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Luteal phase support for in vitro fertilization-embryo transfer – present and future methods to improve successful implantation

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Summary

Purpose: To present reasons for luteal phase deficiency when taking controlled ovarian hyperstimulation (COH) for purposes of inducing multiple oocytes for in vitro fertilization (IVF), and to suggest strategies to overcome the defect. Methods: Treatment options presented include luteal phase support with human chorionic gonadotropin (hCG) injection, progesterone, estradiol, gonadotropin releasing hormone agonists, cytokines, e.g., granulocyte colony stimulating factor, and lymphocyte immunotherapy. Results: hCG and progesterone produce the best results and are comparable or at best a slight edge to hCG but the latter is associated with too high a risk for ovarian hyperstimulation syndrome. Vaginal progesterone is the most efficacious with the least side-effects. Conclusions: Better methods are needed to adequately assess full correction of the luteal phase defect. In some cases the luteal phase defect associated with COH is not correctable and FSH stimulation should be reduced or all embryos frozen and defer transfer to an artificial estrogen progesterone or natural cycle.

Key words: Progesterone; Controlled ovarian hyperstimulation; Human chorionic gonadotropin; Estradiol; Gonadotropin releasing hormone agonist.

Etiology of luteal phase defects with in vitro fertilization-embryo transfer (IVF-ET)

In 1980 Edwards, Steptoe and Purdy suggested that the luteal phase of all stimulated IVF cycles is abnormal [1]. In 1985 and 1989 publications by Check et al., showed lower miscarriage rates in women using clomiphene citrate or human menopausal gonadotropins, not in high dosages as used for IVF but in lower dosages just to achieve ovulation when the luteal phase was supplemented with progesterone [2, 3]. Thus the studies by Check et al. suggested that the luteal phase defect (LPD) reported by Edwards et al. was not related to the process of IVF itself combined with high-dose gonadotropin stimulation but something disruptive about the stimulating drugs.

Further support for this concept was provided by Kerin et al. in 1981 who showed that aspiration of a preovulatory Graafian follicle following spontaneous ovulation did not cause an apparent luteal phase defect [4]. Thus the study by Kerin et al. showed that the removal of large quantities of granulosa cells during oocyte retrieval is not the reason for LPD in stimulated IVF-ET cycles [4].

One study suggested that the injection of human chorionic gonadotropins (hCG) to enable advancement of meiosis to the metaphase II stage would suppress endogenous luteinizing hormone (LH) production by a short loop feedback mechanism and thus causes LPD [5]. However, this potential etiologic factor for LPD in women taking COH for IVF-ET was shown not to be a likely explanation because taking hCG in natural cycles did not down-regulate LH secretion in the luteal phase [6].

The demonstration of LPD from controlled ovarian hyperstimulation (COH) for IVF-ET occurred before the common practice of using gonadotropin-releasing hormone (GnRH) agonist to prevent premature luteinization. Nevertheless, a popular theory arose that LPD was created by the delay in pituitary recovery from suppression by the GnRH agonist [7]. However, if this was the case then the problem would be obviated by the replacement of using a GnRH agonist with a GnRH antagonist protocol. However, Albano et al. published the first of several subsequent studies showing that despite the rapid recovery of pituitary function LPD using GnRH antagonists still persists and pregnancy rates suffer greatly unless supplemented progesterone or hCG injections are given [8]. Thus these studies using GnRH antagonists obviate the popular concept that LPD was related to pituitary suppression by the GnRH agonist.

The prevalent theory today for the etiology of LPD for COH for IVF-ET is related to the supra-physiological concentration of steroids secreted by multiple corpora lutea during the early luteal phase which directly inhibit LH release by negative feedback to the pituitary and the hypothalamus.

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Main Methods of Treating LPD from COH for IVF-ET

Human chorionic gonadotropins

Human chorionic gonadotropin has been found to rescue the corpus luteum in IVF-ET cycles since as early as 1990 [9]. Besides increasing serum estradiol (E2) and progesterone (P) concentrations, hCG may also work by increasing integrin alpha-5, placental protein 14, and relaxin [10-12].

Perhaps by increasing these other luteal peptide hormones besides E2 and P, hCG may be somewhat superior to exclusive P supplementation [13]. Unfortunately luteal support with hCG has been associated with a significant increased risk of ovarian hyperstimulation syndrome [14]. Because of this risk probably P support should be the treatment of choice for most IVF-ET cycles involving the usual COH despite a possible mild superiority in achieving pregnancy with hCG vs P [15]. Human chorionic gonadotropin supplementation could be considered in mild stimulation protocols especially in women with diminished oocyte reserve, women who fail to have sufficient length to the luteal phase or who fail to attain evidence of adequate endometrial P, e.g., failing to attain a homogeneous hyperechogenic endometrial echo pattern by mid-luteal phase despite P therapy, or women who cannot tolerate vaginal or intramuscular P taking standard COH as long as the serum E2 is not too high or there are too many follicles [16, 17].

Progesterone therapy

The two most effective forms of luteal phase P therapy is either intramuscular (IM) or vaginal. The first method of P used for IVF-ET was IM [18]. A large prospective multi-center open label study found no significant differences in pregnancy rates with IM vs vaginal P [19]. Similarly a recent meta-analysis reached the same conclusions [20].

From a side-effect stand point vaginal P is much more tolerated than IM P which can cause severe pain at the injection sites, severe inflammatory reactions with erythema and swelling, and even abscess formation [21]. There are even reports of a rare but very serious complication of eosinophilic pneumonia [22, 23]. For this reason vaginal P is favored over IM administration.

Pregnancy rates in 150 women who conceived with IVF-ET and P was stopped on the day of a positive serum hCG injection or the day after, the day of the oocyte retrieval or even at day 3 ET [40]. One study showed a non-significant trend for higher pregnancy rates with Crinone vs Utrogestan [28]. Another study found fewer side-effects with Crinone vs Utrogestan [29].

A vaginal tablet was introduced to the market – in contrast to the oral micronized P tablet which had been used vaginally by some IVF centers – which was designed to absorb the vaginal secretions and disintegrate into an adhesive powder that adheres to the vaginal epithelium, thus facilitating sustained absorption and also causing less perineal irritation [30]. It is known commercially as Endometrin (vaginal tablets) [31]. We participated in a multi-center randomized prospective trial and found that the dosage of 100 mg 3x/day produced comparable ongoing live delivery rates compared to Crinone 90 mg (8%) once daily [32]. We also participated in a multi-center P trial evaluating a silastic ring with slow release of P (change weekly) and found that it produced comparable pregnancy rates to Crinone. This product will soon be released to the U.S. market.

Oral micronized P (Prometrium) is subjected to first-pass prehepatic and hepatic metabolism and is thus degraded to its 5 alpha and 5 beta reduced metabolites [33]. These reduced metabolites create frequent side-effects of nausea and light headedness and abdominal discomfort. Though the oral Prometrium is able to induce menses in an estrogen replete woman with amenorrhea, studies have shown very little evidence of P secretory effect following endometrial biopsies when given to women with ovarian failure or when estrogen followed by P [34].

In contrast there is an oral P (not available in the United States) that has good oral bioavailability known as dydrogesterone [35]. Appropriate endometrial secretory transformation has been demonstrated with dydrogesterone [36]. A randomized study of IVF-ET cycles found dydrogesterone to produce comparable pregnancy rates compared to micronized P administered vaginally [37]. However other studies found that dydrogesterone is not as effective as vaginal P in establishing in phase endometrium in women with amenorrhea and estrogen deficiency when treated first with estrogen followed by P [38, 39].

There does not appear to be any difference in live delivered pregnancy rates in IVF-ET cycles if P is started the day of hCG injection or the day after, the day of the oocyte retrieval or even at day 3 ET [40]. One study compared the live delivered pregnancy rates in 150 women who conceived with IVF-ET and P was stopped on the day of a positive serum beta-hCG level (78.7%) vs those continuing for three weeks beyond the positive beta-hCG (82.4%) [41]. Obviously, the study did not have enough power to determine if the five extra women who delivered with P extended to three weeks was real or fortuitous but I would rather error on the conservative side and extend the therapy. In fact, it is possible that even an higher successful live delivery rate could be achieved if P was extended to the end of the first trimester as in the practice of this author.
Possible other ancillary therapy for an inadequate corpus luteum

Estrogen supplementation

E2 is secreted in significant amounts by the corpus luteum and reaches a second peak by the mid-luteal phase [42]. During the follicular phase E2 plays a major role in inducing P receptors in the endometrium. Its role in the luteal phase is less clear but it definitely is needed for pregnancies to be maintained. For example, adequate pregnancy rates would not be achieved by embryo transfers using donor oocytes in a graduated estrogen replacement cycle by merely adding P without continuing the E2.

With COH generally there are higher levels of E2 made by the corpus luteum but there are also higher levels of P and yet P supplementation is needed for ideal pregnancy rates following IVF-ET or at least hCG injections to stimulate more P production by the corpus luteum. The question is once there has been adequate priming of the endometrium by follicular phase E2 production with induction of P receptors in the luteal phase is E2 necessary to maintain the progesterone-induced changes in the endometrium? There is a possibility that too much estrogen in the earlier luteal phase may be luteolytic normally by increasing nitric oxide production which causes apoptosis of the luteal cells leading to decreased P production [43-45].

A prospective randomized study added E2 valerate 6 mg to P vaginal suppositories (total 600 mg per day) in patients superovulated but not undergoing IVF-ET and found no difference in outcome [46]. No difference in pregnancy outcome was found with addition of E2 to P vs P alone in a progesterone IVF-ET study using luteal phase GnRH agonist [47]. Some other IVF-ET studies using GnRH agonists have found a mild beneficial effect of adding E2 to P [48, 49]. An IVF-ET study with GnRH antagonists did not find that adding E2 to P was beneficial for improving pregnancy rates in women taking a GnRH antagonist protocol [50].

Luteal phase GnRH agonist

I personally think that adding a GnRH agonist has the most potential to improve live delivered pregnancy rates following COH and IVF-ET since the discovery years ago of using hCG supplementation or P. One of the most fascinating studies was by Tesarik et al. who found that a time mid-luteal nasal spray of buseriline significantly improved live delivered birth rates in estrogen/progesterone primed women receiving donated oocytes [51]. This study showed that it can be beneficial even when there is no corpus luteum [51]. The GnRH agonist could have a direct effect on the endometrium because GnRH receptors in the endometrium have been found [52].

However, the data from Tesarik et al. could also suggest a direct effect of GnRH on the embryo itself [51]. A previous study found that women with singleton pregnancies have higher serum beta-hCG levels when they have had luteal treatment with GnRH agonists compared to pregnant women not receiving a GnRH agonist at the same time post-ovulation [53]. Some data support the concept that the GnRH acts on a GnRH receptor in the placenta and augments hCG output by the early placenta [54].

A subsequent study by Tesarik et al. found that 0.1 mg of triptorelin for six days after oocyte retrieval resulted in increased live delivered pregnancy rates in both GnRH agonist and antagonist IVF-ET cycles versus placebo in which both groups were also supplemented by vaginal P and oral estrogen [55]. We will be presenting data at the 2012 annual meeting of the American Society of Reproductive Medicine showing a 30% in pregnancy rates following embryo transfer but no increase in beta-hCG levels suggesting a direct effect on endometrial GnRH receptors to explain its mechanism of action.

Cytokines

Besides E2 and P which are the major products of the corpus luteum, there are a plethora of cytokines secreted by the corpus luteum. However, based on very high pregnancy rates found in donor oocyte cycles or frozen embryo transfer cycles which are devoid of corpora lutea, it is clear that the secretion of these cytokines is not important for successful pregnancy in most women receiving embryos. However, one cytokine in particular may prove useful for improving the receptivity of the endometrium for successful embryo implantation, and that is granulocyte colony stimulating factor (G-CSF) which is expressed and produced by decidual cells [56-58]. A randomized controlled trial of women with recurrent miscarriage found a significantly improved live delivery rate in women treated with 1 µg/kg/day G-CSF subcutaneously from the mid-luteal phase to the end of the 9th week of gestation [59]. Recently, an intrauterine infusion prior to ovulation of G-CSF was found to significantly increase endometrial thickness in women with persistently thin endometria leading to successful pregnancies in a series of anecdotal cases, and this group is now conducting prospective randomized studies to see if this method could improve embryo implantation following COH and IVF-ET [60].
Methods to determine if luteal support is adequate in IVF-ET cycles

The oldest method to determine adequacy of the luteal phase at the endometrial level is the endometrial biopsy [61]. However, there are great difficulties in the interpretation and many IVF-ET centers no longer use this technique [62]. There are data suggesting that failure to attain a homogeneous hyperechogenic (HH) endometrial echo pattern by mid-luteal phase is associated with much lower pregnancy rates [63]. Increasing the dosage of P from mid-luteal phase in those women not attaining an HH pattern has resulted in improved pregnancy rates [64].

There is evidence that one way P may help implantation is by interacting with P receptors that are induced de novo on gamma/delta T cells by the allogeneic stimulus of the fetal semi allograft causing the expression of the immunomodulatory protein known as the P induced blocking factor (PIBF) [65, 66]. This protein has been found to suppress natural killer cell activity especially by stabilizing perforin granules and causes a shift from thymic helper (TH) cytokines (which evoke cellular immune responses) to TH2 cytokines (which evoke a humoral response which may be immuno-protective) [67, 68].

Recently an ELISA method has been developed that can rapidly measure PIBF [69]. We will be presenting research at the 2012 American Society of Reproductive Medicine meeting showing that PIBF is not only present in high amounts 3 days after embryo transfer but it actually begins to rise 1 hour after embryo transfer. Our ELISA method differs slightly from that of Hudic et al. [69]. If this can be determined it could prompt raising the dosage of P, since we have determined that most of the time low PIBF levels are related to inadequate P exposure [70].

The two main factors involved in secreting PIBF from gamma/delta T cells are the development of P receptors in the gamma/delta T cells and exposure to P at the maternal fetal interface. In a minority of cases the relatively low immunogenicity of the fetus is sometimes for some reason insufficient to properly induce sufficient P receptors in the gamma/delta T cells leading to poor PIBF expression despite adequate P exposure. In this case, injection of the far more immunogenic lymphocytes (i.e., lymphocyte immunotherapy) can increase PIBF expression [71]. Through a highly debatable subject, one study found a 51% ongoing/live delivered pregnancy rate following lymphocyte immunotherapy in women undergoing another IVF-ET cycle (despite failing to achieve a live pregnancy even with average of 4.3 previous embryo transfers) vs only 16% in the controls [72]. Progesterone-induced blocking factor secretion does not require a corpus luteum [73]. However, there are various cytokines and interleukins involved in PIBF secretion but this suggests they are not corpus luteum derived. Thus if a certain level of PIBF after a certain time after implantation is found to be associated with a positive outcome, there is potential for a treatment paradigm of first using P to increase PIBF and if ineffective try lymphocyte immunotherapy.

Other strategies taking into consideration that present techniques fail to completely identify full correction of the luteal phase defect by COH

Sometimes a single case report can accurately present the crux of a problem. A case was reported of a woman with polycystic ovarian syndrome and amenorrhea who failed to conceive despite six years of ovulation induction with luteal phase P support with no other infertility factors identified. Subsequently she had ten IVF-ET cycles with 92 embryos transferred in three of the world's foremost IVF centers but still failed to conceive. A decision was made to perform another IVF cycle but to purposely cryopreserve all the embryos and defer ET in case the COH caused a hostile uterine environment that was not correctable by P supplementation. She was successful with a live delivery following her first and only frozen ET at age 38 [74].

Interestingly three months following her delivery she menstruated and had nine regular menstrual cycles for the first time in her life. She returned for a consult to have another frozen ET, and she was in the early luteal phase. She had not taken P in her previous cycles. She was placed on P this cycle and we prepared for frozen ET the next cycle but she conceived in this natural cycle with just intercourse [75]. This case shows that luteal phase defects exist even without COH especially in women of advanced reproductive age, and P therapy in the luteal phase may successfully improve chance of a live pregnancy [76]. It should be remembered that she failed to conceive after six years of ovulation induction and P supplementation showing that follicle maturing drugs even when used in mild dosages can create an endometrial defect not correctable by P or hCG [74, 75].

Though many IVF centers find very low pregnancy rates following COH and IVF-ET in women with diminished ovarian oocyte reserve and elevated day 3 serum FSH, it has been clearly demonstrated that this observation is not related to defective oocytes prone to meiosis errors but more related to the adverse effect of high FSH dosage [77, 78]. This adverse effect can be negated to a large degree by using mild ovarian stimulation and avoids even low dosages of FSH when the serum FSH level is elevated, and in some instances lowering the FSH by ethinyl estradiol or other means [79-81].

These data underscore the importance of a good cryopreservation program to maximize the chance of conception from a given COH oocyte retrieval cycle and to consider that failure to conceive following the transfer of a normal appearing embryo could be from the COH itself [82, 83].

High-dose COH and cryopreservation may not be the ideal answer for women with diminished oocyte reserve since the adverse effect may be in the embryo itself interfering with some implantation factor present on the embryo [84].
References


Luteal phase support for in vitro fertilization-embryo transfer – present and future methods to improve successful implantation


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Original Articles

Reproductive Biology Section

No evidence to support the concept that low serum dehydroepiandrosterone (DHEA) sulfate (s) levels are associated with less oocyte production or lower pregnancy rates

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The University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School at Camden
Cooper Hospital/University Medical Center, Department of Obstetrics and Gynecology
Division of Reproductive Endocrinology & Infertility, Camden, NJ (USA)

Summary

**Purpose:** To determine if in a population of women with diminished oocyte reserve as evidenced by day 3 serum follicle stimulating hormone (FSH) levels > 12 mIU/ml women with lower dehydroepiandrosterone sulfate (DHEA-s) levels produce fewer oocytes or have lower pregnancy rates following in vitro fertilization-embryo transfer (IVF-ET) compared to women with higher levels. **Methods:** The women were divided into poor responders (producing ≤ 4 oocytes) following oocyte retrieval or good responders (≥ 5 oocytes). Mean DHEA-s levels were compared in poor vs good responders and in the subgroups of those who conceived vs those who did not conceive. **Results:** The data clearly showed no association with low DHEA-s levels and response to controlled ovarian hyperstimulation or pregnancy rates. **Conclusions:** In women with elevated serum FSH low DHEA levels do not suggest that supplementation with DHEA would improve response or pregnancy rate. These data do not preclude the possibility that there is a small subset of women with normal oocyte reserve who also fail to respond to controlled ovarian hyperstimulation for some unknown reason and the problem could be remediable by DHEA supplementation.

**Key words:** Dehydroepiandrosterone sulfate levels; Diminished oocyte reserve; In vitro fertilization-embryo transfer.

Introduction

There are studies that demonstrate marked augmentation of serum insulin-like growth factor I (IGF-I) with oral administration of physiological dehydroepiandrosterone (DHEA) [1-4]. In a small uncontrolled case series of five women Casson et al. claimed that the mean serum estradiol (E2) increased in poor responders to gonadotropins from 266 pg/ml to 939.8 pg/ml after two months of DHEA pretreatment [4]. Casson et al. suggested that improvement in response to gonadotropins by pre-treatment with DHEA is particularly suited for women with low DHEA sulfate levels [4]. It should be noted that the five poor responder cases reported by Casson et al. all had normal serum follicle stimulating hormone (FSH) levels [4].

Subsequently a case was reported by Barad and Gleicher which showed that a 43-year-old woman who had responded poorly with only two oocytes retrieved increased to 18 oocytes with nine months of DHEA supplementation [5]. This was followed by a larger case-controlled series (n = 25) by the same authors who claimed that 16 weeks of DHEA supplementation (25 mg 3 x daily) led to a significantly increased number of fertilized oocytes and an increase number of day 3 embryos [6]. In contrast to the cases reported by Casson et al. where the day 3 serum FSH was normal, the study by Barad and Gleicher only used women with elevated day 3 serum FSH [4-6].

A more recent study by Sonmezzer et al. also suggested improved ovarian response and pregnancy rates and embryo quality in poor responders following DHEA supplementation [7].

A previous study by Haning et al. found that plasma DHEA-s serves as a prehormone for 48% of follicular fluid testosterone during treatment with menotropins [8]. Thus Casson et al. suggested that one possible explanation for their observation of improved responses to gonadotropins in poor responders by pretreatment with DHEA may be by increasing the follicular androgen pool and thus increasing advancement of pre-antral to antral follicles which could then respond to gonadotropins [4].

The present retrospective study aimed to further explore the impact of low serum DHEA-s levels in women with diminished oocyte reserve as evidenced by increased day 3 serum FSH by comparing DHEA levels in those with a lower yield of oocytes vs those with a better response. The study would also determine if lower levels of serum DHEA-s may be associated with lower pregnancy rates following embryo transfer.
Materials and Methods

This was a retrospective study. This study used a population of women < 40 years old with diminished oocyte reserves undergoing in vitro fertilization-embryo transfer (IVF-ET). Diminished oocyte reserve was defined by a day 3 serum follicle stimulating hormone (FSH) level ≥ 12 mIU/ml. DHEA sulfate levels were drawn prior to initiation of follicle stimulating drugs.

Subjects were grouped according to whether the woman was a relatively poor responder (≤ 4 oocytes retrieved) or a relatively good responder (≥ 5 oocytes). Only the first IVF cycle was evaluated to determine oocyte response.

Subjects were also grouped according to those achieving a pregnancy vs those who did not, both in their first cycle and then within three cycles of embryo transfers. Mean DHEA-s levels were compared in each of these cohorts.

Analysis of variance (ANOVA) was used to compare the mean levels of DHEA. Pregnancy rates were compared using Fisher’s exact test.

Results

Evaluating 39 first IVF-ET cycles, the mean serum DHEA-s (µg/dl) for poor responders who did not conceive was 148.0 ± 82.8 vs 143.9 ± 47.7 for those that did conceive (p = NS, ANOVA). The mean serum DHEA-s (µg/dl) for relatively good responders who did not conceive (14 cycles) was 138.5 ± 26.4 vs 103.5 ± 41.9 for those that did conceive (p = NS, ANOVA). In fact, opposite to what might have been expected the mean DHEA-s (µg/dl) level for poor responders (145.7 ± 83.3) was significantly higher than the mean level of good responders (122.3 ± 40.4) (p < .05, ANOVA).

Without controlling for ovarian response and given only one cycle to conceive, 24 IVF-ET cycles had positive pregnancy tests and 37 IVF-ET cycles had negative tests. The mean DHEA-s (µg/dl) levels were 119.1 ± 50.3 for those who conceived vs 151.8 ± 85.6 for those not conceiving (p < .05, ANOVA). Opposite to expectation the mean level of DHEA-s was significantly higher in those women failing to conceive.

Given three cycles to conceive, 52 had positive pregnancy tests and 86 had negative tests. The mean DHEA-s levels were 140.7 ± 57.3 for those who conceived vs 154.1 ± 91.4 for those not conceiving (p = NS, ANOVA).

Because the range of DHEA-s levels was so large we also looked at the difference in pregnancy rates for the ten lowest values and the ten highest values. The mean DHEA-s was 70.4 ± 23.2 for the 10 lowest values vs 243.2 ± 64.4 for the ten highest values (p ≤ 0.05, ANOVA). The clinical (gestational sac at 8 weeks) and exogenous gonadotropins because the chronic elevation of serum FSH down-regulates the FSH receptors in the follicles [9]. This concept was supported by the demonstration that lowering the elevated serum FSH in women in apparent menopause by ethinyl estradiol (the advantage of ethinyl estradiol over other estrogens is that it does not contribute to the serum estradiol measurement) or GnRH agonists or antagonists [18-20].

Thus based on not finding any difference in response when serum DHEA-s levels are low vs normal or with lower DHEA levels in poor responders who fail to achieve pregnancies vs succeed in achieving pregnancies we suspect that the mechanism of improvement in the studies using DHEA supplementation is related to the suppression of FSH and restoration of FSH receptors in the follicle both from conversion of DHEA to estradiol and also resting the ovaries from previous treatment with high levels of exogenous gonadotropins. It has been shown that in women in apparent menopause and in poor responders good follicular response can be achieved by merely stopping the follicle maturing drugs [21, 22].

Based on these other aforementioned studies using DHEA supplementation which showed a positive benefit in response and pregnancy rates, DHEA supplementation can be added to the pharmacologic options in resistant ovary syndrome and premature ovarian failure [23]. The recorded pregnancy rates for this present study support the concept that quality of oocytes from women with diminished oocyte reserve are much more comparable to their age peers with normal oocyte reserve than women of advanced reproductive age [24].

Though it appears that low DHEA-s levels are not etiologic in the low response and poor pregnancy rates seen following traditional higher dosage gonadotropin stimulation, it should be recalled that the original study by Cassen et al. evaluated poor responders with normal serum FSH levels but low DHEA-s [4]. Perhaps this is a unique group where low DHEA-s levels may play an etiologic role in the poor oocyte response. If indeed the mechanism of improvement in ovarian response after pretreatment with DHEA is related to its conversion to estra-
dihydroepiandrosterone and ethinyl estradiol may be more reliable in FSH suppression and devoid of androgen side effects.

References


The sharing of eggs by infertile women who are trying to conceive themselves with an egg recipient for financial advantages does not jeopardize the donor’s chance of conceiving

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Summary

Purpose: To determine if the sharing of oocytes by an infertile woman with an egg recipient for financial advantages has any negative impact on the success rate for the donor. Methods: A matched controlled study was performed comparing pregnancy outcome of women undergoing in vitro fertilization-embryo transfer (IVF-ET) but sharing half of their eggs with a recipient vs women undergoing IVF-ET but not sharing oocytes. Results: Even though more women sharing oocytes deferred fresh transfer and cryopreserved the embryos because of a greater likelihood of ovarian hyperstimulation syndrome, there was no difference in pregnancy rates between the two groups after their first embryo transfer whether it was with fresh or frozen-thawed embryos. Conclusions: Sharing of oocytes by a woman undergoing IVF-ET does not jeopardize her chance of a successful outcome following embryo transfer.

Key words: Infertile egg donors; Sharing of oocytes; Recipient; Pregnancy rates.

Introduction

One source of donor oocytes for recipients in need of oocytes is from infertile women willing to share their harvest of oocytes [1]. The donation is usually associated with some type of relief of the financial burden for the donor’s in vitro fertilization (IVF) cycle.

There are data showing that the pregnancy and implantation rate in recipients using eggs from infertile donors are not reduced when compared to paid donors [2]. One question that arises, however, is whether the sharing of oocytes may be at the expense of a reduction in the pregnancy rate of the donors.

The present study evaluated the outcome of women undergoing controlled ovarian hyperstimulation and oocyte retrieval with sharing half of the oocytes retrieved with a recipient vs women who were not egg donors keeping all the oocytes themselves.

Materials and Methods

Over an 8-year-period infertile women donating half of their retrieved oocytes to recipients in exchange for free IVF services were matched to the next woman going through IVF who did not share oocytes. The match had to be in the same year, the age of patient within six months and the number of eggs retrieved within one (but could be two if otherwise matching would not be done in same year), and the same infertility diagnosis. Pregnancy outcome following the first fresh embryo transfer was then compared.

Sometimes because of the risk for ovarian hyperstimulation, all embryos were frozen. Therefore, the pregnancy rates were also calculated according to the pregnancy rate per first transfer which would include the first frozen embryo transfer if the fresh one was deferred. All embryos were transferred on day three.

Results

There were 325 infertile egg donors having IVF and egg retrieval donating half the eggs to a recipient compared to 325 matched women undergoing IVF-ET who were not donating any eggs. There were 194 fresh embryo transfers of > 2 embryos in donors vs 256 in non-donors.

The results are shown in Table 1. There were no significant differences in clinical or ongoing/delivered pregnancy rates or implantation rates.

There were 101 retrievals in donors where the fresh embryo transfer was deferred but a frozen embryo transfer had been performed within the same time of the study period. The comparable number for non-donors was 46.

The usual reason for not transferring fresh embryos was the risk for OHSS (n = 91 for donors vs 36 in non-donors). Fresh ET was deferred for inadequate endometrial thickness (< 8 mm) or adverse homogeneous hyper-echogenic pattern upon evaluating the endometrium by sonography in ten women in each group.

Embryos were formed in all retrievals. The difference of 22 donors and 15 non-donors having oocyte retrievals and no transfer (fresh or frozen) was that at the close of the study, they had not transferred the frozen embryo as yet.

The pregnancy outcome of the first embryo transfer (fresh or frozen) is shown in Table 2. There were no significant differences in the clinical or ongoing/delivered

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The sharing of eggs by infertile women who are trying to conceive themselves with an egg recipient for financial advantages etc.

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Table 1. — Pregnancy outcome in first fresh embryo transfer of at least two embryos in donors vs non-donors.

<table>
<thead>
<tr>
<th></th>
<th>Donors</th>
<th>Non-donors</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. retrievals</td>
<td>325</td>
<td>325</td>
</tr>
<tr>
<td>No. fresh transfers</td>
<td>202</td>
<td>264</td>
</tr>
<tr>
<td>No. transfers ≥ 2 embryos</td>
<td>194</td>
<td>256</td>
</tr>
<tr>
<td>Average age</td>
<td>31.0</td>
<td>31.1</td>
</tr>
<tr>
<td>No. follicles</td>
<td>8962</td>
<td>4713</td>
</tr>
<tr>
<td>No. eggs retrieved</td>
<td>3500</td>
<td>3406</td>
</tr>
<tr>
<td>No. metaphase II eggs</td>
<td>2938</td>
<td>2801</td>
</tr>
<tr>
<td>No. inseminated</td>
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<td>3060</td>
</tr>
<tr>
<td>No. fertilized</td>
<td>2165</td>
<td>1993</td>
</tr>
<tr>
<td>No. pregnancies</td>
<td>111</td>
<td>135</td>
</tr>
<tr>
<td>% pregnant/ transfers</td>
<td>57.2</td>
<td>52.7</td>
</tr>
<tr>
<td>No. clinical pregnancies</td>
<td>105</td>
<td>124</td>
</tr>
<tr>
<td>% clinical/ transfers</td>
<td>54.1</td>
<td>48.4</td>
</tr>
<tr>
<td>No. chemical</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>No. ectopic</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>No. live/delivered</td>
<td>97</td>
<td>115</td>
</tr>
<tr>
<td>% live/delivered</td>
<td>50.0</td>
<td>44.9</td>
</tr>
<tr>
<td>No. miscarriages</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>% miscarriages</td>
<td>8.6</td>
<td>8.9</td>
</tr>
<tr>
<td>No. embryos transferred</td>
<td>567</td>
<td>780</td>
</tr>
<tr>
<td>Average no. embryos transferred</td>
<td>2.9</td>
<td>3.0</td>
</tr>
<tr>
<td>No. sacs implanted</td>
<td>167</td>
<td>200</td>
</tr>
<tr>
<td>Implantation rate (%)</td>
<td>29.5</td>
<td>25.6</td>
</tr>
<tr>
<td>No. twins</td>
<td>37</td>
<td>43</td>
</tr>
<tr>
<td>% twins/clinical pregnancy</td>
<td>35.2</td>
<td>34.7</td>
</tr>
<tr>
<td>No. triplets</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>% triplets/clinical pregnancy</td>
<td>11.4</td>
<td>7.3</td>
</tr>
<tr>
<td>No. quads</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>% quads/clinical pregnancy</td>
<td>1.0</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Table 2. — Pregnancy outcome in first transfer (includes frozen ET).

<table>
<thead>
<tr>
<th></th>
<th>Donors</th>
<th>Non-donors</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. retrievals</td>
<td>325</td>
<td>325</td>
</tr>
<tr>
<td>No. transfers</td>
<td>303</td>
<td>310</td>
</tr>
<tr>
<td>No. pregnancies</td>
<td>167</td>
<td>158</td>
</tr>
<tr>
<td>% pregnant/ transfers</td>
<td>55.1</td>
<td>51.0</td>
</tr>
<tr>
<td>No. clinical</td>
<td>152</td>
<td>145</td>
</tr>
<tr>
<td>% clinical/ transfers</td>
<td>50.2</td>
<td>46.8</td>
</tr>
<tr>
<td>No. chemical</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>No. live/delivered</td>
<td>138</td>
<td>134</td>
</tr>
<tr>
<td>% live/delivered</td>
<td>45.5</td>
<td>43.2</td>
</tr>
<tr>
<td>No. SAB/TAB/ET</td>
<td>20</td>
<td>14</td>
</tr>
<tr>
<td>% SAB/clinical pregnancy</td>
<td>13.2</td>
<td>9.7</td>
</tr>
<tr>
<td>No. embryos transferred</td>
<td>875</td>
<td>929</td>
</tr>
<tr>
<td>Average no. embryos transferred</td>
<td>2.9</td>
<td>3.0</td>
</tr>
<tr>
<td>No. sacs implanted</td>
<td>243</td>
<td>232</td>
</tr>
<tr>
<td>Implantation rate (%)</td>
<td>27.8</td>
<td>25.0</td>
</tr>
<tr>
<td>No. twins</td>
<td>56</td>
<td>47</td>
</tr>
<tr>
<td>% twins/clinical pregnancy</td>
<td>36.8</td>
<td>32.4</td>
</tr>
<tr>
<td>No. triplets</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>% triplets/clinical pregnancy</td>
<td>7.9</td>
<td>8.3</td>
</tr>
<tr>
<td>No. quads</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>% quads/clinical pregnancy</td>
<td>1.3</td>
<td>2.1</td>
</tr>
</tbody>
</table>

Discussion

The greater number of first transfers being frozen in donors vs non-donors might be related to the tendency for the doctor monitoring the cycle to push the gonadotropins a little more aggressively in oocyte donors to insure enough eggs for donors and recipients. This policy did not seem to adversely affect pregnancy outcome since there was no difference in pregnancy rates or implantation rates following the first embryo transfer despite the fact that frozen transfers accounted for 33.3% of first transfers for donors vs 14.8% of non-donors.

Theoretically the fact that the donor gives away half of the eggs might lead to less top quality embryos to transfer which could theoretically lower the pregnancy rate. The fact that the pregnancy rate in the first fresh embryo transfer showed no difference indicates this was not the case.

The only disadvantage of sharing oocytes is fewer embryos available for future frozen embryo transfers. However, many still have frozen embryos available after the first transfer. If not they could always donate again.

References


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Comparison of pregnancy rates following frozen embryo transfer according to the reason for freezing: risk of ovarian hyperstimulation vs inadequate endometrial thickness

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Introduction

Two reasons for cryopreserving all embryos during in vitro fertilization (IVF) and deferring fresh embryo transfer (ET) is either the risk of ovarian hyperstimulation syndrome (OHSS) or inadequate endometrial thickness at time of peak follicular maturation. Some studies suggest that the frozen/thawed embryos derived from women who hyperstimulate produce normal pregnancy rates and others suggest an inferior pregnancy rate [1, 2]. Though using a graduated oral/vaginal estrogen regimen may increase endometrial thickness, sometimes it does not and the ET occurs despite inferior endometrial thickness. Lower pregnancy rates are found with thin endometria in the late proliferative phase [3].

The objective of this study was to evaluate the efficacy of a modified slow cool embryo freezing technique and at the same time evaluate the effect of deferring ET and cryopreserving all embryos because of risk of OHSS vs cryopreservation for inadequate endometrial thickness.

Materials and Methods

A retrospective study over a 10-year time period was conducted. A requirement was that the source of the embryos were from women who deferred fresh ET either for risk of OHSS or inadequate endometrial thickness in the late proliferative phase on the day of human chorionic gonadotropin (hCG).

A modified slow cool cryopreservation technique was employed in which the programmable freezer was replaced by a rate controlled alcohol bath freezer [4]. A simplified thawing procedure removed the cryoprotectant, 1,2 propanediol, in one step [4]. Assisted embryo hatching was performed on day 3 embryos prior to transfer [5].

Deferring fresh ET with cryopreservation of all embryos was performed for a serum estradiol > 5000 pg/ml or > 25 follicles of ≥ 12 mm average diameter or endometrial thickness of ≤ 7 mm on the day of hCG injection. Women with endometrial synechiae were excluded.

Results

Pregnancy rates for frozen ET in patients whose fresh transfer was deferred is shown in Table 1. For women ≤ age 39 years of age, the clinical pregnancy rate (PR) following frozen ET for those deferring fresh ET for OHSS was 42.8% (389/893) vs 28.7% (25/87) for thin endometria (chi-square analysis showed p = 0.01). The live delivered PRs were 31.9% (285/893) vs 21.8% (19/87) (p = 0.07, chi-square analysis).

Discussion

The lower pregnancy rate for those deferring fresh transfer for thin endometria vs those deferring for risk of OHSS can be partially explained by still failing to attain adequate endometrial thickness despite a graduated estrogen regimen. These data show that attaining an adequate endometrial thickness is important not just for controlled ovarian hyperstimulation (COH) cycles with fresh ET but also for frozen ET without COH.

These data also show that a graduated oral estrogen regimen in lieu of COH is not necessarily a panacea for inadequate endometrial thickness on COH cycles.

Purposeful cryopreservation for risk of OHSS is performed much more commonly than for thin endometria.

Key words: Embryo cryopreservation; Ovarian hyperstimulation; Endometrial thickness.
Table 1. — Pregnancy rates following frozen ET according to reason for deferring fresh ET.

<table>
<thead>
<tr>
<th>Reason for Deferring</th>
<th>Age ≤ 35</th>
<th>36-39</th>
<th>Age ≤ 35</th>
<th>36-39</th>
</tr>
</thead>
<tbody>
<tr>
<td># transfers</td>
<td>746</td>
<td>147</td>
<td>52</td>
<td>35</td>
</tr>
<tr>
<td>% pregnant/transfer</td>
<td>50.9</td>
<td>36.1</td>
<td>40.4</td>
<td>34.3</td>
</tr>
<tr>
<td>(chemical)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% clinical/trans</td>
<td>44.9</td>
<td>32.7</td>
<td>28.8</td>
<td>28.6</td>
</tr>
<tr>
<td>(ultrasound at 8 weeks)</td>
<td>40.8</td>
<td>29.3</td>
<td>25.0</td>
<td>25.7</td>
</tr>
<tr>
<td>% delivered</td>
<td>38.2</td>
<td>27.2</td>
<td>21.2</td>
<td>22.9</td>
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<td>Avg. # embryos transferred</td>
<td>3.1</td>
<td>3.7</td>
<td>2.9</td>
<td>3.5</td>
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<td>Implantation rate (%)</td>
<td>22.2</td>
<td>13.5</td>
<td>15.1</td>
<td>9.0</td>
</tr>
</tbody>
</table>

References


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Induction of final follicle maturation with a gonadotropin-releasing hormone agonist in women at risk of ovarian hyperstimulation syndrome undergoing gonadotropin stimulation and intrauterine insemination: proof-of-concept study

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Summary

Objective: To evaluate the reproductive performance and safety of gonadotropin-stimulated intrauterine insemination (IUI) cycles in women at risk for ovarian hyperstimulation syndrome (OHSS) when final follicle maturation was induced using a gonadotropin-releasing hormone (GnRH) agonist. Materials and Methods: Thirty-three women presenting with a history of cancelled ovarian stimulation for fear of OHSS, underwent repeat gonadotropin ovarian stimulation for IUI. They were all found to be at high-risk for OHSS once more, and were counseled to receive a GnRH agonist to trigger final follicle maturation before insemination. GnRH agonist trigger of ovulation (triptorelin) was given subcutaneously every 12 hours in three repeated doses: 0.3, 0.2, 0.2 mg, respectively. Results: Induction with the agonist was associated with a 30.3% take-home pregnancy rate and 20% miscarriage rate. Multiple pregnancy rates were 26.7%. There were no reported cases of clinically significant moderate/severe ovarian hyperstimulation syndrome. Conclusions: The use of a GnRH agonist to trigger final follicle maturation in stimulated cycles of hyper responders was associated with a favorable reproductive outcome and no incidence of OHSS. The rate of multiple pregnancies nevertheless was found to be uncontrollably elevated, raising serious concerns regarding the safety of this protocol in standard clinical practice in the context of IUI.

Key words: Gonadotropin-releasing hormone agonist; Follicle maturation; Intrauterine insemination; Multiple gestations; Ovarian hyperstimulation syndrome.

Introduction

With the widespread use of human menopausal gonadotropins (hMG) for ovarian stimulation, the risk of developing ovarian hyperstimulation syndrome (OHSS), recognized as the most serious complication of fertility management, has become a primary concern. The most effective secondary preventive measure to avoid OHSS remains the withholding of the human chorionic gonadotropin (hCG) trigger dose and the cancellation of the treatment cycle. The substitution of hCG with a GnRH agonist to trigger final follicle maturation in the context of in vitro fertilization (IVF) and intracytoplasmatic sperm injection (ICSI) cycles has been reported in literature [1, 2]. The induced luteinizing hormone (LH) surge was demonstrated to initiate first meiotic division events successfully, leading to collection of competent metaphase II oocytes [1-5]. The application of the same trigger technique in the context of IUI by contrast has been poorly investigated. For IUI treatment cycles to achieve a successful outcome, the additional steps of follicle rupture and oocyte release are required. It is known through animal data that LH requirements, in terms of both duration and amplitude of the surge, are much more demanding for mechanical follicle rupture to occur than for meiosis to resume [6, 7]. Clinically, very few studies have reported the use of a GnRH agonist for the triggering of ovulation prior to IUI [8-10].

The aim of this interventional analysis was one of a proof-of-concept, which was to investigate whether the use of a GnRH agonist trigger protocol in gonadotropin-stimulated IUI cycles can achieve conception, while monitoring the risks of OHSS and multiple pregnancies.

Materials and Methods

Patients

All initiated gonadotropin-stimulated IUI cycles that ended in a cycle cancellation for risk of OHSS and which were performed at a tertiary fertility center between June 1, 2003 and December 31, 2004 were reviewed. The criteria for cycle cancellation were: (a) estradiol levels \( \geq 1,500 \) pg/ml and/or (b) four or more follicles \( \geq 12 \) mm in diameter. Inclusion criteria included: (a) history of primary infertility; (b) women age range: 18 to 38 years; and (c) first attempted IUI cycle. Exclusion criteria included: (a) evidence of obstructive tubal disease; (b) moderate/severe endometriosis (ASRM Stage III/IV); and (c) and moderate/severe male factor infertility (< 5 million motile sperm post-wash).

Thirty-nine women who in subsequent stimulation cycles were found to meet again the aforementioned cancellation crite-
ria were considered for study. Thirty-three of them were consented to receive a GnRH agonist to trigger follicle maturation instead of cancelling their cycle. Approval for the study was obtained from the Institutional Review Board.

Ovarian stimulation

All eligible women were stimulated using human menopausal gonadotropins (hMG) beginning on day three of their menstrual cycle. Triggering of ovulation using the GnRH agonist was performed when at least one follicle measured ≥ 18 mm in diameter, in the following manner: triptorelin in repeated subcutaneous doses of 0.3, 0.2, and 0.2 mg at 12-hour intervals. IUI was scheduled 36 to 40 hours following the first triggering dose. Potential adverse effects, namely OHSS and multiple gestations, were thoroughly explained to all women throughout the study period. All patients approved to undergo selective embryo reduction in the event of high-order multiple gestations.

Follow-up and management

The women received 4 mg of estradiol and 40 mg of synthetic progesterone orally and daily in two divided doses. Luteal supplementation was begun on the day following IUI and continued until gestational week 11 in the event of pregnancy. OHSS was diagnosed according to the criteria by Navot et al. [11]. The identification of at least one intrauterine gestational sac by ultrasound was considered the basis for a clinical pregnancy. A miscarriage was defined as a pregnancy loss following verification of a positive urinary pregnancy test and prior to 20 weeks of gestation. A pregnancy was considered ongoing if viability was documented by ultrasound beyond 20 weeks of gestation.

Outcome measures

The primary outcome measures were the rates of clinical/ongoing/take-home pregnancies and miscarriages rates. The secondary outcome measures were the incidence of clinically significant moderate/severe OHSS and multiple gestations.

Statistical analysis

Metric and nominal variables were analyzed descriptively for lack of controls. Values are expressed as mean ± standard deviation.

Results

Thirty-three women, who received the GnRH agonist for final follicle trigger, met the inclusion criteria and were considered for evaluation. Patient demographics and stimulation characteristics are shown in Table 1. The primary causes of infertility were polycystic ovary syndrome (PCOS) (n = 23), mild male factor infertility (n = 5), unexplained infertility (n = 4), and minimal endometriosis (n = 1). Mean final serum E2 levels on the day of GnRH agonist trigger were 3,337.5 ± 871.9 pg/ml (range: 1,700 pg/ml to 4,987 pg/ml).

Outcome measures are presented in Table 2. Fifteen (45.5%) of the 33 women cycles achieved pregnancy, of whom three (20.0%) had a miscarriage and four (26.7%) had twin gestations. No cases of high-order multiple gestations were reported. One set of twins were lost at 22 weeks gestation when they presented full cervical dilatation. No incidents of clinically significant moderate or severe OHSS were reported. Ultrasound examinations of the ovaries performed during the menstrual phase of the next cycle in 18 women and between seven and eight weeks gestation in 15 women, revealed normal-appearing ovaries with absence of any corpora lutea exceeding ≥ 12 mm in diameter.

Discussion

The findings of this proof-of-concept study have shown that the use of the GnRH agonist, triptorelin, to trigger final follicle maturation in gonadotropin stimulated IUI cycles at risk for OHSS, is associated with a highly-favorable reproductive outcome, compared to IUI outcomes reported in the literature. These findings constitute an indirect confirmation of the occurrence of LH-mediated ovarian events, namely resumption of meiosis, follicle rupture, and oocyte release following GnRH agonist trigger. These findings contrast with those of IVF/ICSI cycles, in which a series of randomized clinical trials lately casted serious doubts regarding the reproductive performance of GnRH agonists when used as substitutes for hCG for ovulation triggering [3-5]. Although the GnRH agonist trigger protocol was not shown to influence the number and quality of oocytes retrieved [3-5], lower pregnancy and higher miscarriage rates were repeatedly reported in these studies [3, 4, 12]. The compromised reproductive outcome associated with IVF/ICSI cycles
was believed to be due to endometrial/luteal insufficiency, rather than the result of an oocyte/embryo developmental problem [13]. The unusually favorable pregnancy rates found in this study could be interpreted on the basis of the following explanations: (a) estradiol/progesterone combined luteal supplementation was continued until 11 weeks gestation. The early interruption of luteal supplementation was associated with unusually elevated miscarriage rates in one study [3]; (b) it is also possible that the high number of ovulated oocytes from super-ovulated ovaries may have leveraged the presumed endometrial/luteal insufficiency associated with GnRH agonist trigger protocols, acting as a salvage mechanism. Challenging a defective endometrium with a high number of fertilized oocytes may have counterbalanced its restricted reproductive performance.

Proposed mechanisms for the protective effect offered by GnRH agonists against OHSS are the prolonged pituitary down-regulation with reduction of LH support to the corpora lutea and the initiation of intracellular signaling cascade mediating apoptosis with irreversible luteolysis [10, 14-17]. The findings of the present study demonstrated the complete elimination of moderate and severe OHSS in 33 cycles undergoing ovarian gonadotropin stimulation for IUI, despite a very high number of pre-ovulatory follicles, highly-elevated mean final E2 serum levels, and the presence of past history of cycle cancellation due to risk of OHSS (Table 1). The ultrasound findings of normal looking ovaries devoid of any corpora lutea > 12 mm diameter following failed cycles and during the first trimester of pregnancy supports the irreversible luteolysis hypothesis proposed by Nevo et al. [17] despite rising endogenous placental hCG titers. Nevertheless, a final conclusion on this topic cannot be made without proper quantification of risk through prospective controlled trials in larger female populations. It should also be noted that the GnRH agonist trigger protocol described in this study was arbitrarily modified from the conventional single dose to the repeated dose regimen.

The finding of a high multiple pregnancy rate associated with the GnRH agonist trigger protocol when used in the context of IUI cycles in high-responding women, is probably the most significant drawback of this treatment approach. The uncontrollable nature of this complication with potentially very serious perinatal sequel is a major source of concern. The absence of high-order multiple pregnancies despite a high number of pre-ovulatory follicles at the time of ovulation trigger is however intriguing. Potential explanations may be traced to the previously proposed endometrial/luteal insufficiency reducing implantation rates [13, 18-20], and/or to a crowding effect within the super-ovulated ovary increasing the chance of rupture for superficial follicles only and entrapment for deeper ones.

The main limitations of this study were the retrospective collection of the data and the uncontrolled nature of the study, which may have overestimated the size effect of the intervention. The actual effect of the GnRH agonist trigger protocol in pregnancy rates in IUI cycles may also have been skewed due to selection bias as a result of the inclusion criteria in which only young women with high ovarian response and absent tubal and/or male factor infertility were included.

In conclusion, despite the good favorable impact of GnRH agonists in pregnancy outcome and risk of OHSS when used to trigger final follicle maturation in women at risk for OHSS undergoing IUI cycles, this study does not provide safety data regarding the risk of high-order multiple gestations. It should be acknowledged that standard clinical practice dictates mono- or bi-follicular development in stimulated IUI cycles, and that multi-follicular growth is best managed by cycle cancellation.

References


Induction of final follicle maturation with a gonadotropin-releasing hormone agonist in women at risk of ovarian etc.


*Endocrine*, 2000, 12, 61.


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Oocytes from women of advanced reproductive age do not appear to have an increased risk of zona pellucida hardening

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Summary

Purpose: To test the hypothesis that very advanced reproductive age leads to an increased risk of zona pellucida hardening by comparing fertilization rates and rates of failed fertilization with conventional oocyte insemination vs intracytoplasmic sperm injection (ICSI). Methods: Women aged ≥ 45 were given the option of ICSI vs conventional oocyte insemination in circumstances where there was no male factor present. They were advised of the theoretical benefit of ICSI overcoming zona hardening but also advised that ICSI might lower pregnancy rates and is more costly. Results: There were 364 cycles evaluated and 74% chose ICSI. The failed fertilization rates were similar – 28.4% (66/232) for ICSI vs 26.5% (35/132) for conventional insemination. The fertilization rates were similar 56.0% with ICSI vs 50.9% with conventional oocyte insemination. Conclusion: Based on similar fertilization and failed fertilization rates in women aged ≥ 45 undergoing IVF-ET, zona hardening does not appear to be a consequence of reproductive aging.

Key words: Reproductive aging; Zona pellucida hardening; Intracytoplasmic sperm injection; In vitro fertilization-embryo transfer; Pregnancy rates.

Introduction

Some researchers suggest that oocytes obtained from women of very advanced reproductive age may also have increased zona pellucida hardening. Intracytoplasmic sperm injection (ICSI) may overcome zona hardening in these patients. The objective of this study was to determine if the oocytes obtained from women of advanced reproductive age (≥ age 45) have a tendency toward zona hardening. The assumption was made that if zona hardening was present, the use of ICSI would increase the fertilization rate and decrease the frequency of failed fertilization when compared with conventional insemination.

Materials and Methods

Women aged ≥ 45 undergoing in vitro fertilization (IVF-ET) with husbands with normal semen parameters (≥ 8 x 10⁶ million motile sperm per ml, morphology by strict criteria ≥ 4% normal, absence of antisperm antibodies, hypoosmotic swelling test ≥ 50%) were given the option of inseminating their oocytes conventionally or by ICSI. They were advised of the possible benefit of ICSI for zona pellucida hardening, though there was little proof. Furthermore, they were advised that there are some data suggesting higher pregnancy rates with conventional oocyte insemination, which is a much less costly option [1-4].

Results

The fertilization rates of those women having IVF cycles with no fertilization and poor fertilization were compared according to method of fertilization. The results are shown in Table I.

There were no significant differences between fertilization rates whether conventional insemination or ICSI was performed (chi-square). Similarly, choosing conventional oocyte insemination did not lead to higher rates of failed fertilization.

Discussion

The data clearly show that there is no evidence to support the concept of zona pellucida hardening with advanced reproductive age. A comparison of fertilization rates following conventional oocyte insemination vs ICSI in women ≥ age 45 were similar, as was the rate of completely failed zona hardening.

One would argue as to how one can be sure that ICSI can overcome zona hardening. The evidence for this is provided by the marked improvement of fertilization rates of cryopreserved oocytes (which are well known to have zona hardening) by ICSI [5].

References

Oocytes from women of advanced reproductive age do not appear to have an increased risk of zona pellucida hardening.

Table 1. — Fertilization rates of women 45 and older using their own eggs according to method of fertilization.

<table>
<thead>
<tr>
<th></th>
<th>ICSI</th>
<th>Total eggs</th>
<th>Conventional</th>
<th>1 egg retrieved</th>
<th>Conventional</th>
<th>2 or more eggs retrieved</th>
<th>Conventional</th>
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</thead>
<tbody>
<tr>
<td># cycles</td>
<td>232</td>
<td>132</td>
<td>117</td>
<td>63</td>
<td>115</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td># eggs retrieved</td>
<td>727</td>
<td>414</td>
<td>117</td>
<td>63</td>
<td>610</td>
<td>351</td>
<td></td>
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<tr>
<td># metaphase II retrieved</td>
<td>586</td>
<td>399</td>
<td>117</td>
<td>63</td>
<td>469</td>
<td>308</td>
<td></td>
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<tr>
<td># inseminated</td>
<td>586</td>
<td>399</td>
<td>117</td>
<td>63</td>
<td>469</td>
<td>336</td>
<td></td>
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<tr>
<td># fertilized</td>
<td>328</td>
<td>203</td>
<td>65</td>
<td>39</td>
<td>263</td>
<td>164</td>
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<tr>
<td>% fertilized (zero excluded)</td>
<td>56.0</td>
<td>50.9</td>
<td>55.6</td>
<td>61.9</td>
<td>56.1</td>
<td>48.8</td>
<td></td>
</tr>
<tr>
<td># cycles w/0% fert.</td>
<td>66</td>
<td>35</td>
<td>52</td>
<td>24</td>
<td>14</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>% cycles w/0% fert.</td>
<td>28.4</td>
<td>26.5</td>
<td>44.4</td>
<td>38.1</td>
<td>12.2</td>
<td>15.9</td>
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</table>


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General Section

Ethnic disparities in perioperative management among foreigners residing in Japan

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Summary

The objectives of this research were to examine the current status of perioperative treatment among foreigners, to elucidate the health status/outcome disparities that contribute to ethnic differences, and to recommend counter-measures to rectify these ethnic disparities. The authors identified 36 non-Japanese and 111 Japanese females who underwent gynecological surgery from 2004 to 2009 at a single institution. Electronic medical records were reviewed and telephone survey was conducted in order to obtain patient background, preoperative, operative, and postoperative data. The non-Japanese group showed significantly larger number of uninsured, shorter length of stay (LOS), higher rate of emergency surgery, and higher cases of spinal anesthesia. There were significant differences in length of residency in Japan and LOS among four foreign countries. Seventy-nine percent of patients contacted by phone understood informed consent from doctors, 73.7% understood explanation in operating room (OR), and 84.2% understood explanation from anesthesiologists. This research was the first survey of the ethnic disparities in perioperative management among foreign patients treated in Osaka. The authors have demonstrated differences in operative method, emergency surgery, anesthesia, and American Society of Anesthesiologists physical status (ASA-PS) due to the difference in disease structure, language, and culture. It is recommended that the barriers between non-Japanese patients and medical staff are rectified during the perioperative period when mutual understanding is needed the most.

Key words: Foreign-residents in Japan; Perioperative; Gynecological surgery; Ethnic disparities.

Introduction

Since the 1980s, the number of registered foreign residents in Japan has increased continuously and their stay tends to be prolonged. According to a survey conducted by the Ministry of Justice [1] in 2008, the number of legally-registered foreigners had reached 2,217,000, which corresponds to 1.74% of the overall Japanese population.

Many foreign residents are subjected to cultural stress due to issues such as language, racial discrimination, education, healthcare, and these stresses prevent them from conceiving, delivering, and raising children in Japan [2-5]. For example, the current foreigner program in maternal and child healthcare (MCH), such as providing the MCH handbook in other languages, is not working to full capacity and is far from reaching the objectives of providing quality and accessible services to foreign residents. The majority of foreign residents are unaware of the range of services offered for maternal and child healthcare [6]. Population statistics for foreign residents in Japan show that 74% are in the reproductive age group [6] and their prolonged stay indicates that a further increase in them with gynecological and obstetric chronic illness who will undergo surgery can be expected. The number of perioperative medical errors which induce serious health disorders are expected to increase due to the rise in the overall number of surgical operations.

Studies of health inequalities have been the subject of vast quantities of research within the last decade, and address the significant differences with respect to perioperative treatment, health status, and outcome according to countries such as the United States, England, and so on. Numerous studies have found that races such as Hispanics and Africans are likely to have less clinical follow up and worse clinical outcomes as compared to Caucasians [7, 8]. Hispanics and Africans are in worse health conditions from the beginning of their hospitalization. Even if communicated, it is difficult for these ethnic groups to obtain enough information and knowledge about their diseases due to race and educational level [9, 10]. A recent study found that socio-economic status (SES) is strongly associated to patients’ choice of their treatment methods [11, 12]. Evidence that ethnicity and race are predictors of screening disparities, treatment variations, and health outcomes has been reported in medical and surgical literature [13-18]. However, there is no national report evaluating health disparities in perioperative treatment/health between non-Japanese and Japanese patients. Language barriers and cultural differences may become an obstacle to appropriate healthcare, and can induce misinterpretation even if translated [19, 20].

Thus, the purpose of the study was to examine the current status of perioperative treatment among foreigners residing in Japan, to elucidate the health status/outcome disparities that contribute to ethnic difference, and to recommend counter-measures to rectify those ethnic disparities.
Materials and Methods

Subjects
The authors identified 36 non-Japanese patients and 111 Japanese patients who underwent gynecological surgery from 2004 to 2009 at General Hospital C which serves as the primary provider of acute health care needs for Osaka and Eastern Hyogo district dwellers. In this study, the authors included obstetrical surgery, such as cesarean section during gynecological surgery.

Record review
The authors conducted a retrospective analysis of data including descriptive analysis of relevant clinical variables. Electronic medical records were reviewed in order to obtain data in four major categories: patient background, preoperative, operative, and postoperative data. These data were compared between non-Japanese and Japanese patients. Patient background included: age, length of residency in Japan, nationality, native language, marital status, husband’s nationality, Japanese language level, and insurance status. Preoperative data included the American Society of Anesthesiologists physical status (ASA-PS) and use of interpreter. ASA-PS grading system was created is imply to assess the degree of a patient’s “sickness” or “physical state” prior to selecting the anesthetic or prior to performing surgery. Operative data included: comprehension of explanation in operating room (OR), emergency surgery, operative method, anesthesia method, intraoperative blood loss, hemoglobin (Hb) and platelet levels. Postoperative data included: pain control frequency (analgesic use), patient-controlled analgesia (PCA) frequency, ambulation, length of stay (LOS), removal of urinary and epidural catheters, and medical cost.

Telephone survey
Telephone survey was conducted in order to obtain data in three major categories: comprehension of informed consent/anesthesia explanation, patients’ supportive environment, and use of interpreter. Scale ranging from “very good” to “not at all” was used to evaluate foreign patients’ own comprehensions of informed consent and anesthesia explanation.

Ethical consideration
The authors obtained an appropriate approval from the Institutional Review Boards at Kobe University before conducting the survey.

Statistical analyses
The differences in the distribution of baseline characteristics between the two (non-Japanese and Japanese) or four ethnic groups (Chinese, Korean, Philippino, and Latin American) were tested using the Chi-square test or Fisher’s exact test, the Mann-Whitney’s U test, the Student’s t-test, and Kruskal-Wallis test for categorical and dichotomous variables and analyses of variance (ANOVA) with Scheffe’s F post hoc test, Student’s t-test, Mann-Whitney’s U test, and Kruskal-Wallis test for comparison of continuous variables. Quantitative data were presented as means and standard deviations. All statistical analyses were carried out using STATCEL. Statistical significance was expressed as p values and 95% confidence intervals (CIs). A p value of < 0.05 was considered significant.

Results
Characteristics of patients are shown in Table 1. Foreign patients’ length of residency in Japan was 8.4 ± 6.6 (mean ± SD) years. Mean age at hospitalization was significantly younger in non-Japanese compared to Japanese (29.8 years vs 32.9 years, p = 0.02). There was no significant difference in marital status (p = 0.05). The distribution of husbands’ nationality was Japanese (44.8%), same nationality (24.1%), different nationality (3.5%), and unknown (27.6%). The distribution of foreign patients’ nationality was Chinese (19.4%), Korean (13.9%), Philippino (22.2%), Peruvian (5.6%), Brazilian (5.6%), and others (33.3%). The distribution of Japanese skill was daily (55.6%), babble (19.4%), scarce (13.9%), and unknown (11.1%). Larger proportions of non-Japanese had no insurance compared to Japanese patients (8.3% versus 0.0%, p < 0.01). LOS was significantly shorter in non-Japanese compared to Japanese patients (p < 0.01).

Comparison of operative method and anesthesia between non-Japanese and Japanese patients is shown in Table 2. There were 147 cases of gynecological surgery analyzed, including cesarean section (n = 66), ectopic pregnancy surgery (n = 18), ovarian tumor surgery (n = 28), hysterectomy (n = 16), and others (n = 14). Larger proportions of non-Japanese patients were diagnosed with ectopic pregnancy compared to Japanese patients (27.8% vs 7.2%, p < 0.01).

Table 1. — Comparison of patient characteristics between non-Japanese and Japanese patients.

<table>
<thead>
<tr>
<th></th>
<th>Non-Japanese (n = 36)</th>
<th>Japanese (n = 111)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stay in Japan (yrs)</td>
<td>19 8.4 ± 6.6</td>
<td>111 32.9 ± 6.8</td>
<td>0.02</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>36 29.8 ± 7.2</td>
<td>111 32.9 ± 6.8</td>
<td>0.02</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>28 77.8%</td>
<td>85 76.6%</td>
<td>0.50</td>
</tr>
<tr>
<td>Partner</td>
<td>1 2.8</td>
<td>2 1.8</td>
<td></td>
</tr>
<tr>
<td>Unmarried</td>
<td>6 16.7</td>
<td>13 11.7</td>
<td></td>
</tr>
<tr>
<td>Husband</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japanese</td>
<td>13 44.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Same nationality</td>
<td>7 24.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Different nationality</td>
<td>1 3.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nationality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chinese</td>
<td>7 19.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Korean</td>
<td>5 13.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Philippino</td>
<td>8 22.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peruvian</td>
<td>2 5.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brazilian</td>
<td>2 5.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>12 33.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japanese</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>20 55.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Babble</td>
<td>7 19.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scarce</td>
<td>5 13.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insurance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>32 88.9%</td>
<td>110 99.1%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>No</td>
<td>3 8.3</td>
<td>0 0.0</td>
<td></td>
</tr>
<tr>
<td>Public assistance</td>
<td>1 2.8</td>
<td>1 0.9</td>
<td></td>
</tr>
<tr>
<td>Length of stay (LOS)</td>
<td>36 7.9 ± 2.6</td>
<td>111 10.4 ± 7.2</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Medical cost (1000 yen)</td>
<td>36 227.0 ± 194.6</td>
<td>111 270.0 ± 181.9</td>
<td>0.92</td>
</tr>
</tbody>
</table>

Statistical Analysis: Student’s t-test, Chi-square test, and Mann-Whitney’s U test.
Moreover, LOS tended to be shorter in non-Japanese than in Japanese patients (6.5 ± 1.2 days vs 8.0 ± 2.6 days, \( p = 0.16 \)). Among cesarean section cases, the proportion of low ASA-PS tended to be higher (66.7% vs 48.1%, \( p = 0.20 \)) in non-Japanese patients. In addition, the amount of blood loss tended to be lower (10.2 ± 4.3 × 10^2 g versus 9.3 ± 6.9 × 10^2 g, \( p = 0.20 \)) and Hb level tended to be higher (11.2 ± 1.4 mg/dl versus 10.6 ± 1.3 mg/dl, \( p = 0.14 \)) in non-Japanese patients.

Comparison of perioperative data among four nationalities is shown in Table 5. Among four nationalities including Chinese, Korean, Philippino, and Latin American, certain differences were found in the length of residence in Japan (\( p = 0.045 \)) and LOS (\( p < 0.01 \)) in Latin Americans than that in Chinese, Koreans, or Philippinos. Latin Americans tended to have higher body mass index (BMI) (\( p = 0.06 \)), about four times higher frequency of using pain control (\( p = 0.10 \)), and higher percentage of planned surgeries (\( p = 0.16 \)) compared to other three nationalities. Latin Americans had a higher proportion of high (2-3E) ASA-PS (\( p = 0.42 \)) and Chinese were more likely to refuse to shower (\( p = 0.69 \)) during the postoperative period.

Foreign patients’ comprehension of informed consent is shown in Table 6. Among 36 foreign patients, 52.8% (19 patients) could be contacted by phone. Patients contacted were: 36.8% Chinese, 21.1% Philippino, 16.8% Korean, 10.5% Brazilian, and 5.3% Indian, Russian, and Bolivian. Their Japanese language level showed: 63.2% daily, 15.8% babble, and 21.1% scarce. Overall 78.9% of patients contacted understood informed consent from surgical doctors, 73.7% of patients understood explanation in OR, and 84.2% of patients understood explanation provided by anesthesiologists. Almost all patients contacted had some support from family or friends, and about half of patients contacted had the use of an interpreter.

### Discussion

This was the first survey reporting ethnic disparities in perioperative management among foreign patients in a hospital in Osaka. This research showed major differences in operative method, emergency surgery, anaesthesia, and ASA-PS due to the difference in disease structure, language, and culture. In detail, differences and tendencies were found between non-Japanese and Japanese surgeries such as ectopic pregnancy surgery and cesarean section. At postoperative period, shower frequency tended to differ between non-Japanese and Japanese patients. Moreover, differences were found among four nationalities such as Chinese, Korean, Philippino, and Latin American. During the telephone survey, a large number of patients stated that they had good comprehension of the informed consents and those with Japanese ability were somewhat good to excellent. In other words, it was more difficult for patients that did not speak Japanese.

In overall gynecological patients, foreigners have shown to correlate with multiple factors: age, insurance, LOS, operative method, emergency surgery, anesthesia

---

Table 3. — Comparison of postoperative events between non-Japanese and Japanese patients.

<table>
<thead>
<tr>
<th>Event</th>
<th>Non-Japanese (n = 36)</th>
<th>Japanese (n = 111)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shower</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>25</td>
<td>89</td>
<td>0.18</td>
</tr>
<tr>
<td>No</td>
<td>11</td>
<td>22</td>
<td>0.46</td>
</tr>
<tr>
<td>Use of PCA (times)</td>
<td>36</td>
<td>111</td>
<td>0.94</td>
</tr>
<tr>
<td>Pain control (times)</td>
<td>17</td>
<td>82</td>
<td>0.26</td>
</tr>
<tr>
<td>PCA removal (day)</td>
<td>17</td>
<td>75</td>
<td>0.55</td>
</tr>
<tr>
<td>Urine catheter removal (day)</td>
<td>35</td>
<td>111</td>
<td>0.46</td>
</tr>
</tbody>
</table>

Statistical Analysis: Student’s t-test, Chi-square test, and Mann-Whitney’s U test.

The percentage of emergency surgery was significantly higher in non-Japanese compared to Japanese patients (41.7% vs 23.4%, \( p = 0.02 \)), and the proportion of spinal anesthesia was significantly higher in non-Japanese patients (36.1% vs 19.8%, \( p = 0.03 \)), while the proportion of epidural combined anesthesia was lower. The percentage of low (1-1E) ASA-PS tended to be higher in non-Japanese compared to Japanese patients (63.9% vs 47.7%, \( p = 0.09 \)).

Comparison of postoperative events between non-Japanese and Japanese patients is shown in Table 3. Non-Japanese patients tended to refuse to shower during the postoperative period (\( p = 0.18 \)). There was no significant difference in the use of pain control or removal of PCA or urine catheter between non-Japanese and Japanese patients.

Comparison of perioperative data in ectopic pregnancy surgery and cesarean section between non-Japanese and Japanese patients is shown in Table 4. Among ectopic pregnancy cases, the amount of intraoperative blood loss was significantly lower in non-Japanese than in Japanese patients (\( p < 0.01 \)). The percentage of low ASA-PS and laparotomy cases tended to be higher (60.0% vs 25.0%, \( p = 0.16 \)) in non-Japanese compared to Japanese patients.

## Statistical Analysis

Student’s t-test, Chi-square test, and Mann-Whitney’s U test.

method, and intraoperative blood loss. Number of foreign patients insisted to be discharged from hospital prior to the recommended date mainly due to the following reasons: did not want to be absent from work, stress due to a language barrier between the patient and medical staff, did not like hospital meals, and so on. The rate of uninsured patients was significantly higher in non-Japanese patients. In particular, 8.3% of foreign patients who had no insurance were put under difficult circumstances or had a weak social status such as: using an insurance card which belonged to a friend, delivering a child whose father was a married man, and so on. Lack of insurance may affect mortality by several mechanisms because payer status can affect many processes of healthcare [21]. In addition, it was also noted that there was a gap in the knowledge of foreigners regarding the medical insurance system [6], and this resulted in foreign patients without health insurance.

Emergency surgery was strongly associated with the high percentage of ectopic pregnant surgery, the increased use of spinal anesthesia, and decreased use of a combination of epidural and spinal anesthesia, which played a role in ethnic variations in the receipt of the treatments. Nevertheless, foreign patients showed a ten-

### Table 4. — Comparison of perioperative data between non-Japanese and Japanese patients who underwent ectopic pregnancy surgery or cesarean section.

<table>
<thead>
<tr>
<th></th>
<th>Ectopic pregnancy surgery</th>
<th>Cesarean section</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-Japanese (n = 10)</td>
<td>Japanese (n = 8)</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Planned</td>
<td>3 30.0%</td>
<td>2 25.0%</td>
</tr>
<tr>
<td>Emergency</td>
<td>7 70.0%</td>
<td>6 75.0%</td>
</tr>
<tr>
<td>ASA-PS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-1E</td>
<td>6 60.0%</td>
<td>2 25.0%</td>
</tr>
<tr>
<td>2-3E</td>
<td>4 40.0%</td>
<td>6 75.0%</td>
</tr>
<tr>
<td>Operative approach</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laparotomy</td>
<td>6 60.0%</td>
<td>2 25.0%</td>
</tr>
<tr>
<td>Laparoscopy</td>
<td>4 40.0%</td>
<td>6 75.0%</td>
</tr>
<tr>
<td>Blood loss (x10^2 g)</td>
<td>10 3.9 ± 6.3</td>
<td>8 11.6 ± 6.2</td>
</tr>
<tr>
<td>Hb (mg/dl)</td>
<td>9 11.4 ± 1.9</td>
<td>8 11.2 ± 1.5</td>
</tr>
<tr>
<td>PLT (10^4/mm^3)</td>
<td>9 28.4 ± 18.5</td>
<td>8 25.2 ± 5.4</td>
</tr>
<tr>
<td>LOS (day)</td>
<td>10 6.5 ± 1.2</td>
<td>8 8.0 ± 2.6</td>
</tr>
<tr>
<td>Pain control (times)</td>
<td>10 1.7 ± 1.9</td>
<td>8 2.0 ± 1.5</td>
</tr>
<tr>
<td>Blood loss (x10^2 g)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb (mg/dl)</td>
<td>9 11.4 ± 1.9</td>
<td>8 11.2 ± 1.5</td>
</tr>
<tr>
<td>PLT (10^4/mm^3)</td>
<td>9 28.4 ± 18.5</td>
<td>8 25.2 ± 5.4</td>
</tr>
<tr>
<td>LOS (day)</td>
<td>10 6.5 ± 1.2</td>
<td>8 8.0 ± 2.6</td>
</tr>
<tr>
<td>Pain control (times)</td>
<td>10 1.7 ± 1.9</td>
<td>8 2.0 ± 1.5</td>
</tr>
</tbody>
</table>

### Table 5. — Comparison among four nationalities (Chinese, Korean, Philippino, and Latin American).

<table>
<thead>
<tr>
<th></th>
<th>Chinese (n = 7)</th>
<th>Korean (n = 5)</th>
<th>Philippino (n = 8)</th>
<th>Latin American (n = 6)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
</tr>
<tr>
<td>Stay in Japan (yrs)</td>
<td>7 6.3 ± 4.3</td>
<td>3 17.0 ± 8.9</td>
<td>4 11.5 ± 5.7</td>
<td>3 5.3 ± 1.2</td>
<td>0.045</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>7 29.7 ± 4.0</td>
<td>5 32.6 ± 5.5</td>
<td>8 28.5 ± 7.6</td>
<td>6 31.3 ± 13.7</td>
<td>0.53</td>
</tr>
<tr>
<td>Blood loss (x10^2 g)</td>
<td>7 4.6 ± 7.5</td>
<td>5 7.1 ± 4.4</td>
<td>8 3.0 ± 4.5</td>
<td>6 5.7 ± 5.0</td>
<td>0.35</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>7 21.3 ± 4.5</td>
<td>4 20.9 ± 3.5</td>
<td>8 20.9 ± 2.8</td>
<td>5 30.4 ± 9.5</td>
<td>0.06</td>
</tr>
<tr>
<td>Hb (mg/dl)</td>
<td>7 11.5 ± 1.7</td>
<td>4 10.6 ± 2.4</td>
<td>8 11.0 ± 1.1</td>
<td>6 12.2 ± 1.6</td>
<td>0.52</td>
</tr>
<tr>
<td>PLT (10^4/mm^3)</td>
<td>6 20.1 ± 5.5</td>
<td>4 24.2 ± 3.0</td>
<td>8 33.3 ± 18.6</td>
<td>6 25.8 ± 4.7</td>
<td>0.13</td>
</tr>
<tr>
<td>Pain control (times)</td>
<td>7 1.0 ± 1.2</td>
<td>5 1.4 ± 2.1</td>
<td>8 1.1 ± 1.6</td>
<td>6 4.7 ± 3.1</td>
<td>0.10</td>
</tr>
<tr>
<td>Use of PCA (times)</td>
<td>3 0.7 ± 1.2</td>
<td>2 3.5 ± 3.5</td>
<td>5 1.2 ± 1.1</td>
<td>3 4.7 ± 4.6</td>
<td>0.25</td>
</tr>
<tr>
<td>PCA removal (day)</td>
<td>6 2.0 ± 1.2</td>
<td>3 3.0 ± 1.0</td>
<td>4 3.0 ± 1.4</td>
<td>3 3.7 ± 1.5</td>
<td>0.46</td>
</tr>
<tr>
<td>LOS (day)</td>
<td>7 6.1 ± 2.3</td>
<td>5 6.8 ± 1.3</td>
<td>8 7.6 ± 2.4</td>
<td>6 10.8 ± 1.7</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Medical cost (1000 yen)</td>
<td>7 277.1 ± 242.9</td>
<td>5 225.0 ± 258.8</td>
<td>8 244.6 ± 248.8</td>
<td>6 185.3 ± 106.9</td>
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<tr>
<td>Sugery</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Planned</td>
<td>5 71.4%</td>
<td>1 20.0%</td>
<td>5 62.5%</td>
<td>5 83.3%</td>
<td>0.16</td>
</tr>
<tr>
<td>Emergency</td>
<td>2 28.6</td>
<td>4 80.0%</td>
<td>3 37.5</td>
<td>1 16.7</td>
<td></td>
</tr>
<tr>
<td>Operative approach</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-laparoscopy</td>
<td>5 71.4%</td>
<td>4 80.0%</td>
<td>5 62.5%</td>
<td>6 100.0%</td>
<td>0.41</td>
</tr>
<tr>
<td>Laparoscopy</td>
<td>2 28.6</td>
<td>1 20.0%</td>
<td>3 37.5</td>
<td>0 0.0</td>
<td></td>
</tr>
<tr>
<td>ASA-PS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-1E</td>
<td>5 71.4%</td>
<td>3 60.0%</td>
<td>6 75.0%</td>
<td>2 33.3%</td>
<td>0.42</td>
</tr>
<tr>
<td>2-3E</td>
<td>2 28.6</td>
<td>2 40.0%</td>
<td>2 25.0</td>
<td>4 66.7</td>
<td></td>
</tr>
<tr>
<td>Shower</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4 57.1%</td>
<td>4 80.0%</td>
<td>5 62.5%</td>
<td>5 83.3%</td>
<td>0.69</td>
</tr>
<tr>
<td>No</td>
<td>3 42.9%</td>
<td>1 20.0%</td>
<td>3 37.5</td>
<td>1 16.7</td>
<td></td>
</tr>
</tbody>
</table>

Statistic Analysis: Kruskal-Wallis test, ANOVA, Scheffe’s F post hoc test, Chi-square test, and Mann-Whitney’s U test.
Table 6. — Foreign patients' comprehension and supportive environment.

<table>
<thead>
<tr>
<th>Nationalities n = 19</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Chinese</td>
<td>7</td>
</tr>
<tr>
<td>Philippino</td>
<td>4</td>
</tr>
<tr>
<td>Korean</td>
<td>3</td>
</tr>
<tr>
<td>Brazilian</td>
<td>2</td>
</tr>
<tr>
<td>Indian</td>
<td>1</td>
</tr>
<tr>
<td>Russian</td>
<td>1</td>
</tr>
<tr>
<td>Bolivian</td>
<td>1</td>
</tr>
</tbody>
</table>

Informed consent from Doctors

| Very good | 13 |
| Good      |  2 |
| Not so much |  2 |
| Not at all  |  0 |
| Unknown    |  2 |

Explanation in OR

| Very good | 13 |
| Good      |  1 |
| Not so much |  1 |
| Not at all  |  2 |
| Unknown    |  2 |

Explanation from anesthesiologist

| Very good | 14 |
| Good      |  2 |
| Not so much |  1 |
| Not at all  |  0 |
| Unknown    |  2 |

Supportive environment

| Family |  7 |
| Friend  |  7 |
| Both    | 11 |
| Unknown | 11 |
| Interpreter | 4 |
| Always  |  4 |
| Sometimes |  7 |
| Not at all  |  7 |
| Unknown    |  1 |

It seemed likely that the data including emergency surgery, anesthesia method, and ASA-PS were affected by the difference in disease structure between non-Japanese and Japanese patients. In order to exclude the effect of disease structure, further analysis was conducted focusing on specific diseases, such as cesarean section and ectopic pregnancy surgery between non-Japanese and Japanese patients. In ectopic pregnancy patients, foreigners' health status/outcome showed to correlate with multiple factors, such as: lower ASA-PS, higher rate of laparotomy, less intraoperative blood loss, and shorter LOS among foreign patients with ectopic pregnancy under laparotomy. In reference to the fact that severity of ectopic pregnancy was associated with intraoperative blood loss, it renders generalizations or conclusions difficult. There were some patients who wanted to be discharged within a few days after surgery. These circumstances may possibly be incurred by somewhat insufficient informed consents on laparoscopic surgery performed in foreign patients. Regarding cesarean section, foreign patients' health status/outcome showed to be correlated with several factors: higher rate of emergency surgery and lower ASA-PS.

In this study population, nationalities were associated with length of residence in Japan, pain control frequency, ASA-PS, and shower frequency. Interestingly, it seemed that Latin Americans were more likely to feel pain. However, Japanese nurses often perceived that Latin Americans overreacted to pain, but were actually prone to feel pain. Larger number of Latin Americans had higher ASA-PS and had complications such as electrocardiogram (ECG) abnormality, diabetes mellitus, obesity, and so forth. Chinese were more likely to refuse to shower during the postoperative period compared to Japanese, which showed a good example of a cultural difference in hygiene standards. This may be caused by their cultural background that Chinese do not shower after surgery or delivery.

During the telephone survey, most patients stated that they understood informed consents, explanation in OR, and explanation from anesthesiologists. However, this self-administered telephone survey was doubtful because the ward nurses who administered care to foreign patients attested that they all had difficulties in language (data not shown). In addition, it also seemed likely that those with higher grade of ASA-PS patients such as Latin Americans, were unable to be contacted by telephone. Foreigners from Latin America tended to speak only their native language and were unable to speak neither Japanese nor English. As a consequence, they tended to have wider communication gaps compared to other foreigners. Further approach such as interpreter system and multilingual resources should also overcome language barriers: some aspects which are clarified through another research during the perioperative period.

This study had several potential limitations. First, the proportions of foreigners’ nationalities may not be representative of Japan today; second, foreign patients who were thought to have less Japanese ability such as Latin Americans, were difficult to be contacted by telephone; third, a recall bias could have affected the telephone survey results; and fourth, the authors had a limited number of data which made a further factor analysis difficult. However, this retrospective analysis was the first report of a comparison between non-Japanese and Japanese patients undergoing gynecological surgery in Japan. The strength of this study was the two-way approach applied to foreign patients by record review and telephone survey.
In conclusion, the authors have reported the first survey of the ethnic disparities in perioperative management among foreign patients in a certain hospital in Osaka. This research showed major differences in operative method, emergency surgery, anesthesia, and ASA-PS due to the difference in disease structure, language, and culture. In detail, differences and tendencies were found between non-Japanese and Japanese patient surgeries such as ectopic pregnancy surgery and cesarean section. It is recommended that the barriers between non-Japanese patients and medical staff are rectified during perioperative times when mutual understanding is immensely required. Future investigations should include an analysis of a larger number of subjects.

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References


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Kobe 654-0142 (Japan)
e-mail: matsuoh@tiger.kobe-u.ac.jp
Obstetric and neonatal outcome after assisted fertilization and spontaneous conception: a comparative study

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³Interbalkan Medical Center, Thessaloniki
⁴Technological Educational Institute of Thessaloniki (Greece)

Summary

Purpose: The widespread use of assisted reproduction technology (ART) is accompanied by concerns for potential adverse outcomes. The aim of the present study was to evaluate the impact of ART in obstetric and neonatal outcome. Methods: Data from labor ward records from 913 consecutive births were analyzed retrospectively, and the obstetric and neonatal outcomes of pregnancies after ART were compared with those after natural conception. Results: No major complications were noted after ART. A higher probability of cesarean section, lower gestational age at birth, lower birth weight and hospitalization in the Neonatal Intensive Care Unit (NICU) was noted after ART, as compared with spontaneous conception. However, after exclusion of multifetal pregnancies, there was no significant difference in outcomes, except for cesarean section rates. Conclusions: The higher proportion of multiple pregnancies after ART is associated with lower gestational age at birth, lower birth weights and higher NICU hospitalization rates.

Key words: Obstetric outcome; Neonatal outcome; Assisted reproductive technology (ART); Assisted fertilization; Spontaneous conception.

Introduction

The use of assisted reproductive technology (ART) has been steadily increasing in Western countries during the last decades [1, 2]. The main reason for this trend appears to be the ever increasing number of women in developed countries who delay pregnancy until an age when fertility is physiologically reduced. This phenomenon is further enforced by the advances and availability of ART itself [3]. A major concern arising from the widespread use of ART is the potential risk of poor obstetric and postnatal outcomes after assisted fertilization, as compared with spontaneous conception. However, it is not clear if the causes of such adverse outcomes lie in ART or infertility itself and/or the etiology of infertility [3-5]. Furthermore, though it is well established that iatrogenic multifetal pregnancies lead to increased morbidity after assisted fertilization, it is not yet clear to what extent singleton pregnancies might lead to increased morbidity as well [3, 4]. In the present study, the obstetric and neonatal outcomes of births from pregnancies after use of ART were compared to those of pregnancies after natural conception.

Materials and Methods

Study population

Data from 913 consecutive pregnancies were analyzed retrospectively. Data was retrieved from labor ward records, containing information about pregnancies beyond 24 weeks gestation ending in birth (either live or stillbirth). Obstetric and neonatal outcomes in pregnancies after use of ART were compared with those after spontaneous conception in both multiple and singleton (n = 913), as well as in singleton pregnancies only (n = 863), after exclusion of multiple pregnancies. Obstetric outcome was compared in terms of mode of delivery and gestational age at birth; neonatal outcome was compared in terms of birth weight and days of hospitalization in the Neonatal Intensive Care Unit (NICU). Infertility treatment and obstetric management were conducted in all cases by one consultant in a single IVF-center and a single medical center for obstetric care. Prenatal screening for fetal anomalies was also performed by one specialist.

Statistical analysis

Linear or logistic regression analyses were conducted to adjust for covariates when the outcome was continuous or binary, respectively. The independent samples t-test was used to check for differences of continuous variables (e.g., mean days in NICU). The chi-square test was used to check for independence of nominal variables. P values less than 0.05 were considered statistically significant. SPSS version 16.0 (Chicago, IL, USA) was used for the analyses.

Results

Patient characteristics

An overview of descriptive statistical data from all singleton and multiple pregnancies ending in birth regarding maternal age, parity, mode of delivery, gestational age at birth, birth weight, and hospitalization in the NICU after assisted fertilization or spontaneous conception is presented in Table 1. After exclusion of multiple pregnancies, an overview of similar data from singleton pregnancies is presented in Table 2. No data from first and second trimester miscarriages were available in labor ward records.
Table 1. — Overview of data from all pregnancies (multiple and singleton).

<table>
<thead>
<tr>
<th></th>
<th>Assisted fertilization</th>
<th>Spontaneous conception</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of pregnancies</td>
<td>126</td>
<td>787</td>
</tr>
<tr>
<td>Number of neonates</td>
<td>160</td>
<td>804</td>
</tr>
<tr>
<td>Mean maternal age</td>
<td>35.6 (± 4.9)</td>
<td>32.5 (± 4.2)</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Para 0</td>
<td>104</td>
<td>413</td>
</tr>
<tr>
<td>Para ≥ 1</td>
<td>22</td>
<td>374</td>
</tr>
<tr>
<td>Mode of delivery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal</td>
<td>27</td>
<td>413</td>
</tr>
<tr>
<td>Cesarean</td>
<td>99</td>
<td>374</td>
</tr>
<tr>
<td>Gestational age at birth</td>
<td>36.5 (± 1.8)</td>
<td>37.2 (± 1.6)</td>
</tr>
<tr>
<td>≥ 37 weeks</td>
<td>83</td>
<td>663</td>
</tr>
<tr>
<td>&lt; 37 weeks</td>
<td>43</td>
<td>124</td>
</tr>
<tr>
<td>Birth weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>2,645.2 (± 661.7)</td>
<td>3,039.2 (± 503.7)</td>
</tr>
<tr>
<td>≥ 2,500 g</td>
<td>103</td>
<td>719</td>
</tr>
<tr>
<td>&lt; 2,500 g</td>
<td>57</td>
<td>85</td>
</tr>
<tr>
<td>NICU*</td>
<td>46</td>
<td>88</td>
</tr>
</tbody>
</table>

* Number of neonates hospitalized.

Table 2. — Overview of data from singleton pregnancies only.

<table>
<thead>
<tr>
<th></th>
<th>Assisted fertilization</th>
<th>Spontaneous conception</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of pregnancies</td>
<td>93</td>
<td>770</td>
</tr>
<tr>
<td>Mean maternal age</td>
<td>35.7 (± 4.9)</td>
<td>32.4 (± 4.2)</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Para 0</td>
<td>80</td>
<td>402</td>
</tr>
<tr>
<td>Para ≥ 1</td>
<td>13</td>
<td>368</td>
</tr>
<tr>
<td>Mode of delivery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal</td>
<td>27</td>
<td>413</td>
</tr>
<tr>
<td>Cesarean</td>
<td>66</td>
<td>357</td>
</tr>
<tr>
<td>Gestational age at birth</td>
<td>37.1 (± 1.4)</td>
<td>37.3 (± 1.3)</td>
</tr>
<tr>
<td>≥ 37 weeks</td>
<td>72</td>
<td>649</td>
</tr>
<tr>
<td>&lt; 37 weeks</td>
<td>21</td>
<td>121</td>
</tr>
<tr>
<td>Birth weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>2,999.9 (± 483.9)</td>
<td>3,079.7 (± 461.7)</td>
</tr>
<tr>
<td>≥ 2,500 g</td>
<td>82</td>
<td>707</td>
</tr>
<tr>
<td>&lt; 2,500 g</td>
<td>11</td>
<td>63</td>
</tr>
<tr>
<td>NICU*</td>
<td>12</td>
<td>78</td>
</tr>
</tbody>
</table>

* Number of neonates hospitalized.

Data from 913 consecutive births were analyzed; 126 after assisted fertilization (13.8%) with 160 neonates and 787 after spontaneous conception (86.2%) with 804 neonates. Overall, there were 863 singleton (94.5%) and 50 multiple pregnancies (5.5%); there were 93 singleton (73.8%) and 33 multiple pregnancies (26.2%; 31 twins and two triplets) after use of ART and 770 singleton (97.8%) and 17 multiple pregnancies (2.2%; all twins) after natural conception. The mean maternal age was 33.0 years overall; 35.6 after assisted fertilization and 32.5 years after spontaneous conception.

Mode of delivery

Cesarean section was performed in all multiple pregnancies, regardless of the mode of conception. In singleton pregnancies, cesarean section was performed in most cases after use of ART (in 66 out of 93 cases – 71%). In contrast, vaginal delivery was the mode of delivery in most cases of singleton pregnancies after spontaneous conception (in 413 out of 770 cases – 53.6%). Using logistic regression analysis adjusted for maternal age and parity, we found that delivery by cesarean section was more likely than vaginal delivery (including operative vaginal delivery) in pregnancies after assisted fertilization as compared with pregnancies after spontaneous conception (OR 3.64, 95% CI; p < 0.0001). Exclusion of multiple pregnancies from this analysis did not alter conclusions (OR 1.87, 95% CI; p < 0.014).

Gestational age

For both singleton and multiple pregnancies mean gestational age at birth was 36.5 (± 1.8) after use of ART and 37.2 (± 1.6) after spontaneous conception; after exclusion of multiple pregnancies, mean gestational age at birth for singletons was 37.1 (± 1.4) and 37.3 (± 1.3), respectively. Preterm birth rates (i.e. birth before 37 weeks of gestation) after assisted fertilization or spontaneous conception were as follows: 1) for singletons 21 out of 93 (22.6%) and 121 out of 770 (15.7%), respectively, and 2) for multiple pregnancies 22 out of 33 (66.7%) and three out of 17 (17.6%), respectively.

Using linear regression analysis adjusted for maternal age and parity, we found that gestational age at birth was significantly higher in spontaneously conceived pregnancies than in pregnancies after use of ART (0.9 weeks, R = 0.239). Using an independent samples t-test this association remained statistically significant (p < 0.005). In singleton pregnancies however, linear regression analysis adjusted for maternal age and parity showed that gestational age at birth was not significantly related with the mode of conception. Furthermore, using Pearson’s χ²-test, there was no significant difference in the occurrence of preterm births (i.e. birth prior to 37 weeks of gestation) between the two groups.

Birth weight

For both singleton and multiple pregnancies mean birth weight was 2,645.2 g (± 661.7) after assisted fertilization and 3,039.2 g (± 503.7) after spontaneous conception; after exclusion of multiple pregnancies, mean birth weight was 2,999.9 g (± 483.9) and 3,079.7 g (± 461.7), respectively. Low birth weight rates (i.e. below 2,500 g after use of ART or spontaneous conception were as follows: 1) for singletons 11 out of 93 (11.8%) and 63 out of 770 (8.19%) neonates, respectively, and 2) for multiple pregnancies 22 out of 33 (66.7%) and three out of 17 (17.6%) neonates, respectively.

Using linear regression analysis adjusted for maternal age and parity, we found that birth weight was significantly higher (340.4 g, R = 0.28) in neonates born after spontaneously conceived pregnancies than after ART. However, in singleton pregnancies only, there was no statistically significant difference in birth weight between the two groups. Furthermore, using Pearson’s chi-square-test, there was no significant difference in the incidence of low-birth weight singletons (i.e., with birth weight <
2,500 g) between the two groups (i.e. ART vs spontaneous conception).

Neonatal Intensive Care Unit (NICU) hospitalization

Twelve singletons (12.9%) and 34 neonates from multiple pregnancies (50.7%) after ART were hospitalized in the NICU. Among children conceived spontaneously 78 singletons (10.1%) and ten from multiple pregnancies (29.4%) were hospitalized in the NICU. There were no perinatal deaths, neither in pregnancies after ART nor after spontaneous conception.

Using the chi-square test and independent samples t-test, we found that hospitalization of neonates in the NICU was more likely (χ²-test; p < 0.0001) and lasted longer (independent samples t-test; p < 0.0001) in pregnancies after ART than after spontaneous conception. Conclusions were not altered after multiple regression analysis to adjust for maternal age, mode of delivery and parity (ANOVA, p < 0.0001). However, analysis in singleton pregnancies after exclusion of multiple pregnancies using the chi-square test and the independent samples t-test showed that hospitalization of neonates in the NICU was not significantly related with the mode of conception.

Discussion

In the present study, data from 913 consecutive pregnancies ending in live birth have been analyzed retrospectively, and obstetric and neonatal outcomes were compared between pregnancies after the use of assisted fertilization and spontaneous conception. This analysis showed that after use of ART cesarean section was more likely compared with pregnancies after natural conception. Exclusion of multiple pregnancies from this analysis did not alter conclusions. These findings are consistent with those of previous studies, which have shown that cesarean delivery rates were higher after ART, even in singleton pregnancies [6-8]. Management of pregnancies after assisted reproduction as high-risk pregnancies seems to be the main reason for the increased cesarean rates in such cases [5].

We also found that gestational age at birth and birth weight were lower following assisted fertilization as compared with pregnancies after spontaneous conception. However, exclusion of multiple pregnancies from this analysis showed that there were no significant differences in singletons, between the two groups. In other studies previously published [5-7, 9-17], gestational age at birth and birth weight were also lower after ART, even in singleton pregnancies.

Another finding in the present study was that hospitalization in the NICU was more likely in pregnancies after use of ART than after spontaneous conception. However, exclusion of multiple pregnancies from this analysis showed that in singletons there were no significant differences in days of hospitalization in the NICU between the two groups. These findings are in line with those of previous studies, suggesting that the iatrogenic increase in the rates of multiple pregnancies contributes to the relatively high neonatal morbidity in pregnancies after ART [4, 5, 7, 9, 10].

Conclusion

Our findings, consistent with those of previously published studies [4-17], show that in pregnancies after assisted fertilization there is a higher probability of cesarean section, lower gestational age at birth, lower birth weight and a higher risk of hospitalization in the NICU, than in pregnancies after natural conception. Though these findings have been observed in part even in singleton pregnancies, the iatrogenic increase of multifetal pregnancies appears to be the main contributing factor to the increase of these risks after assisted fertilization. Hence, with the implementation of single embryo transfer such problems could be reduced or even eliminated, without compromising the primary goal of providing healthy babies to infertile couples. Furthermore, besides improving neonatal morbidity, single embryo transfer could possibly decrease associated healthcare costs as well.

References


Obstetric and neonatal outcome after assisted fertilization and spontaneous conception: a comparative study


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Diagnostic laparoscopy findings in unexplained infertility cases

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Summary

Objective: Evaluation of diagnostic laparoscopy findings in 600 unexplained infertility cases. Materials and Methods: A total of 600 diagnostic laparoscopies performed between 1995 and 2008 were investigated. Laparoscopies were performed in the proliferative phase of the cycle. General anesthesia was performed in all cases. Results: Normal genital findings were determined in 47.50% of primary infertile cases and in 47% of secondary infertile cases. Pelvic adhesion was the most frequent finding encountered and it was seen at a rate of 20% in the primary infertility group and 18% in the secondary infertility group. Endometriosis was determined to have a rate of 15% in the primary infertility group and 11.5% in the secondary infertility group. Conclusion: Laparoscopy has an important place in the diagnosis and planning in the treatment of infertility. Planning the convenient treatment for patients will prevent both economic loss and time loss.

Key words: Infertility, Diagnostic laparoscopy.

Introduction

Infertility is one of the most important health problems for individuals in the young age group. If pregnancy does not occur in a one-year period despite unprotected intercourse, causes of infertility should be investigated [1]. Baseline tests for infertility investigation consist of determination of mid-luteal progesterone level, semen analysis and hysterosalpingography in the evaluation of tubal patency. Endoscopic evaluation of the pelvic cavity is necessary in cases of suspicion of pelvic adhesions [2]. Laparoscopy is used in the diagnosis and treatment of infertility, pelvic pain, ectopic pregnancy, endometriosis and neoplasm. However, with the finding of a broad field of use, especially IVF-ET in recent years, either diagnostic or operative laparoscopy has begun to decrease in value for evaluation of infertility. In our study, we discuss the findings of diagnostic laparoscopy that we performed frequently until the beginning of the year 2000 but which today we nearly never use in evaluation of unexplained infertility.

Materials and Methods

In our study, 600 diagnostic laparoscopies performed due to a diagnosis of unexplained primary infertility between January 1995 and May 2008 were investigated. Couples having normal spermogram, hormone profile, ovulation and hysterosalpingography but not achieving pregnancy were considered as unexplained infertility. Laparoscopies were performed in the proliferative phase of the cycle. General anesthesia was performed in all cases. First, the urinary bladder of the patient in the lithotomy position was emptied and sterile drapes were placed after all cases. First, the urinary bladder of the patient in the lithotomy position was emptied and sterile drapes were placed after all cases. Then the patient was placed in the Trandelenburg position and then pelvic evaluation was performed. In each case, two 5-mm accessory trocars, one in the suprapubic region and one in the left lower quadrant, were inserted and manipulation of tubes and ovaries was performed by the instruments inserted through these regions, and the determined pathologies were removed. The procedure ended following a methylene blue test. After surgery, CO2 in the abdomen was emptied as much as possible and trocar incisions were closed. The patients were discharged approximately 8-24 hours after the operation.

Results

When the total 800 cases were analyzed according to age, it was determined that 84% of patients were between 21-35 years old, 9% were ≥ 20 years old, and 7% were between 36-40 years old. Mean age was 25.7 (19-40) years in the primary infertility group and 29.6 (22-40) years in the secondary infertility group. Duration of infertility was 6.8 years in the primary infertility group and 5.7 years in the secondary infertility group. Four hundred of our cases were primary infertiles and 200 were secondary infertiles. When the findings of laparoscopy were evaluated in the primary infertility group, pelvic adhesion was determined in 20% of cases, endometriosis in 15%, tubal pathologies in 4.25% of cases, and normal findings were observed in 47.5% of the cases. In the secondary infertility group, pelvic adhesions were determined in 18% of cases, endometriosis in 11.50%, tubal pathology in 7.50%, and pelvic operations in 7.50% of the cases whereas normal findings were observed in 47% of the cases (Table 1).
Laparoscopy, which is defined as observation of the abdominal cavity through an optic system, is widely used for both diagnostic and operative purposes today. Diagnostic laparoscopy is used most commonly in the differential diagnosis of infertility, endometriosis, chronic pelvic pain, acute abdomen and in the diagnosis and differential diagnosis of pelvic and other abdominal masses. In infertility cases, laparoscopy is an important diagnostic and treatment method for evaluation of tubal, ovarian, uterine and peritoneal factors. Tubal and pelvic pathology is responsible for 14-33% of female infertility and the diagnosis can only be made by hysterosalpingography and laparoscopy [3-6]. In 509 laparoscopic procedures performed in infertile cases by Hamid et al. [7], pelvic adhesion was determined to be 20%, tubal pathology 15% and endometriosis 9% of cases. In our study, pelvic adhesion was determined in 20% of the primary infertile cases and 18% of the secondary infertile cases. Federici et al. [8] determined endometriosis in 24.5% of cases in which they performed laparoscopy and stated that this was an important cause of infertility. In our study, endometriosis was determined in 15% of the primary infertile cases and in 11.50% of secondary infertile cases; this percentage is lower than that of Federici et al.

As a result of direct observation of the pelvic organs, diagnosis of endometriosis and pelvic adhesions can easily be made. In our study, these two pathologies were the most commonly encountered pelvic pathology, thus showing the significance of laparoscopy in diagnosis and removal of the present pathology.

In conclusion, performance of diagnostic laparoscopy in diagnosis and planning of treatment of unexplained infertility will allow both removal the of pathology (if there is) and choice of a more objective treatment method for patients.

References

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Table 1. — Laparoscopy findings.

<table>
<thead>
<tr>
<th>Results</th>
<th>Primary infertility (400)</th>
<th>Secondary infertility (200)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>25.65 ± 2.7</td>
<td>29.60 ± 4.3</td>
</tr>
<tr>
<td>Duration of infertility (years)</td>
<td>6.75 ± 4.4</td>
<td>5.7 ± 4.6</td>
</tr>
<tr>
<td>Pelvic adhesion</td>
<td>80 20 36 18</td>
<td></td>
</tr>
<tr>
<td>Endometriosis</td>
<td>60 15 23 11.50</td>
<td></td>
</tr>
<tr>
<td>Tubal pathology</td>
<td>17 4.25 15 7.50</td>
<td></td>
</tr>
<tr>
<td>Pelvic operation</td>
<td>14 3.50 15 7.50</td>
<td></td>
</tr>
<tr>
<td>Ovarian cyst</td>
<td>10 2.50 4 2</td>
<td></td>
</tr>
<tr>
<td>Congenital anomaly*</td>
<td>10 2.50 2 1</td>
<td></td>
</tr>
<tr>
<td>Normal finding</td>
<td>190 47.50 94 47</td>
<td></td>
</tr>
<tr>
<td>Other**</td>
<td>20 5 11 5.50</td>
<td></td>
</tr>
</tbody>
</table>

*Uterus, tube, ovary, **Tb, myoma, paraovarian cyst.
Pain and breastfeeding: a prospective observational study

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²Department of Woman’s Health, Sapienza University, Rome (Italy)

Summary

Objective: To demonstrate that pain affects the goodness of breastfeeding. Materials and Methods: Seventy-nine patients were interviewed regarding satisfaction in breastfeeding, tiredness, uterine pain, nipple and other pain, and analgesic use at day three and at first, second, third, and fourth week after birth. Data regarding the mode of delivery were recorded from medical charts. Milk formula supplements, bottle use, pacifier use, and nipple shields use were considered as variables suggesting unsuccessful breastfeeding. Results: At third day after delivery, it appeared that analgesic use was significantly associated with milk formula supplementing, bottle use, less satisfaction in breastfeeding, and more tiredness. At first week after delivery, the presence of pain differing from nipple and uterine pain was more likely associated with milk formula supplementing, bottle use, pacifier use, less satisfaction in breastfeeding, and more tiredness. At third week after delivery, nipple pain was directly related to tiredness, while it increased the odds of adding milk formula and using a bottle. Conclusion: Pain affects the goodness of breastfeeding.

Key words: Pain; Breastfeeding; Delivery; Cesarean section; Analgesic drugs.

Introduction

The irrefutable advantages of breastfeeding for babies, mothers, society, as well as for the environment, have been pointed out so far by many organizations and researchers. Many strategies to prevent breastfeeding discontinuation have been developed by midwives and caregivers to attain the goal of exclusive maternal breastfeeding for at least the first six months, as advocated by World Health Organization (WHO) / United Nation Children’s Fund (UNICEF). Clinician support and prevention / treatment of depressive symptoms should be useful for avoiding breastfeeding discontinuation [1], while proper baby positioning may be helpful in preventing sore nipples [2], and nipple-related pain, that could lead to breastfeeding discontinuation [3].

The authors believe that pain during breastfeeding may lead to its discontinuation, independently from other factors. It has been noted that pain reported in some kind of conditions after delivery may affect breastfeeding [4-9]. Those reports, however, were not aimed to determine how much pain levels may negatively affect breastfeeding. Additionally, a few studies aimed to assess that pain control after delivery was useful for breastfeeding [10, 11]. In the authors’ opinion, the topic should be better investigated and in more detail, because they feel that pain independently affects both milk production and milk secretion (lactogenesis phase II), as well as baby breast positioning and attaching.

For example, it has been reported that cesarean sections (CS) may affect successful breastfeeding [9, 12]. This is due to some difficulties in providing early breastfeeding support related to CS (bonding, early breast attachment, and rooming in). However, a lower milk production was present in patients who underwent CS and those reporting higher levels of pain during breast pumping [5].

Therefore the authors assessed if self-reported pain and analgesic drugs use during the first month after delivery may have influenced the goodness of breastfeeding.

Materials and Methods

A prospective observational study of 79 healthy women supported for breastfeeding after birth was carried out. The patients agreed to participate in the study and were randomly enrolled in the “Fatebenefratelli Villa San Pietro” Hospital in Rome (Italy). Patients were interviewed at day three and contacted by phone at the first, second, third, and fourth week after birth. Data about patient characteristics, mode of delivery, tears after birth, and drug use were collected from medical charts. At the third day, first, second, third, and fourth week after delivery, patients were asked to quantify level of satisfaction in breastfeeding (from 0 to 10), level of tiredness during breastfeeding (from 0 to 10), level of nipple pain (from 0 to 10), level of uterine pain (from 0 to 10), presence of pain elsewhere (yes/no), as well as use of analgesic drugs (yes/no), milk formula supplements (yes/no), bottle-feeding (yes/no), nipple shields (yes/no) and pacifiers (yes/no).

Effective breastfeeding was not achieved if milk formula supplements were given or if bottles or pacifiers were used. Moreover, using nipple shields may be a sign of incorrect attachment of the baby to the breasts. Such variables were chosen to assess the goodness of breastfeeding.

Therefore, it was assessed if self-reported pain and analgesic drugs use during the first month after delivery were statistically significant.
Results

Overall, 46 (57%) patients delivered spontaneously. CSs were 33 (41.8%). Just one patient underwent vacuum extractor-aided delivery. The mean age was 29.7 (± 3.48).

Table 1 illustrates rates of patients using milk formula supplements, bottle, pacifier, and nipple shield use, with mean values (± standard deviations) according to mode of delivery.

<table>
<thead>
<tr>
<th>Mode of Delivery</th>
<th>Milk formula supplements</th>
<th>Bottle</th>
<th>Pacifiers</th>
<th>Nipple shields</th>
<th>Satisfaction in breastfeeding</th>
<th>Tiredness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous delivery (n 45 - 57%)</td>
<td>7 (15.6%)</td>
<td>7 (15.6%)</td>
<td>5 (11.1%)</td>
<td>12 (26.7%)</td>
<td>9 ± 1.35</td>
<td>4.8 ± 1.70</td>
</tr>
<tr>
<td>Cesarean section (n 33 - 41.8%)</td>
<td>18 (54.5%)</td>
<td>18 (54.5%)</td>
<td>4 (12.1%)</td>
<td>16 (48.5%)</td>
<td>8.8 ± 1.29</td>
<td>4.7 ± 1.68</td>
</tr>
<tr>
<td>Vacuum (n 1 - 1.3%)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>10</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 2 shows pain scores and analgesic use rates in cesareans and spontaneous deliveries. Pain was usually reported in CS incision (24 cases at third day and 18 at first week), in vaginal-perineal tear sutures, in episiotomies (eight cases at third day) and in hemorrhoids (two cases at third day). More rarely, musculoskeletal back pain (two cases at third day) was reported, and one patient reported kidney pain at third day.

At third day after delivery, it seemed that analgesic use was significantly associated with milk formula supplementing (odds ratio 5.195; CI 95% 1.555 – 17.355; p = 0.007), bottle using (odds ratio 5.829; CI 95% 1.721 – 19.743; p = 0.005), pacifier using (odds ratio 3.681; CI 95% 1.053 – 12.866; p = 0.041), less satisfaction in breastfeeding (standardized coefficient -0.245; CI 95% -1.280 – -0.068; p = 0.030) and more tiredness (standardized coefficient 0.274; CI 95% 0.255 – 1.983; p = 0.012).

At first week after delivery, nipple pain was directly related with tiredness (standardized coefficient 0.256; CI 95% 0.042 – 0.450; p = 0.019) while it increased the odds of adding milk formula and using a bottle (odds ratio 1.760; CI 95% 1.097 – 2.822; p = 0.019).

It should be noted that multivariable models did not reach significance, suggesting overfit for some variables.

Discussion

Effective breastfeeding (i.e. exclusive breastfeeding for at least six months) is linked to several aspects that are impossible to objectify and standardize in clinical studies. Hurst [13] indicated that lactogenesis phase II may be affected by internal and external environments.
Pain and breastfeeding: Incidence of multiple breast-attaching or breastfeeding support. However, it has been indirectly reported that many kinds of pain may affect breastfeeding overall [4, 5, 7, 8]. In the present sample, mean pain scores and analgesic use rated higher in CS patients. Therefore, the authors feel that ineffective breastfeeding after CS is linked with pain. Pain may negatively affect the endocrine system in relationship with the central nervous system [16-18]. In light of this hypothesis, the goodness of breastfeeding should be linked to mechanisms involving pain control; the present data support this hypothesis. The best predictor of ineffective breastfeeding seemed to be the need for analgesic drugs at third day and the presence of any pain at first week.

Pain may directly affect mood; such an aspect explains both the negative correlation between pain during breastfeeding and satisfaction score given during breastfeeding, and the positive correlation between pain and tiredness during breastfeeding.

It should be pointed out that uterine and nipple pain levels were low overall, and did not relate to the goodness of breastfeeding in this study (with the exception of nipple pain at third week). Breton et al. [19] reported that oxytocin had an antinociceptive role in lamina I-II neurons, enhancing the antinoiceptive effect of GABAergic neurons. Interestingly, in patients who underwent CS, Moore et al. [11] revealed better pain control and satisfaction with no differences in breastfeeding effectiveness by administering preoperative gabapentin 600 mg. Other authors [10] reported that pain control after cesareans facilitated breastfeeding. Therefore, one could speculate that the physiologic oxytocin production during breastfeeding could be useful for controlling nipple and uterine discomfort. This may prove useful even in controlling some mood disorders during breastfeeding.

This study had some limitations; it should be pointed out that many variables which may be involved in breastfeeding were not assessed. Therefore, one should construct a study in which these variables are assessed in a multivariable model. Such kind of study requires much more than seventy-nine patients to reach statistical significance. Therefore, the data presented should be considered interesting for further research. Moreover, the authors feel that a prospective observational study is not able to explain physiopathologic mechanisms underlying milk production in patients with pain. Pain levels after delivery should be investigated in association with stress hormone increases and central pain control pathways. This will provide evidence for further analgesic interventions.

In conclusion, this study highlights that pain affects the goodness of breastfeeding irrespective from mode of delivery. It is important to stress that every kind of pain should be treated in order to favor the success of breastfeeding.

References


The former is related to a complex hormonal milieu, emotional status, and anatomical characteristics of the breasts and nipples, while the latter is related to behavior. It is easy to suggest that breastfeeding support affects the external environment. However, factors affecting the internal environment, such as pain and stress, may compromise even breastfeeding support. Evidence that stress hormones may affect milk production and secretion involving prolactin and oxytocin behavior has been reported in the literature [14, 15].

It has been reported that patients who underwent CS [9, 12], patients with complicated vaginal deliveries [15], or ones reporting nipple pain [6], may experience ineffective breastfeeding. In the present sample, it seemed that patients who underwent CS were more likely to add milk formula, use bottle, and pacifiers. It would appear that clinical conditions may have affected the goodness of breastfeeding due to ineffectiveness in bonding, baby breast-attaching or breastfeeding support. However, it has been indirectly reported that many kinds of pain may affect breastfeeding overall [4, 5, 7, 8]. In the present sample, mean pain scores and analgesic use rated higher in CS patients. Therefore, the authors feel that ineffective breastfeeding after CS is linked with pain. Pain may negatively affect the endocrine system in relationship with the central nervous system [16-18]. In light of this hypothesis, the goodness of breastfeeding should be linked to mechanisms involving pain control; the present data support this hypothesis. The best predictor of ineffective breastfeeding seemed to be the need for analgesic drugs at third day and the presence of any pain at first week.

Pain may directly affect mood; such an aspect explains both the negative correlation between pain during breastfeeding and satisfaction score given during breastfeeding, and the positive correlation between pain and tiredness during breastfeeding.

It should be pointed out that uterine and nipple pain levels were low overall, and did not relate to the goodness of breastfeeding in this study (with the exception of nipple pain at third week). Breton et al. [19] reported that oxytocin had an antinociceptive role in lamina I-II neurons, enhancing the antinoiceptive effect of GABAergic neurons. Interestingly, in patients who underwent CS, Moore et al. [11] revealed better pain control and satisfaction with no differences in breastfeeding effectiveness by administering preoperative gabapentin 600 mg. Other authors [10] reported that pain control after cesareans facilitated breastfeeding. Therefore, one could speculate that the physiologic oxytocin production during breastfeeding could be useful for controlling nipple and uterine discomfort. This may prove useful even in controlling some mood disorders during breastfeeding.

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In conclusion, this study highlights that pain affects the goodness of breastfeeding irrespective from mode of delivery. It is important to stress that every kind of pain should be treated in order to favor the success of breastfeeding.

References

Pain and breastfeeding: a prospective observational study


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Clinicopathological characteristics of adnexal lesions diagnosed during pregnancy or cesarean section

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Summary

Objective: The diagnosis of an incidental adnexal lesion during pregnancy has become more common after the widespread use of routine ultrasonography (US). The aim of this study was to examine the diagnostic approach, management strategy and the pathological findings in cases of adnexal lesions that were diagnosed and treated during pregnancy in our department. Materials and Methods: This was a 15-year retrospective study. Cases of adnexal lesions detected during routine prenatal care by US or while performing cesarean section, between January 1996 and December 2010 at Aretaieion Hospital of the National University of Athens, were analyzed. Results: In this study period 39 cases of adnexal lesions were diagnosed during pregnancy or cesarean section. The age of the women was between 21 and 40 years (mean age 32.4). Surgical excision of the lesions was decided in 32 cases and conservative treatment was followed in the remaining seven cases. Surgical removal of the lesions was performed during cesarean section in 13 cases of term gestations and in four cases of preterm gestations in which pregnancy termination was considered necessary. Laparotomy during the antepartum period led to excision of adnexal lesions in 15 cases. Histology revealed benign ovarian lesions in 25 cases (78.1%), borderline ovarian tumors in two cases (6.3%), malignant ovarian tumors in four cases (12.5%) and adenocarcinoma of the appendix in one case (3.1%) presenting as an ovarian mass. Discussion: The management of cases diagnosed with adnexal lesions during pregnancy remains controversial. According to the literature, the estimated risk of malignancy for adnexal masses during pregnancy is low (2-3%) and complications of these lesions are extremely rare. These data suggest that adnexal masses could be managed conservatively if possible with US follow-up. On the other hand, the results of this study showed a higher incidence of malignancy among adnexal lesions that were surgically treated (15.6%). Conclusion: Surgical intervention and histological examination in cases suspicious for malignancy at US and clinical findings remain the treatment of choice even during pregnancy.

Key words: Adnexal lesions; Ovarian cancer; Pregnancy; Cesarean section.

Introduction

The diagnosis of an asymptomatic adnexal lesion during pregnancy has become more common after the widespread use of routine ultrasonography (US). According to the literature 1-2% of pregnant women are diagnosed with an adnexal mass [1, 2]. The most commonly diagnosed adnexal masses during pregnancy after histological evaluation are mature cystic teratomas, endometrioid cysts and corpus luteum cysts [3]. On the other hand, the risk of malignancy for adnexal lesions diagnosed during pregnancy is only 2-3% [4-7]. Despite this low incidence of ovarian cancer among adnexal lesions observed during pregnancy, it is considered to be the second most frequent gynecological cancer complicating pregnancy [4]. The therapeutic approach in cases of asymptomatic adnexal lesions that persist during pregnancy remains controversial. The difficulties in the preoperative differential diagnosis of these lesions and the possibility of malignancy that is not always easily excluded according only to US findings, suggest that surgical intervention and histological examination are often necessary for the final diagnosis.

Women with obvious US findings of benign, small in diameter, simple ovarian cysts, without vascularization or solid components, could undergo conservative management during pregnancy with routine US follow-up. In these cases, whenever a cesarean delivery is performed for obstetrical indications, ovarian cystectomy can be performed at that time, avoiding the possible adverse effect of surgery and anesthesia during the antepartum period to the fetus and the mother [8]. This approach is reinforced by the fact that US can assist in determining which patients are at risk for malignancy and require antepartum surgery, as opposed to those with benign indications in which postponing the surgery until the delivery or postpartum period seems to be the ideal strategy [8, 9].

In cases of mature cystic teratomas there are studies [10, 11] which suggest the surgical removal during the second trimester because these lesions influenced by hormonal changes during pregnancy seem to have a higher growth rate.

The aim of the present study was to analyze the diagnostic approach, management strategy, surgical outcome and final pathological findings in cases of adnexal lesions that were diagnosed and treated during pregnancy in our department.

Materials and Methods

This was a 15-year retrospective study. During the period between January 1996 and December 2010, there were 39 cases of persistent adnexal lesions diagnosed during either routine...

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pregnancy, as incidental finding while performing cesarean section and examination of the adnexae.

Patients with adnexal masses diagnosed during pregnancy that resolved spontaneously and did not require surgical management were excluded. Also, seven out of these 39 cases had benign US characteristics and conservative treatment without a surgical approach was decided. None of these patients underwent surgery even after the postpartum period. These cases were excluded as well from the present study. The rest of the 32 pregnant women diagnosed with adnexal lesions underwent surgical intervention. All lesions were removed and sent to the pathology laboratory for macroscopic and microscopic examination.

Data collection included age, gestational age (at the time of diagnosis, surgery and delivery), US findings, surgical, maternal and neonatal outcome, histological type of the lesions and possible adjuvant therapy that followed.

**Results**

During the study period there were 32 pregnant women diagnosed with adnexal lesions that required surgical management. The age of the women was between 21 and 40 years (mean age 32.4).

Of the 32 cases, nine patients (28.1%) underwent elective exploratory laparotomy during the second trimester, while in the same gestational period six cases (18.8%) had emergency exploratory laparotomy (5 from torsion and 1 due to rupture). Also, in four preterm gestations (12.5%) exploratory laparotomy and cesarean section at the same time were performed because of suspicious clinical and US findings that led to the termination of the gestation. In 13 cases (40.6%) of term gestations adnexal lesions were removed during cesarean section (in 7 cases these masses were incidental findings while performing cesarean section and examination of the adnexae).

In 28 cases (87.5%) the adnexal lesions were unilateral, while in four cases (12.5%) bilateral. In the vast majority of the cases (81.3%) the masses were cystic or partly cystic measuring between 5 and 20 cm in maximum diameter (mean diameter 12.5 cm). In 18.7% of the cases the adnexal tumors were found to be solid, measuring between 3.5 and 12 cm in maximum diameter (mean diameter 6.5 cm).

Histology revealed benign ovarian lesions in 25 cases (78.1%) (Table 1). The most common benign adnexal lesions were the luteinizing ovarian cysts, diagnosed in 14 cases. Also, in three cases there were extensively luteinized ovaries with ectopic decidual nodules of the omentum discovered during cesarean section. In six cases histology revealed the presence of cystadenoma (5 serous and 1 mucinous) in which cystectomy was performed. The other two cases of benign lesions were an endometrioid cyst and a bilateral mature cystic teratoma which were entirely removed.

Borderline ovarian tumors were diagnosed in two cases (6.3%) in which surgical intervention was performed during the antepartum period. Both cases were treated conservatively with unilateral salpingo-oophorectomy and were classified at Stage IA according to the FIGO staging system.

Malignant tumors were diagnosed and removed in five cases (15.6%). In a case of a 33-year-old Greek woman who underwent cesarean section for obstetrical indications at term gestation, a mass was diagnosed while performing the examination of the right adnexa, rising from the appendix, with a maximum diameter of 2.5 cm. Frozen section of the tumor was positive for adenocarcinoma. Right salpingectomy and regional lymphadenectomy followed. Of the 20 removed lymph nodes one was found positive for malignancy. The patient received adjuvant chemotherapy and remains well without evidence of disease.

In one case of preterm gestation, bilateral Krukenberg tumors, metastatic from gastric cancer, were excised at termination of the gestation at the 28th week. Cesarean section was performed and a male stillborn preterm neonate was delivered. Total abdominal hysterectomy with bilateral salpingo-oophorectomy followed.

In another case of preterm gestation in which the US findings led to termination of the gestation with cesarean section, frozen section of the lesion and final histological examination of the surgical specimen showed ovarian serous cystadenocarcinoma. The patient underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy and omentectomy after cesarean section. Staging according to FIGO after exploratory laparotomy and histological examination was IIa and the patient received adjuvant chemotherapy with cisplatin and paclitaxel.

Finally, two cases of dysgerminoma both at Stage Ic were diagnosed after cesarean section followed by unilateral salpingo-oophorectomy, biopsies of the contralateral ovary, omentectomy and elective pelvic lymphadenectomy in a term and preterm gestation, respectively. Diagnosis of the masses was performed with the use of routine US in the case of preterm gestation, while in the other case it was an incidental finding while performing the cesarean section. Both patients had an excellent perinatal outcome and received chemotherapy with cisplatin and etoposide.

Twenty-four term neonates were born (75%) with an Apgar score of 10 at 5 min and adequate weight. They required no incubators. Eight preterm neonates were born.
(25%) with satisfactory outcomes. Of the 15 women who underwent exploratory laparotomy during the antepartum period seven had vaginal delivery, while in the other eight cases cesarean section was performed.

Discussion

Most pregnant women with adnexal tumors are asymptomatic [4, 12-14]. In the present study, 78.1% of patients were asymptomatic and diagnosis was an incidental finding mainly arrived at by chance during US examination for routine prenatal monitoring, or during a cesarean section. US is considered to be the best diagnostic approach to detect adnexal lesions in pregnant and non-pregnant women [15]. Several studies suggest that the sonographic characterization of the adnexal masses can be sufficient to determine which patients are truly at increased risk for malignancy versus those who can be followed-up expectantly [16, 17]. With color Doppler, a pulsatility index below 1.0 in a morphologically suspect area would suggest malignancy [18]. Magnetic resonance imaging (MRI) could be useful in association with US to identify the characteristics of the mass preoperatively. This examination is particularly useful in pregnant women when the differential diagnosis of an adnexal mass from possible leiomyoma is difficult [19-21]. In our study the vast majority of adnexal masses were diagnosed during routine US examination or while performing cesarean section for obstetrical indications.

In 1963, Munndell suggested that excision of an ovarian mass during pregnancy was indicated for three reasons: 1) elimination of a possible cause of dystocia, 2) danger of torsion, rupture, or hemorrhage, and 3) danger of malignancy [22]. Recent studies support the removal of all persisting adnexal masses in the second and third trimester owing to the risk of malignancy [23]. On the other hand the most numerous and recently informed study by Leiserowitz et al. [24] showed an incidence of 2.15% for ovarian cancer among pregnant women with adnexal masses. These data are similar to results coming from other studies [4-7, 13]. The low incidence of malignancy among adnexal masses during pregnancy and the sufficient results of Doppler US in the differential diagnosis between benign and malignant lesions led to the strategy of exploratory laparotomy during pregnancy only for persistent masses with suspicious for malignancy sonographic characteristics.

Remarkable is that our study showed an increased incidence of malignancy among pregnant women diagnosed with adnexal masses that were surgically treated (15.6%). According to these results surgery should not be delayed if there is high suspicion of malignancy or if the patient’s clinical condition requires urgent surgical treatment. Surgery with adequate staging remains the cornerstone of ovarian cancer diagnosis and therapy during pregnancy. The decision to perform conservative or radical surgery depends on histology, degree of extension, patient’s age and desire for fertility preservation. Emergency laparoscopy or laparotomy is indicated for complications such as torsion or rupture.

Most adnexal masses diagnosed during pregnancy are small functional cysts with a maximum diameter less than 5 cm. These lesions could be managed conservatively if the US characteristics are not suspicious for malignancy. If there is a larger mass (maximum diameter more than 6 cm), if its structure is more complex with solid components, if there is ascites or if it persists beyond the 16th week of gestation, surgery should be performed to rule out malignancy [6, 14, 16, 24]. A delay in elective surgery is suggested until weeks 16-18 if there is suspicion of a low malignancy mass, thus reducing the risk of miscarriage due to hormonal independence of the corpus luteum starting at this gestational age.

In contrast with other studies [25] which suggested that an adnexal mass might be associated with an adverse perinatal outcome, we did not recognize differences in perinatal mortality, congenital malformations or Apgar scores of neonates between cases with and without these lesions.

Differences according to the epidemiology of benign ovarian lesions during pregnancy were also observed between our study and previous studies [3, 8]. In the present study the most common benign adnexal lesions were the luteinizing ovarian cysts and not the mature cystic teratomas. The incidence of endometrioid cysts among adnexal lesions diagnosed and treated during pregnancy was extremely low in our study as well.

In conclusion, surgical intervention and histological examination in cases suspicious for malignancy at US and clinical findings remain the treatment of choice even during pregnancy. The generally good prognosis for pregnant women diagnosed with ovarian cancer may be due to early-stage diagnosis of the disease because of both the widespread use of routine US examination for prenatal monitoring and the increased percentage of cesarean section for delivery.

References

Clinicopathological characteristics of adnexal lesions diagnosed during pregnancy or cesarean section


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Hysterectomy prevention using the uterine hollow obliterations (HYUNHO) method for placenta previa

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Summary

Objective: We have invented a method of hysterectomy prevention called the uterine hollow obliteration (HYUNHO) method to preserve the uterus and fertility after treating placenta previa or accreta. Methods: Eighty patients underwent cesarean section because of placenta previa between January 2003 and December 2009. All patients eligible for the study were evaluated by follow-up and a telephone questionnaire about fertility, menstruation recovery, and complications. Results: The success rate on preserving the uterus with the HYUNHO method was 96.2%. Three cases required additional procedures, including a cesarean hysterectomy or uterine artery embolization (UAE), two cases underwent a cesarean hysterectomy after delivery, and one case underwent UAE. Conclusion: The HYUNHO method is a safe, easy method for placenta previa, although it should be evaluated in a randomized controlled trial.

Key words: Hysterectomy; Placenta previa; Uterine artery embolization.

Introduction

Postpartum hemorrhage (PPH) is a serious complication in patients with placenta previa and a leading cause of severe maternal morbidity and mortality. Placenta previa is a dangerous condition due to massive PPH before delivery. Obstetricians evaluate the severity of placenta previa by ultrasonography (US) and color Doppler US using the vascular invasion of the placenta implantation site before a cesarean section. Placenta previa is an indication for cesarean section, but if conservative management fails, cesarean hysterectomy or uterine artery embolization (UAE) is a choice. If effective methods are developed for placenta previa during a cesarean section, it may reduce cesarean hysterectomy.

Materials and Methods

After obtaining approval from the institutional review board, we performed a prospective observational study including all pregnant women who underwent hysterectomy prevention using the uterine hollow obliteration (HYUNHO) method for placenta previa between January 2003 and December 2009 at a tertiary university hospital. The HYUNHO method was performed on 80 patients by the same obstetrician.

We classified the patients into two groups; group 1 included patients with marginal, and partial placenta previa, and group 2 included patients with total placenta previa with or without accreta. In all cases, fetal growth and fetal well-being were assessed by routine US and color Doppler US before delivery after the second trimester. The same obstetrician operated on all patients and routinely used the HYUNHO method. All patients were treated with uterotonic medical management such as oxytocin, ergot derivatives, prostaglandins, and bimanual uterine massage during cesarean section. Patients were monitored with continuous pulse oximetry, as well as for heart rate and blood pressure, and for urine output with an indwelling catheter. Two large-bore intravenous cannulae were inserted in the central vein, and immediate rapid fluid replacement with crystalloids, Ringer’s lactate, or Hartmann’s solution was continued. Transfusions of blood and coagulation factors were performed in every patient if the hemoglobin level was less than 7 g/dl, or if vital signs were unstable according to hypovolemia. We followed-up all patients at the first week, first month, and at one year. We checked the history and conducted pelvic and US and color Doppler US examinations.

Clinical data were collected from medical records. Major complaints, clinical, and laboratory findings as well as comorbidity data were collected, analyzed, and investigated. We attempted to contact all patients from the cohort to determine the long-term outcome of the HYUNHO method. Patients were asked about breastfeeding duration, menstruation history, pelvic pain, dysmenorrhea, and vaginal discharge. Additionally, patients were asked about their desire for subsequent pregnancies, attempts to conceive or contraception, and fertility by telephone.

Statistical analyses were performed using the Student’s t-test, chi-square test, and Fisher exact test, as appropriate. A p value < 0.05 was deemed statistically significant. Statistical analyses were performed using SPSS.

Description of the HYUNHO method

1) Patients were placed in a supine position under anesthesia. 2) The abdomen was opened with an appropriately sized Pfannenstiel skin incision. 3) Upon entering the abdomen, a lower transverse segment incision was made after dissecting the bladder. 4) The bleeding points were identified after manually delivering the baby and placenta. 5) The operator classified the delivery as group 1 or 2 after delivery of the baby and placenta. 6) The multiple heavy bleeding points in the endometrium were sutured with chromic gut 1-0 and in the myometrium with no. 1 Vicryl (Ethicon, Somerville, NJ, USA).

The obstetrician determined whether there was a marginal or partial placenta previa without placenta accreta (group 1). For...
Hysterectomy prevention using the uterine hollow obliterations (HYUNHO) method for placenta previa

Figure 1. — Hysterectomy prevention by the uterine hollow obliterations (HYUNHO) method.

A) The uterus was obliterated from the cervix to the closest lower incision site by chromic gut 1-0. The cavity of the uterine cervix was obliterated with chromic gut 1-0.

B) The posterior uterine wall was sutured to the anterior uterine wall by chromic gut 1-0. The 1/2 lumen of the uterus was obliterated with sutures.

Group 1: A, Group 2: A+B.

1) The HYUNHO method blocks the uterine artery blood supply from the cervix.

2) The HYUNHO method blocks the uterine artery blood supply from the utero-ovarian vessels.

3) The HYUNHO method results in compression and tamponade on the placental implantation site.

4) Suturing using the HYUNHO method creates a small uterine cavity. After the remaining uterine fundal cavity is filled with blood, blood and hematoma control the blood by their own limited space.

5) We sutured with absorbable suture materials (chromic gut or Vicryl), which may be cut by tension of the uterine cavity and are easily absorbed to reduce the endometrial cavity defect.

Rationale for the HYUNHO method

The HYUNHO method results in compression and tamponade on the placental implantation site. Suturing using the HYUNHO method creates a small uterine cavity. After the remaining uterine fundal cavity is filled with blood, blood and hematoma control the blood by their own limited space. We sutured with absorbable suture materials (chromic gut or Vicryl), which may be cut by tension of the uterine cavity and are easily absorbed to reduce the endometrial cavity defect.

Table 1. — Comparison of clinical variables between the primary treatment group and the failure group.

<table>
<thead>
<tr>
<th>Variable</th>
<th>HYUNHO method (n = 73)</th>
<th>Cesarean hysterectomy or uterine artery embolization</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years ± SD)</td>
<td>32.1 ± 3.8</td>
<td>29.7 ± 4.0</td>
<td>0.231</td>
</tr>
<tr>
<td>Gravida (± SD)</td>
<td>2.7 ± 1.8</td>
<td>3.0 ± 1.7</td>
<td>0.831</td>
</tr>
<tr>
<td>Parity (± SD)</td>
<td>0.6 ± 0.8</td>
<td>0 ± 0.0</td>
<td>0.193</td>
</tr>
<tr>
<td>Hemoglobin level at initial (± SD, g/dl)</td>
<td>11.5 ± 1.4</td>
<td>9.5 ± 1.9</td>
<td>0.009</td>
</tr>
<tr>
<td>Hemoglobin level at discharge (± SD, g/dl)</td>
<td>9.9 ± 1.4</td>
<td>10.5 ± 1.6</td>
<td>0.437</td>
</tr>
<tr>
<td>Hematocrit level at discharge (± SD, %)</td>
<td>29.8 ± 4.0</td>
<td>31.2 ± 4.3</td>
<td>0.483</td>
</tr>
<tr>
<td>Amount of blood loss (± SD, cc)</td>
<td>828.9 ± 443.7</td>
<td>3125.0 ± 2868.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Blood transfusion (± SD, pints)</td>
<td>1.8 ± 2.3</td>
<td>9.0 ± 6.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Operation time (± SD, minutes)</td>
<td>59.5 ± 17.8</td>
<td>276.5 ± 51.6</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*HYUNHO, hysterectomy prevention by uterine hollow obliteration method.

Table 2. — Patient follow-up data after the HYUNHO method.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N</th>
<th>Average ± SD, change parameters (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactation duration (months)</td>
<td>68</td>
<td>4.6 ± 3.6</td>
</tr>
<tr>
<td>Menstrual restart after delivery</td>
<td>73</td>
<td>2.6 ± 1.7</td>
</tr>
<tr>
<td>Dysmenorrhea change after delivery</td>
<td>73</td>
<td>More severe dysmenorrhea 5 (7.1)</td>
</tr>
<tr>
<td>Menstrual amount change</td>
<td>73</td>
<td>No change 73/73 (100)</td>
</tr>
<tr>
<td>Menstrual duration change</td>
<td>73</td>
<td>More longer 2/73 (2.7)</td>
</tr>
<tr>
<td>Fertility</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>Contraception</td>
<td>54</td>
<td>54/73 (73.9%)</td>
</tr>
<tr>
<td>No pregnancy</td>
<td>1</td>
<td>1/73 (1.3%)</td>
</tr>
<tr>
<td>One child and one spontaneous abortion</td>
<td>2</td>
<td>2/73 (2.7%)</td>
</tr>
<tr>
<td>One gravity (pregnancy 1 time)</td>
<td>11</td>
<td>11/73 (15.0%)</td>
</tr>
<tr>
<td>Two gravity (pregnancy 2 times)</td>
<td>5</td>
<td>5/73 (6.8%)</td>
</tr>
</tbody>
</table>

After finishing the operation, we followed-up the patients at one week, one month, and one year later using color Doppler US (Figure 2A-C).

Results

From January 2003 through December 2009, 80 patients who gave birth at a tertiary university hospital were diagnosed with placenta previa. Their mean age was 32.0 ± 3.8 years, and the mean parity was 0.5 ± 0.7; 34 patients (42.5%) were primiparous. The mean gestational age was 35.6 ± 1.9 weeks, with 18 (22.5%) preterm deliveries (<37 weeks). Group 1 placenta previa occurred in 23 cases, 19 marginal, four partial. Group 2 included 57 cases (45 total placenta previa, 12 total placenta previa with accreta). Among group 2, two patients (cases A and B total placenta previa) underwent cesarean hysterectomy, and one patient (case C total placenta previa with placenta accreta) was treated with UAE for bleeding refractory to the HYUNHO method. The overall patient mortality rate was 0%. Two patients were admitted to the intensive care unit (2.5%), and the mean length of hospital stay was 7.5 days. The success rate of the HYUNHO method was 96.2%. We evaluated complications of fever, necrosis...
of the uterine cavity, infection, and wound disruption. No patient had a fever (>38.5°C), and the mean operating time was 59.5 ± 17.8 minutes. The mean estimated blood loss was 828.9 ± 443.7 ml. One patient had subcutaneous wound disruption, so we resutured without another complication. All patients were administered prophylactic intravenous antibiotic therapy with 3 g cefazolin. We conducted a pelvic examination and examined US and color Doppler US (Figure 2). Clinical variables were compared between the primary treatment group and the failure group (Table 1).

Failure group

Three cases (cases A, B, and C) were failed by the HYUNHO method. Cesarean hysterectomy was performed in two cases (cases A and B) after the HYUNHO procedure. One case (case C) received additional UAE after the HYUNHO procedure. Two cases (cases A and B) had total placenta previa, and both had severe pelvic endometriosis with adhesions on the cu-de-sac. Thus, the uterus was distended after the HYUNHO procedure, and bleeding occurred due to an adhesion on the uterine posterior wall, so a hemoperitoneum occurred. One case (case C) had total placenta previa with placenta accreta. The patient wanted another method performed to preserve the uterus, so we decided on UAE after the HYUNHO procedure.

Follow-up evaluation

We interviewed 73 patients by telephone questionnaire and follow-up. Of the 73 patients who had undergone the HYUNHO procedure, all had returned to normal menstruation, with the timing depending on breastfeeding and contraceptive use (Table 2). Three patients underwent bilateral tubal ligation during the operation, and 51 of the 73 patients used condoms. No other urinary problems occurred. Eighteen cases had a healthy baby after the HYUNHO procedure (10 males, 8 females), and the mean body weight of the newborns was 3,044 ± 327 g. After 1 and 5 min, all groups had Apgar scores of 8.8 ± 0.4 and 10.0 ± 0.0, respectively. None of the 18 cases had placenta previa at the second operation.

Discussion

We provide the following management algorithm for placenta previa [1]. Placenta previa severity was suspected by US and color Doppler US before cesarean section [2]. Group 1 and group 2 were divided after delivery of the placenta [3], and we routinely performed conservative management with uterotonics [4]. For group 1 cases, we only sutured from the anterior uterine endometrium to the posterior uterine endometrium including the half of the myometrium which is located on the upper segment of the
cervical region [5]. For group 2, we sutured the uterine cavity of the upper segment of the uterine incision in the same way facing the myometrium in front of uterus and the one at the back of the uterus facing the myometrium in front of the uterus and the one at the back of the uterus [6]. After the HYUNHO method, we inserted and dilated the cervix and endometrium by Hagar at one week and one month.

The HYUNHO method was applied only for placenta previa. The HYUNHO method includes compressing the uterine cavity with sutures. We confirmed menstruation pattern, urinary problems, and fertility after the operation using a telephone questionnaire. The HYUNHO method was easy and resulted in a short operation time with few complications. The success rate for preserving the uterus was 96.2%.

The B-Lynch surgical technique for postpartum bleeding, which uses a brace for external compression, was reported in 1997 [1]. Many combined methods have been reported for placenta previa including the B-Lynch suture with the Bakri balloon method, Affronti suture, and B-Lynch suture [1]. The B-Lynch suture method and recombinant activated factor VII have been used simultaneously for placenta increta [2]. Uterine cavity packing is controversial for placenta previa due to the risk of infection or concealed hemorrhage; however, some have reported that it is successful for placenta previa when used with other methods such as internal iliac artery ligation or suturing the placental bed [3]. Despite the introduction of new surgical techniques to control postpartum hemorrhage, a previous cesarean delivery with placenta previa or accreta is a major risk factor for an emergency cesarean hysterectomy [5]. UAE has been performed for over 30 years and is a safe and effective procedure that preserves a patient’s reproductive capacity. However, 50-60% of UAE failures are due to placenta accreta rather than uterine atony [6]. Furthermore, UAE cannot be performed in every hospital. Uterine compression suture techniques provide an alternative to cesarean hysterectomy for postpartum hemorrhage. The HYUNHO method is expected to result in success. Our two cases of failure had severe pelvic endometriosis with cul-de-sac adhesions. After suturing and emptying, the upper portion of the uterus was distended, and the posterior uterine cul-de-sac and the serosa vessels started bleeding, which was a very rare failure factor. We experienced no accreta or pyometra with the HYUNHO method. Our patients wanted to have additional children, and placenta previa did not recur at the second delivery time after the HYUNHO procedure. However, it is necessary to be cautious using the HYUNHO method for an endometriosis adhesion in the posterior cul-de-sac, as deep infiltrated endometriotic lesions create bleeding. Therefore, if endometriosis with a cul-de-sac adhesion is observed during the operation, we recommend that other methods be added.

PPH is a serious complication for obstetricians and patients. The HYUNHO method should be used only for placenta previa or placenta previa with accreta. We confirmed that the HYUNHO method was simple and safe, and preserved the uterus and fertility during follow-up but randomized controlled trials should be carried out.

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References


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Polymorphisms in angiotensin-converting enzyme and glutathione s-transferase genes in Turkish population and risk for preeclampsia

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3Bursa ART Center, Bursa (Turkey)

Summary

Aims: This study was conducted to investigate whether insertion/deletion (I/D) polymorphism of angiotensin-converting enzyme (ACE) gene and polymorphisms in glutathione S-transferase (GST) M1 and T1 genes are associated with increased risk for preeclampsia. Materials and Methods: Sixty-three patients with hypertensive disorder of pregnancy and 85 controls were evaluated in a prospective case-control study. All subjects were genotyped by polymerase chain reaction (PCR) followed by agarose gel electrophoresis. Results: Allele frequencies of ACE gene I/D polymorphism were found significantly different between preeclampsia and the control groups (p = 0.001). Differences in genotype frequencies of ACE gene I/D polymorphism between the two groups were statistically significant (p = 0.004). Individuals homozygous for D allele were more likely to develop preeclampsia (OR = 2.29; 95% CI, 1.39 - 3.79), whereas heterozygous individuals were not at increased risk (OR = 0.92; 95% CI, 0.56 - 1.49), compared to individuals homozygous for I allele. The differences in frequencies of functional and null alleles of GSTM1 and GSTT1 genes between the two groups were not significant (p = 0.46 and p = 0.44, respectively). Conclusion: ACE gene DD genotype was found to be associated with increased risk of preeclampsia development, whereas the authors did not find any significant relationship with polymorphisms of the GSTM1 and GSTT1 genes and preeclampsia.

Key words: Gene; Polymorphism; Angiotensin-converting enzyme; Glutathione s-transferase; Preeclampsia.

Introduction

The role of genetic factors in pregnancies complicated by preeclampsia is still unclear. Several lines of evidence suggest a relationship between various components of metabolizers of xenobiotics and endogenous toxins, renin-angiotensin system (RAS), and preeclampsia [1-3]. There is growing evidence that polymorphisms of genes that encode the associates of those families, could possibly be responsible from the genetic part of the genesis of preeclampsia [4-6].

Deficient placentation characterized by inadequate trophoblast invasion into maternal spiral arterioles is considered one of the major pathophysiologic mechanisms of preeclampsia. Previous studies revealed that RAS mediates physiological remodeling of spiral arterioles throughout the pregnancy [7] and has a role in fluid-electrolyte balance, as well as blood pressure regulation [8]. Thereby, inappropriate activation of the RAS could play a role in the development of preeclampsia. Serum levels of angiotensin-converting enzyme (ACE), as one of the key components of the RAS, are reported to be decreased in states of preeclampsia [9]. In recent studies, differences in the ACE activity and uteroplacental circulation are found to be reliably associated with Insertion/Deletion (I/D) polymorphism of the ACE gene [10, 11]. There is conflicting data in the literature regarding the relationship between ACE gene I/D polymorphism and preeclampsia. Some of the published researches have suggested a significant interaction [6, 11, 12-14], while others could not demonstrated any connection [9, 15, 16].

Vascular endothelial damage is another important mechanism in the development of preeclampsia [17]. Significantly, lipid peroxides and endogenous toxins that are produced in vivo are responsible from this damage to the endothelium [18]. Imbalance between toxic substances and detoxifying enzymes has an increasing effect on oxidative stress and therefore, causes placental and maternal vascular endothelial damage [19]. Gluthathione S-transferases (GST) are the group of enzymes that are involved in the metabolization of toxic substances. In this regard, they are thought to play a role in the pathogenesis of preeclampsia. GST enzymes are responsible for the detoxification of wide variety of chemicals by nucleophilic addition of gluthathione to electrophilic centers of the substrates. They have an important role in protecting the tissue from oxidative damage. There are four major groups of GST enzymes-alpha (α), mu (M), pi (P), theta (T). All have been found to be genetically polymorphic. Deletion polymorphisms have been found for gluthathione S-transferase M1 (GSTM1) and gluthathione S-transferase T1 (GSTT1) genes. Approximately 45% and 20% of Caucasians bear the non-functional alleles for GSTM1 and GSTT1, respectively. The relation between polymorphisms of the both GST genes and preeclampsia has been investigated, however researchers are not yet able to find any strong evidence [20, 21].
In the present study, the authors aimed to investigate whether genetic polymorphisms on intron 16 in the ACE gene and genetic polymorphisms in GSTM1 and GSTT1 genes are varied between preeclamptic patients and the controls.

Materials and Methods

Subjects

Sixty-three unrelated pregnant women with hypertensive disorder in pregnancy (19 patients with preeclampsia and 44 patients with severe preeclampsia) and 85 healthy pregnant unrelated controls were enrolled in the study between May 2009 and March 2010 at the Obstetrics and Gynecology Department of Uludag University. All of the participants were singletons and were in their third trimester. All participants were Caucasians with average socioeconomic status. Preeclampsia was defined as demonstration of systolic blood pressure measurement above 140 mm Hg and diastolic blood pressure reading above 90 mm Hg in at least two different occasions at more than six hours apart in a previously normotensive women after 20th gestational weeks of pregnancy, in association with proteinuria more than 300 mg/l in a 24-hour urine collection. Severe preeclampsia was defined as presence of one of the following criteria: systolic blood pressure measurement above 160 mm Hg or diastolic blood pressure measurement above 110 mm Hg on two occasions at least six hours apart, more than five grams urinary protein excretion in 24 hours, cerebral or visual disturbances, pulmonary edema or cyanosis, and epigastric or right upper quadrant pain. The patients of the control group were followed up with blood pressure measurements until sixth week after delivery to ensure that they did not develop preeclampsia. Women with chronic hypertension, diabetes, preexisting vascular, and chronic renal diseases were excluded from the study. The study was approved by the Ethical Committee of Uludag University. All participants were fully informed and agreed to give written informed consent.

Extraction of DNA with genomic analysis

Peripheral blood samples of 3 ml were obtained from preeclamptics and controls into tubes prepared with ethylenediaminetetraacetic acid (EDTA) as anticoagulant. Genomic DNA was extracted from circulating leukocytes with salting out procedure and was stored at −20°C until studied. All of the DNA samples collected from participants that met the criteria of the study were examined and included in the present report without any elimination. Genotyping for insertion (I) and deletion (D) alleles of the ACE gene, and deletion polymorphisms of GSTM1 and GSTT1 genes was carried out on the basis of amplification with polymerase chain reaction (PCR) technique. DNA isolation was performed with DNA isolation kit (Dr. Zeydani Laboratories Ltd., Ankara, Turkey) according to the instructions of the manufacturer. Laboratory work was conducted blinded to the clinical status of the subjects. I/D polymorphism on intron 16 of the ACE gene was determined by using a respective primer pair. As PCR is known to have a tendency to preferentially amplify the shorter D allele rather than the other longer I allele when both alleles are present, confirmation was done by a second PCR amplification with insertion of specific primer pair that recognizes insertion-specific sequence for subjects who are homozygous for D allele. This avoided misdiagnosing of ID genotypes as DD and increased the specificity for DD genotyping. Primer pair sequences were shown in Table 1.

Table 1. — Primer sequences.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Forward Primer</th>
<th>Backward Primer</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE I/D</td>
<td>Forward 5'-GCC CTC TGC TAA CAA GTC CTA C-3'</td>
<td>Backward 5'-TCA CCG GAT CAT GGC CAG CA-3'</td>
</tr>
<tr>
<td>GSTM1</td>
<td>Forward 5'-GAA CTC CCT GCT GCT CCT CAT ATC TC-3'</td>
<td>Backward 5'-GTC CCA GCC CTC CCA TGC CCA TAA-3'</td>
</tr>
<tr>
<td>GSTT1</td>
<td>Forward 5'-GTC TCT ATT ACT GGT CCT CAC ATC TC-3'</td>
<td>Backward 5'-GAT GTC CCA GCC CTC CCA TAA-3'</td>
</tr>
<tr>
<td>Albumin</td>
<td>Forward 5'-GCC CTC TGC TAA CAA GTC CTA C-3'</td>
<td>Backward 5'-GTC CCA GCC CTC CCA TGC CCA TAA-3'</td>
</tr>
</tbody>
</table>

PCR was conducted by using 100 ng genomic DNA, 500 mmol of each primer, 0.5 mmol/l each of the four dNTPs, one unit of Taq DNA polymerase, three mmol/l MgCl2, 50 mmol/l KCl, 10 mmol/l Tris HCl, 0.001% gelatin, pH 8.3 in a total volume of 25 µl. Thermocycling procedure was performed by first denaturation for five minutes at 94°C, followed by a second denaturation for 30 seconds in 94°C. Afterwards it was continued by 35 cycles that consisted of primer annealing for one minute at 57°C (in second procedure where DD genotype verified, was set to 63°C), extension step for two minutes at 72°C. The procedure ended with final extension for ten minutes at 72°C. The bands standing for amplified I and D alleles of ACE gene were separated on 2% agarose gel, and then stained by ethidium bromide. As a result, amplification band of 190 bp which stands for DD genotype, bands of 490 bp and 190 bp representing ID genotype, and 490 bp band of ID genotype were formed. In the second analysis used as confirmation, amplification band of 335 bp was observed which represented the presence of insertion allele.

The method performed to detect deletion polymorphisms of GSTM1 and GSTT1 genes was the same as described above. Primer pairs for albumin are co-amplified as internal controls. PCR yielded 350 bp, 219 bp, and 459 bp products representing albumin, GSTM1 and GSTT1 genes, respectively.

Statistical analysis

Statistics were performed using Statistical Package for the Social Sciences software version 17.0 (SPSS Inc., Chicago, IL, USA). Mean values with standard deviations were calculated for the descriptive variables of the subjects. Student’s t test was used to compare characteristics between study and control groups for the continuous variables that are normally distributed. Chi-square test with continuity correction was conducted for the categorical variables. Hardy-Weinberg equilibrium was tested for allele and genotype frequencies of ACE gene I/D polymorphism for both groups. After obeying the equilibrium, binary logistic regression model was applied to calculate odds ratios (OR) of specific ACE gene polymorphic variants. The level of statistical significance was defined as p < 0.05.
The clinical characteristics and demographic data of 63 women with preeclampsia and 85 control subjects were presented in Table 2. Mean values of maternal age, gravidity, parity, and body mass index (BMI) of the preeclamptic women did not differ significantly from the control individuals (p > 0.05). Mean values of gestational age, and systolic and diastolic blood pressure were significantly lower in the preeclamptic group than in the control group. Distribution of the polymorphic variants of the ACE gene I/D polymorphism was found significantly different between the preeclampsia and the control groups (Table 3). Frequencies of the genotypes in study group were in Hardy-Weinberg equilibrium (χ² = 0.118, p = 0.73), as well as in the control group (χ² = 0.013, p = 0.91). Of the total 65 preeclamptic women, 32 (50.8%) were homozygous DD genotype, 25 (39.7%) were heterozygous, and six (9.5%) were homozygous II genotype. In the control group, 22 (25.9%) of them were homozygous for DD genotype, 25 (39.7%) were heterozygous, and 25 (39.7%) were homozygous II genotype. The genotype distribution of GSTM1 and GSTT1 genes in patients and controls were presented in Table 3. Patients having functional GSTM1 gene were 56% and GSTT1 gene were 73%. These findings did not differ statistically from that of controls, in which 47% and 65% had a functional glutathione S-transferase M1 and T1 gene, respectively. Of the patients with preeclampsia, 44% lacked a functional GSTM1 gene, and 27% lacked a functional GSTT1 gene. Similar to those findings, 53% and 35% of the individuals in control group lacked a functional GSTM1 or GSTT1 gene, respectively. The difference in frequencies of both alleles of GSTM1 genes between the two groups were found statistically insignificant, and presence of non-functional gene was found to have no effect in susceptibility to preeclampsia (OR = 1.40; 95% CI, 0.685 - 2.862). The authors could not find any association between non-functional GSTT1 gene and increased risk for preeclampsia (OR = 1.46; 95% CI, 0.671 - 3.185).

**Results**

The clinical characteristics and demographic data of 63 women with preeclampsia and 85 control subjects were presented in Table 2. Mean values of maternal age, gravidity, parity, and body mass index (BMI) of the preeclamptic women did not differ significantly from the control individuals (p > 0.05). Mean values of gestational age, and systolic and diastolic blood pressure were significantly lower in the preeclamptic group than in the control group. Distribution of the polymorphic variants of the ACE gene I/D polymorphism was found significantly different between the preeclampsia and the control groups (Table 3). Frequencies of the genotypes in study group were in Hardy-Weinberg equilibrium (χ² = 0.118, p = 0.73), as well as in the control group (χ² = 0.013, p = 0.91). Of the total 65 preeclamptic women, 32 (50.8%) were homozygous DD genotype, 25 (39.7%) were heterozygous, and six (9.5%) were homozygous II genotype. In the control group, 22 (25.9%) of them were homozygous for DD genotype, 25 (39.7%) were heterozygous, and 25 (39.7%) were homozygous II genotype. The genotype distribution of GSTM1 and GSTT1 genes in patients and controls were presented in Table 3. Patients having functional GSTM1 gene were 56% and GSTT1 gene were 73%. These findings did not differ statistically from that of controls, in which 47% and 65% had a functional glutathione S-transferase M1 and T1 gene, respectively. Of the patients with preeclampsia, 44% lacked a functional GSTM1 gene, and 27% lacked a functional GSTT1 gene. Similar to those findings, 53% and 35% of the individuals in control group lacked a functional GSTM1 or GSTT1 gene, respectively. The difference in frequencies of both alleles of GSTM1 genes between the two groups were found statistically insignificant, and presence of non-functional gene was found to have no effect in susceptibility to preeclampsia (OR = 1.40; 95% CI, 0.685 - 2.862). The authors could not find any association between non-functional GSTT1 gene and increased risk for preeclampsia (OR = 1.46; 95% CI, 0.671 - 3.185).

**Discussion**

Preeclampsia, which is the leading cause of maternal and fetal mortality, has been suggested to have a potent familial basis. Although the exact genetic nature remains unknown, susceptibility to preeclampsia is thought to result from complex interactions between maternal and fetal genotypes, maternal predisposing factors, and environmental factors. Polygenic and multifactorial penetrances have been reported, as well as genomic imprinting with preferential expression of the maternal alleles. In many researches regarding genetics of preeclampsia, several gene loci have been explored [5, 13].

Due to the central role of RAS on body fluid-electrolyte regulation and vascular remodeling of the placenta in pregnancy, it is thought to account for a major role in the etiology of the genetics of preeclampsia. ACE gene as a member of RAS which catalyses the conversion of angiotensin I to angiotensin II, which is a potent vasconstrictor, has been investigated recently. From the studies in Chinese population, it was found that genetic variation in ACE gene locus is related with increased risk of pregnancy-induced hypertension and preeclampsia [12, 22].
Mello and co-workers were in agreement with the previous studies and reported diminished uteroplacental blood supply in preeclamptic Italian women that bear ACE DD genotype in contrast to patients with ID and II genotypes [11]. Beyond this statement, they found DD genotype in relation with the risk of recurrent preeclampsia and fetal growth restriction.

In the present study, the authors found that frequency of D allele is significantly higher in preeclamptic cases rather than in control subjects. Data from the present study suggests that individuals who are homozygous for D allele have increased risk for developing preeclampsia. Nevertheless, the authors could not demonstrate in this study that individuals who are heterozygous for D allele were at increased risk to develop preeclampsia. The results regarding allele frequencies and genotype frequencies were in concordance with each other, representing an increased risk of preeclampsia with the homozygosity for D allele. The current study provides evidence that there is a relationship between ACE I/D polymorphic variants and preeclampsia. However, the latter two results from this study have clinical importance in understanding possible genetic transmission model of ACE I/D polymorphism in preeclampsia.

In the current study, the authors did not find any statistically significant difference in frequencies of GSTM1 and GSTT1 polymorphisms between normal and preeclamptic subjects. These results were in corroboration with previous studies. There is a high prevalence of null alleles of GSTM1 and GSTT1 genes in humans, but interestingly the presence of homozygous nonfunctional alleles appear to have no effect on corresponding activity, and thus, is not related to GSTM1 and GSTT1 related placental oxidative stress or endothelial damage in preeclampsia pathogenesis.

In conclusion, data from this study suggests that ACE gene DD genotype is related with increased risk for developing preeclampsia. This association warrants further investigation. GSTM1 and GSTT1 polymorphisms are not directly associated with preeclampsia.

References


Detection of placenta elasticity modulus by quantitative real-time shear wave imaging

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Summary

Objective: To explore the clinical values in detecting the placental elastic modulus using real-time quantitative shear wave elasticity imaging. Methods: A total of 30 women in the late pregnancy stage without complications and having normal, single pregnancies, as well as normal fetal growth, amniotic fluid index, and anterior placenta were selected. A real-time elasticity imaging system was used to randomly select regions of interest at the central and edge of the placenta. The elastography imaging mode was launched to measure the elasticity of the elastic modulus of these placental parts. A total of 15 measured values were obtained at the placental center and edge for each pregnancy case. Umbilical artery and uterine artery pulsatility index (PI) values for 18 cases were also randomly measured. Results: The average value of 30 placental edges of the elastic modulus (n = 15) was (7.60 ± 1.71) kPa. The average value of the 30 placental central elastic modulus (n = 15) was (7.84 ± 1.68) kPa. No significant difference was observed between placenta central and edge elastic modulus. The PI mean value of umbilical artery in 18 cases was 0.94, whereas the average PI values of the uterine artery was 0.83. No linear correlation was found among the elastic modulus, the placental uterine artery PI values, and the umbilical artery PI values (p > 0.05). Conclusion: No difference between the placental center of normal pregnancies and the edge of the elastic modulus was detected. The elastic modulus of the placenta could be obtained in the best position. The placenta varied greatly between elastic modulus. No correlation was found between the placental elastic modulus, the uterine artery, and umbilical artery PI values. Real-time shear wave elasticity imaging technology can provide morphological evidence of placental function, which may emerge as a new clinical assessment approach.

Key words: Shear; Elasticity imaging; Placental function.

Introduction

Elastography is a recently developed ultrasound (US) imaging technology, the basic principle of which is to impose an internal or external dynamic or static excitation on a tissue so that this tissue will respond to displacement, velocity, or strain, among others. Using the US imaging method, along with digital signal processing and digital image processing technology, elastography produces a visual display of information or quantifies the expression of this response. The elastic modulus is the ratio between stress (excitation) and strain (response). The elasticity imaging technique can be used to estimate tissue elastic modulus directly or indirectly [1]. The traditional static method has numerous clinical limitations because of a number of uncertain, complex factors. The shear-wave based dynamic method is a new approach that can quantitatively detect the absolute value of the elastic modulus of a region of interest by detecting the shear wave velocity triggered by acoustic radiation pulses [2]. In the formula $E = 3pc^2$, $E$ is the elastic modulus, $c$ is the shear wave velocity, and $p$ is tissue density. Thus, shear-wave velocity in an organization at supersonic speeds, thereby producing a “Mach cone” phenomenon, increasing the shear wave generation, improving communication efficiency, enabling flexibility in ensuring real-time imaging of shear waves, and ensuring patient safety. In addition, ultra high-speed imaging (Ultrafast) can capture a shear wave, the velocity of which is significantly lower than that of a sound, resulting in shear-wave ultra-high-temporal resolution images. Furthermore, this Ultrafast feature allows the measurement of the absolute value of organization elasticity through a quantitative analysis of tissue elasticity (QBOX) system, thus improving the detection repeatability and providing a reliable basis for flexible imaging in clinical applications and studies.

Birth weight and intrauterine growth pattern determine neonatal morbidity, mortality, and long-term prognosis. These two factors can help determine whether the birth survival rate of low-for-gestational-age children is low or if the occurrence of adult degenerative diseases, such as hypertension and type II diabetes, will increase [3]. The fetal nutrient supply capacity of the placenta is a primary factor determining intrauterine growth [4]. Therefore, the diagnosis and treatment of placental insufficiency is an effective method of reducing neonatal morbidity and mortality and improving quality of life.

In the present paper, real-time shear wave elasticity imaging was used to quantitatively detect placental elastic modulus, to explore the clinical value of this technology in assessing placental function, and to provide a reference index for the diagnosis of placental dysfunction.
Materials and Methods

General data

A total of 30 patients with singleton, late-stage pregnancies were randomly selected from April to June 2011 at the Department of Fetal Medicine Ultrasound of the First Affiliated Hospital of Jinan University. These patients were without pregnancy-related complications. They had normal fetal growth, amniotic fluid index, and anterior placenta. The patients were aged 29 ± 0.38 years (21 to 39 years), and fetal gestational age was 33.93 ± 3.99 weeks (28 to 41 weeks).

Method

A real-time shear wave elasticity imaging US diagnostic apparatus (Supersonic AixPlorer, probe SE12-3, frequency 3 MHz to 12 MHz, Supersonic, France) with a mechanical index, MI < 1.0, and heat index, TI < 0.5, was used in the current study. The edge of the placenta and the central organization were positioned using conventional 2D ultrasound. Regions of interest were randomly selected. The pregnant women breathed when the fetus was quiet to avoid excessive pressure on the abdominal wall. Once the elastography mode was started, three measurements were frozen after an image was stabilized. Q-BOX was then used to assess the measurements.

The diameter of the sampling frame was set to 15 mm. Each measurement included a maximum, minimum, average, and standard deviation, less than 30% of which was considered as an effective measure. The average was taken as part of the elastic modulus of the placenta. A total of 15 of the measured values were obtained in the center and edge of the placenta of each pregnant woman (Figure 1). Finally, umbilical artery and uterine artery PI values of the 18 cases were randomly measured.

Statistical analysis

Measurement data are shown as mean ± standard deviation. The elastic modulus of the placental center and the edge were compared using a paired t-test. The relationship among the placenta elastic modulus, the umbilical artery, and uterine artery PI values of the 18 cases were randomly measured.

Results

Comparison of the elastic modulus

The placental edge elastic modulus was measured in 30 groups (n = 15). The maximum was 12.36 ± 1.77 kPa, and the minimum was 5.15 ± 1.31 kPa or an average of 7.84 ± 1.68 kPa. No statistically significant difference was found between the central placental and the edge of the elastic modulus (t = 0.529, p > 0.05) (Table 1).

Placental distribution of elastic modulus

The average elastic modulus of each placental edge and the central elastic modulus were determined. The maximum was 12.53 ± 1.24 kPa, and the minimum was 5.34 ± 1.24 kPa, with a mean of 7.70 ± 1.61 kPa (Table 1, Figure 2).

<table>
<thead>
<tr>
<th>No.</th>
<th>Placenta central elastic modulus (kPa)</th>
<th>Elastic modulus edge of the placenta (kPa)</th>
<th>Placenta average elastic modulus (kPa)</th>
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</thead>
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<tr>
<td>1</td>
<td>7.53 ± 2.42</td>
<td>7.55 ± 1.58</td>
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<td>2</td>
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<td>3</td>
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<td>6.83 ± 1.40</td>
<td>5.43 ± 0.85</td>
<td>6.15 ± 1.35</td>
</tr>
<tr>
<td>24</td>
<td>6.50 ± 1.35</td>
<td>6.84 ± 0.71</td>
<td>6.67 ± 1.07</td>
</tr>
<tr>
<td>25</td>
<td>8.12 ± 1.50</td>
<td>9.66 ± 1.10</td>
<td>8.87 ± 1.52</td>
</tr>
<tr>
<td>26</td>
<td>7.69 ± 1.35</td>
<td>8.85 ± 1.64</td>
<td>8.17 ± 1.57</td>
</tr>
<tr>
<td>27</td>
<td>6.82 ± 0.67</td>
<td>7.65 ± 0.74</td>
<td>7.29 ± 0.79</td>
</tr>
<tr>
<td>28</td>
<td>6.46 ± 1.16</td>
<td>5.42 ± 0.84</td>
<td>5.96 ± 1.13</td>
</tr>
<tr>
<td>29</td>
<td>8.41 ± 1.06</td>
<td>10.38 ± 1.44</td>
<td>9.03 ± 1.59</td>
</tr>
<tr>
<td>30</td>
<td>12.73 ± 1.12</td>
<td>12.36 ± 1.77</td>
<td>12.53 ± 1.24</td>
</tr>
</tbody>
</table>

Table 2. — Relationship between placenta elastic modulus, umbilical artery and uterine artery PI values in 18 cases.

<table>
<thead>
<tr>
<th>No.</th>
<th>Elastic modulus of the placenta (Kpa)</th>
<th>Umbilical artery PI values</th>
<th>Uterine artery PI values</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.54 ± 2.02</td>
<td>0.86</td>
<td>0.78</td>
</tr>
<tr>
<td>2</td>
<td>9.60 ± 2.34</td>
<td>0.91</td>
<td>0.8</td>
</tr>
<tr>
<td>3</td>
<td>6.93 ± 1.63</td>
<td>0.76</td>
<td>0.97</td>
</tr>
<tr>
<td>4</td>
<td>8.36 ± 1.63</td>
<td>1.01</td>
<td>0.76</td>
</tr>
<tr>
<td>5</td>
<td>6.98 ± 1.17</td>
<td>1.06</td>
<td>0.83</td>
</tr>
<tr>
<td>6</td>
<td>10.15 ± 1.56</td>
<td>0.92</td>
<td>0.85</td>
</tr>
<tr>
<td>7</td>
<td>10.57 ± 1.84</td>
<td>1.16</td>
<td>0.87</td>
</tr>
<tr>
<td>8</td>
<td>5.57 ± 1.02</td>
<td>0.71</td>
<td>0.84</td>
</tr>
<tr>
<td>9</td>
<td>7.33 ± 1.56</td>
<td>1.02</td>
<td>1.11</td>
</tr>
<tr>
<td>10</td>
<td>6.44 ± 1.25</td>
<td>0.93</td>
<td>0.86</td>
</tr>
<tr>
<td>11</td>
<td>6.37 ± 1.38</td>
<td>1.01</td>
<td>0.77</td>
</tr>
<tr>
<td>12</td>
<td>5.34 ± 1.24</td>
<td>1.1</td>
<td>0.88</td>
</tr>
<tr>
<td>13</td>
<td>8.57 ± 1.42</td>
<td>0.89</td>
<td>0.9</td>
</tr>
<tr>
<td>14</td>
<td>6.15 ± 1.35</td>
<td>1.37</td>
<td>0.72</td>
</tr>
<tr>
<td>15</td>
<td>6.67 ± 1.07</td>
<td>0.85</td>
<td>0.66</td>
</tr>
<tr>
<td>16</td>
<td>8.87 ± 1.52</td>
<td>1.02</td>
<td>1.03</td>
</tr>
<tr>
<td>17</td>
<td>8.17 ± 1.57</td>
<td>0.66</td>
<td>0.77</td>
</tr>
<tr>
<td>18</td>
<td>7.29 ± 0.79</td>
<td>0.74</td>
<td>0.85</td>
</tr>
</tbody>
</table>

Table 1. — Placenta central, marginal and average elastic modulus of 30 cases.

No linear correlation was shown among placenta elastic modulus value, umbilical artery PI, uterine artery PI values.

Relationship among the placenta, umbilical artery elastic modulus, and uterine artery PI values

A total of 18 pregnancy cases were randomly selected to measure umbilical artery and uterine artery PI values.
The maximum value of umbilical artery PI was 1.37, and the minimum was 0.66, or an average of 0.94. Uterine artery maximum PI was 1.11, and the minimum was 0.63, or an average of 0.83. Umbilical artery and uterine artery PI values were less than the corresponding 95th percentile for gestational age [5, 6]. The correlation coefficient of the placenta and the umbilical artery elastic modulus PI values were $r = 0.10$, $t = 0.40$ ($p > 0.05$). No linear correlation was found among the placenta, umbilical artery elastic modulus PI value, and the uterine artery PI values (Table 2).

Discussion

Elasticity imaging technology has been clinically used for over ten years. This technology was initially used to identify benign and malignant breast lesions. The usefulness of this technology has been widely recognized through a large-sample, multi-center clinical study [7]. The elasticity imaging of the thyroid, prostate, and other organs provides a reliable basis for identifying and diagnosing diseases [8, 9].

The real-time shear wave elasticity imaging technique has been used in quantitative studies of abdominal organs. This technique is a preferred approach because of its imaging depth, reproducibility, and measurability, among other superior aspects. This imaging technique reportedly allows a close correlation between liver fibrosis type and tissue elasticity values [10]. However, no relevant reports have been carried out on real-time elastography of the placenta.

Exploring the causal relationship that results in the further dysfunction of placental complications in pregnancy is the ultimate goal of this series of studies. Using shear wave elasticity imaging for real-time expression, the present study sought to determine whether placenta-specific morphology or the morphological changes occurring during pregnancy indirectly reflect placental function.

In the present study, all cases involved normal pregnancies. Fetal growth and development corresponded to gestational age. Amniotic fluid index was normal. The umbilical artery and uterine artery PI values were within the normal range, that is, the clinical significance of placental function was normal. Therefore, the measured elasticity of the placental modulus should also be normal. A 10 cm detection depth for the SE12-3 probe was the most appropriate. The depth of the posterior wall of the placenta at late pregnancy usually exceeds 10 cm, as was the anterior placenta in the current study.

During the measurement process, the results can be affected by the high sensitivity of the instrument, fetal movement, breathing activity, and excessive pressure to the abdominal wall. These confounding factors were avoided. Measurements were also frozen after three image stabilization to improve measurement accuracy and repeatability. In addition, the interference of the above-mentioned factors on the measured values increase heterogeneity. The sampling window was placed at a lower elasticity. The average standard deviation of less than 30% can also minimize measurement error.

The edge and central areas of normal pregnancy placental elastic modulus were measured. No significant difference between the two was found using a paired t-test, indicating that the placental center and edge can both represent the placental elastic modulus. This finding indicates that the posterior wall of the placenta could also be measured extending to the wall. The edge elastic modulus of the depth within 10 cm represents the placental elasticity modulus. This condition resolves the effect of the location of the placenta on the measured values during the sampling process.

The placental elastic modulus ranged from $12.53 \pm 1.24$ kPa to $5.34 \pm 1.24$ kPa, or an average of $7.70 \pm 1.61$ kPa. The significant variations in the elastic modulus may be attributable to the following. First, the method by which the varying degrees of placental tissue calcification in different parts could affect the elasticity value changes
Detection of placenta elasticity modulus by quantitative real-time shear wave imaging

References


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during late pregnancy was unclear. Second, the relationship between the results and sample size might require further exploration.

The best indicators of the placenta are: 1) Abnormal umbilical artery PI values resulting from abnormal placental function; 2) Abnormal uterine artery PI values resulting in placental dysfunction; and 3) Umbilical artery and uterine artery PI values before and after the load. The present study found no linear correlation among the umbilical artery, uterine artery PI values, and the corresponding placental elastic modulus, suggesting that the elastic modulus of the placenta may be a specific or sensitive indicator of placental function measurement. The occurrence of jet lag when the elastic modulus and placental blood flow index became unusual, and the factors that resulted in the difference in severity require further study.

The capability of the placenta to transfer nutrients depends on several factors, including the maternal–fetal nutrient exchange surface area, the overall shape and ultrastructure of the placenta, blood flow, and the concentration of transport proteins, nutrients and anabolic hormones, among others [11]. Current clinical evaluation of placental function also depends on several factors, including the placental area that indirectly reflects the exchange volume [12], the direct reflection of placental perfusion flow index [13], the indirect reflection of the perfusion of the fetal placenta (umbilical artery) or the artery resistance index (uterine artery) of the mother, and the reflection of the synthesis of placental hormones and biochemical parameters [14].

However, no approach can accurately reflect placental function at present. Therefore, the relationships among intrauterine growth retardation, gestational hypertension, diabetes, and other pregnancy complications, as well as placental function and pregnancy outcome cannot be explored. Information on these relationships will clinically guide the timely termination of a pregnancy.

Real-time shear wave elasticity imaging is a method for tissue characterization, which can indirectly reflect the placental forms through the placenta elastic modulus and can provide the morphological basis for assessing placental function. The present work has demonstrated that the proposed approach could become an emerging technology in providing better clinical diagnosis based on abnormal placental function, following the paths taken by three-dimensional US, Doppler, hormone levels, and other related methods.
Three-dimensional ultrasound and three-dimensional power Doppler improve the preoperative evaluation of complex benign ovarian lesions

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³Department of Hygiene, Epidemiology and Medical Statistics, Medical School University of Athens
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⁵2nd Department of Obstetrics and Gynecology, Aretaieion Hospital, University of Athens (Greece)

Introduction

Transvaginal ultrasonography (TVUS) is a well-established imaging modality for the preoperative evaluation of ovarian masses according to visualization of specific structural characteristics and vascular parameters [1]. A reliable preoperative differential diagnosis between benign and malignant lesions can alter the surgical management of adnexal masses and therefore affect the prognosis [2]. Benign masses can be effectively managed with laparoscopy which is associated with lower morbidity and a shorter hospital stay, whereas in case of suspected malignancy, referral to a gynecological oncologist is required [3].

Although the accuracy of the subjective assessment of the ultrasound image of an ovarian mass by an expert is considered to be high, certain cases of complex ovarian lesions are still difficult to correctly classify [4]. The introduction of three-dimensional ultrasound (3D-US) and three-dimensional power Doppler ultrasound (3DPD-US) in the last decade has opened up new possibilities in the evaluation of ovarian masses. Main advantages of 3D-US include: the visualization of three image planes, 3D color display of blood flow, digital volume storage available at any time, and reconstruction of 3D plastic images [5]. Previous studies have demonstrated that 3D imaging techniques can enhance and facilitate the morphologic and functional evaluation of both benign and malignant ovarian lesions [6, 7]. Also, different scoring systems have been proposed for the morphological indexing assessment of an adnexal mass in order to determine the likelihood of malignancy [6, 8]. Current scoring systems proposed include: morphological assessment of ovarian lesions with gray-scale ultrasound, alone or combined with additional Doppler-velocimetric indices, CA125 values, and clinical parameters [4, 9].

The aim of this study was to determine whether the use of 3D-US and 3DPD-US as adjuncts to B-mode-US and the evaluation of findings according to a specific scoring system could facilitate the preoperative classification of complex benign ovarian lesions.

Materials and Methods

The authors prospectively analyzed the preoperative sonographic reports of 29 patients aged 16 - 56 years (mean age 33 years) who presented complex adnexal ovarian masses. Patients presenting a unilateral complex ovarian mass who were examined by an experienced sonographer and underwent elective surgical treatment (laparoscopy or laparotomy) were eligible for...
Three-dimensional ultrasound and three-dimensional power Doppler improve the preoperative evaluation of complex benign etc.

Table 1. — Sonographic scoring criteria for the assessment of an ovarian lesion.

<table>
<thead>
<tr>
<th>B-</th>
<th>US</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wall structure</td>
<td>Smooth</td>
<td>0</td>
</tr>
<tr>
<td>Low level irregularities</td>
<td>Papillarities</td>
<td>2</td>
</tr>
<tr>
<td>Shadowing</td>
<td>Present</td>
<td>0</td>
</tr>
<tr>
<td>Septa</td>
<td>None or thin = 3 mm or less</td>
<td>0</td>
</tr>
<tr>
<td>Thick &gt; 3 mm</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Solid parts</td>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Low solid pattern</td>
<td>High solid pattern</td>
<td>1</td>
</tr>
<tr>
<td>Echogenicity</td>
<td>Sonolucent</td>
<td>0</td>
</tr>
<tr>
<td>Mid level echo</td>
<td>High level echo</td>
<td>2</td>
</tr>
<tr>
<td>Peritoneal fluid</td>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Present</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

3D-US

Surface | Regular | 0 |
| Low level irregularity | 1 |
| High level irregularity | 2 |
| Relationship with the surrounding structures | Normal | 0 |
| Low level disturbance | High level disturbance | 1 |
| 3DPD-US | Linear vessel arrangement | 0 |
| Disturbed vessel arrangement | 1 |
| Chaotic vessel arrangement | 2 |
| Branching pattern | Simple | 0 |
| Moderate | 1 |
| Complex | 2 |

Table 2. — Correlation between histopathologic and 2D sonographic findings.

<table>
<thead>
<tr>
<th>Histopathological diagnosis</th>
<th>Cystic</th>
<th>Mixed</th>
<th>Septations</th>
<th>Papillarities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrioma (16)</td>
<td>9</td>
<td>7</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Dermoid cyst (7)</td>
<td>1</td>
<td>6</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Cystadenoma (4)</td>
<td>serous (2)</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>mucinous (2)</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hemorrhagic corpus luteum (2)</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 3. — Scores obtained after the evaluation of the sonographic characteristics of each ovarian lesion according to the proposed scoring system.

<table>
<thead>
<tr>
<th>2D score</th>
<th>Range</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>2D + 3D score</td>
<td>Range</td>
<td>Mean</td>
</tr>
<tr>
<td>2D + 3D + 3DPD score</td>
<td>Range</td>
<td>Mean</td>
</tr>
<tr>
<td>Endometrioma</td>
<td>0 - 6</td>
<td>3.19</td>
</tr>
<tr>
<td>Dermoid cyst</td>
<td>5 - 8</td>
<td>6.71</td>
</tr>
<tr>
<td>Cystadenoma</td>
<td>0 - 3</td>
<td>2</td>
</tr>
<tr>
<td>Hemorrhagic corpus luteum</td>
<td>5 - 6</td>
<td>5.5</td>
</tr>
</tbody>
</table>

Results

A total of 29 women presenting a unilateral ovarian mass were recruited for the study and underwent transvaginal gray-scale, 3D and 3DPD ultrasound examination. Histological analysis of ovarian lesions identified 16 endometriomas, seven teratomas, four cystadenomas and two hemorrhagic corpus luteum cysts. Table 2 presents the correlation of the histological diagnosis with the presence of septa or papillary projections and the cystic or solid appearance of the lesion. Dermoid cysts and hemorrhagic corpus luteum cysts presented more complex features and thus more conspicuous morphology. None of the cases in this study were characterized by chaotic vessel arrangement or complex branching patterns which are associated with malignancy.

At the end of the scanning session, the scores obtained by different types of ovarian masses according to B-mode or 3D/3DPD ultrasound modalities applied were evaluated and are shown in Table 3. According to B-mode-US findings, only seven endometriomas had a score less or
equal to three (44%), and were preoperatively classified as low risk for malignancy. The addition of 3D-US and 3DPD-US increased the accuracy to 56% (nine cases) and 94% (15 cases), respectively (Figure 1A). All cases of dermoid cysts included in the study were misinterpreted as high risk lesions according to B-mode scoring. Subsequent examination with 3D-US reduced the risk in one case, and the addition of 3DPD-US correctly classified another three cases (Figure 1B). All four cystadenomas were accurately graded as low risk masses with B-mode-US, 3D-US and 3DPD-US examinations. Both hemorrhagic corpus luteum cysts were initially misinterpreted by B-mode-US as high risk ovarian lesions due to rather high scores indicating ovarian malignancy, but the addition of 3D-US and 3DPD-US findings provided the correct diagnosis in one case (Figure 1C).

The overall diagnostic accuracy of sonographic examination of ovarian lesions with the aid of B-mode was 38% and increased to 48% and 83% with the addition of 3D-US and 3DPD-US, respectively. Other parameters of diagnostic performance, such as specificity and false positive rate, could not be estimated because the study group included only benign cases.

Discussion

Conventional B-mode TVS is usually considered the first-line imaging technique for the accurate characterization of ovarian lesions according to the subjective evaluation of ultrasound findings. However, this approach may fail to distinguish complex benign ovarian lesions and also to detect malignancy in lesions without conventional “malignant” morphology [13]. The findings in this study indicate that assessment of morphological characteristics and vascularization of ovarian lesions using 3D-US and 3DPD-US as adjuncts to B-mode-US, and evaluation according to a standardized scoring system, seem to improve the diagnostic accuracy in cases of complex benign adnexal mass.

Complex adnexal masses, such as endometriomas, can present diverse sonographic features which may resemble those of an ovarian carcinoma [14]. In this study, according to B-mode-US and 3D-US findings, just seven endometriomas had a score less than three and nine endometriomas less than six, respectively, which suggested low risk for malignancy. After the 3DPD-US examination, 15 out of 16 endometriomas included in the study were correctly visualized as benign. Qualitative analysis of tumor vascularity by 3DPD-US examination in these cases can be proven valuable, since it can distinguish the linear vessel pattern of a benign tumor and correctly guide diagnosis [15]. Similarly, dermoid cysts typically appear as heterogeneous masses with irregular hypoechoic and hyperechoic areas with posterior shadowing not separated by septa or homogeneous hyperechoic masses with regular capsule and posterior shadowing [2]. However, these masses are characterized by a great variability in sonographic appearance renders their correct interpretation as low risk lesions more challenging [14]. All the presented cases were initially considered suspicious for malignancy according to the B-mode score, mainly due to the presence of solid irregular inner contents. Additional examination with 3D-US changed the risk in one case, whereas the use of 3DPD-US changed the preliminary diagnosis in another three cases and assigned them as low risk category. Absence of vascularity within the solid part of the mass, linear appearance, and regular branching of the peripheral vessels demonstrated with the 3DPD-US, assisted in the correct classification of dermoid cysts.

A recent multicenter study included cystadenomas, either serous or mucinous, in the adnexal masses that present diagnostic difficulties on the basis of sonographic findings [4]. No ovarian cystadenoma in this study gave the wrong impression of malignant lesion by its B-mode scores due to its solid component. Three-dimensional visualization of the regular surface of solid components protruding into the cystic cavity and linear vessel architecture in the periphery of the lesion (3DPD-US criterion) correctly indicated a benign lesion. Furthermore, both hemorrhagic corpus luteum cysts were misinterpreted by B-mode-US and 3D-US examinations, as the morphologic scores obtained were high that may be associated to the presence of papillary projections, indicating ovarian malignancy; however, the addition of 3DPD-US imaging modality classified one case as low risk. The age of hematoma within a corpus luteum cyst affects the sonographic appearance of a hemorrhagic corpus luteum.
cyst, and if acutely imaged may simulate a solid mass due to the presence of heterogeneous echoes.

Multicenter studies have demonstrated that experienced ultrasound examiners using high-end ultrasound systems are able to correctly discriminate between benign and malignant adnexal masses in >90% cases based on morphological and Doppler assessment [4]. However, in a small proportion of cases even an experienced ultrasound examiner will find it difficult to determine whether the mass is most likely to be benign or malignant and the false positive rate is about 25% [4, 16]. In particular, a mass with papillary projections, multilocularity, low-level echogenicity of cystic fluid, and moderate vascularization with color Doppler ultrasound examination seem to be the most difficult to classify. There is ample evidence that both 3D-US and 3DPD-US are reproducible techniques among examiners and could be useful in selected cases in which conventional B-mode-US cannot confidently lead to a definite diagnosis [5]. Three-dimensional ultrasound images facilitate the recognition of the ovarian lesion anatomy and relationship with other pelvic structures, the accurate visualization of the surface features, the evaluation of the intracystic morphology, and the analysis of the tumor vasculature. In addition, the 3D-US mode allows the exploration of the outlet wall surface with the surface rendering an increasingly precise description of lesion anatomy via the acquisition of multiple sections, rotation, and reconstruction of the plastic image of the mass without increasing the scanning time.

In this study, the addition of 3D-US appeared to improve the evaluation of the lesion’s architecture and was associated with a significant decrease in false-positive findings. Moreover, morphological assessment of mass vascularity as depicted by 3D power Doppler seems to further add positively in the analysis of the tumor vasculature. In addition, the 3D-US technique allows the exploration of the outlet wall surface with the surface rendering an increasingly precise description of lesion anatomy via the acquisition of multiple sections, rotation, and reconstruction of the plastic image of the mass without increasing the scanning time. The findings in the present study demonstrate that the 3D-US and 3DPD-US in the conventional ultrasound evaluation of adnexal masses and the evaluation of the findings according to the proposed scoring system could improve the identification of complex benign ovarian lesions. A more accurate classification of ovarian lesions could be explained by the meticulous investigation of the lesion anatomy and the qualitative analysis of the vascularity architecture with the aid of 3D imaging. However, possible advantages of this approach demonstrated in our preliminary study should be validated in randomized clinical trials that will recruit a large sample size and include malignant cases as well. Moreover, it should be noted that the 3D power Doppler criteria were descriptive and may be replaced by quanti-
tive criteria of vascularization, such as flow index and vascularization index, resulting in a less subjective evaluation system. A reliable preoperative classification of complex ovarian lesions will establish the optimal surgical management affecting positively the prognosis in each case.

References


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Comparison of electrolytic status (Na\(^+\), K\(^+\), Ca\(^{2+}\), Mg\(^{2+}\)) in preterm and term deliveries

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Summary

Purpose of investigation: The objective of this study was to evaluate the electrolytic status of Na\(^+\), K\(^+\), Ca\(^{2+}\), and Mg\(^{2+}\) in serum and red blood cells in idiopathic preterm and term deliveries. Methods: The study included 105 pregnant women diagnosed with idiopathic premature delivery (study group) and 36 pregnant women with physiologically term delivery (controls). Samples of mother’s blood were collected and analyzed for the level of electrolytes in the serum/plasma and red blood cells. Results: Measured values of magnesium in red blood cells in the study group were far lower than physiological values, intracellular calcium levels were higher in the study group compared to levels measured in the controls. Sodium concentrations in cells were significantly lower in subjects with premature delivery. Conclusion: The magnesium intracellular level is the best representative value of magnesium in the body.

Introduction

Is the physiological mechanism of contraction and electrolytic status of the gravid uterus always the same? Electrolytic status is vitally important for biochemical processes in the cell. Recognition of intracellular processes, enzymatic activity, effects of neurohormonal factors, interacting effects and relation of electrolytes, particularly the correlation of intracellular deficit of magnesium, and altered concentrations of sodium, potassium, and calcium, allows for a more thorough and precise understanding of uterine contractions both in term and idiopathic preterm deliveries [1].

From the current aspect of electrophysiology in spite of numerous non-clarified facts, the mechanism of contractions of the gravid uterus is in direct relation with slow, voltage-gated channels and their interaction with intracellular processes. The change of electric potential in cell membranes controlling the cellular calcium level, as well as feedback on the cell membrane which is regulated by intracellular events, defines muscle cell tonus [2, 3]. Out of all electrolytes, magnesium is the most important regulator of cellular function and an essential activity factor of over 320 enzymes [4, 5]. Magnesium is an integral part of the intracellular processes such as oxidative phosphorylation, membrane transport, muscular contractions, and neural conduction, and it is involved in the synthesis of nucleic acids and proteins [6]. The most valuable discovery regarding the role of magnesium is the knowledge that the concentration of free magnesium ions in the cell regulates metabolic activity of the cell.

Smooth muscle contraction is closely related to cellular metabolism and electrophysiological characteristics of the cell. Smooth muscles are so-called oxidative tissue with more than 80% of ATP supplied from oxidative phosphorylation in mitochondria which requires magnesium ions to proceed. Until now, it is known that smooth muscle contraction is initiated by Ca\(^{2+}\) bonding to calmodulin, and such formed complex activates the kinase of the myosin light chain. It is considered that the presence of Mg\(^{2+}\) ion is necessary for modulation of the kinase of the myosin light chain as well as for identification of site and mode of action of the respective enzyme [7-11]. If there is any magnesium deficit in the cell, it brings about the impairment of physiological processes.

Magnesium is the most important bivalent cation in the cell. Less than 1% of total body magnesium is found in circulating blood, and therefore, the evaluation and analysis of serum magnesium concentration is not the true indicator of magnesium level [12-14]. The objective of our study was to evaluate the electrolytic status of Na\(^+\), K\(^+\), Ca\(^{2+}\), and Mg\(^{2+}\) in extracellular (serum) and intracellular (red blood cell) compartments in idiopathic preterm and term deliveries.

Materials and Methods

A randomized clinical study based on fundamental physiological principles was carried out. The study included 105 pregnant women diagnosed with idiopathic premature delivery (study group) and 36 pregnant women with physiologically term delivery (controls). The study group consisted only of pregnant women at 28-36 gestational weeks with preterm delivery whose etiology could not be explained by etiological agents, i.e. the study excluded all premature births whose causes could have been due to maternal or fetal factors (e.g., multifetal pregnancy, hypertension, diabetes mellitus, amnionitis, PROM, urogenital tract infections, IUGR, macrosomia, polyhydramnios, oligoamnios, etc.). The controls involved women with physio-
logic pregnancy and with term delivery between 38 and 42 gestational weeks.

Other than regular biochemical analyses, a sample of mother’s blood was collected and analyzed for the level of electrolytes as follows: sodium, potassium, magnesium and calcium in serum/plasma (extracellular compartment) and red blood cells (intracellular compartments). The method of AAS – atomic absorption spectrophotometry – was used to read the values of the respective electrolytes. The procedure involved the sampling of 5 ml of heparinized blood centrifuged at 3,000 rounds per minute and plasma was used for dilution of electrolytes.

**Plasma**

To determine sodium and potassium in plasma, 1:100 dilution (0.1 ml plasma/10 ml water) was prepared. To determine calcium and magnesium, LaCl3 - 0.2% (5 ml) was added for precipitation of phosphates and prevention of formation of potassium and magnesium phosphates which could have interfered with their values.

**Red blood cells**

Red blood cells were washed three times by 0.9% NaCl in 1:1 ratio (2 ml WBC and 2 ml saline) and used for preparation of electrolyte dilution. Upon centrifuging it, supernatant was decanted and the procedure was repeated three times. Thereafter, washed erythrocytes were diluted by deionized water. For sodium and potassium determination, 1:100 dilution (0.1 ml erythrocytes/10 ml water) and 1:1,000 dilution was prepared, respectively. Calcium and magnesium were diluted in 1:100 ratio with addition of LaCl3, as in plasma.

For dilutions prepared in this way, electrolytes were determined by reading the values on the AAS according to standards of known concentrations. The AAS SP 192 produced by Pye Unicima Ltd. functions as flame spectrophotometry. Solution elements in contact with a burner (acetylene) are transferred to free atoms. The light source emission is characteristic for each element at specific wave lengths. Accordingly, magnesium is determined at 285.2 nm, calcium at 422.7 nm, sodium at 589 nm and potassium at 766.5 nm.

Reference values for plasma were as follows: Na+ (135-148 mmol/l), K+ (4.09-4.73 mmol/l), Mg2+ (0.65-1.05 mmol/l), Ca2+ (2.12-2.62 mmol/l). Reference values for red blood cells were: Na+ (117 ± 2.10 mmol/l), Mg2+ (2.30 ± 0.24 mmol/l), K+ (125 ± 10.6 mmol/l), Ca2+ (0 ± 0.10 mmol/l). The values were directly obtained by expression in mmol/l of blood.

Statistical data processing included: descriptive parameters (mean value, standard deviation, standard error and median), Student’s t-test (with probability p < 0.01 and p < 0.05), χ² test (p < 0.05), Fisher’s exact test, Mann-Whitney U-test (p < 0.05), and McNemar’s test.

**Results**

The mean age of pregnant women with premature delivery was 25.14 ± 4.40 years, and 26.11 ± 5.10 years (t = 1.092) in the controls. In both groups, the majority of pregnant women was primipara (76/67.7% of the study group and 20/55.6% of the controls), χ² test = 1.705. In multiparas, former pregnancies in the experimental group were terminated at gestational week 39.03, and in the controls at gestational week 38.33 (t = 1.453).

The results revealed that the average gestational week at the time of delivery in the study group was 33.60 ± 2.05 (the least being week 27), and in the controls 39.17 ± 1.48 weeks, t = 15.015 (p < 0.01).

The concentration of the analyzed bivalent magnesium ion within the extracellular space in the premature delivery group was at the lowest normal limits (0.93 ± 0.14 mmol/l), while measured values in pregnant women with term delivery were within optimal physiological values (1.12 ± 0.11 mmol/l). In spite of the fact that the obtained results were reviewed rather strictly within tolerable limits, statistical analysis yielded quite different figures, i.e., t = 7.435 (p < 0.01).

Measured values of magnesium in red blood cells are illustrated in Table 1; values in subjects with premature delivery were far lower than physiological values, accounting for 0.86 ± 0.22 mmol/l. In control subjects, the values of intracellular magnesium were 2.19 ± 0.12 mmol/l. The Mann-Whitney U test recorded U = 36.00, Z = 9.770. Such result indicated that intracellular magnesium level in subjects with premature delivery was significantly lower in relation to intracellular level in the group of subjects with term delivery (Table 1).

Analysis of the results, as presented in Table 2, demonstrated no significant difference of calcium concentration in the extracellular compartment in either group.

Cellular calcium level was 0.63 ± 0.18 mmol/l in subjects with premature delivery, and 0.47 ± 0.18 mmol/l in the controls. The measurements of intracellular calcium showed that in both groups there was a significantly higher calcium level compared with physiological values, and further analysis of the obtained results found a difference between these two groups (p < 0.01), meaning that significantly higher values were recorded in subjects with premature delivery (Table 2).

The results of serum sodium concentrations were within physiological limits in both groups and there was no significant difference (154.62 mmol/l vs 147.51 mmol/l).

The obtained results of sodium concentrations in the cell, as demonstrated in Table 3, showed that there was a significant difference (p < 0.01), with lower values in subjects with premature delivery. Considering that blood samples were collected from both groups at the time of delivery, i.e., at the time of full activity, the obtained sodium values in the intracellular space were the result of depolarizing activity of the cell membrane which generally precedes the contraction of all cells, even the uterine muscle cells (Table 3).

The values of major intracellular monovalent ion - K ion (potassium), which determines the positivity of the external cell membrane surface and magnitude of the resting membrane potential, were within physiological limits in both groups (4.44 ± 0.60 mmol/l in the experimental and 4.28 ± 0.63 mmol/l in the controls).

Measurements of potassium concentrations in the cell revealed that the values were lower in both groups in relation to reference physiological values, but a significant difference was found between these two groups. In ery-
thromocytes of women with preterm delivery, the values were 56 ± 11.08 mmol/l, and in the controls 91.56 ± 12.08 mmol/l (t = 16.104; p < 0.01). The results supported the role of depolarized activity during the action potential as the trigger of contractions of the uterine muscle cells.

**Discussion**

Premature delivery is one of the most important individual problems of perinatal medicine. Multiple facts with a predominating impact can affect the occurrence of preterm delivery [15, 16]. One of the most frequent unrecognized and untimely, diagnosed electrolyte disorders is magnesium deficit. Plasma magnesium level is a poor indicator of magnesium status in the body [17].

The obtained results showed that the level of plasma magnesium was within physiological limits in both groups, and they themselves could not indicate hypomagnesemia. The fact that these results could not be relied on was confirmed by findings of the cell compartment – red blood cells. Intracellular space is the only valid indicator of the actual status, i.e., electrolytic level of magnesium, because this bivalent cation is predominantly intracellular electrolytes, and, in normal serum magnesium concentrations, intracellular hypomagnesemia may be, and often is, present [18, 19]. Our sample verified the aforementioned.

The results suggested that in case of idiopathic premature delivery, intracellular hypomagnesemia was present in borderline values of serum magnesium: given the known role of magnesium in intracellular processes, it may cause a series of reactions giving rise to elevated cell excitability. The role of magnesium is seen in neuronal activity, cardiac excitability, vasomotor tonus, and muscular contractions, which is all the result of its modulatory potential.

One of the modulatory potentials of magnesium is the control of cellular calcium level [20]. Magnesium by magnesium-dependent enzymes directly affects calcium influx through cell membranes as well as the release of calcium from intracellular depots through membranes of the sarcotubular system [21, 22].

In both groups, serum calcium values were at lower physiological limits, which entirely corresponded with the fact that the subjects were giving birth, meaning that uterine activity (muscular contractions) was present.

So far, it has been only concluded that there is a rise of intracellular calcium, which by a known mechanism brings about muscular contractions, but the etiological factor causing the development has been completely neglected [23]. Our results showed that there was a significant increase of intracellular calcium concentrations in both studied groups, but also that there was a significant difference between these groups. It supports the observation that increased intracellular calcium concentration is necessary for muscular contractions, but the trigger of the uterine contraction mechanism is different in preterm and term deliveries.

Cellular processes proceed as chain reactions, and therefore any disorder cannot be observed as an isolated phenomenon. It is known that magnesium affects the cell membrane and significantly changes its action potential. Changed levels of sodium and potassium, particularly in the intracellular space, are the direct result of cellular hypomagnesemia and the effect of magnesium on Na and K biochemistry. The presence of hypomagnesemia causes the stimulation of transport systems of Na-channels, K-channels, Na⁺, K⁺ and Cl⁻-transport, K⁺ Cl⁻, co-transport, and Na/H exchange [24].

In red blood cells, there is a direct relation between K⁺/Mg²⁺ and Na⁺/Ca²⁺ concentrations.

In our study, plasma sodium levels were within physiological limits in both groups. What attracts special attention is the level in intracellular sodium. In both groups, there was a significant rise in sodium concentration. More marked hypernatremia was found in subjects with premature delivery, intracellular hypomagnesemia was present in a lesser degree of this group in comparison with subjects having premature delivery. Significantly lower intracellular sodium values in preterm delivery showed that depolarization activity had a certain but not decisive role in the initiation of the uterine muscular cell contractions, with constant focus on recorded higher intracellular calcium level and low level of its physiological antagonist – magnesium. It verifies a predominant effect of action potential to pathogenetic mechanisms of term delivery [25].

The analysis of results of K⁺ level in red blood cells
revealed a higher degree of hypokalemia in the group of subjects with premature delivery, what was certainly the result of the hypomagnesemia effect on Na⁺ and K⁺ membrane transport.

Hypomagnesemia is always followed by varying degrees of hypokalemia, and it is beyond doubt that the role of magnesium and its activity as an intracellular metabolism controller and modulator of enzymatic catalyzed processes is an important individual causative agent of higher cell excitability of the excitable tissues [26].

**Conclusion**

Hypomagnesemia in intracellular space increases the excitability of uterine smooth muscle, altering the permeability of cell membrane for Ca²⁺, N⁺, and K⁺, and enhancing the release of calcium from the intracellular depots thus preventing its re-accumulation. In term delivery, the increase of intracellular sodium concentration interferes with action potential which is the major factor – trigger of initiation of the uterine contraction. If an adequate level of intracellular magnesium were provided during pregnancy, it would certainly result in fewer premature deliveries caused by initiation of the uterine contractions due to electrolytic imbalance in the cell.

The magnesium ion is a crucially important element for biochemical processes in the cell.

**References**


Lymphedema of the arm after surgery for breast cancer: new physiotherapy

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Summary

Secondary lymphedema of the upper limb is a complication which can be found in patients who have undergone surgical breast cancer treatment with an axillary dissection. Lymphedema following breast cancer treatment remains a long-term disabling complication which cannot be treated in a decisive and radical manner. The objective of the treatment is to limit complications, to try to preserve the remaining lymphatic system and to develop new anastomosis. It consists of a specific decongestive physiotherapy, which may include a specific lymphatic drainage and skin mobilization, reducing bandages including Mobiderm (Thuasne), and sub-bandage muscular exercises. However variations in the therapy have been recorded by different teams.

Our experience in treating lymphedema in Tunisia takes into consideration the epidemiological, climatic, cultural and socio-economic conditions of the country. The difference in our treatment compared to what is being advocated elsewhere essentially consists of the no muscular exercise while wearing a bandage. This is compensated for by daily domestic activities, by prolonging the first two phases of treatment (the intensive phase and the stabilization phase), and by the use of the hydro gel dressing Hydrosob (Hartmann) to prevent blisters induced by the pressure imposed by Mobiderm studs of the bandage on the skin, and also by the superimposition of two types of Mobiderm bandages (small and large blocks).

Key words: Lymphedema; Breast cancer; Tunisia; Decongestant treatment of lymphedema.

Introduction

Lymphedema is the accumulation of protein-rich lymphatic liquid in the interstitial space, particularly in subcutaneous fat, affecting the secondary lymphoid organs of the upper limb of 14 to 28% of patients who undergo surgical breast cancer treatment by axillary dissection [1, 2].

Breast cancer is the most common cancer affecting women around the world. In African countries, standardized effects are less than 30/100,000 women [3]. In Tunisia, 17% of women with breast cancer are under the age of 35 years [3]. In this country, the diagnosis is made in most cases at an advanced stage (60% of patients are diagnosed at Stage II or III) [4], leading to invasive surgery of voluminous tumors (4 cm in diameter on average) [3, 4]. This invasive surgical treatment is associated with a large dissection and consequent additional treatments: chemotherapy and/or cobalt radiotherapy. The latter causes different skin symptoms of variable severity: erythema [5], dry dermatitis and exudative dermatitis, and dermal fibrosis which may appear and change over time. These reactions slow down or even offset new lymphatic anastomoses (indeed, they aggravate secondary lymphatic insufficiency with the appearance of post-radiation fibrosis [6]). As for chemotherapy, it is accompanied by a loss of proteins through vomiting, which may generate osmotic problems and lymph retention.

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which in the long-term can cause disability. It is then difficult to provide support for long term patients.

We present the details of our use of specific physiotherapy for this pathology.

Materials and Methods

Treatment

The main objective of the treatment is to minimize complications, to try to preserve the remaining lymphatic system and to develop new anastomoses to provide patients with more autonomy and a better quality of life. We stress the importance of hygiene [16-19], as well as specific decongestive physiotherapy. The latter includes specific lymphatic drainage, tissue mobilization, reducing bandages, and finally exercises under bandages.

The treatment should be preceded by questioning the patient about her marital status [2, 17], her living conditions (presence of animals and other possibly harmful factors), details of the history of illness and other examinations and treatments. We stress the importance of radiologic exploration in eliminating all pathologies associated with edema (such as deep thrombo- phlebitis, recurring metastatic and ganglion extensions) [20]. For patients with a heart deficiency, close monitoring has to be maintained by a cardiologist, since the treatment provokes a liquid surcharge in the heart. The questioning should be followed by a clinical assessment undertaken by the physiotherapist. It should include an inspection (staining loss, hair loss, transverse folds, mycosis, vesicles) [21], palpation (skin temperature, fattening, fibrosis...), assessment of measurements (with photos); and joint, muscular, sensory and functional checks [1, 13].

In our experience, the treatment of lymphedema is normally done according to the CHARDON-BRAS protocol. It includes lymphatic drainage, tissue mobilization, and specific decongestive physiotherapy. The latter includes specific lymphatic drainage, tissue mobilization, reducing bandages, and finally exercises under bandages [1]. Specific lymphatic drainage (digital pressure with spread fingers) consists of techniques whose aim is neuro-vegetative stimulation of the lymphatic system of the superficial skin. These techniques were developed by Schiltz in 1989 [13]. Tissue mobilization performed by hand is deeper; it consists of gentle transverse and longitudinal stretching which foster slipping of different underlying skin and muscle tissues. We stress the importance of radiologic exploration in eliminating all pathologies associated with edema (such as deep thrombophlebitis, recurring metastatic and ganglion extensions) [20]. For patients with a heart deficiency, close monitoring has to be maintained by a cardiologist, since the treatment provokes a liquid surcharge in the heart. The questioning should be followed by a clinical assessment undertaken by the physiotherapist. It should include an inspection (staining loss, hair loss, transverse folds, mycosis, vesicles) [21], palpation (skin temperature, fattening, fibrosis...), assessment of measurements (with photos); and joint, muscular, sensory and functional checks [1, 13].

In our practice, we proceed as follows: Since we do not have all the bandages, we use a Medica 315 cotton bandage which is carefully inserted between the fingers (Figure 2) and then wrapped around the arm in tilted circles to avoid a tourniquet effect. Prior to that, we interpose a Hydrosob (Figure 1) [22]: bandage at the elbow. It consists of a gel cushion whose composition includes 60% of water to avoid aggressive friction on the skin at the elbow. We then lay on the Mobiderm 33 cm x 1 m pad, which includes small blocks (5 mm x 5 mm) (Figure 6). The Mobiderm 15 mm x 15 mm (Figure 3) is used to reinforce the effect. We finally place the Flexiedial or Biflex (Figure 6) bandage, which is left in place all day. The patient removes the Biflex bandage at night. For this phase, all bandages are in semispecia (Figure 4 and Figure 5) to the elbow and spiral covering (1/3, 2/3) on the arm, in order to ensure their strength and to increase back pressure.

During the weaning phase, the patient needs to become more autonomous. She should learn how to perform auto-drainage and tissue mobilization from the physiotherapist. No friction should occur when laying the bandages. Chardon recommends [1] wearing a custom made Mobiderm sleeve at night. In Tunisia, since there are no Mobiderm sleeves available, the patient uses bandages which are placed at the end of the day, in the stabilization phase. The patient should have moderate activity, and the Biflex should be removed before going to bed.

Unlike the Chardon therapy, which includes several phase I and phase II cycles, depending on the evolution of the lymphedema, the duration of the phase I therapy is increased to 21 days and the duration of phase II to six months, without repeating these two phases in recurring cycles.

Different types of situations are encountered which can generally be classified in three large groups according to the appearance of the lymphedema and its association or not with an infection (Table 2). The presentation of the lymphedema determines the therapy for the patient. It should be taken into consideration that the treatment presented above is for lymphedema installed after the end of cancer treatment. The variants of this treatment are presented in Table 2. The variants are either related to the duration of the treatment or its association with antibiotic therapy.

Postsurgery lymphedema is easier to treat since the treatment lasts one to two weeks. It is limited to the drainage and mobilization of the tissue and stretching of open channels, with the
identification of the causes of installation. We stress the need for prevention [16-23]. Lymphedema associated with an infection requires antibiotic treatment. This treatment delays the support by the physiotherapist for six weeks. However, positive results are noticeable after two months of treatment on average.

**Discussion**

Lymphedema of the upper limb after breast cancer treatment remains an evolving chronic illness which can, over the long term, cause disability. It is induced by the association of several mechanical and biochemical factors which may be overlooked. There are specific anatomical sites which have been found by Kubik [24]. This may explain the appearance or disappearance of different types of post-operative edemas or their delayed appearance. In both transitory and chronic lymphedema cases, the treatment is essentially preventive [16-19]. It is important to trace harmful causal factors [13] in order to adopt the most efficient treatment.

In 2003, support of the lymphedema was the subject of consensual work at the International Society of Lymphology [25]. There were specific recommendations for secondary lymphedema of the arm after breast cancer treatment. The same basic techniques for the treatment were reported by different teams: manual lymphatic drainage, multilayer bandages and muscular activity under bandage. However variations according to the teams were observed.

### Table 1. — Steps of treatment.

<table>
<thead>
<tr>
<th>Phase</th>
<th>Duration</th>
<th>Frequency</th>
<th>Means</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attack phase</td>
<td>21 Days</td>
<td>Every day</td>
<td>Lymphatic drainage: 40 min at the beginning of the treatment</td>
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<td></td>
<td></td>
<td></td>
<td>Tissue mobilization: Bandage:</td>
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<td>10 min</td>
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<td>1 cotton Band</td>
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<td></td>
<td>1 Plate Mobiderm®</td>
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<td></td>
<td></td>
<td></td>
<td>1 or 2 Flexideal®</td>
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<td></td>
<td></td>
<td></td>
<td>1 Band Biflex® 16’</td>
</tr>
<tr>
<td>Stabilization</td>
<td>Six-month</td>
<td>1 to 2 days</td>
<td>Lymphatic drainage: 20 min</td>
</tr>
<tr>
<td>phase</td>
<td>period</td>
<td></td>
<td>Tissue mobilization: Bandage:</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>10 min</td>
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<td></td>
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<td>1 hydro gel dressing Hydrosol®</td>
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<td></td>
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<td>1 cotton Band</td>
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<td>1 Plate mobiderm®</td>
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<td>1 Band Biflex® 16’</td>
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<tr>
<td>Autonomy phase</td>
<td>Long-term</td>
<td></td>
<td>Autodrainage lymphatic</td>
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<td></td>
<td>Automobilization</td>
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<td></td>
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<td>Autobandage:</td>
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<td>1 Band Biflex® 16’</td>
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</tbody>
</table>

### Table 2. — Variants of treatment according to the appearance of the lymphedema and its association or not with an infection.

<table>
<thead>
<tr>
<th>Type of lymphedema</th>
<th>Characteristics</th>
<th>Factors starting &amp; factors of risk</th>
<th>Specificity of the treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphedema</td>
<td>&lt; 3 or 4 cm</td>
<td>Surgery</td>
<td>Prevention</td>
<td>Recovery of the volume of arm and mobility in 15 days</td>
</tr>
<tr>
<td>postoperation</td>
<td>transient evolution</td>
<td>Surgical drains</td>
<td>Open string stretching Body’s lymphatic drainage Tissue mobilization of the upper limb</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Immobilization</td>
<td>Tissue mobilization</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphedema</td>
<td>Asymmetry in size and volume of the two limbs</td>
<td>Lack of prevention</td>
<td>Preventing complications of the upper limb</td>
<td>Variable recovery</td>
</tr>
<tr>
<td>installed after</td>
<td>Insidious onset</td>
<td>High blood pressure</td>
<td>Manual lymphatic drainage Tissue mobilization Reducing Bandage</td>
<td></td>
</tr>
<tr>
<td>treatment of breast cancer</td>
<td>Slow Painless at the beginning</td>
<td>Obesity slow transit/constipation Sedentarity Garments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphedema</td>
<td>Sudden increase in the pain volume + infection characteristics (blush heat)</td>
<td>Infection entrance through skin on lymphatic stasis</td>
<td>Antibiotics (6 wks min.) Rest</td>
<td>Good progress after 21 characteristics</td>
</tr>
<tr>
<td>following an</td>
<td></td>
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<tr>
<td>infectious episode</td>
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...
The objective of the support is to limit complications, particularly infection [26], to preserve the remaining lymphatic system, and eventually to develop new anastomoses to increase autonomy and the quality of life of the patient over the long term. We note a psychological effect (change of body image) [18] and physical ones (increase in the volume of the limb and a decrease of the force of movement), which result in decreased autonomy.

Specific decongestive physiotherapy elaborated by a physiotherapist is the main element in the treatment of this pathology. It is important to remember that the following treatments should not be applied on the indurated arm [17]:

- Electrotherapy due to risk of burns
- Vacuotherapy on the limb (LPG method or endermology)
- Pulley therapy for compensation and charge risks and articulatory work along a fixed axis.
- Application of all possible sources of heat (infrared, fang therapy, hot pack)
- Use of weights, pumps, resistance exercise, gymnastics.

Figure 1. — Interposition of Hydrosob.
Figure 2. — Anti-edema cotton bandage (Medica 315/Gasoni-Sigvaris) application in spiral covering, protecting and reinforcing aponeurosis and increasing the drainage during physical effort (see Figure 5).
Figure 3. — Superimposition of the mobilizing Mobiderm bandage (10 cm x 3 m) with blocks of 15 x 15 mm.
Figure 4. — Superimposed elastic bandage(s) of cotton Flexideal (Thuasne), maintained in place by a compressive Biflex (Thuasne) bandage, facilitating drainage, even in the case of inactive patients.
Figure 5. — Anti-edema cotton bandage (Medica 315/Gasoni-Sigvaris) after removal of Biflex (Thuasne) bandage at night (since it exerts considerable pressure).
Figure 6. — “Final cover” with Biflex (Thuasne) bandage (left in place all day).
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- Massage of the indured arm which carries a risk of skin distension with a reverse effect on the lymphedema. It is also important to remember that inadequate treatment may make the lymphedema worse.

Other factors that can reduce efficiency of the treatment: A slow transit (chronic constipation) can prevent good lymphatic drainage.

Tightly fitting clothes (bra, inadequate prosthesis, etc.) which can have a tourniquet effect on return circulation. We stress the importance of physical effort (walking, swimming) to avoid complications resulting from potential stasis in adipose tissue.

For the treatment itself, good daily hydration of the skin is necessary to limit the effects of induced irritation by the Mobiderm blocks. The treatment is only effective when there is muscular contraction. We recommend that the patient uses the arm under bandage in her daily life. Furthermore, there should be good cooperation between the physiotherapist and the patient. The acceptance of the treatment by the patient is greater if the support is personnel and adapted to each case, with rigorous monitoring of the health checks during the different phases of the therapy.

Our experience in the treatment of lymphedema in Tunisia highlights certain modifications when compared to the methods recommended by CHARDON-BRAS. These are mainly due to adaptation to local climatic, cultural and social-economic conditions. Our patients do not necessarily have domestic help and have, therefore, to perform daily domestic activities despite their bandage. This compensates for the lack of muscular exercises under bandage. The ambulatory application of the lymphedema treatment in Tunisia is reduced during the hot months (May to October). Lymphedema is further aggravated by the summer heat. The bandage treatment in these conditions often induces blisters under the Mobiderm blocks on the skin. The frequency of therapy sessions also decreases in summer, and we note an increase of the duration of the first two phases of the treatment, namely the intensive phase and the stabilization phase. In addition, a HydroSorb bandage is included as a preventive measure.

Finally, we propose a different bandage superposition from that of CHARDON-BRAS. We superimpose two types of Mobiderm (small and large blocks) and recommend a system which is less rigid than the strapping or the sticky non elastic assembly.

In conclusion, the treatment of arm lymphedema after therapy for breast cancer is not entirely uniform and does not follow strict rules. It requires an adaptation approach by the physiotherapist and the patient.

References


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Oral supplementation with antioxidant agents containing alpha lipoic acid: effects on postmenopausal bone mass

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Summary

Purpose of investigation: Oxidative stress impacts many age-related degenerative processes, such as in postmenopausal bone loss and in antioxidant defenses that are significantly decreased in elderly osteoporotic women. The authors evaluated the effect of oral supplementation with antioxidant agents containing alpha lipoic acid (ALA) on bone mineral density (BMD) of osteopenic postmenopausal women. Materials and Methods: Fifty postmenopausal women with osteopenia (–2.5 < T-score < –1) were prospectively enrolled and randomly assigned to orally receive ALA and other antioxidant agents (vitamin C, vitamin E, and selenium) plus calcium and vitamin D3 (n = 25), or only calcium and vitamin D3 (n = 25). The BMD was estimated at baseline and after 12 months of treatment by heel quantitative ultrasonometry (QUS). Results: Forty-four patients completed the one-year study: 23 in the ALA group, 21 in the control group. The treatment of ALA group led to a better estimated BMD compared to the control group (0.401 ± 0.026 vs 0.388 ± 0.025 g/cm²), although this difference barely achieved a statistical significance (p = 0.048). Conclusion: These findings, although in a small population, could suggest that oral supplementation with antioxidant agents containing ALA may mitigate bone loss in osteopenic postmenopausal women.

Key words: Alpha lipoic acid; Menopause; Osteoporosis.

Introduction

Alpha lipoic acid (ALA), or thiotic acid, is a vitamin-like fatty acid produced by the human organism and found in small amounts in several foods: muscle meats, heart, kidney, liver and, to a lesser degree, fruits and vegetables. ALA is involved in the Krebs cycle and plays a key role in the cellular energetic metabolism with an insulin-like stimulation of glucose uptake and utilization [1]. In particular, ALA is a naturally occurring cofactor for the mitochondrial enzymes pyruvate-dehydrogenase and alpha-ketoglutarate-dehydrogenase, then it increases acetylcholine (ACh) production by activation of choline-acetyltransferase and increases glucose uptake, thus supplying more acetyl-CoA for the production of ACh [2]. Moreover, ALA is also a powerful antioxidantizing agent [3-5]. In particular, ALA chelates redox-active transition metals, thus inhibiting the formation of hydroxyl radicals and also scavenges reactive oxygen species (ROS), thereby increasing the levels of reduced glutathione [6-11]. In addition, ALA down-regulates the expression of redox-sensitive pro-inflammatoryary proteins, including tumor necrosis factor (TNF) and inducible nitric oxide synthase (iNOS) [12, 13]. Furthermore, ALA can scavenge lipid peroxidation products, such as hydroxynonenal and acrolein [14, 15].

Oxidative stress plays a pivotal role in the pathogenesis of various diseases and many age-related degenerative processes, including aging, cancer, atherosclerosis, inflammation, diabetes, and Parkinson’s disease [16]. Many studies have been conducted confirming the clinical benefits of ALA, including recent findings that ALA offers enhancing effects on hypertension, coronary heart disease, metabolic syndrome, peripheral neuropathy including diabetic neuropathy, and brain function including Alzheimer’s disease [17]. Clinically, ALA has been widely used for long time, including in ischemia reperfusion injury [18], diabetic neuropathy [19], HIV infection [20], and neurodegenerative diseases [21]. Furthermore, several sources of evidence have suggested a possible link between oxidative stress and bone loss: directly, by osteoclast-generated superoxide contributing to bone degradation, and indirectly, by induction of the osteoclast differentiation [22-24]. Moreover, some antioxidant defenses (e.g., vitamins C, E, and selenium) are markedly decreased in osteoporotic women [25] and ROS accumulation in the bone marrow is associated with bone loss in estrogen-deficient mice [26].

Epidemiological studies have found an association between dietary intake of vitamins C and E and bone mass / risk of hip fractures [27-29], and the administration of antioxidants, such as vitamins C and E and N-acetylcysteine, showed beneficial effects in individuals with osteoporosis [30-33]. Also ALA could have a therapeutic role in reducing bone loss associated with increased oxidative stress [34], although its clinical effect has not been determined.

Therefore, bone loss may also be hypothetically reduced by administration of antioxidant agents and the aim of this prospective comparative study was to evaluate the effect of oral supplementation of antioxidant agents containing ALA and powerful biological thiol antioxidant, on bone mineral density (BMD) of osteopenic postmenopausal women.
Materials and Methods

A group of consecutive osteopenic postmenopausal women (n = 50) was enrolled in this prospective study. Women were randomly divided into two groups: ALA group (n = 25) received, for twelve months, oral tablets containing ALA (300 mg), vitamin C (50 mg), vitamin E (5 mg) and selenium (2.75 mg), twice daily; plus oral tablets containing calcium (500 mg) and vitamin D3 (400 IU), twice daily; the control group (n = 25) only received oral calcium (500 mg) and vitamin D3 (400 IU) with the same posology and for the same period.

The patients were selected according to the following inclusion criteria: age ≥ 45 years; clinical and hormonal diagnosis of postmenopause (serum estradiol levels < 110 pmol/l, serum follicle-stimulating hormone (FSH) levels > 30 IU/l); osteopenia (-2.5 < T-score < –1). The exclusion criteria were: early menopause (< 45 years); body mass index (BMI) ≥ 30; bone disorders except osteopenia; use of hormone replacement therapy (HRT) or other bone-active agents less than six months before enrolment.

The authors evaluated the T-score in the enrolment phase and the estimated BMD at baseline and after 12 months of treatment, by means of heel quantitative ultrasonometry (QUS). BMD estimate was performed with a bone sonometer applied to the non-dominant foot. Ultrasound frequency of 0.6 MHz was used to measure estimate BMD as g/cm² (CVs 3% for BMD, absolute precision 0.014 g/cm²).

All values are presented as the mean value with range or standard deviation (SD). The statistical analysis was used by unpaired Student t-test. The level of statistical significance was set at p < 0.05.

Results

The study period of twelve months was completed by 44 patients out of 50 enrolled (23 in the ALA group and 21 in the control group). The women completing the study had a mean age of 60.1 years (range 49 - 75) and a BMI of 27.7 kg/m² (range 21.7 - 29.9); the menopause mean age was 50.7 years (range 45 - 56) and the mean duration of menopause was 9.5 years (range 1 - 27 years).

By group, the mean age in the ALA group was 60.7 ± 7.3 years and the BMI 27.3 ± 2.2 kg/m²; in the control group, the mean age was 59.5 ± 6.5 years and the BMI 28.1 ± 1.5 kg/m². Concerning bone assessment, the baseline estimated BMD was 0.399 ± 0.028 g/cm² and 0.391 ± 0.022 g/cm² in the ALA and control group, respectively. The complete clinical baseline characteristics of the study population were detailed in Table 1 and there were no significant differences (p > 0.05).

The treatment with ALA-containing antioxidant agents led to a significant better estimated BMD compared to the control group only receiving calcium and vitamin D3 (0.401 ± 0.026 vs 0.388 ± 0.025 g/cm²). Nevertheless, this difference only reached the statistical significance (p = 0.048) (Figure 1).

Discussion

The decrease in estrogen circulating levels during menopausal transition represents the main cause of bone loss [35]. A rapid decrease is, however, evident within the first five to ten years following menopause [36]. The physiological bone remodelling in this period is characterized by a relevant prevalence of resorption due to an increase of osteoclast pool size and activity, but the mechanisms through which estrogen deficiency stimulates bone resorption and impairs bone formation remain controversial and include direct effects of estrogen on osteoclasts and indirect effects that are cytokines-mediated. In addition, there is recent and increasing evidence that bone loss can also be mediated by oxidative stress [22-24].

Oxidative stress plays a pivotal role in many age-related degenerative processes, such as in case of postmenopausal bone loss by means of superoxide direct action and increase of osteoclastic differentiation [22-24]: estrogen deficiency lowers thiol antioxidant defenses in bone cells, thereby increasing ROS levels, which in turn induce expression of TNF, which causes bone loss [37]. A partial confirmation of these findings is the significant decrease of exogenous (vitamins A, C, and E) and endogenous (uric acid, superoxide dismutase, and glutathione peroxidase) antioxidizing agents in elderly osteoporotic women [25], and ROS accumulation in the bone marrow of ovariectomized mice with bone loss [26]. In particular, ovariectomy causes a substantial decrease in the levels of glutathione and thioredoxin that are the major tissue thiol antioxidants; which have been shown to prevent bone loss induced by estrogen deficiency [22-24].

ALA is a potent biological antioxidant and has been used to improve age-associated cardiovascular, cognitive, and neuromuscular deficits and has been implicated as a modulator of various inflammatory signaling pathways [7-9, 38-42]. More recently, the clinical role of ALA has been better defined as an inducer of cellular signaling pathways, insulin mimetic / hypotriglyceridemic agents, vasorelaxant / anti-hypertensive compounds, metal chelator and an adjuvant for neurocognitive function [17]: ALA may be effective in treating Alzheimer’s disease and related dementias [43]; intravenous infusion reduces symptoms of diabetic peripheral neuropathy [44-46]; dietary supplementation prevents hypertension, insulin resistance, and aorta superoxide production in a rat model of hypertension induced by chronic glucose feeding [47]; ALA has recently been shown to exert potent antiobesity effects by suppressing hypothalamic adenosine monophosphate-activated protein kinase activity [48].

Moreover, there are some in vitro evidences suggesting
that ALA, like other thiol antioxidant agents, could have a therapeutic role in halting or reducing bone loss associated with increased oxidative stress: ALA suppresses osteoclastogenesis by direct inhibition of the receptor activator of nuclear factor-kappaB ligand (RANKL) mediated signals [49]; ALA showed to prevent bone resorption induced by RANKL and TNF-α [50]; a pretreatment of human bone marrow stromal cells (hBMSCs) with ALA prevented the apoptosis induced by TNF-α and hydrogen peroxide [34]. However, in the typical Western diet, ALA is not sufficiently supplied by diet and de novo synthesis takes place in the heart, liver, and testis [51], hence the concentration of free ALA in the circulation is very low and supplementation is necessary to reach potential therapeutic levels [34].

The purpose of this comparative investigation was to evaluate in vivo the effect of a 12-month oral supplementation with ALA, plus other antioxidant agents such as vitamin C, vitamin E, and selenium, on the BMD of a subset of 50 osteopenic postmenopausal women. BMD was measured with an ultrasound method, heel QUS measured on the non-dominant foot [52-54], not considered as the gold standard in the diagnosis of postmenopausal osteoporosis, but able to estimate the bone density decrease and predict the risk of fractures with respect to the conventional dual energy X-ray absorptiometry technique [55-59].

The results in the 44 patients that completed this one-year study showed that the association of antioxidant agents containing ALA to calcium and vitamin D3 led to a better estimated BMD compared to the control group, but significantly greater at the trochanter (+4.6%, \( p = 0.022 \)) after adjustment for BMI [60]. Furthermore, this experience confirms the association between dietary intake of vitamins C and E and bone mass [27-29] and their beneficial effects in osteoporotic patients [30-33]. Finally, the selenium supplementation and these clinical results are consistent with the evidence of decrease of glutathione peroxidase (selenium-containing) in elderly osteoporotic women [25].

Nevertheless, it should be noted that an analysis, not including ALA, of women participating in the large study Women’s Health Initiative (WHI) does not support an independent association between intake or serum concentrations of antioxidants (vitamins A, C, E, retinol, beta-carotene, and selenium) and BMD [61].

**Conclusions**

This comparative study, although limited by a small population, showed that the oral supplementation of osteopenic postmenopausal women with ALA plus other antioxidant agents (vitamin C, vitamin E, and selenium) had favorable effects by mitigating bone loss compared to the supplementation of calcium and vitamin D3 only. Even if the molecular impact of ALA and other antioxidant agents on bone turnover is yet not fully clear, it is apparent that oral supplementation could be clinically effective against oxidative stress-induced bone loss. Because current evidences mainly originate from *in vitro* studies, in particular regarding ALA, further controlled trials are needed to determine the potential to prevent bone loss, including postmenopausal osteoporosis.

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Oral supplementation with antioxidant agents containing alpha lipoic acid: effects on postmenopausal bone mass


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Perinatal outcome associated with nuchal umbilical cord

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Summary

Introduction: Nuchal umbilical cord (NUC) is a possible complication of pregnancy which can be associated with adverse perinatal outcome. Materials and Methods: A retrospective study was done at the County Emergency Hospital Timisoara, Romania, between January 2009 and December 2010 and included cases with NUC at the time of delivery. Outcome variable related to the mothers and newborns were studied. Results: The incidence of NUC in the studied period was 8%. Most were primiparous. There were no significant statistical differences between vaginal births and cesarean section with one minute Apgar scores higher than 8. Five percent of the studied group presented intrauterine fetal death. Conclusions: The presence of NUC implies more attention but are not associated with increased rate of operative vaginal or cesarean delivery. One minute Apgar scores in these cases are comparable. NUC can be a cause of IUFD.

Key words: Nuchal umbilical cord; Fetal distress; Intrauterine fetal death; Vaginal birth; Cesarean section.

Introduction

The umbilical cord (UC) has a very important role in connecting the developing fetus to the placenta. The apparition of the cord wraps - defined as a 360º, single or multiple wrap around the fetus’ s neck - is considered a random event, caused by excessive fetal movement or a long UC [1]. Various factors related to the UC can influence the fetal blood flow through the umbilical cord vessels throughout pregnancy, labor, and delivery. It can have serious undesirable effects on the health of the fetus and newborn. NUC can be diagnosed antepartum using ultrasound (US) examination, but the complications are unpredictable and unpreventable. An umbilical cord accident (UCA) can conduct to intrauterine fetal death (IUFD), which is a form of sudden antenatal death syndrome (SADS). In these cases, the umbilical venous or umbilical arterial blood flow is compromised and the fetus dies. Incerti et al. demonstrated that UCA may occur in 15% or more of all SADS cases [2]. The main objective of the study was to identify any correlation between maternal, fetal, and placental factors, the mode of delivery and the perinatal outcome of the cases with NUC at the time of delivery. The secondary objective was to demonstrate that NUC could be a cause of IUFD.

Materials and Methods

In the present study the recorded number of births with NUC were counted as well as the total number of deliveries in a tertiary hospital – Department of Obstetrics and Gynecology of the County Emergency Hospital Timisoara, Romania. Respectively the authors found 397 cases with NUC from the 5025 births recorded from January 2009 to December 2010.

Results

Gestational age was based on the obstetrical method that uses the last menstrual cycle. In the study, term infants were defined as those born at or after 37 weeks of gestation and preterm infants were defined as those born between 28 and 36 weeks of gestation. Multipara was defined as women who had had two or more births and grand multipara was defined as women who had given birth five or more times.

Data were collected from different sources. Demographic data, including age, parity, provenance (urban/rural), obstetric history, and associated pathology were provided by patient medical records. Data related to the delivery were extracted from the delivery records and included gestational age, pregnancy type (single/multiple), fetal presentation at the time of delivery, mode of delivery, and the reasons for cesarean section (C-section), and details related to the placenta. Details about the newborns included birthweight, Apgar scores, sex, details related to NUC, associated pathologies or congenital anomalies were also extracted from the newborn’s paper records.

For statistical analysis the SPSS computer application was used. More statistical tests were applied to analyze the data: chi square ($\chi^2$), Kruskall-Wallis, Mann-Whitney, and correlation analysis.

In the studied period 8% of the births were complicated with NUC. The mean maternal age was 27.7 ± 5.5 years; 11% (43) of the women were under the age of 20, 21% (238) were aged between 21-30, 28% (111) were aged between 31-40, and 1% (5) were 41 years of age or older. The urban/rural ratio showed that 54% were urban and 46% were rural. A total of 229 women (58%) were delivering their first child. NUC was present in 168 cases, (42%) in multipara, and just 13 cases (3%) of NUC in grand multipara.

The number of cases with NUC at the moment of birth increased until 40 weeks. After this term the number of cases decreased. In the cases with prematurity there were 37 pregnancies (9%) between 28-36 weeks. The gesta-
Perinatal outcome associated with nuchal umbilical cord

The mean of the newborn weight at birth was 3,257.6 ± 519.2 g. It is remarkable that the one-minute Apgar score varied between 8-10 in 92% of cases (Figure 1). There were 20 (5%) IUFDs. In these cases no other reason for fetal death were identified. An association was established between NUC and IUFD (test $\chi^2$, $p = 0.027$, $\alpha = 0.05$).

Vaginal delivery was carried out in 64% of the pregnancies and videextraction was used in 5% of these cases. The decision for cesarean birth was made by balancing the risks and benefits to mother and baby. The Apgar scores of the newborns by vaginal delivery and by C-section are presented in Table 3. The differences are statistically insignificant (test Mann-Whitney, $p = 0.096$). The percentage of patients with vaginal deliveries with the one-minute Apgar score from 8-10 was not significantly different in comparison with the C-sections (test $\chi^2$, $p = 0.308$, $\alpha = 0.05$).

The reasons for the cesarean births were grouped into eight categories (Table 4). The dystocia group included all cases in which the fetus was not able to progress down the birth canal and the size of the baby compared to the size of the mother’s pelvis implied a difficult vaginal delivery. This category represents 11% of all cesarean sections. Cases with uterine fibroma and with placental previa were included in obstruction or severe distorsion of the birth canal and represented 4%. Previous C-sections were described in 13% of cases. In the studied group, the fetuses were in normal position before the delivery – head downward in most cases (97%). There were 7% of C-sections performed due to abnormal position of the fetus in the uterus. Fetal distress represented 23% – as a single or associated reason for the C-section. It was the single reason for the Cesian section, or was associated with other reasons. Placental abruption was present in three cases. Two of these were associated with pregnancy-induced hypertension which could be the reason for the C-section. The C-section was performed in case of fetal anomaly or IUFD (3% of cases).

| Table 1. — Mean Apgar score in different gestational age groups. |
|---------------------|---------------------|---------------------|
| Group of gestation  | N       | Apgar score        | Std. Deviation   | Minimum | Maximum |
| 28-33 weeks        | 14      | 3.9                | 2.5               | 0       | 10      |
| 34-36 weeks        | 23      | 7.1                | 3.4               | 0       | 10      |
| 37-40 weeks        | 337     | 8.8                | 1.7               | 0       | 10      |
| 41-42 weeks        | 23      | 9.1                | 0.7               | 8       | 10      |
| Total              | 397     | 8.6                | 2.1               | 0       | 10      |

| Table 2. — Results of two by two groups’ comparison of the Apgar score. |
|---------------------|---------------------|---------------------|
| Weeks of gestation by group | Weeks of gestation by group | Calculated $p$ |
| 28-33 weeks        | 34-36 weeks         | < 0.001*            |
| 34-36 weeks        | 37-40 weeks         | < 0.001*            |
| 37-40 weeks        | 41-42 weeks         | 0.003               |
| 34-36 weeks        | 41-42 weeks         | 0.984               |

*significant differences.

| Table 3. — Mean one-minute Apgar score of the newborns by vaginal and C-section. |
|---------------------|---------------------|---------------------|
| Type of birth       | N       | Apgar score        | Std. Deviation   |
| Vaginal             | 255     | 8.5                | 2.1              |
| C-Section           | 142     | 8.9                | 2.2              |

| Table 4. — List of reasons for cesarean section. |
|---------------------|---------------------|
| Indication for the cesarean section | Cases |
| Dystocia            | 26 (18%)            |
| Obstruction or severe distortion of the birth canal | 5 (4%) |
| Previous cesarean birth | 19 (13%) |
| Position of the fetus within the uterus | 10 (7%) |
| Fetal distress       | 32 (23%)            |
| Problems with UC     | 1 (1%)              |
| Placental abruption  | 3 (2%)              |
| Health of the mother | 51 (36%)           |
| Health of the baby   | 4 (3%)              |

It is remarkable that the one-minute Apgar score varied between 8-10 in 92% of cases (Figure 1). It is an insignificant, direct, and very low correlation between Apgar score and NUC (Spearman coefficient = 0.04, $p = 0.428$), and was the same situation when NUC was correlated with the gestational age (coefficient Spearman = 0.032, $p = 0.519$). The mean of one minute Apgar score was related to gestational age. The largest mean one-minute Apgar score was in babies delivered post-term (Table 1). There were significant differences between the Apgar score in the described gestational age groups (test Kruskall-Wallis, $p < 0.001$). Values of the Apgar score were used to compare two by two groups using the Mann-Whitney test (Table 2).
Discussion

The study identified one NUC of every 13 deliveries (8%). Studies have described approximately 20-33% of pregnancies with NUC at term [3]. Other studies have reported a frequency between 18-25% of deliveries [4, 5]. Some studies suggest that NUC at delivery is not associated with perinatal outcomes [6]. Still other studies demonstrate that NUC has been associated with an increased risk for adverse outcome [7, 8]. The wrap of the UC was associated with higher birth weights and a fewer C-sections [9-11]. In the present group 60% of newborns weighed more than 3,500 g and just 36% were born by C-section.

Although the observation that NUC is present more often in primiparas, other studies identified the presence of NUC mostly in multiparas and still others did not find any relation between multiparity and NUC [12]. Moreover more male fetuses than female born with NUC has also been described in other studies [13].

In the third trimester of gestation, the most common cause of fetal demise is the complication of UC [14]. In UC accidents, the UC is constricted. This results in periods of hypoxia for the fetus which are described as unusually long periods of kicking or struggling. Therefore it is important to educate pregnant women to pay attention to these movements, especially when there is a large increase in kicking. It is not known how much time is needed for a fetus to die in cases when the UC is constricted. Unfortunately a common time of fetal death is during maternal sleep. Studies suggest that the event could be related to circadian rhythms [15-17]. In these cases various placental changes can appear with blood flow disruption or increased resistance [18, 19]. In the studied period, 37% of all IUFDs were attributed to an UC accident, which is a previously unrecognized complication in pregnancies after assisted reproductive techniques [20]. In the studied group, 4% of the pregnancies were obtained after sterility or infertility treatment; no IUFD occurred.

Ghosh demonstrated that in post-term pregnancies where NUC is present, there is an increased risk of fetal distress and operative intervention during labor, and thus delivery should be performed [21]. In the present study in the post-term pregnancies, 6% of the cases presented NUC and no IUFD occurred.

In the studied group the mode of delivery was predominantly vaginal (64%). Other studies described a higher incidence of natural birth (84.21%) [13]. Because of the blood flow changes in cases with NUC, it has been hypothesized that it could be the reason for reduced fetal weight at birth [4, 22, 23]. In the studied group, the average fetal weight was under 3,200 g.

Conclusions

The presence of NUC does not result in slightly lower Apgar scores at one minute, mainly as a consequence of higher operative delivery rates. A good perinatal outcome resulted in the cases with natural birth so C-section delivery was not necessary – just in cases that presented documented fetal distress. NUC can complicate the result of birth, therefore in these cases the delivery requires more attention. Monitoring during labor is very important in all these cases. If any signs of fetal distress appear, C-section is recommended. The study concludes that the presence of NUC implies a possible fetal risk and NUC could be a reason for IUFD.

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Intrauterine balloon tamponade as management of postpartum haemorrhage and prevention of haemorrhage related to low-lying placenta

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Summary

The aim of the present study was to evaluate the effectiveness of Bakri balloon in preventing and treating postpartum haemorrhage (PPH). Intrauterine Bakri balloon was used in a total of 16 patients with two different purposes: prophylactic placement of the balloon after caesarean section (CS) in six patients with low-lying placenta and therapeutic placement in ten patients with persistent bleeding from uterine atony, after spontaneous delivery, and administration of uterotonic. Intrauterine Bakri balloon was a successful approach in controlling and preventing PPH in all 16 patients. The median nadir hematocrit was 26.6% in six patients who underwent CS and 25.6% in ten patients with persistent bleeding after spontaneous delivery. The intrauterine balloon was in place for a duration of 24 hours. The median balloon infusion volume was 345 ml (range 250-455). No complications were reported. Bakri balloon tamponade was a useful measure in treating PPH unresponsive to pharmacological therapy in patients who delivered vaginally. Moreover, it was able to prevent persistent bleeding in patients who underwent CS for central placenta previa.

Key words: Postpartum bleeding; Uterine tamponade; Balloon technology; Fertility sparing.

Introduction

Postpartum haemorrhage (PPH) is often a sudden, life-threatening delivery complication. It is one of the leading causes of maternal morbidity and mortality [1, 2], responsible for 140,000 maternal deaths worldwide each year (one every four minutes) [3]. Recently, several guidelines regarding PPH management have been formulated. They involve a stepwise approach, with an escalation of intervention: from less-invasive methods, as uterine rubbering, and uterotonic agents, to more aggressive techniques such as peripartum hysterectomy. Actually, the UK survey revealed that, for those women who do not respond to a combination of uterotonic drugs, hysterectomy remained the most common surgical procedure [4]. Taking into account the serious problems related to surgical management of PPH as uterine atony, shock, renal failure, and coagulopathy) and adverse effect on fertility, alternative measures have to be sought [5, 6].

Uterine tamponade was one of the principal methods of achieving haemostasis in case of PPH since 1856 (cotton gauze was usually used to pack the uterus) [7, 8]. Today, there is resurgence of the use of uterine tamponade as conservative option in treating PPH with balloon technology. The aim of the present report was to evaluate the real effectiveness of Bakri balloon not only in treating PPH after vaginal delivery, but also in preventing excessive bleeding in patients with low-lying placenta who are candidates to elective caesarean section (CS).

Materials and Methods

The present study was conducted at the University Department of Gynecology and Obstetrics of L’Aquila between January 2009 and December 2011. A first group of patients who underwent CS for central placenta previa, and a second group of patients who experienced persistent bleeding from uterine atony after spontaneous delivery were candidates for uterine balloon tamponade. In patients who had CS, Bakri balloon was placed immediately after manual removal of afterbirth. At the same time, they received oxytocin (20 U in 500 ml of normal saline) and ergometrine intramuscularly (0.25 mg). The application technique of the device was similar to the original one explained by Bakri et al. during CS: the distal end of the balloon shaft was passed through the cervical opening with an assistant pulling that end vaginally. The uterine incision was sutured before filling the balloon with saline solution. After completing CS procedure, a vaginal pack was applied around the balloon shaft. In patients with persistent postpartum bleeding, the initial pharmacological approach with high-dose oxytocin (40 U in 500 ml of normal saline) and intramuscular ergometrine has not achieved haemorrhagic control. In these patients, the balloon was placed inserting the proximal end through the cervical opening, followed by vaginal packing. The amount of saline instilled to inflate the balloon ranged from 250 ml to 455 ml, depending on the size and capacity of the uterus. In all cases the balloon was filled while visualizing the uterine response to increasing tamponade. All patients had an indwelling Foley catheter to monitor the urine output and a broad-spectrum antibiotic cover for prophylaxis. Patients were kept under constant surveillance with control of hemogram, arterial pressure, and cardiac frequency six and twelve hours after the placement of the balloon. The balloon was held for a duration of 24 hours. The authors considered the procedure to be successful if the bleeding was stopped after the balloon was inflated.

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Results

Ten women had vaginal deliveries (three of them were primiparous) and six women had elective CS. Onset of the labour was spontaneous in seven cases and induced in three of ten vaginal deliveries. Elective CS was performed for central placenta previa in all six cases. The age of the patients ranged from 20 to 44 years (median 31.1). The median estimated blood loss was 512 ml (range 300-680) in the group of patients who had CS and 955 ml (range 600-1,500) in women who experienced PPH after vaginal delivery. The median nadir hematocrit was 26.6% in women who had elective CS (down from a pre-operative median hematocrit of 35%) and 25.6% after vaginal delivery (down from 30.5%). The balloon and the Foley catheter were removed after 24 hours. The median balloon infusion volume was 345 ml. All patients had spontaneous diuresis. No genital and/or urinary infections were observed. No patients were transfused and no complications were observed. In all 16 cases balloon tamponade was performed successfully, achieving haemostasis, minimizing uterine blood loss, and avoiding the need of peripartum hysterectomy.

Discussion

The management of PPH involves a stepwise series of procedures to stop uterine bleeding [9]. Although hysterectomy is a definitive treatment, there is a growing desire to preserve fertility, particularly in young women [10]. Uterine tamponade is one of the earliest methods for the management of PPH [11]. With recent appearance of balloon technology, medical community still shows a renewed interest in uterine tamponade as a conservative approach to PPH. Currently, a variety of such balloons are available; in descending order of relative cost they include: the Sengstaken-Blakemore tube, the Bakri balloon, Rusch balloon, Foley catheters, and the condom catheter balloon. Bakri balloon has the advantage of easy applicability and at the same time, easy removal (without the problem of traumatic friction of endometrial, endocervical or vaginal surfaces). In this study the authors found that Bakri balloon tamponade was highly effective in the management of PPH unresponsive to standard pharmacological management. All ten cases of PPH after vaginal delivery were controlled with balloon tamponade. Moreover, Bakri balloon tamponade was an effective mean of prevention of severe postpartum bleeding in patients having elective CS for central placenta previa. The purpose of our study was to evaluate the possible use of Bakri balloon as a preventative method of postpartum haemorrhage in patients showing risk factor for PPH as central placenta previa. Despite the small size of the sample, this report denotes an encouraging result in using Bakri balloon tamponade both as conservative management of PPH and as a mean of prevention of obstetric haemorrhage in women at risk, with the consequent reduction of aggressive surgery and without adverse effects on fertility.

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Clinical course and complications of HELLP syndrome according to time of onset

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Summary
Objective: To evaluate the impact of gestational age on clinical laboratory findings and maternal-perinatal outcomes in patients with HELLP syndrome. Method: A retrospective review of 74 patients with HELLP syndrome between January 2007 and October 2010 was performed. Data were stratified into two groups by gestational age at the onset of disease: group 1 (< 34 weeks) and group 2 (≥ 34 weeks). Clinical signs and symptoms, laboratory findings, and maternal and perinatal outcomes were evaluated. Results: No differences were observed between the two groups in the clinical and laboratory characteristics according to onset of HELLP syndrome except for gravidity, parity, and delivery interval. Maternal complications did not differ between the groups. The perinatal mortality rate was 22.9% in total and it was 43.2% in group 1. Conclusions: The time of onset of the HELLP syndrome mainly affects neonatal outcomes. To assess the effect on maternal morbidity more studies are needed.

Key words: HELLP syndrome; Maternal and perinatal outcomes; Temporizing management.

Introduction
Severe preeclampsia, particularly HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome is associated with significant maternal and perinatal morbidity and mortality [1]. Maternal organ systems such as the central nervous system (CNS), lungs, liver, kidneys, and systemic vasculature are susceptible to excessive inflammation and endothelial damage in HELLP syndrome [2]. It is essential to confirm the diagnosis and appropriate clinical management to avoid these multisystemic complications. The debate regarding the definition, diagnosis, etiology, and management of this syndrome is considerable [3]. It has a heterogeneous presentation and a clinical course similar to preeclampsia.

The terminology of early and late onset preeclampsia according to gestational age at the onset of preeclampsia is used largely, as a reflection of the severity of the disease and different etiopathogenesis [2]. Gestational age plays an important role in disease management and also impacts the short-term perinatal morbidity and mortality. Unfortunately, there is insufficient data regarding the impact of gestational age on the clinical course and maternal outcome in HELLP syndrome. It has been demonstrated that some clinical and laboratory parameters predict the severity of HELLP syndrome or disease outcomes, but there remains an ongoing debate and controversy about the potential use in clinical practice [4]. No predictors of adverse maternal and perinatal outcomes were identified in a review by Magee et al. [5] for severe preeclampsia. The time of onset of HELLP syndrome is important for perinatal outcome, and the effect on maternal outcome and management should be demonstrated.

The goal of this study was to evaluate the impact of gestational age on clinical laboratory findings and maternal-perinatal outcomes in patients with HELLP syndrome.

Materials and Methods
A retrospective review of the data of patients with diagnosed HELLP syndrome managed at Cukurova University, School of Medicine, Department of Obstetrics and Gynecology between January 2007 and October 2010 was conducted. This study was exempted from ethical approval by the Local Ethics Committee. The study groups consisted of mostly referred patients because of the tertiary unit. The patients were divided into two groups according to onset of HELLP syndrome. Group 1 (n = 37) consisted of patients with early onset disease (< 34 weeks of gestation) and group 2 (n = 37) consisted of patients with late onset disease (≥ 34 weeks of gestation). Clinical and laboratory findings, and maternal and perinatal outcomes were compared between the groups.

Patients were classified as having hypertension, severe preeclampsia, and eclampsia according to the criteria of the American College of Obstetricians and Gynecologist [6]. HELLP syndrome was defined as the presence of hemolysis which defined lactate dehydrogenase (LDH) ≥ 600 U/l or serum total bilirubin levels > 1.2 mg/dl, elevated liver enzymes, serum aspartate aminotransferase (AST) > 70 U/l and low platelet counts (< 100,000/mm³). Typical cases are those that develop before 20 weeks, and beyond 48 hours postpartum, and those that presented with some of the signs and symptoms of preeclampsia without the usual hypertension or proteinuria [7], diabetes mellitus, epilepsy, hepatic, and renal diseases were excluded from this study. At admission hematocrit, hemoglobin, platelet count, liver enzymes, LDH, uric acid, coagulation tests (prothrombin time, partial thromboplastin time, bleeding time), renal function tests (blood urea nitrogen, creatinine), and spot urinary proteinuria were determined. The patients were strictly monitored with blood pressure and urine output measurements and frequent assessment of symptoms. Laboratory assessments of platelet count, liver and renal function tests, LDH, and uric acid values were carried out every six hours. Blood products were administered to patients with existing severe anemia or coagulation abnormalities. Gestational age was determined according to the last menstrual period or first/early second trimester ultrasonography (US). All patients with HELLP syndrome routinely received magnesium sulfate as a 4.5 g IV loading dose before a 2 g maintenance dose per hour. All cases

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Statistical analyses were carried out using the Statistical Package for Social Sciences (SPSS version 16.0; SPSS Inc., Chicago, IL, USA). Data are shown as mean ± SD, minimum-maximum value or percent. Student’s t-test and Mann-Whitney U tests were used to determine differences for comparison of groups for parametric and nonparametric data. Statistical significance was set at p < 0.05.

Results

A total of 6,622 deliveries occurred during the study period, and 85 of all deliveries were complicated by HELLP syndrome (1.2%). This high prevalence is due to the fact that most patients were referred because of a tertiary unit. Seventy-four of these patients were included in the study because atypical presentation of HELLP syndrome. In this study, 11 patients were excluded due to an atypical presentation. Some studies showed that hypertension may be mild or absent in patients with HELLP syndrome and up to 13% of cases do not have proteinuria [4, 9, 10]. HELLP syndrome may be

Table 1. — Demographic characteristics and clinical findings of the patients according to the time of onset of HELLP syndrome.

<table>
<thead>
<tr>
<th>HELLP</th>
<th>Mean ± SD</th>
<th>Median (min-max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early onset (n = 37)</td>
<td>Late onset (n = 37)</td>
<td>Total (n = 74)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>30.5 ± 6.4</td>
<td>28.7 ± 6.4</td>
</tr>
<tr>
<td>Parity</td>
<td>30 (17-43)</td>
<td>30 (18-45)</td>
</tr>
<tr>
<td>Gravidity</td>
<td>3 (1-8)</td>
<td>1 (1-7)</td>
</tr>
<tr>
<td>Gestational age (week)</td>
<td>31.4 (21-35.6)</td>
<td>36.6 (33-40.4)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>162.2 ± 28.7</td>
<td>157.3 ± 28.2</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>107.8 ± 19.3</td>
<td>104.3 ± 17.6</td>
</tr>
<tr>
<td>Delivery interval (day)</td>
<td>2 (1-37)</td>
<td>1.2 ± 1.2</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>1374.3 ± 517.4</td>
<td>2480.4 ± 671.6</td>
</tr>
<tr>
<td>Proximal symptoms</td>
<td>22 (73.0)</td>
<td>29 (78.4)</td>
</tr>
<tr>
<td>Postpartum HELLP</td>
<td>2 (7.0)</td>
<td>20 (54.1)</td>
</tr>
<tr>
<td>Recurrent preeclampsia</td>
<td>4 (10.8)</td>
<td>3 (8.1)</td>
</tr>
<tr>
<td>IV antihypertensive requirement</td>
<td>31 (83.8)</td>
<td>31 (83.8)</td>
</tr>
<tr>
<td>Transfusion requirement</td>
<td>9 (24.3)</td>
<td>10 (27.0)</td>
</tr>
<tr>
<td>Twin pregnancy</td>
<td>3 (8.1)</td>
<td>2 (5.4)</td>
</tr>
<tr>
<td>Administering of betamethasone</td>
<td>16 (43.2)</td>
<td>1 (2.7)</td>
</tr>
</tbody>
</table>

*p = n, percent; * = p < 0.005.
Table 2. — Laboratory findings of patients according to time of onset of HELLP syndrome.

<table>
<thead>
<tr>
<th>HELLP</th>
<th>Mean ± SD</th>
<th>Median (min-max)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early onset (n = 37)</td>
<td>Late onset (n = 37)</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>12.6 ± 2.0</td>
<td>12.3 ± 1.4</td>
</tr>
<tr>
<td>Htc (%)</td>
<td>37.1 ± 5.7</td>
<td>36.8 ± 4.5</td>
</tr>
<tr>
<td>Pk (×10⁹ per l)</td>
<td>38.2 (20-48)</td>
<td>37.1 (27.5-45)</td>
</tr>
<tr>
<td>White cell count (×10³ per l)</td>
<td>13.0 ± 5.7</td>
<td>12.8 ± 6.1</td>
</tr>
<tr>
<td>AST (U/l)</td>
<td>13.3 (3.2-28.4)</td>
<td>10.9 (3.2-26.5)</td>
</tr>
<tr>
<td>ALT (U/l)</td>
<td>237.1 ± 282.0</td>
<td>233.6 ± 281.2</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>18.0 ± 11.0</td>
<td>14.2 ± 7.5</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>7.2 ± 2.1</td>
<td>7.4 ± 2.1</td>
</tr>
<tr>
<td>LDH (U/l)</td>
<td>1051.9 ± 523.7</td>
<td>949.2 ± 416.5</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>37.1 ± 5.7</td>
<td>36.8 ± 4.5</td>
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*p < 0.05; **p = 0.766.

Table 3. — Maternal and fetal outcomes according to time of onset of HELLP syndrome.

<table>
<thead>
<tr>
<th>HELLP</th>
<th>n (%)</th>
<th>Early onset</th>
<th>Late onset</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIC</td>
<td>9 (24.3)</td>
<td>7 (18.9)</td>
<td>16 (21.6)</td>
<td></td>
</tr>
<tr>
<td>Eclampsia</td>
<td>3 (8.1)</td>
<td>4 (10.8)</td>
<td>7 (9.5)</td>
<td></td>
</tr>
<tr>
<td>ARDS</td>
<td>1 (2.7)</td>
<td>1 (2.7)</td>
<td>2 (2.7)</td>
<td></td>
</tr>
<tr>
<td>Ablatio placenta</td>
<td>0 (0.0)</td>
<td>2 (5.4)</td>
<td>2 (2.7)</td>
<td></td>
</tr>
<tr>
<td>ATI</td>
<td>1 (2.7)</td>
<td>1 (2.7)</td>
<td>2 (2.7)</td>
<td></td>
</tr>
<tr>
<td>ICU admission</td>
<td>7 (18.9)</td>
<td>9 (24.3)</td>
<td>16 (21.6)</td>
<td></td>
</tr>
<tr>
<td>Class I (&lt; 50 x 10³)</td>
<td>5 (13.5)</td>
<td>7 (19.1)</td>
<td>12 (16.2)</td>
<td></td>
</tr>
<tr>
<td>Class II (50-100 x 10³)</td>
<td>21 (56.8)</td>
<td>21 (56.8)</td>
<td>42 (56.8)</td>
<td></td>
</tr>
<tr>
<td>Class III (&gt; 100 x 10³)</td>
<td>11 (29.7)</td>
<td>9 (24.3)</td>
<td>20 (27.0)</td>
<td></td>
</tr>
<tr>
<td>Fetal outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oligohydramniosi</td>
<td>10 (27.0)</td>
<td>9 (24.3)</td>
<td>19 (25.7)</td>
<td></td>
</tr>
<tr>
<td>IUGR</td>
<td>14 (37.8)</td>
<td>16 (43.2)</td>
<td>30 (40.5)</td>
<td></td>
</tr>
<tr>
<td>Stillbirth</td>
<td>2 (5.4)</td>
<td>1 (2.7)</td>
<td>3 (4.1)</td>
<td></td>
</tr>
<tr>
<td>Low APGAR score</td>
<td>15 (40.5)</td>
<td>2 (5.4)</td>
<td>17 (23.0)</td>
<td></td>
</tr>
<tr>
<td>NICU admission</td>
<td>31 (83.8)</td>
<td>13 (35.1)</td>
<td>44 (59.5)</td>
<td></td>
</tr>
<tr>
<td>Low birth weight</td>
<td>34 (91.9)</td>
<td>9 (24.3)</td>
<td>43 (58.1)</td>
<td></td>
</tr>
<tr>
<td>Perinatal mortality</td>
<td>16 (43.2)</td>
<td>1 (2.7)</td>
<td>17 (22.9)</td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.05; **p = 0.766.

Develop in the antepartum or postpartum period, and postpartum presentation may be as high as 30% [4]. In our series, HELLP syndrome developed in nine postpartum patients (12.2%), and eight of them were in the late onset group. The onset of clinical findings in this group of patients was within 48 hours postpartum. Women with a history of preeclampsia are at increased risk of preeclampsia and other adverse pregnancy outcomes in subsequent pregnancies. The magnitude of this risk depends on gestational age at time of disease onset and severity of disease. In our study, seven patients had a history of preeclampsia (9.5%). In a study which evaluated the recurrence risk of delivery before 34 weeks of pregnancy due to early onset of hypertensive disorder, the risk has been determined to be approximately 8% [11]. Prodomal symptoms have been reported with a frequency ranging from 30-90% [2]. The incidence of one or more prodomal symptoms in our study population was 75.7%. These results remind us of the importance of close follow-up of prodomal symptoms in the antenatal and postpartum period.

The purpose of this study was to discuss the impact of gestational age on maternal outcome, clinical findings, and laboratory parameters in patients with HELLP syndrome. We compared clinical and laboratory findings of patients in terms of onset of HELLP syndrome, and observed no differences between the two groups, except for gravidity and parity, and delivery interval. Yıldırım et al. [12] evaluated maternal complications according to gestational age and used 28 weeks of gestation for the threshold value; they observed no significant differences between the groups. Approximately 9-16% of HELLP syndrome cases are reported to be associated with eclampsia and it is reported that this association decreased as gestational age increased [13]. The ratio of eclampsia seen with HELLP syndrome was 7.9% in our study population and was not different between the groups. In another study [14] eclampsia did not appear to contribute to a significant adverse impact on the course or outcome of pregnancies complicated by HELLP syndrome.

Identifying patients with increased perinatal or maternal adverse outcomes could facilitate management of these patients. The initial evaluation of laboratory data may not provide predictions of complications. Haddad et al. [13] reported that laboratory parameters of HELLP syndrome are not independent risk factors for adverse maternal outcomes and management should be based on clinical endpoints rather than on laboratory parameters alone. According to Cavtaykar et al. [15] clinical complaints may help in predicting prognosis better than laboratory findings. However, Martin et al. [3] stated that laboratory data are more important to consider; the researchers found higher maternal morbidity rates in class 1 HELLP syndrome (class 1 defined as a platelet count ≤ 50,000 cells/mm³). In this study we compared the classification of HELLP syndrome by the Mississippi-Triple Classification System with onset of the disease, and did not find significant differences in onset of the disease. Yucesoy et al. [16] proposed that low platelet counts, LDH, AST, and ALT at the time of admission could be useful in predicting the severity of HELLP syndrome [17, 18]. However, Ganzevoort et al. [19] showed that accurate prediction of the clinical
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course of disease and patients, development of additional maternal complications with severe hypertensive disorders of pregnancy were not feasible at admission. Another study aimed at determining identification of preeclamptic women at risk of adverse outcomes [20]. An important effect of this study might be identification of preeclamptic women at the lowest risk of adverse outcomes. Gestational age at admission is a strong prognostic indicator for adverse infant outcome for preeclampsia [21]. This study demonstrated that the time of onset of disease was strongly associated with neonatal outcome but did not demonstrate an association with maternal outcome, laboratory findings, and clinical course of HELLP syndrome. The most important limitation of this study was that it was retrospective and there were not enough cases for decision-making for maternal outcomes according to time of onset of the disease.

Conclusion

The key clinical issue is to predict the complications of HELLP syndrome. Clinical presentation, symptoms, laboratory tests, and the time of onset of disease should be evaluated carefully to predict maternal and perinatal complications in HELLP syndrome.

References


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Fertility in women survivors of hematological malignancies: what is the real role of GnRH analogue treatment?

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¹Clinic of Obstetrics and Gynecology, ²Clinic of Hematology and Bone Marrow Transplantation, ³Department of Surgery
Teaching Hospital “SM della Misericordia”, Udine (Italy)

Summary

Purpose of investigation: The aim of this study was to evaluate the ovarian function in women who received or not gonadotropin-releasing hormone (GnRH) analogue co-treatment compared to the control group that did not receive it. Materials and Methods: This study analyzed 124 patients affected by hematological diseases between 1998 and 2007. The data were analyzed using R (v 2.9.1). Results: In the women treated with GnRH analogue, the authors found 33% post-treatment secondary amenorrhea and 6% had a pregnancy post-treatment, while in the other group the prevalence were respectively 49% and 4% (p n.s.). Moreover, in multivariate analysis the authors found bone marrow transplantation to be a risk factor for secondary amenorrhea, while the association of chemotherapeutic regimens is an experimental one. Whereas several investigators have demonstrated that GnRH-a inhibit chemotherapy induced ovarian follicular depletion in the rat [4], uncertainty remains regarding application in humans.

Conclusion: The authors found no statistical evidence to support that Gn-RH analogue treatment preserves ovarian follicular reserve during hematologic cancer treatment, but more evidence must be obtained.

Key words: Fertility; Hematologic disease; GnRH analogue treatment.

Introduction

Cancer is not rare in reproductive age young women [1]. The improved long-term survival of adolescents and young women treated for cancer has resulted in an increased focus on the effects of chemotherapy on ovarian function and its preservation. One of the major quality issues for young cancer survivors is preserving gonadal function and fertility [2].

It is known that the alkylating agents are associated with the highest risk of infertility. Then the most common significant long-term toxicity of chemotherapy in women is premature ovarian failure. Early loss of ovarian function not only jeopardizes the patients with a premature menopause and the related complications, but it is also associated with loss of fertility. Furthermore, women in Italy, like in the Western world, have been delaying initiation of childbearing to later in life. As cancer survivors, they face the risk of developing premature ovarian failure (POF) before they even consider having children. The prevalence of POF as a late medical sequel is, however, not as well-documented. Patients whose ovarian function recovers immediately after treatment or who maintain ovarian function, may still face risk of developing POF several years after therapy [3].

For the variations in type and dose of chemotherapy, the type of cancer, the time available before onset of treatment, the patient’s age and the partner status, renders each case unique and requires a different strategy of fertility preservation. The number of options is growing continuously: the use of gonadotropin-releasing hormone analogues (GnRH-a) as a co-treatment during chemotherapeutic regimens is an experimental one. Whereas several investigators have demonstrated that GnRH-a inhibit chemotherapy induced ovarian follicular depletion in the rat [4], uncertainty remains regarding application in humans.

The aim of this study was to evaluate the ovarian function in women who received GnRH-a co-treatment and in women who were treated with the same chemotherapy for hematologic diseases, without the agonist or only with estroprogestinic treatment.

Materials and Methods

This prospective non-randomized study analyzed 124 patients affected by hematological diseases treated in the Hematological Clinic and in the Obstetrics and Gynecological Clinic at the University Hospital of Udine between 1998 and 2007. The patients were affected mainly by: Hodgkin lymphoma, non-Hodgkin lymphoma, acute lymphoblastic leukemia, and acute myeloid leukemia (Table 1). The authors considered women with available clinical follow-up data in the five years after treatment. The authors categorized the patients into two groups: the first group treated with monthly depot injection of 3.75 mg GnRH-a (D-TRP6-GnRH-a; Decapeptyl C.R.; Ferring, Germany) for all the duration of chemotherapy, and the second group without GnRH-a treatment. The inclusion in the treatment or control group was a woman’s personal choice.

In this study the authors considered the following outcomes: the pregancy rate after chemotherapy, amenorrhea after chemotherapy, and the climacteric syndrome after chemotherapy. The authors took into account the following factors: characteristics of menstrual periods before and after chemotherapy, chemotherapeutic agents, associated radiotherapy, hematological pathology, bone marrow transplantation, physiologic, and gynecological history.
The data were analyzed using R (v 2.9.1). The authors used bi-variate analysis (chi-square or Fisher exact test, Wilcoxon test or t-test, and monovariate logistic regression) and multivariate analysis (multivariate logistic regression). The authors considered statistically significant a p < 0.05.

The GnRH-a treatment protocol was approved by the human ethical committee at the University of Udine. After informed consent, the GnRH-a administration was timed as early as possible, usually within ten to 14 days before starting chemotherapy.

In seven cases, where the hematologists indicated urgency to the initiation of chemotherapy, the interval was shorter. POF was defined as persistent hypergonadotropic amenorrhea (FSH > 40 U/l in two occasions) and low E2 levels. During the study period, these protocols were used: 1) for Hodgkin lymphoma (HL) ABVD: adriamycin 25 mg/m2, bleomycin 10 mg/m2, vinblastin 6 mg/m2, dacarbazine 375 mg/m2 (all the drugs were given on day 1 and 15); 2) for non-Hodgkin lymphoma CHOP: cyclophosphamide 750 mg/mq on day 1, doxorubicin 50 mg/mq on day 1, prednisone 100 mg/die on day 1, vincristine 1.4 mg/mq on day 1, rituximab 375 mg/mq on day 1 and 7 of chemotherapy.

### Results

The authors analyzed 124 patients treated of which 98 were still in follow-up or had completed the five years follow-up. The mean age of the women included in this study was 27.84 (± 8.82) years.

Group 1 included 33 women treated with GnRH-a, and about 24% of these (8/33) were co-treated with progestin treatment. These 33 women were treated for an average of 7.17 months (± 6.43). Group 2 included 45 women without treatment, or treated only with progestin treatment in 40% of the cases (18/45).

In Table 1 the authors show the population characteristics and observed no statistically significant difference, except for the lower prevalence of nulliparous women in the control group (p < 0.05). Before the start of chemotherapy, regular menstruation was presented in 91% (30/33) of the patients treated with GnRH-a and in 90% (25/39) of the patients in the control group (p = 0.550).

There was no statistical difference (p = 0.490) in the incidence of gynecological diseases between the group treated with GnRH-a (9%) and the control group (5%).

In Figure 1, the hematological diseases are divided into two study groups: Acute Lymphoid Leukemia (ALL); Acute Myeloid Leukemia (AML); Acute non Lymphoid Leukemia (ANLL); Hodgkin Lymphoma (HL); Chronic Myeloid Leukemia (CML); Non-Hodgkin Lymphoma (NHL); Castleman disease; Multiple Mieloma (MM); Idiopathic Thrombocytopenic Purpura (ITP); Essential Thrombocytemia (ETC); Werlhof disease.

In the two groups, Hodgkin disease, non-Hodgkin lymphoma, acute myeloid leukemia, and acute lymphoid leukemia were uniformly represented. The overall mortality prevalence was 14% (18/124) without considering the specific pathology.

In Table 2 the authors analyzed the chemotherapeutic regimens divided into risk categories considering the previous published data. The high-risk chemotherapeutic regimens were more prevalent in the group not treated with GnRH-a, and this group included all bone marrow transplantations. While the low-risk regimens were higher in the group treated with GnRH-a-Cyclophosphamide was used in about 30% of cases. In addition, cyclophosphamide was used in 33% (11/33) of women treated with GnRH-a and 29% (13/45) of non-treated women (p = 0.674).

In Table 1 the authors also considered the different prevalence of radiotherapy and bone marrow transplantation between the two groups and there was no difference that achieved statistical significance. Furthermore, the authors performed a logistic bi-variate analysis without finding statistical significance of GnRH-a treatment for the following outcomes: protection for amenorrhea post-therapy OR 0.52 (CI 0.95 0.21-1.33, p 0.172); achievement of pregnancy post-therapy OR 1.39 (CI 0.19-10.39, p 0.750); and protection against climacteric syndrome OR 0.42 (CI 0.08-2.22, p 0.307).

Among the considered outcomes, the authors analyzed two more in detail: pregnancy achievement after therapy and secondary amenorrhea after therapy. As shown before and in Table 1, there was no significant difference in pregnancy prevalence between treated and non-treated women with GnRH-a. Also the other possible predictors (histological type, treatment options, and age) were not significantly correlated to pregnancy achievement. Considering amenorrhea post-therapy at a maximum of five years follow-up, the authors confirmed GnRH-a not to be statistically significant protective (Table 3).

While radiotherapy was protective (OR 0.3 CI 0.95 0.1 - 0.9, p < 0.05) and the bone marrow transplantation was a risk factor for amenorrhea post-therapy (OR 7.2 CI 0.95 2.4 - 21.5 p < 0.05) in univariate and multivariate analyses after correction for age, parity, histological type and other treatment options.

### Discussion

Modern chemotherapy and radiation therapy regimens have enabled many girls and reproductive age women to survive their cancers, but at the cost of rendering them sterile due to ovarian failure. The GnRH-a as fertility-preserving agents is highly debated in hematology and most of the studies are criticized for their lack of randomization and the different and shorter follow-up periods for treatment and control groups. The most numerous studies were not randomized and resulted in favour of GnRH-a efficacy to spare fertility [5, 6].

The incidence of chemotherapy-induced amenorrhea is related to patient age, the specific agents used, and the total dose administered. Therefore, the authors carefully compared the study and control group for each of these parameters. Neither the age nor the dosages of the various cytotoxic drugs were significantly different between the two groups. Moreover, there was no significant difference in the incidence of POF between the two groups (33% vs 49% p = 0.170).

The cumulative dose of the alkylating agent, which is
Outcomes

Haematological diagnosis

Hodgkin’s lymphoma 52% (17/33) 35% (16/45) 0.160
Non-Hodgkin’s lymphoma 30% (10/33) 27% (12/45) 0.720
Acute myeloid leukemia 15% (5/33) 9% (4/45) 0.390
Chronic myeloid leukemia 0% (0/33) 11% (5/45) 0.070
Other malignancies 3% (1/33) 18% (8/45) 0.070

Oncological treatment

Chemotherapy 100% (33/33) 100% (45/45) 1.000
Number of cycle of chemotherapy 6 (4-6) 6 (4-6) 1.000
Radiotherapy 49% (16/33) 32% (14/44) 0.140
Bone marrow transplant 27% (9/33) 44% (20/45) 0.120

Outcomes

Pregnancy after therapy (5 years follow-up) 6% (2/33) 4% (2/45) 0.750
Amenorrhea 33% (11/33) 49% (22/45) 0.170
Polymenorrhea 3% (1/33) 0% (0/45) 0.240
Oligomenorrhea 0% (0/33) 0% (0/45) 1.000
Dyspareunia 3% (1/33) 2% (1/45) 0.820
Climacteric syndrome 6% (2/33) 13% (6/45) 0.300

Among one the most important parameters determining the risk of ovarian damage in this study, was the same in the group with Gn-RH-a (33.3% ciclophosphamide) and in the control group (28.8%).

Older women have a higher risk of ovarian failure and permanent infertility in comparison with younger women, since primordial follicle reserve declines with age [7]. For this reason in this protocol, the authors treated with GnRH-a only patients with an age between 15 and 36 years. The incidence of ovarian dysfunction after chemotherapy is strictly dependent on the doses of alkylating agents, and it has been calculated that the total dose of ciclophosphamide induced amenorrhea in a 40-year-old woman is four times less than the equivalent dose in a 20-year-old girl. Alkylation agents are gonadotoxic, producing damage to the ovarian reserve (primordial follicles) because they are not cell cycle-specific drugs [8]. If GnRH-a are given during the follicular phase of the cycle, they may actually cause a flare effect and create the opposite of the desired impact [9]. For this reason the authors, after informed consent, suggested the GnRH-a administration as early as possible, usually within ten to 14 days before starting chemotherapy. Future studies should examine GnRH antagonists instead of agonists for the achievement of a faster hypogonadotropic milieu, eliminating the waiting period of 7-14 days [10, 11]. However, in a recent study Danforth et al. [12] demonstrated in rodents that GnRH antagonists did not protect the ovary from the damaging effects of ciclophosphamide. Whereas the GnRH agonist significantly minimized the follicular depletion caused by ciclophosphamide, the GnRH antagonists did not prevent the gonadotoxic effect. This observation, although preliminary, raises concerns regarding the ability of GnRH-agonists to substitute the agonists.

It has been well-established that chemotherapy with total body irradiation followed by allogeneic or autologous bone marrow transplantation causes permanent elevation of gonadotrophin levels and amenorrhoea in 92-100% of female patients [13]. The authors confirmed this data, but the association of chemotherapy with radiotherapy and no bone marrow transplantation resulted to be protective.

The possibility of administering an adjuvant treatment that may decrease the gonadal damage caused by an otherwise successful treatment is attractive [14-16]. It has been suggested that inhibition of the pituitary-gonadal axis may reduce the rate of folliculogenesis and consequently render the germinal epithelium less susceptible to the gonadotoxic effects [17].

In hematologic malignancies, different studies [5, 6, 18-20] suggested a statistical significant improvement in the preservation of ovarian function by the use of GnRH-a in keeping with this study. The authors found no statistical significance but GnRH-a seems to be protective for amenorrhea post-therapy (OR 0.5 CI.95 0.2 - 1.3, p = 0.172), a promoting factor for a pregnancy post-therapy OR 1.4 (CI.95 0.2 - 10.4, p = 0.75), and protective for the climacteric syndrome OR 0.42 (IC 0.1 - 2.2, p = 0.307).

There are some important factors that differ between studies. First, the time of follow-up is important because POF is related to the age of women and menopause is a...
Fertility in women survivors of hematological malignancies: what is the real role of GnRH analogue treatment?

In this study the authors considered a follow-up of five years while the majority of studies took in consideration a short follow-up period. Second, POF and depletion of ovarian reserve are two different endpoints: 1) secondary amenorrhea associated with hormonal dosages will determine the actual diagnosis of POF but will not estimate the ovarian reserve depletion in the cohort of women with resumption of menstruation [21]; 2) ovarian reserve depletion could be estimated in two ways longer follow-up times to establish time to menopause and hormonal dosages.

Different hormonal dosages have been proposed for the estimation of ovarian reserve depletion. The FSH measurements on the second or third day of the menstrual period was found to be reliable and if it exceeded 12 mIU/ml (20 mIU/ml by radioimmunoassay), the probability of pregnancies was very low [22]. Likewise, elevation of estradiol levels above 75 pg/ml on the second or third day of the menstrual period is also associated with compromised fertility [23]. However recent studies found anti-Müllerian hormone (AMH) to be more reliable. AMH is expressed by granulosa cells [24] and its expression is initiated in the smallest growing follicles and declines in the early antral stages as one follicle is selected for dominance and the rest of them become atretic. In a recent study, compared to estradiol and FSH, AMH showed a more rapid and sustained change after chemotherapy [25]. However all these hormonal methods are limited as any other test while the time to menopause seems a more reliable method to establish the ovarian reserve damage because the aim should be to say to a 30 years-old woman the average risk to develop menopause during the next ten years in taking or not GnRH-a, in comparison to the normal population. For example the answer should be the menopause in the average of population is at x years; if you take GnRH-a it will be 1 year before; if you do not it will be 2 years before.

In a recent review, Badawy et al. took in consideration all randomized studies with GnRHa for preservation of ovarian function during gonadotoxic chemotherapy [26-30]. However they considered different tumors other than hematologic and two extremely recent randomized studies were missing, therefore in Figure 2 the authors analyzed the GnRH-a value in breast and hematologic cancer including the two new randomized studies. Furthermore, in case of the ZORO study the authors considered the 24 months outcome instead of the six months (*) [27]. In Figure 2 the two new studies are one for breast cancer (**) and one for hematological cancer (***) [31, 32]. The first point that can be observed is that no significance is achieved among breast or hematological cancers but the majority of studies are in favor of GnRH-a efficacy. The second point is that in the whole randomized studies of hematological pathologies have enrolled only 65 women, while Blumenfeld alone in a non-randomized study have evaluated 157 women [6]. The authors agree with Blumenfeld when he says that some studies are giving conclusion without enough evidence [33] and all need randomized studies with longer follow-ups that are not only assessing hormonal levels, but also the prevalence of evident diagnosis of POF during longer follow-ups.

Moreover, patients undergoing myelosuppressive therapy are at high-risk of menorrhagia during thrombocytopenia. In patients with cancer receiving aggressive chemotherapy, the authors used GnRH-a treatment to prevent thrombocytopenia-associated menorrhagia [34]. In conclusion in these patients, the authors suggested before the beginning of conventional chemotherapy regimens, the GnRH-a co-treatment because it prevents menorrhagia and could preserve ovarian function, but other further evidence is required to confirm the effect of treatment of GnRH-a in preservation of fertility in young patients exposed to chemotherapy.
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Determining the optimal fentanyl dose for dilation and curettage procedures

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²Aydın Maternity and Childcare Hospital, Aydın (Turkey)

Summary

Aim: This study attempted to determine an optimal dose of fentanyl, a drug frequently used in dilation and curettage (D&C) procedures, which is commonly performed as a brief outpatient intervention. Methods: The optimal fentanyl dose was determined using Dixon’s up-and-down method. The study was accomplished with a beginning fentanyl dose of 1 µg kg⁻¹ with a step size of 0.1 µg kg⁻¹ fentanyl. Results: The ED₅₀ [95% confidence interval (CI)] for fentanyl for successful anesthesia in D&C procedures was found to be 0.45 (0.35-0.55) µg kg⁻¹ and the ED₉₅ value was 0.50 (0.45-0.60) µg kg⁻¹. Conclusion: This dose is considerably lower than the standard dose that is used at present, which is 1 µg kg⁻¹. To the best of our knowledge, the current study is the first to show that a significantly reduced dose of fentanyl can be as effective as higher doses in D&C procedures using Dixon’s up-and-down method.

Key words: Fentanyl; Dilation and curettage; Optimal dose.

Introduction

Dilation and curettage (D&C) is one of the most frequently performed gynecological procedures and one that is both brief in duration and undertaken as an outpatient procedure. A dose of 1 µg kg⁻¹ fentanyl is commonly used as an analgesic in D&C [1] to alleviate significant pain that is likely to be involved in the procedure [2, 3].

While a fentanyl dose of 1 µg kg⁻¹ is frequently used for this procedure, to the best of our knowledge there is no study in the literature that has used Dixon’s up-and-down method to determine the optimal dose of fentanyl for D&C [4].

The aim of this study was to determine the optimal dose of fentanyl, a drug frequently used in D&C procedures, using Dixon’s up-and-down method.

Material and Methods

The study was conducted at the Adnan Menderes University Hospital. Patients willing to participate in the study completed a written informed consent.

Patients who met the inclusion criteria and who were about to undergo a D&C procedure were included in the study. The research was carried out with a total of 30 patients.

Patients between the ages of 18-60 assessed as I or II in the physical status classification of the American Society of Anesthesiologists (ASA) were enrolled in the study. Patients requiring intubation of the trachea or the use of a laryngeal mask, pregnant patients, patients who had reactive airway disease or a body mass index of > 35 kg/m², those with liver, kidney or lung disease, neuromuscular disease, as well as other patients who were to undergo the procedure as an emergency intervention were excluded from the study.

The patients were placed on an overnight fast and premedication was not administered. In the operating room, an intravenous (IV) cannula was first secured to the dorsum of the patient’s hand and an infusion of lactated Ringer’s solution was initiated. All patients in the operating theater were subjected to standard monitorization with a five-lead ECG noninvasive blood pressure and pulse oximetry.

The first patient was given an IV bolus dose of fentanyl 1 µg kg⁻¹ (Fentanyl citrate, USP 50 mcg/ml; Abbot Laboratories, Chicago, IL). New fentanyl doses were determined using Dixon’s up-and-down method according to the response received on the previous test doses. A step size of 0.1 µg kg⁻¹ was used for fentanyl in the study. An effort was made to determine the optimal fentanyl dose using Dixon’s up-and-down method, which has been used in many other previous studies to determine optimal dosage of various medications used in anesthesia. If successful anesthesia could not be attained in the D&C procedure, the next patient was administered a fentanyl dose increased by 0.1 µg kg⁻¹. If the procedure was successfully performed, the next patient’s fentanyl dose was reduced by 0.1 µg kg⁻¹.

A successful D&C procedure was defined as absence of recurring movement during the procedure and serious increase or decrease in hemodynamic signs; also, the non-presence of side effects of fentanyl such as dose-related respiratory depression.

The patient was administered 3-min preoxygenation prior to the induction of anesthesia. Following the fentanyl infusion, the patient’s basal measurements were taken. Later, lidocaine (Jetocaine simlex ampule; Adeka Pharmaceutical, Istanbul, Turkey) IV 1 mg/kg was administered. Anesthesia induction was achieved in the patients with propofol (Propofol 1% Fresenius, Fresenius Kabi, Australia GmbH), and sustained with a facemask with 60% nitrous oxide (N₂O) in oxygen with a fresh gas flow of 4 l/min⁻¹. Blood pressure, heart rate and oxygen saturation were recorded during the procedure. Clinically significant hypotension and bradycardia were defined as a reduction of mean arterial pressure and heart rate by > 30% compared to the basal measurement during the induction of anesthesia. The procedure ended when the gynecologist pronounced the intervention completed.

Statistical analysis

Statistical analysis for the study was carried out with the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL,
Table 1. — Patient characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>38.9 ± 10.3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>67.6 ± 10.6</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160.7 ± 8.56</td>
</tr>
<tr>
<td>Anesthesia time (min)</td>
<td>9.2 ± 0.88</td>
</tr>
<tr>
<td>ASA physical status</td>
<td>I/II (n)</td>
</tr>
<tr>
<td></td>
<td>14/16</td>
</tr>
<tr>
<td>Duration of surgery</td>
<td>7.47 ± 1.14</td>
</tr>
</tbody>
</table>

Table 2. — The 50% effective dose (ED50) and 95% effective dose (ED95) of fentanyl.

<table>
<thead>
<tr>
<th>Dose</th>
<th>ED50 (µg kg^-1)</th>
<th>ED95 (µg kg^-1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.45 (0.35-0.55)</td>
<td>0.50 (0.45-0.60)</td>
</tr>
</tbody>
</table>

USA), Version 14.0; p values < 0.05 were considered significant.

Data is expressed as mean ± standard deviation (SD). The study attempted to determine the optimal fentanyl dose using Dixon’s up-and-down method.

The analysis of the values for a 50% effective dose (ED50) were based on the calculation of the mid-point concentration of all independent pairs of patients displaying a crossover concentration. The ED50 was accepted as the average of the crossover midpoints in each pair. A probit test was also used for the up-and-down sequences and making the calculation of a mean fentanyl dose possible with a confidence interval (CI) of 95%.

A probit test that offered the best-fitting sigmoid curve was used to determine the maximal likelihood estimators of the model variables.

Results

A total of 30 patients participated in the study. Characteristics of the subjects are shown in Table 1.

The ED50 (95% CI) for fentanyl, obtained with probit analysis, found for successful anesthesia in D&C procedures was 0.45 (0.35-0.55) µg kg^-1 and the ED95 value for fentanyl was 0.50 (0.45-0.60) µg kg^-1 (Table 2).

Discussion

One of the most common outpatient operations performed in the obstetrics and gynecology branch of medicine is the D&C procedure. Significant pain is an expected outcome of this surgery. The reason for the pain is generally related to cervical dilation and tissue extraction required during the procedure [5]. An important consideration in the operation is the patient’s movement in response to pain. Because sharp tools, curettes, are used in the operation, patient movement during the procedure may lead to uterine rupture. Movement may also cause injuries of the intraabdominal organs such as the intestines and urinary tract [6]. This potential danger is an important factor to consider in terms of its significant potential for morbidity and even mortality. It is of great importance in terms of patient comfort, to ensure that she feels no pain during the procedure [7].

Opioids are the choice analgesic drugs in D&C. One of the opioids that is most commonly used because of the various advantages it offers is fentanyl. Fentanyl is a synthetic opioid. Fentanyl specifically interacts with the opioid µ receptor and is somewhat effective on δ and κ-opioid receptors [8]. Fentanyl’s cost advantage and its fast-acting effects give the molecule an edge over many other opioids [9]. At the same time, availability of fentanyl in suitable preparations other than in IV form contributes to making it a drug that is used effectively and successfully today [10-12].

Although fentanyl is frequently used in D&C procedures, to the best of our knowledge, the literature contains no reference of any research that has used Dixon’s up-and-down method to determine an optimal dose of fentanyl for D&C.

An analysis was performed to find the ED50 value (95% CI) for fentanyl for successful anesthesia in D&C procedures. This study is significant in that, it is the first study to use Dixon’s up-and-down method to show that fentanyl can be just as effective in markedly reduced doses in D&C procedures.

Fentanyl is commonly used as an analgesic in brief gynecological surgery and the practical, non-evidence-based dose that is generally administered is 1 µg kg^-1 [1]. In a study we carried out previously, it was found that fentanyl was effective in smaller doses of up to even 0.5 µg kg^-1 [13]. We found that smaller doses not only achieved analgesia but side effects were reduced as well. Moreover, the added advantage of faster recovery times in the group studied contributed to the conclusion that small doses of fentanyl could be as effective as higher doses for outpatient surgery.

The use of Dixon’s up-and-down method was one of the strengths of our study. Dixon’s up-and-down method has been frequently and successfully used to determine optimal dose studies [14-16]. While conventional techniques of determining doses call for numerous subjects, Dixon’s up-and-down method significantly reduces the number of cases needed to make the determination. While reducing the number of subjects needed in a study, Dixon’s up-and-down method still provides the opportunity to obtain similarly successful outcomes that can serve to determine optimal dosage.

There were some limitations to the study. One was the issue of blinding. The anesthesiologist participating in the study could not be blinded to the fentanyl dose. On the other hand, he was unaware of the basic purpose of the study. At the same time, the person evaluating the study and giving the instructions to increase or decrease the dose of the drug was an independent analyst who was blinded to the fentanyl dose. From this perspective, we believe that the study did achieve blinding to a significant extent.

Up-and-down methods are based on a simple sequential design that is used to define the dose at the 50th quantile (ED50), reducing the total number of subjects needed for the computation.

Because of the interest of anesthesiologists in the ED95, this is often calculated using the isotonic regression estimator with the CIs derived by bootstrap sampling. Despite the fact that isotonic regression provides a
Determining the optimal fentanyl dose for dilation and curettage procedures

backdrop analysis for determining ED50 with a smaller bias and tighter CIs as compared to standard probit or logit regression, which usually produce biased estimators [16, 17], extrapolating ED95 from small up-and-down data may fail to yield an exact calculation.

Another limitation of the study was defining successful anesthesia for the D&C procedure when a facemask is being used. We defined successful anesthesia in this case as the absence of recurring movement during the procedure, no serious increase or decrease in hemodynamic data, and the non-presence of dose-related side effects of fentanyl such as respiratory depression [18].

A recommendation might be to have future studies explore the duration of time in the operating room and in post anesthesia care unit when the ED50 or ED95 of fentanyl determined in the present study are administered, as well as to review the status of patients in terms of early discharge from the hospital. In taking a brief and global look into the practical application of significantly reducing the opioid dosage to the levels determined in the present study, and with the consideration that this procedure is a very common surgical intervention, another worthwhile study would be to compare costs for this dose with the costs of conventional 1 µg kg⁻¹ doses of fentanyl [19].

In conclusion, the use of Dixon’s up-and-down method to determine an optimal fentanyl dose for successful D&C procedures yielded the results that the ED50 (95% CI) value for fentanyl for successful anesthesia in D&C procedures was 0.45 (0.35-0.55) µg kg⁻¹ and the ED95 value was 0.50 (0.45-0.60) µg kg⁻¹, a significantly lower dose than the standard dose currently administered.

The study is significant in that it is the first study, to the best of our knowledge, that has used Dixon’s up-and-down method to show that significantly reducing fentanyl doses in D&C procedures may produce the same effect as the currently accepted standard dose of 1 µg kg⁻¹.

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Prediction of fetal macrosomia with ultrasound parameters and maternal glycemic controls in gestational diabetes mellitus

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Summary

Purpose of investigation: Evaluation of ultrasound measurements of fetal adipose subcutaneous tissue (ASCT), abdominal circumference (AC), liver length (LL), and amniotic fluid index (AFI) in prediction of fetal macrosomia (FM) and gestational diabetes mellitus (GDM). Materials and Methods: In a prospective clinical trial, 280 pregnant women underwent 100 g oral glucose tolerance test (oGTT) at 28th week of gestation (wg) and measurements of AC, LL, AFI, and ASCT at 32nd, 34th, 36th, and 38th wg. Results: For GDM, the best sensitivity was achieved by ACST at 32nd and 34th wg, the best specificity by LL at 32nd wg (90.6%), the best area under the curve (AUC) by LL at 34th wg (0.944). For FM the best sensitivity was achieved by AC at 32nd, 34th, 36th, and 38th wg and by ASCT at 34th wg (94.2%), and the best AUC at 38th wg for AC (0.974). Conclusion: Ultrasound parameters of glycemic control were good predictors of FM and GDM.

Key words: Gestational diabetes mellitus; Ultrasonography; Fetal adipose subcutaneous tissue; Fetal liver length; Amniotic fluid index; Fetal abdominal circumference.

Introduction

The reported prevalence of gestational diabetes mellitus (GDM) is 30% to 40% in a population of high-risk women for GDM [1]. Fetal macrosomia (FM) is one of the common adverse outcomes associated with GDM. It occurs in a significant proportion of fetuses of women with GDM, despite relatively good glycemic control [2]. A review of articles from different regions of the world with a documented prevalence of FM reveals a wide range (1% - 28%) in different countries. The prevalence was ≤ 3% in Nigeria [3] and Taiwan [4]; whereas Denmark [5] and Croatia [6] had a prevalence of ≥ 20%.

The sonographic diagnosis of FM is imprecise, and false diagnosis is common [7]. The prediction of FM may have considerable effects on obstetric management, even when the estimated fetal weight (EFW) is below the threshold that mandates Cesarean delivery [7]. EFW is based on biometric data (various combinations of femur length, head circumference, abdominal circumference, and other parameters) collected during the ultrasonographic examination and then incorporated into well-established regression formulas. Macrosomia due to GDM is different from FM due to other predisposing factors. Macrosomic infants of GDM mothers tend to have greater total body fat, greater shoulder and upper-extremity circumferences, greater upper-extremity skin-fold measurements, and smaller head-to-abdominal-circumference ratios than macrosomic infants of healthy mothers [8]. To overcome these drawbacks, alternative ultrasound markers for FM have been proposed which take advantage of the presumed correlation between subcutaneous fat deposition and fetal weight. Some of these markers are also indicators of glycemia control [9] and good predictors of GDM as well [1].

The aim of this study was to evaluate diagnostic performances of ultrasound indicators of glycemia control in prediction of FM and GDM.

Materials and Methods

The study was carried-out in the Institute for Gynecology and Obstetrics, Clinical Center of Serbia, Belgrade. The study population comprised of pregnant women diagnosed with GDM. The exclusion criteria were multiple gestation, confirmed fetal anomaly, pre-pregnancy hypertension, and pathological oral glucose tolerance test (oGTT) values, diabetes mellitus type 1 or 2, age < 18 years, maternal-fetal ABO incompatibility (titer > 1:30), maternal diseases and long-term medical treatments that might have affected glucose metabolism. A total of 280 pregnant women were enrolled in the study. At 28 weeks of gestation (wg), the study participants underwent oGTT and at 32nd, 34th, 36th, and 38th wg ultrasound exams, but the sonographers were blinded to the results of the oGTT of study participants. Dating was established by accurate menstrual history confirmed by sonography prior to 20 weeks. The ultrasound exams were performed using a ECO Ceel Toshiba, variable 2-5 MHz transducer (Toshiba Medical Systems, Ltd, Tokyo, Japan) and the Accuvix V100, Medison, variable 2-8 MHz transducer (Medison Co., Ltd, Seoul, Korea). Measurements of fetal adipose subcutaneous tissue (ASCT), fetal liver length (LL), amniotic fluid index (AFI) and abdominal circumference (AC), were measured using standard techniques [10-13].
Table 1. — Prediction of gestational diabetes mellitus and fetal macrosomia by ultrasound parameters of glycemic control.

<table>
<thead>
<tr>
<th>Week</th>
<th>AUC</th>
<th>p</th>
<th>CO Sn</th>
<th>Sp</th>
<th>AUC</th>
<th>CO Sn</th>
<th>Sp</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td>AC</td>
<td>0.910 (0.88 - 0.94) &lt; 0.001</td>
<td>300</td>
<td>0.897</td>
<td>0.777</td>
<td>0.953 (0.93 - 0.98) &lt; 0.001</td>
<td>304.5</td>
</tr>
<tr>
<td></td>
<td>ASCT</td>
<td>0.937 (0.90 - 0.97) &lt; 0.001</td>
<td>7.45</td>
<td>0.936</td>
<td>0.866</td>
<td>0.865 (0.80 - 0.95) &lt; 0.001</td>
<td>7.45</td>
</tr>
<tr>
<td></td>
<td>AFI</td>
<td>0.833 (0.78 - 0.89) &lt; 0.001</td>
<td>165.5</td>
<td>0.679</td>
<td>0.837</td>
<td>0.857 (0.79 - 0.91) &lt; 0.001</td>
<td>153.5</td>
</tr>
<tr>
<td></td>
<td>LL</td>
<td>0.942 (0.91 - 0.97) &lt; 0.001</td>
<td>47.5</td>
<td>0.872</td>
<td>0.906</td>
<td>0.882 (0.84 - 0.92) &lt; 0.001</td>
<td>47.5</td>
</tr>
<tr>
<td>34</td>
<td>AC</td>
<td>0.903 (0.87 - 0.94) &lt; 0.001</td>
<td>318</td>
<td>0.923</td>
<td>0.738</td>
<td>0.965 (0.94 - 0.99) &lt; 0.001</td>
<td>325.5</td>
</tr>
<tr>
<td></td>
<td>ASCT</td>
<td>0.931 (0.90 - 0.96) &lt; 0.001</td>
<td>7.75</td>
<td>0.936</td>
<td>0.797</td>
<td>0.919 (0.88 - 0.96) &lt; 0.001</td>
<td>7.95</td>
</tr>
<tr>
<td></td>
<td>AFI</td>
<td>0.856 (0.80 - 0.91) &lt; 0.001</td>
<td>156.5</td>
<td>0.872</td>
<td>0.718</td>
<td>0.863 (0.81 - 0.92) &lt; 0.001</td>
<td>178.5</td>
</tr>
<tr>
<td></td>
<td>LL</td>
<td>0.944 (0.91 - 0.97) &lt; 0.001</td>
<td>49.5</td>
<td>0.885</td>
<td>0.866</td>
<td>0.914 (0.88 - 0.95) &lt; 0.001</td>
<td>49.5</td>
</tr>
<tr>
<td>36</td>
<td>AC</td>
<td>0.885 (0.84 - 0.93) &lt; 0.001</td>
<td>338</td>
<td>0.885</td>
<td>0.757</td>
<td>0.973 (0.96 - 0.99) &lt; 0.001</td>
<td>344.5</td>
</tr>
<tr>
<td></td>
<td>ASCT</td>
<td>0.923 (0.84 - 0.95) &lt; 0.001</td>
<td>8.25</td>
<td>0.885</td>
<td>0.797</td>
<td>0.952 (0.93 - 0.98) &lt; 0.001</td>
<td>8.45</td>
</tr>
<tr>
<td></td>
<td>AFI</td>
<td>0.856 (0.81 - 0.91) &lt; 0.001</td>
<td>155</td>
<td>0.846</td>
<td>0.743</td>
<td>0.875 (0.82 - 0.93) &lt; 0.001</td>
<td>179.5</td>
</tr>
<tr>
<td></td>
<td>LL</td>
<td>0.917 (0.88 - 0.95) &lt; 0.001</td>
<td>51.5</td>
<td>0.936</td>
<td>0.752</td>
<td>0.927 (0.89 - 0.96) &lt; 0.001</td>
<td>52.5</td>
</tr>
<tr>
<td>38</td>
<td>AC</td>
<td>0.890 (0.85 - 0.93) &lt; 0.001</td>
<td>357</td>
<td>0.859</td>
<td>0.782</td>
<td>0.974 (0.96 - 0.99) &lt; 0.001</td>
<td>364.5</td>
</tr>
<tr>
<td></td>
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<td>0.918 (0.88 - 0.95) &lt; 0.001</td>
<td>8.55</td>
<td>0.923</td>
<td>0.738</td>
<td>0.953 (0.92 - 0.98) &lt; 0.001</td>
<td>8.85</td>
</tr>
<tr>
<td></td>
<td>AFI</td>
<td>0.834 (0.78 - 0.89) &lt; 0.001</td>
<td>154.5</td>
<td>0.782</td>
<td>0.767</td>
<td>0.870 (0.81 - 0.93) &lt; 0.001</td>
<td>168.5</td>
</tr>
<tr>
<td></td>
<td>LL</td>
<td>0.914 (0.88 - 0.95) &lt; 0.001</td>
<td>55</td>
<td>0.879</td>
<td>0.757</td>
<td>0.952 (0.93 - 0.98) &lt; 0.001</td>
<td>57.5</td>
</tr>
</tbody>
</table>


**Discussion**

The prevalence of FM and GDM in the present study were similar to comparable populations in Europe [5, 6]. The EFW is based on biometric data collected during the ultrasound examination. This exam is often obtained as close to delivery as possible to best estimate the fetal weight at birth. Unfortunately, these late exams have relatively poor positive and negative predictive values for fetal macrosomia, which limits their clinical utility for the individual patient [14-16]. Performing ultrasound exam so close to delivery can also present technical challenges such as decreased amniotic fluid and a fetal vertex well-engaged in the pelvis, which may limit visualization and accuracy. Various investigators have sought to overcome these limitations by performing series of ultrasonographic examinations earlier in the third trimester and predicting EFW on the basis of trends of fetal growth determined from earlier scans [17-19]. These were the reasons for this study design, which included evaluation of ultrasound parameters of glycemic control performed remotely from delivery to predict FM.

Sensitivity of ultrasound parameters of glycemic control in prediction of FM in this study ranged from 75% to 94.2%. Usual cut-off value of AC ultrasound measurement > 35 cm at term as an accurate method in identifying FM with high sensitivity (87.50%) and specificity (84.74%) [20], has lower diagnostic value comparing the proposed cut-off values for AC, ASCT, and LL during 32th, 34th, 36th, and 38th wg. Also, the utility of the proposed cut-off values were supported by a high AUC on ROC analysis. The best AUC in this study were achieved by LL at 34th wg (0.944), by ASCT at 32th wg (0.942), and by ACST at 36th wg (0.923). ROC curves indicated that measurements of AC, ASCT, and LL are superior to sonographic measurements of other fetal soft tissue (cheek-to-cheek diameter, upper arm subcutaneous tissue, and EFW...
derived from it) achieved in the study of Chauhan and colleagues [21], where the AUC was 0.73 and where two methods (upper arm or thigh subcutaneous tissue and ratio of thigh subcutaneous tissue to FL) were poor diagnostic tests (range of AUC 0.52 ± 0.06 to 0.58 ± 0.07). EFW based on upper arm soft tissue thickness and cheek-to-cheek diameter in their study (areas 0.70 and 0.67, respectively) were not better than the present predictions by ASCT, AC, and LL for detecting macrosomic fetuses [21].

Ultrasound screening for fetal biometry and abnormality is widely practiced and has defined sonographic markers of GDM which include those ultrasound parameters of glycemic control evaluated in this study (ACST, AFI, LL and AC). The authors report that their sensitivity ranged from 67.9% to 93.6% and specificity from 71.8% to 86.6%. This is in accordance with their previous study [1], where sensitivity of AC, AFI, and ACST in GDM prediction ranged from 51.5% to 60.6%, whereas specificity ranged from 81.8% to 94.7%. These findings were unexpected, bearing in mind that in previous study the authors had studied a population that had just been diagnosed with GDM, while in the current study, the participants were diagnosed with GDM at 28th wg and treated with dietary regime and moderate physical activity. This confirms that sometimes this regime is insufficient in acquiring good metabolic control, which is in accordance with another previous study [9]. Moreover, Evers concluded that the postprandial glucose excursions are not always reflected in the HbA1c level [22]. Consequently, intermittent hyperglycemia (usually with normal HbA1c) could be more important than chronic hyperglycemia (usually with higher HbA1c) in causing accelerated fetal growth [23]. In addition, Jovanovic stated that “macrosomia despite normoglycemia should rather state macrosomia because of undetected (postprandial) hyperglycemia [24]”.

Conclusion

Ultrasound parameters of glycemic control could be an additional tool in predicting FM even more remotely from delivery and term, and also in detection of GDM if this entity is not diagnosed through usual screening periods at 24th to 28th wg because of organizational oversights or other reasons.

References


Prediction of fetal macrosomia with ultrasound parameters and maternal glycemic controls in gestational diabetes mellitus


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Comparison of pregnancy outcomes in different localizations of uterine fibroids

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Zekai Tahir Burak Women’s Health Research Hospital, Ankara (Turkey)

Summary

Objective: The basic aim of this study is to compare the pregnancy outcomes in cases with uterine fibroids located at the anterior and posterior uterine walls. Materials and methods: A total of 84 pregnant women with a diagnosis of uterine myoma larger than 30 millimeter (mm) in diameter were included in the study to determine the obstetric outcomes. In 64 (76.20%) patients, myomas were detected at the anterior uterine wall (group 1), while 20 (23.80%) were detected at the posterior uterine wall (group 2). All patients were followed monthly until the end of pregnancy. Demographic and obstetric characteristics were compared between the two groups. Results: There were no significant differences in age, gravidity, parity, and myoma size between the two groups. A significant difference existed between the groups with regard to pelvic pain. Posterior located fibroids were associated with more pelvic pain (p = 0.001). No difference was observed between the two groups with regard to the rates of preterm delivery, bleeding in early pregnancy, infants with small for gestational age, and hospitalization period during pregnancy. Women with posterior located myomas had significantly higher miscarriage rates. Conclusion: Our findings suggest that pregnancies with uterine fibroids are at increased risk for complications. Posterior located fibroids larger than 30 mm in diameter are associated with severe pelvic pain compared to anterior located fibroids.

Key words: Fibroids; Pregnancy; Pelvic pain.

Introduction

Fibroids are benign smooth muscle cell tumors of the uterus. They are a very common finding in women of reproductive age. Although they are extremely common, with an overall incidence of 40% to 60% by the age of 35 years and 70% to 80% by the age of 50 years their precise incidence remains unclear [1]. The diagnosis of fibroids in pregnancy is not simple. Only 42% of large fibroids (> 5 cm) and 12.5% of smaller fibroids (3 - 5 cm) can be diagnosed during physical examination [2]. During pregnancy, it is difficult to differentiate fibroids from physiologic thickening of the myometrium by ultrasound [3-6]. Therefore the prevalence of uterine fibroids during pregnancy is likely underestimated. The relationship between uterine fibroids and adverse pregnancy outcome is not clearly understood. It has been reported that they are associated with adverse pregnancy outcomes such as increased rate of spontaneous miscarriage, preterm labor, placenta abruption, malpresentation, labor dystocia, cesarean delivery, and postpartum hemorrhage [7].

The authors of the present study believe that posterior versus anterior fibroids may have a different impact on pregnancy outcome. In the present study, the pregnancy outcome in cases with uterine fibroids located at the anterior uterine wall and posterior uterine wall were compared.

Materials and Methods

The present was a retrospective study over a 24-month period, between June 2008 and June 2010. A total of 84 pregnant women who had uterine fibroids greater than 30 millimeter (mm) in size were included in the study. Ultrasound examination is routinely performed during early pregnancy in our hospital. So singleton pregnancies at a maximum of 12 weeks gestation diagnosed with fibroids were included in the study. In case of multiple fibroids, patients were categorized according to the maximum size of the fibroid located at the anterior or posterior uterine wall. The fibroid location was studied in relation to placental implantation. The type of fibroids found in the women analyzed (submucosal, intramural, subsierosal, are also reported). Patients were divided into two groups: group 1 included pregnancies with uterine fibroids detected at the anterior uterine wall (n = 64), and group 2 consisted of pregnancies with uterine fibroids detected at the posterior uterine wall (n = 20). There were no obstetric risk factors such as fertility treatments, hypertensive disorders, gestational diabetes mellitus, or multiple pregnancies in any of the patients.

The following clinical characteristics were noted: maternal age, number of pregnancies, and gestational age at diagnosis. In the standard regular antenatal follow-up model, women made visits to the clinics once a month for the first six months of pregnancy, once every two to three weeks for the next two months, and then once a week until delivery. Localization and size of myomas were noted. Obstetric characteristics including miscarriage, vaginal bleeding, pelvic pain, small for gestational age (SGA), mode of delivery, delivery time, birth weight, Apgar score at one and five minutes, admission to neonatal intensive care unit (NICU) were assessed. The local ethics institutional board approved this study.

The statistical analysis for the data was done with SPSS version 11.0 (SPSS Inc., Chicago, IL). The normal distribution of all studied parameters was checked with Kolmogorov - Smirnov test. Data were analyzed on an intent - to - treat basis with parametric (Student t test) and nonparametric statistics (chi-square, Mann Whitney-U test) where appropriate. A p value < 0.05 was established as statistically significant.

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Results

During the 24-month period of the study, a total of 84 patients were collected. In 64 (76.20%) patients, myomas were detected at the anterior uterine wall (group I) while 20 (23.80%) were at the posterior uterine wall (group 2). The mean age of the patients was 34.07 ± 5.21 (22 - 46) years. Twenty-two (26.20%) patients were primigravid, 62 (73.80%) were multigravid. The mean size of the myoma was 57.44 ± 23.62 (30 - 132) mm. The final measurement of myoma was recorded just prior to delivery. Fibroids increased in size in 50 (59.5%) of our patients and remained almost constant in 34 (40.5%) patients. No decrease in size in any of the patients in the study were found. Thirty-four (40.47%) patients had multiple myomas.

There were no significant differences in age, gravidity, parity, and myoma size between the two groups (Table 1). A significant difference existed between the two groups with regard to pelvic pain. Posterior located fibroids were associated with more pelvic pain (p = 0.001). No difference was observed between the two groups with regards to the rates of patients with increase in size, preterm delivery, bleeding during early pregnancy, SGA infants, and hospitalization during pregnancy. Thirty-three (39%) patients were hospitalized during their pregnancy for different indications before delivery. Women with posterior located myomas had significantly higher miscarriage rates (Table 1). No submucosal fibroids were detected in any of the patients studied.

A total of 11 (13%) patients had fibroids which were located retroplacentally. Eight of them were in group I, and three of them were in group 2 (Table 1). All the patients with retroplacental fibroids experienced bleeding during early pregnancy. Three of them in group I had SGA babies and another two had preterm labor. In group 2, out of three patients, two had preterm deliveries and one patient had SGA baby.

Twenty-five (29.80%) of the patients experienced severe pelvic pain mostly during the early second trimester and lasted about five days and they were hospitalized for this. Seventeen (85%) of these had myomas on the posterior uterine wall and the mean size of the myoma was 55.7 mm. Eight (12.5%) patients with myomas on the anterior wall had severe pelvic pain. The difference was significant (Table 1). We detected cystic changes through ultrasound that indicated the development of red degeneration only in seven of 25 patients who had severe pain. Twenty-five (29.76%) patients suffered from bleeding in early pregnancy and 15 patients (17.90%) had spontaneous miscarriages. The mean gestational age at delivery was 37.79 ± 1.69 (33 - 40) weeks. The mean birth weight was 3,169.41 ± 525.83 (2,100 - 4,200) grams. Of the 69 pregnancies, 39 (56.52%) were delivered by cesarean section and 30 (43.47%) vaginally. Malpresentation rate was 42% (29 out of 69) followed by previous section and labor dystocia. Myomectomy was performed during cesarean section in 21 (30%) patients, in which three of them required blood transfusion, and hysterectomy was performed in one patient who also needed blood transfusion. No patients had uterine atony or postpartum hemorrhage after delivery. Seven (8.30%) patients had SGA baby. Twenty preterm deliveries were seen. None of the newborn admitted NICU.

Discussion

Approximately 10% to 30% of women with fibroids develop complications during pregnancy [7]. In this study 46 (54.7%) patients were hospitalized during their pregnancy for different indications before delivery. Prospective studies have shown that the majority of fibroids (60% - 78%) do not demonstrate any significant changes in size during pregnancy [8, 9]. In contrast to this, the authors found that fibroids increased in size in 50 (59.5%) of the patients studied. Growth was remarkable especially during the first and the second trimester, with almost no growth observed during the third trimester. It has been previously reported that all fibroids decrease in size during third trimester [9, 10]. In this study, no decreases in size were found in any of the patients studied.

Pain is the most common complication of fibroids in pregnancy, and is most often seen in women with large fibroids (> 5 cm) during the second and third trimesters of pregnancy [3, 7]. Approximately 30% of the patients in this study suffered from severe localized abdominal pain, mostly during early second trimester which lasted about five days. Most of these had myomas in the posterior uterine wall and the mean size of the myoma was 55.7 mm. If fibroids show heterogeneous echogenic pattern or cystic changes in ultrasound, this indicates the development of red degeneration [10]. There are three main theories to explain the severe pain associated with red degeneration. First, rapid growth results in tissue anoxia, necrosis, and infarction [7, 11]. Second, the growing uterus causes a change of the blood supply to the

<p>| Table 1. Characteristics and prognosis of cases with uterine fibroids located at anterior uterine wall (group I), and posterior uterine wall (group II). |
|---------------------------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>Group I (n = 64)</th>
<th>Group II (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)*</td>
<td>33.5 ± 4.8</td>
<td>35.6 ± 6.1</td>
</tr>
<tr>
<td>Gravida**</td>
<td>3 (1 - 8)</td>
<td>3 (1 - 7)</td>
</tr>
<tr>
<td>Parity**</td>
<td>2 (0 - 6)</td>
<td>2 (0 - 5)</td>
</tr>
<tr>
<td>Size of myoma (mm)*</td>
<td>57.9 ± 23.3</td>
<td>55.9 ± 25.1</td>
</tr>
<tr>
<td>Final size of myoma (mm)*</td>
<td>68.2 ± 29.9</td>
<td>67.1 ± 28.7</td>
</tr>
<tr>
<td>Increase in size (no., %)</td>
<td>35 (54)</td>
<td>15 (75)</td>
</tr>
<tr>
<td>Pain (no., %)</td>
<td>8 (12.5)</td>
<td>17 (85)</td>
</tr>
<tr>
<td>Preterm delivery (no., %)</td>
<td>18 (28.1)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Bleeding in early pregnancy (no., %)</td>
<td>19 (30.2)</td>
<td>6 (30)</td>
</tr>
<tr>
<td>SGA (no., %)</td>
<td>6 (9.4)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Miscarriage (no., %)</td>
<td>8 (12.5)</td>
<td>7 (35)</td>
</tr>
<tr>
<td>Hospitalization during gestation (no., %)</td>
<td>29 (45.3)</td>
<td>17 (85)</td>
</tr>
<tr>
<td>Delivery time (weeks)**</td>
<td>38 (33-40)</td>
<td>39 (34-40)</td>
</tr>
<tr>
<td>Birth weight (grams)*</td>
<td>3146.5 ± 512.3</td>
<td>3264.6 ± 591.7</td>
</tr>
<tr>
<td>Myomectomy during cesarean section (no., %)</td>
<td>17 (26.6)</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Intramural myoma (no., %)</td>
<td>42 (65.6)</td>
<td>13 (65)</td>
</tr>
<tr>
<td>Subserosal myoma (no., %)</td>
<td>22 (34.4)</td>
<td>7 (35)</td>
</tr>
<tr>
<td>Retro-placental myoma (no., %)</td>
<td>8 (12.5)</td>
<td>3 (15)</td>
</tr>
</tbody>
</table>

*Values are mean ± Standard deviation; **Values are median (minimum-maximum); SGA: Small for gestational age; Ns: Nonsignificant.
fibroid which leads to ischemia and necrosis [12]. Third, the release of prostaglandins from cellular damage within the fibroid results in pain, which is supported by the observation that ibuprofen and other prostaglandin synthetase inhibitors effectively and rapidly control fibroid pain [7]. The authors detected cystic changes in ultrasound that indicated the development of red degeneration only in seven of 25 patients who had severe pain. There might be some other mechanisms associated with pain. Pain was conservatively managed through bed rest, hydration, and analgesics.

Most authorities agree in avoiding to perform a myomectomy during cesarean delivery due to risk of severe hemorrhage [13-16]. Myomectomy was performed in 21 (25%) of the patients during cesarean delivery. Most of them had pedunculated subserosal fibroids; in one case, it was difficult to facilitate safe delivery of the fetus. All of them however, were safely delivered, but a blood transfusion was needed in three of them. Hysterectomy was performed in one patient due to a challenged safe delivery of the fetus because of severe adhesions due to prior cesarean sections and multiple myomas.

Numerous studies have shown that uterine fibroids are a risk factor for cesarean delivery [3, 10, 17-21]. The risk of fetal malpresentation also increased [17, 19]. In the present study, the cesarean rate was 56%. The leading indication was malpresentation, followed by previous section and labor dystocia. No patients had uterine atony or postpartum hemorrhage after delivery.

It has been reported that spontaneous miscarriage rates are greatly increased in pregnant women with fibroids [22]. The current miscarriage rate was 17.90% and occurred during the first trimester.

Retrolaplacental fibroids are likely to interfere with placentation and may clinically cause bleeding, intrauterine growth restriction, or placental abruption [23]. In the present study, 11 patients (13%) had fibroids located retrolaplacently, and all experienced bleeding during early gestation. Four of them had SGA babies and another four had premature delivery. The numbers are still insufficient to draw any conclusions regarding the effect of retrolaplacental fibroids in the pregnancy outcome.

One limitation of this study was that the ultrasound evaluation of posterior fibroids was more difficult and less accurate than evaluation of anterior fibroids. Posterior fibroids are not easy to study in pregnancy, but the authors believe that posterior uterine wall fibroids may not have escaped ultrasound detection because the initial diagnosis was confined to an early gestational age window. Fibroids seem to increase the risk for adverse pregnancy outcome, but there was no control group in consisting pregnant women without a fibroid. Since there was no control group, the authors could not determine the increased risk ratio and this was another major limitation of the study.

In conclusion, in light of the small sample number of cases, the authors can state that pregnancies with uterine fibroids are at increased risk for complications. Pelvic pain during the second trimester was the most common complication; especially posteriorly located large fibroids are associated with severe pelvic pain which can be managed conservatively by bed rest, hydration, and analgesics.

References

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The optical trocar in gynecological surgery: clinical and technical outcomes

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Summary
Optical trocars have been introduced as an alternative technique for obtaining access to the peritoneal cavity. The advantage is that each layer of the abdominal wall can be identified avoiding inadvertent injuries due to a lack of vision. From March 2010 to March 2011, 138 women underwent laparoscopy for benign diseases. They were submitted to gynecological laparoscopy for direct optical access. There was no evidence of vascular injuries. This study confirms that the optical trocar is a safe, rapid, and effective method, that offers a real perception of the safety of the entrance into the abdomen.

Key words: Optical trocar; Gynecological laparoscopy; Laparoscopic entry techniques; Laparoscopic complications.

Introduction
Laparoscopy is a very common procedure in gynecology, especially for the treatment of benign conditions. Over the past three decades, the laparoscopic technique has significantly evolved and it is now accepted as the first choice for the management of most gynecological problems [1, 2]. Several studies comparing laparoscopy and laparotomy performed for benign gynecological diseases demonstrated that the risk of minor complications is 40% lower with laparoscopic vs “open” surgery; on the other hand, the risk of major complications is similar [3].

The initial entrance into the abdominal cavity for establishing pneumoperitoneum is a very important and critical step during laparoscopy [4]. The literature demonstrates that at least 50% of major complications occur during the first phase of the procedure [5, 6]. The available methods include closed or open techniques [2, 7].

The blind Veress needle introduction for the creation of pneumoperitoneum is followed by the blind trocar insertion [8]. The basic concept of the open Hasson technique is to create a small skin incision, directly incising all the layers of the abdominal wall one by one (including the anterior peritoneum) and then entering the abdomen [9]. Another technique is represented by a direct trocar which enters into the abdominal cavity without prior Veress needle and pneumo-insufflation. Initial entrance can be performed with a disposable trocar designed with a shield that partially retracts and exposes a sharp tip as it encounters resistance during the passage through the abdominal layers; when the shield reaches the peritoneal cavity, it springs forward and covers the sharp tip. The optical trocar allows a clear visualization of the abdominal tissue planes on the monitor which are separated (not cut) under steady vision by advancement of the edge of the cannula. There is no evidence that one of these techniques is superior or inferior to the other entry methods currently available, and there is no clear consensus as to the optimal method of the entry into the peritoneal cavity. The closed-entry with the use of the Veress needle is the most popular approach for gynecological laparoscopists [10]. Although this technique is generally considered to be safe, several injuries (major and minor) to numerous abdominal structures have been reported (0.9/1000) [11]. Blind entrance, using the Veress needle and the first or the direct trocar, may cause several lesions (vascular, bowel, and abdominal wall injuries). The optical trocars have been introduced as an alternative technique for obtaining access to the peritoneal cavity (traversing the tissue planes under direct view). The theoretical advantage of these trocars, which allow a clear optical entry, is that each layer of the abdominal wall can be identified, avoiding the inadvertent injuries due to a lack of vision [12]. However, they have not obtained a large approval among laparoscopists.

Materials and Methods
From March 2010 to March 2011, a total of 138 women underwent laparoscopic surgery for simple ovarian cysts, sacsosalpinx, extraterine pregnancies, uterine myomas, chronic pelvic pain (adhesions and endometriosis), and sterility. They were all submitted to gynecological laparoscopy for the direct optical access with a bladeless trocar. All the patients were evaluated with a Pap smear (or human papilloma virus (HPV)-DNA test), bimanual examination, and pelvic ultrasound to exclude a premalignant or a malignant condition. Women with previous abdominal surgery and obese patients were not excluded from the study (these conditions were not considered as confounding factors). The maximum diameter of the ovarian cysts and of the uterine myomas was ten cm. The procedures were carried out under general anesthesia by endotracheal intubation. The patient was placed in a steep Trendelenburg position of 45° causing the
intraperitoneal organs to move (dislocate towards the diaphragm) and liberating the operative field of the pelvis and of the lower part of the abdominal cavity. A small, appropriate, intra-umbilical longitudinal incision was performed and the abdominal wall was pulled up with a countertraction by both the first operator and the first assistant; a 12-mm disposable bladeless trocar (Endopath trocar, Ethicon Endo-Surgery, Inc., Cincinnati, OH, USA) with a 0° laparoscope (inserted into the cannula) was advanced into the wound. Under constant direct vision, with a gentle rotating motion combined to a moderate pressure, the trocar was advanced sequentially through the layers of the abdominal wall, from the subcutaneous tissue (white/yellow) to the rectus sheath (bright white) and the peritoneum (translucent, vascular). This movement provides the dilating and the separating of the tissue planes, not their cutting. The peritoneum typically extends over the tip, which offers a classical image of a white ring. If an adhesion is present, a white reflection appears in the center of the ring; on the contrary, a dark area suggests a free abdominal cavity (absence of adhesion to the abdominal wall). The peritoneum is punctured and, in many cases, the unmistakable respiratory movement of the intestinal loops can be identified; the intra-abdominal position of the trocar is confirmed and insufflation can be started. All the patients were generally healthy (ASA I-II); their problems were related to benign gynecological conditions. They presented the following characteristics: average age of 38.1 years (range 21-63), average body mass index (BMI) of 25.2 (range 20-31). The previous abdominal operations (31 cases) included both laparoscopy and laparotomy (12 laparoscopy, 15 Pfannenstiel, 4 transverse incisions). The range of the follow-up period was one to 12 months and no late complications occurred.

Results

In this study, the following parameters were evaluated: occurrence of major and minor vascular injuries, occurrence of major and minor bowel and urological injuries, blood loss, time required for trocar insertion, and the creation of pneumoperitoneum. In all the procedures, no problems or difficulties were encountered during the initial placement of the optical trocar. There was no evidence of any vascular injury (major and/or minor injuries). At times, a slight bleeding (accrued from the small vessels of the abdominal wall) which occurred during the first phase of the laparoscopy, but this blood loss did not prevent the operator from introducing the trocar nor did it interfere with visual control in the monitor. No lesion occurred to the intraperitoneal organs and/or to the omentum, to the bladder and/or to the ureters. There were no port-site hernias; the closure of the fascia was not considered a necessary step and it was carried out in only nine cases (based on the clinical assessment of the surgeon). The average time for the introduction of the trocar and the establishment of pneumoperitoneum was 61.5 seconds; if the patient had had a previous surgery, this time was 72.3 seconds. There was no necessity of conversion to open laparoscopy or laparotomy. In one case, the presence of a peri-umbilical omental adhesion did not give rise to any problems, because the continuous visual control allowed to find a space (an area which was free of adhesion) through which the trocar was inserted into the abdominal cavity. The patients, after assessing the most important clinical parameters, were discharged on day-1 postoperatively. The range of the follow-up period was one to 12 months and no late complications occurred.

Discussion

This study confirmed that the optical trocar can be used for the first abdominal access as a safe, efficacious, and feasible approach. This method can be considered an alternative route to other techniques, both closed and open entries, and it can be proposed to minimize visceral and vascular lesions [13]. Generally, these complications occur when the intraperitoneal structures are located very close to the insertion area of the blind trocar (or of the Veress needle) or when these devices penetrate into the retroperitoneal space. Major vascular injury during the first phase is a highly-feared complication of the procedure. This represents the major cause of death due to laparoscopic early complications. These lesions may occur when the blind Veress needle enters into the abdomen prior to pneumoperitoneum or when the first blind trocar is inserted (prior or after insufflation). The proximity of the anterior wall to the retroperitoneal major vascular structures is apparently the reason for these serious complications. The aorta, the inferior vena cava, and the iliac vessels are strongly exposed and prone to severe or fatal lesions; in fact, in some cases, such as in very thin patients, the distance between the anterior and the posterior layers of the peritoneum is really exiguous (three to five cm).

Intestinal perforation represents one of the three principles causes of death (the main: vascular injury and other complications associated to anesthesia). These lesions, which often are diagnosed in the postoperative period and not immediately, can be detected or avoided with the use of the visual access device. The optical trocar allows an excellent visualization of the abdominal wall layers and its blunt tip can avoid lesions to the vessels and to the gastrointestinal (GI) tract during the entry into the peritoneal cavity. This risk is obviously higher in patients with previous abdominal surgery due to a more likely occurrence of visceral and omental adhesions. Even when complications are encountered, the optical trocar has the advantage of allowing immediate recognition and the repair of injuries (otherwise these could be missed and might lead to serious sequelae, such as peritonitis and sepsis or death, if their diagnosis is delayed).

---

**Table 1. — Procedures and indications for laparoscopic surgery using an optical trocar.**

<table>
<thead>
<tr>
<th>Procedures/Indications</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hysterectomy</td>
<td>13</td>
</tr>
<tr>
<td>Myomectomy</td>
<td>7</td>
</tr>
<tr>
<td>Adnexectomy</td>
<td>24</td>
</tr>
<tr>
<td>Ovarian cysts enucleation</td>
<td>31</td>
</tr>
<tr>
<td>Tubal pregnancy</td>
<td>11</td>
</tr>
<tr>
<td>Chronic pelvic pain (adhesions/endo.)</td>
<td>27</td>
</tr>
<tr>
<td>Sterility</td>
<td>20</td>
</tr>
<tr>
<td>Sactosalpinx</td>
<td>5</td>
</tr>
</tbody>
</table>

---
The optical trocar in gynecological surgery: clinical and technical outcomes

The limit of this study was that a comparison with other techniques of primary port-entry was not performed; on the other hand, no complications occurred. Although visual control is continuous, the risk of injuries still exists, and some data, based on the international literature, show that this technique cannot entirely avoid the initial trocar-related incidents. The optical device offers the possibility for the surgeon to assess, under direct vision with a monitor, every traversed layer of the body wall, the exact position of the vessels (avoiding bleeding and the consequent hematoma which requires a laparotomy) and, especially in patients with previous midline laparotomy, potential adhesions of the intra-abdominal organs to the anterior peritoneal sheet. Therefore, after the cautious and safe entrance into the abdomen, the risk of lesions to the urological and GI tract and to the abdominal vascular tree is very low (bladder and ureteral injuries are more likely to occur during oncological procedures, urogynecological operations, and the treatment of deep endometriosis).

In conclusion, this technique can be considered a rapid and effective method and it can offer a real perception of the safe entrance into the abdomen. The optical trocar is disposable and its cost is reasonable. The authors’ experience with this type of trocar in a large population with various characteristics (Italians or not, wide range of BMI, and patients of all ages, postmenopausal or not) has been excellent and this method has become their first choice for obtaining entry into the abdomen and initiating pneumoperitoneum.

References

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Does vaginal pH affect the efficacy of dinoprostone in cervical ripening/labor duration?

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Summary

Background: Prostaglandins are effective in the ripening of the cervix and facilitating labor induction. Vaginal pH is probably an important factor in the effectiveness of vaginal prostaglandins. The aim of this study was to evaluate the effect of vaginal pH on the function of prostaglandin vaginal tablet during labor. Methods: This is a double-blinded clinical trial study of 147 pregnant primigravid treated in the Yahynejad Hospital of Babol (Iran) from January 2006 to December 2007. Initial pH was measured during vaginal examination with nitrazin paper and the Bishop score was determined. All women received vaginal dinoprostone inserted in the posterior fornix of the vagina for cervical ripening and the second dose was administered if the uterine contractions were inadequate. Reassessments of the Bishop score after 12 hours, duration of latent and active phases, and also the duration of the second stage of labor were compared between the two groups with low or high vaginal pH. Results: The incidence of Cesarean section was lower in women with high vaginal pH but was not statistically significant. The Bishop score after 12 hours, latent phase, and second stage durations were not different in the two groups of high or low vaginal pH, but active phase duration in patients with high pH was significantly shorter than those with low pH (p = 0.019). Conclusion: High vaginal pH influences the function of prostaglandin tablet as a reduction in duration of the active phase of labor.

Key words: Vaginal PH; Prostaglandin; Cervix ripening; Dinoprostone; Labor duration.

Introduction

Labor induction is commonly used in obstetrics [1]. Optional labor induction can increase the Cesarean section incidence rate up to three times [2, 3]. Since Cesarean section is accompanied with the risk of undesired maternal outcomes, most specialists agree with the opinion that optional labor induction is not reasonable in term pregnancies unless there is an indication for termination of the pregnancy [4, 5]. While the maternal or fetal benefits of induction overcome the benefits of continuing pregnancy, labor induction is indicated. Among these indications, emergency conditions, such as rupture of membranes with chorioamnionitis or severe preecclampsia, can be suggested. Rupture of the membranes in the absence of labor, with an uncertain condition of the fetus, and post-date pregnancy are other indications for labor induction [6-8].

With the use of prostaglandins E2 (PGE2), dinoprostone is one of the methods used for cervical ripening. Prostaglandins work in different ways to ripen the cervix and it seems that prostaglandin E especially increases the activity of collagenase in the cervix. Prostaglandins also increase elastase, glycosaminoglycan, dermal sulphate, and hyaluronic acid and by adding intracellular calcium they cause myometrial muscle contraction [9]. Prostaglandins are organic acids which have diminished dissolution ability in aqueous solution and low pH. Although the vagina has a low pH in normal conditions, several factors such as lower genital tract infections, bacterial vaginosis, and rupture of the membrane can alter vaginal pH. There are a few studies on the vaginal pH effect on the cervical response to prostaglandins. Ramsey et al. evaluated the effect of vaginal pH on the efficacy of PGE2 tablet and came to the conclusion that high pH can accelerate the delivery course [10]; there are however controversial results in some studies [11, 12]. To shorten the duration of elective induction of labor and lessen maternal morbidity the authors decided to perform this study, using a cervical ripening method (dinoprostone). This study was conducted to evaluate the association of vaginal pH with the effect of prostaglandin vaginal tablet for cervical ripening/labor induction.

Materials and Methods

This is a single-arm clinical trial study of 147 pregnant primigravid women with an age range of 16 to 35 years treated in the Department of Obstetrics and Gynecology of Yahynejad Hospital, Babol University of Medical Science in Babol (Iran) from January 2006 to December 2007. The ethics committee of the University approved the study and all patients signed an informed consent. All cases were prescribed labor induction and termination of pregnancy due to post-term pregnancy. These women had a singleton pregnancy and the fetuses had cephalic presentation. Their Bishop score was 5 or less and no contraindication of vaginal delivery was present and their uterine contractions had not yet begun. All individuals were informed of the process prior to participation in the study and had signed a written consent. Exclusion criteria were: known sensitivity to prostaglandin, ruptured membranes, the probability of chorioamnionitis, prior history of uterine surgery, a previous Cesarean delivery, and previous induction of labor in the current pregnancy.

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Labor processing

All patients were admitted 12 hours before the initiation of labor induction and monitored to be assured that no uterine contractions or fetal distress was present. Then they were examined using a speculum and a sample of cervico-vaginal liquid from external cervical os and superior region of the vagina was obtained by a cotton swab and the vaginal pH was determined by narrow-range pH paper (Hydrion pH paper, Sigma Chemical Co, St Louis, MO). A vaginal examination was then performed to determine cervical conditions with regards to Bishop score [13]. If the situation was suitable, vaginal tablet of PGE2, including 3 mg of dinoprostone was placed into the posterior fornix of the vagina. Placing PG tablet and determining Bishop score at onset and 12 hours later was performed by a physician who was unaware of the vaginal pH condition. Women with fewer than three uterine contractions within ten minutes and an intact amniotic membrane received a second dose of the tablet after six hours. Twelve hours after receiving the initial dose of the drug, the Bishop score was once again measured. If after 12 hours of time, there was still no proper contraction pattern, oxytocin (Aburahian Co. Tehran, Iran) was administered. Oxytocin infusion was begun at an initial rate of 2 mu/min, with 2 mu/min increased at 20-minute intervals to a maximum dose of 30 mu/min, until an adequate uterine contraction pattern developed. In cases of uterine hyperstimulation, the tablet was removed from the vagina and the patients’ position was altered to the left side, oxygen and hydration were provided, and then the maternal and fetal conditions were constantly re-evaluated; if there was no improvement in the fetal condition, or if fetal distress was repeated during the beginning of contractions, they were put to Cesarean section. In individuals who had a proper improvement in their labor course, the results regarding Bishop score after 12 hours, the duration of the latent phase of labor (from the beginning of regular contractions to 3-5 cm dilatation of cervix), active phase (from 3-5 cm cervical dilatation to full dilatation), and the second stage of labor (from full cervical dilatation to fetal expulsion) [14], was recorded in both groups with high or low vaginal pH. With a pH break point of 4.5 (“normal” vaginal pH) and a high vaginal pH group (> 4.5), two populations were created for comparison [10].

Data was statistically analyzed using SPSS statistical software for Windows version 13.0 (SPSS Inc, Chicago, IL, USA). Statistical tests such as Fisher’s Exact and Mann-Whitney were used. A p value less than 0.05 was considered statistically significant.

Results

The average age of the studied individuals was 23 years. Among 147 pregnant women, 114 individuals (77.3%) had low and 33 cases (22.7%) had high vaginal pH. From these 147 individuals, 70 (50.3%) underwent Cesarean section and 73 (49.7%) had normal vaginal delivery. The delivery method in the two groups with regards to low or high vaginal pH was not significant (p = 0.638), but the duration of active phase in patients with high pH was lower than low pH which was significant (p = 0.019). On the other hand, the duration of the second stage of labor showed no significant difference between the two groups (p = 0.678) (Table 2). In both groups with low or high vaginal pH, after 12 hours with a Bishop score of approximately 10 possessed the most frequent percentage and there was no significant difference between the two groups (p = 0.362) (Figure 1). No adverse effects were reported by the patients.

Discussion

This study aimed to determine the relation of vaginal pH with the efficacy of PGE2 vaginal tablet on cervical ripening and labor induction. The results of the study revealed that after administration of PGE2 tablet in primigravid pregnant women, the duration of the active phase in individuals with high pH was lower than those with low vaginal pH (p = 0.019). Ramsey et al. evaluated the effect of vaginal pH on the function of dinoprostone gel and showed that the time of entering into the active phase, full dilatation, and delivery was obviously shorter in women with high vaginal pH compared with women with a low vaginal pH [10], which is similar to this study.

In the Onen et al. study, vaginal pH had a significant effect on the duration of latent and active phases of delivery following the administration of dinoprostone vaginal insert [15]. Perry et al. showed intracervical dinoprostone decreased time to delivery without increasing the rate of Cesarean section, post-partum infections, or other labor complications [16].

In a research performed by Chandra and et al., the effect of vaginal pH on the function of vaginal misoprostol was studied and the time required for vaginal delivery...
in both high and low vaginal pH had no difference [12]. However, in another research conducted by Ramsey et al., the effect of vaginal pH on the efficacy of on labor induction was studied and the high or low pH of the vagina did not have a noticeable effect on the function of PGE2 tablet and the time of entrance into the active phase of labor and the required time for vaginal delivery had no significant difference in the two studied groups [11]. These results were confirmed in another study of Ramsey et al., that the required time until the entrance to the active phase of labor, full dilatation, and delivery after receiving misoprostol had no difference in the two groups with low or low pH [17].

Furthermore in the present study, the Bishop score 12 hours after administration of prostaglandin vaginal tablet did not show a significant difference between the two groups with low and high vaginal pH. Some researchers also showed no difference in the Bishop score 12 hours after administration of dinoprostone gel in the two groups with low or high vaginal pH [10]. On the other hand, in the present study, the Cesarean section rate in women with low or high vaginal pH showed no difference. Gunalp et al. discovered that the Cesarean section rate and unwanted maternal or fetal outcomes following the administration of misoprostol had no difference in both groups with low or high vaginal pH [18]. In the Chandra et al. study, after administration of vaginal tablet of misoprostole, the maternal or fetal complications showed no difference in the two groups with high or low vaginal pH [12].

**Conclusion**

The results of this research revealed that vaginal pH may have an important influential effect on the function of prostaglandin tablet as reduction in the duration of the active phase of labor in high vaginal pH. The vaginal microenvironment may account for the disparate efficacy of the prostaglandins. Some factors can alter the normal acidic vaginal pH. This factor may be considered in women to attempt cervical ripening/labor induction with dinoprostone tablet.

The authors noted one weak point of this study. Another study might be designed as a case-control to compare those who did not take dinoprostone vs those who did take it to evaluate labor duration. A well-designed study that modifies vaginal pH as a primary variable and evaluates the effect of vaginal pH on the overall efficacy of the dinoprostone tablet could be considered.

**Acknowledgment**

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**References**


Does vaginal pH affect the efficacy of dinoprostone in cervical ripening/labor duration?


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Evaluation of utero-ovarian hemodynamics in relation to fertility and stage of endometriosis

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Introduction
Endometriosis refers to whenever a functioning endometrium is found outside the uterine cavity. Consequences are numerous and the most serious is infertility that occurs in 20-50% of women [1, 2]. While medication proved to be an adequate therapy for mild stage endometriosis, laparoscopic treatment is often the only solution for moderate and severe stages.

A prerequisite for the fertility capacity of female genital tract includes, among others, optimum utero-ovarian and endometrial blood flow. These parameters have been separately studied from a number of perspectives, particularly in in vitro fertilization (IVF) programs, as important predictors of the implantation success [3-5].

Endometriosis is most often accompanied by essentially altered hemodynamics of the uterus and ovaries. This is a consequence of the endometrial hot-beds that often and deeply infiltrate the uterine tissue, oviducts, as well as other, surrounding structures. Therefore the stage of the disease, as well as the site of endometriosis hot-bed are essential in the assessment of utero-ovarian hemodynamics and, consequently, of the fertility capacity. The aim of this study was to determine whether and to what extent utero-ovarian blood flow differs between a group of women with moderate and/or severe endometriosis versus a group of healthy women.

Materials and Methods
During the period from July 2010 to January 2011, color Doppler ultrasonography findings of 54 infertile women finally diagnosed with endometriosis in moderate (35 cases) or severe form (19 cases), and for 45 women without endometriosis (without any infertility-inducing disease).

Patients were subjected to conventional transvaginal and color Doppler examination using 5 MHz transvaginal transducer.

The examination was performed during the proliferative or ovulatory phase of the menstrual cycle (11th to 14th day), with patients in the same position, at approximately the same time of the day, whereby conditions were created to ensure objectivity and comparability of the findings.

Color Doppler mode was used for blood flow imaging. After obtaining continuous image of the flow waveform flow imagery, the average of three to five cardiac cycles was determined for the electronic calculation of PI and RI values from the Doppler spectrum, using the following relationships:

\[ RI = \frac{\text{peak systolic frequency} - \text{end-diastolic frequency}}{\text{peak systolic frequency}} \]

\[ PI = \frac{\text{peak systolic frequency} - \text{end-diastolic frequency}}{\text{mean systolic frequency}} \]

Statistical analysis was performed using the SPSS software package, version 13.0. Statistical significance between the examined groups was assessed using Fisher’s exact test, Chi – square test, Student’s test, Mann – Whitney U test. Results were considered significant when the and p value was less than 0.05.

Results
Regarding most of the demographic features, there were no substantial differences between the test and control group. Only the average age of patients with severe-stage endometriosis was significantly higher (34.4 ± 4.28 years), compared to both: the control group (30.8 ± 4.28 years) and the group of patients with moderate-stage endometriosis. (31.2 ± 5.92 years, p = 0.047). Duration of infertility was significantly longer (7.11 ± 2.98 years versus 5.4 ± 2.90 years), and the mean parity was significantly lower in the group of patients with severe endometriosis (1.05 ± 0.23 versus 1.34 ± 0.48).
Dismenorea, dispareunia, and annovulation were present in a significantly large number of cases (about 70% - 95% cases) both in moderate and severe endometriosis. Somewhat greater probability of all stated symptoms in severe endometriosis was not statistically significant, on the accepted level of reliability. The exception is pelvic pain which appeared significantly more often in Stage IV endometriosis. Irrespective of considered stage, endometriosis was most often found in the ovaries, sacro-uterine ligaments, peritoneum, and rectovaginally. Regarding severe endometriosis, it is significantly more often found in the ovaries and rectovaginally, compared to moderate endometriosis (Table 1).

Blood PI in both uterine and ovarian arteries, did not differ significantly in relation to the endometriosis stage. However, the average RI in these arteries was of significantly higher value in the severe forms of endometriosis. Comparison of either studied stages of endometriosis with the control group shows that both hemodynamic values were significantly higher at the level of the uterus and ovaries (Table 2).

**Discussion**

Pain and infertility are the primary manifestations of the presence of endometriosis, and the dominant one in cases classified as Stage III and IV of this disease [6-8]. Negative effects of the presence of endometriosis are manifested through the anamnestic indicators, particularly in case of severe endometriosis. Patients with this stage of the disease are on the average older, with longer duration of infertility and with lower parity. Based on these results, a conclusion appears obvious regarding the importance of timely application of an adequate treatment for the mild and moderate stage of endometriosis.

The results of this study indicate that particular attention should be paid to the symptoms according to the individual stages of endometriosis. It appears that the symptoms do not differ significantly in studied stages, except for the presence of pain that is much more often a symptom in severe endometriosis. Considering more common locations on the oviducts, rectovaginally, and on sacro-uterine ligament, as well as the deep infiltration of the lesions in case of severe endometriosis, the larger number of cases with the pain is quite logical. Earlier studies have confirmed that the localization of endometrial deep-infiltrated lesions, as a specific entity, is similar and that they are mostly responsible for the presence of pain [6, 8, 9-11].

The association between endometriosis and infertility is related to the fact that endometriosis may induce inflammation of the pelvic minor organs and the peritoneum. In advanced stage of endometriosis, female reproductive function is hindered on all levels.

Disturbed anatomic relations inside the pelvis minor are determined by the presence of adhesive fibrous formations, and jeopardized fertility capacity is further compromised with increased level of inflammation mediators. Consequences of such anatomic-functional mismatches are inadequate hemodynamic parameters, as indicated by altered blood flow to the ovaries and uterus.

### Table 1. — Clinical parameters in the test groups with moderate and severe endometriosis

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Moderate (n = 35)</th>
<th>Severe (n = 19)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvic pain</td>
<td>26 (74.3%)</td>
<td>18 (94.7%)</td>
<td><strong>0.030</strong></td>
</tr>
<tr>
<td>Dismenorea</td>
<td>28 (80.0%)</td>
<td>18 (94.7%)</td>
<td>0.071</td>
</tr>
<tr>
<td>Dispareunia</td>
<td>28 (80.0%)</td>
<td>16 (84.2%)</td>
<td>0.352</td>
</tr>
<tr>
<td>Annovulation</td>
<td>24 (68.6%)</td>
<td>16 (84.2%)</td>
<td>0.106</td>
</tr>
</tbody>
</table>

### Table 2. — Comparison of hemodynamic parameters between the test groups with moderate/severe endometriosis and the control group.

<table>
<thead>
<tr>
<th>Localization</th>
<th>Moderate endometriosis (n = 35)</th>
<th>Severe endometriosis (n = 19)</th>
<th>Control group (n = 45)</th>
<th>p*</th>
<th>p**</th>
<th>p***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI</td>
<td>2.74 (2.31 - 3.80)</td>
<td>3.00 (2.65 - 3.58)</td>
<td>2.60 (1.56 - 2.97)</td>
<td>0.814 &lt; 0.001*</td>
<td>0.011*</td>
<td></td>
</tr>
<tr>
<td>RI</td>
<td>0.83 (0.76 - 0.92)</td>
<td>0.90 (0.83 - 0.96)</td>
<td>0.65 (0.57 - 0.73)</td>
<td><strong>0.016</strong> &lt; 0.001*</td>
<td>&lt; 0.001*</td>
<td></td>
</tr>
<tr>
<td>Ovary</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI</td>
<td>0.94 (0.80 - 1.09)</td>
<td>0.94 (0.80 - 1.26)</td>
<td>0.75 (0.46 - 0.96)</td>
<td>0.079 &lt; 0.001*</td>
<td>&lt; 0.001*</td>
<td></td>
</tr>
<tr>
<td>RI</td>
<td>0.85 (0.78 - 0.97)</td>
<td>0.88 (0.81 - 0.97)</td>
<td>0.60 (0.50 - 0.81)</td>
<td><strong>0.011</strong> &lt; 0.001*</td>
<td>&lt; 0.001*</td>
<td></td>
</tr>
</tbody>
</table>

Data are represented as the median value ± standard deviation or the number of cases (%). * significant p < 0.05.

**Conclusion**

The hemodynamic parameters of uterine and ovarian arteries are considerably different in women with moderate and severe stage of endometriosis compared to
healthy women. Resistance to blood flow in uterine and ovarian arteries and in their branches shows greater sensitivity as the indicator of higher stage, progressed endometriosis, compared to the PI value.

References


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Effects of vaginal versus oral misoprostol to terminate second-trimester pregnancy

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Summary
Objectives: Using surgical methods compared to medical methods, such as misoprostol for termination of pregnancy, has several side effects. This study was performed in order to compare the effect of vaginal and oral misoprostol in second-trimester pregnancy termination (14 - 24 weeks). Materials and Methods: The authors performed a clinical trial study in 40 pregnant women at 14 to 24 weeks of gestation and candidates for medical interruption of pregnancy. All patients received 600 µg of vaginal misoprostol as primary dosage and then, were placed randomly in two groups consisting of 20 patients that received 400 µg of vaginal or oral misoprostol, every four hours, up to three doses. If the abortion was incomplete, oxytocin was used. Twenty-four hours after the procedure, uterine sonography was performed in all patients and if residue was found, the patients were then candidates for curettage. Results: Seventeen patients (85%) in the vaginal group and 17 patients (85%) in the oral group had successful pregnancy interruption. The mean interval until the discharge of pregnancy products in the vaginal group (15 / 42 ± 7 / 8) showed no significant difference compared to the oral group (12 / 65 ± 7 / 8) and no significant differences in side-effects were found between the two groups. Conclusion: Oral misoprostol is as effective as vaginal misoprostol in performing second-trimester abortion. It appears that the vaginal misoprostol primary dose together with the continuation of oral dose is not more effective compared to the vaginal misoprostol method alone.

Key words: Second trimester; Pregnancy termination; Misoprostol, Abortion.

Introduction
The termination of pregnancy in second-trimester is performed for various reasons, such as: fetal abnormality, preterm premature rupture of membranes, intrauterine fetal death, and severe maternal disease [1]. Surgical methods to terminate second-trimester pregnancy have been used for many years. During the last decade however, there has been much improvement in treatment without risk, more effective, and non-surgical abortion in second-trimester pregnancy [2, 3]. In medical therapy, different medicines can be used in order to induce an abortion. One of these medicines is misoprostol which is the industrial analogue of prostaglandine E1 that has effects on labor and abortion induction and is a good alternative to surgical methods performed in second-trimester abortion [4]. Due to fewer side-effects, lower cost, and possibility of storing it at normal room temperature, misoprostol is mostly considered among the variety of prostaglandine choices for second-trimester abortion [5]. There is some debate regarding the ideal dosage and the method of prescription, due to the different pharmacokinetics available [6]. It is prescribable as oral, sublingual, rectal, intramuscular, intravenous, and intraamniotic liquid, but is mainly used in vaginal and oral forms [7]. Many clinical research studies have shown that the vaginal use of misoprostol is more effective than oral [8] and in some studies the success of the oral method is greater [9], while the others also indicated similar effects of these methods in termination of pregnancy in the second trimester [10]. According to contradictory findings of prior studies, for the purpose of examining and comparing the effects of vaginal misoprostol and combination of vaginal and oral forms in second-trimester abortion, one study was designed and performed in Rohany Hospital in Babol (North of Iran) in 2009-2010.

Materials and Methods
This study was performed in a clinical trial method setup and 40 patients referred to therapeutic centers of Babol Medical University for second-trimester (14 to 24 weeks of pregnancy) abortion were enrolled. Interruption of pregnancy was indelated for maternal and fetal reasons. The characteristics of the patients were: nulliparity, parity 1 to 3, absence of pain and uterine infections, Bishop score less than 4, the patients multiparity, corioamnionitis in bedridden time in hospital, and uterine incision. Exclusion criteria from the study included complete abortion in clinic, asthma, glaucoma, renal, hepatic, and cardiac diseases. An informed consent to enter the study was received from all patients. Uterine sonography was performed in all patients during the 48 hours before being bed-ridden and the pregnancy age had been calculated according to the sonography. Patients were randomly placed in two groups of 20 persons. Demographic characteristics such as age, height, body mass index (BMI), parity, and gestational age were recorded 600 µg of misoprostol was given as the vaginal primary dose to all patients, and then in one group, 400 µg of misoprostol was prescribed vaginally every four hours in three
dosages, and oral dosages were prescribed in the other group. If discharge of pregnancy products was incomplete after these dosages, oxytocin was used to complete the process. During treatment, the patients suffering from anaphylaxis, fever, and severe diarrhea were excluded from the study. After 24 hours of pregnancy products discharge, uterine sonography was performed in all patients and if oral residual was more than 2 cm, the patients were then candidates for curettage. Hemoglobin and hematocrit for all patients were previously checked before the initial treatment and 24 hours after abortion and they were recorded. Upon completing the treatment process, the two groups were examined to determine the amount of reaction to misoprostol, duration of the discharge from the initiation of treatment, the frequency of oxytocin used to help pregnancy termination, and the average of amounts of misoprostol taken in both groups, the number of side-effects (fever, diarrhea, and severe bleeding), decrease in Hb level, the need for blood transfusion, and the need of curettage. All parameters were examined and data analysis was then performed by using SPSS software and statistical tests, chi-square and T-test; p < 0.05 was considered significant.

Results

The patients of these two therapy groups of oral and vaginal misoprostol, had no statistically significant differences with regard to age, nulliparity, weight, BMI, and gestational age (p > 0.05) (Table 1). Differences in the number of successful embryo fetal excretions and the mean duration of the process from the initiation of treatment, between the groups was not significant. The side-effects of the oral misoprostol group included diarrhea (5%), and severe bleeding (5%), and in the vaginal misoprostol group, fever (10%) and diarrhea (15%), which showed no significant differences. The difference between the groups regarding the need for curettage to evacuate the residue of pregnancy immediately after excreting the fetus was not significant (Table 2).

Discussion

This study aimed to compare the effect of vaginal and oral misoprostol after the primary dosage in order to terminate second-trimester pregnancy. The results of this study did not show significant differences with regard to successful termination of pregnancy between these two therapeutic groups of oral and vaginal misoprostol. There was also no significant difference between the two groups with regards to the duration of pregnancy termination, side-effects, and the need for curettage.

In a study by Feldman et al., on 43 patients who were candidates for pregnancy termination in the second trimester, the patients were placed in a vaginal misoprostol group (22 persons) and oral misoprostol group (21 persons). At first, they were all prescribed 800 µg of vaginal misoprostol. They were then divided into two groups and prescribed 400 µg of vaginal or oral misoprostol based on a selective method every eight hours. For mean duration of pregnancy termination from the initiation of treatment in the first 24 hours of the above-mentioned study, there was no significant difference between the oral (15.9 ± 2.3 hours) and vaginal (21.1 ± 3.5 hours) therapeutic groups, and also there was no significant difference with regard to the side-effects between these two groups [10], which is consistent with the results of the current study.

Also in the study by Kurshid et al., on 100 patients who were candidates for pregnancy termination in the second trimester, patients were placed in two groups consisting of 30 women. At first all patients received 800 µg of vaginal misoprostol and then 400 µg oral or vaginal misoprostol of four dosages every eight hours for patients of both groups. With regard to termination of pregnancy in the first 24 hours the vaginal group (80%) was significantly more than the oral group (32%). Furthermore, the mean interval of pregnancy termination from initiation of treatment in successful vaginal group (16/12 ± 6/1 hours) was significantly less than the oral group (32/5 ± 6/12 hours) [11], which was not consistent with the results of the current study. Since our case series is smaller than the study of Kurshid, the difference of these studies may be related to this fact or the different effects of the drug in various races. There was no significant difference between the oral groups (18%) and vaginal groups (13%) according to the need for curettage [11], which is consistent with the results of the present study.

Similarly, in the study by Behrashi et al., in 60 pregnant women in the second trimester who were candidates for pregnancy termination, the patients were placed in two groups consisting of 30 women that received vaginal or oral misoprostol with the primary dose of 400 µg and it was continued for three doses every six hours. The successful termination of pregnancy in the vaginal group
Effects of vaginal versus oral misoprostol to terminate second-trimester pregnancy

(86.7%) was significantly higher compared to the oral group (43.3%) [12], which is inconsistent with the results of the current study. Since in the present study in both groups, the first dose had been prescribed vaginally, and vaginal absorption of misoprostol is more effective than oral absorption, this would explain the differences encountered between these studies. With respect to the mean duration of the process between the vaginal group (9.2 ± 4.2 hours) and oral group (12.7 ± 7.3 hours), no significant difference was shown. Also with respect to the side-effects, there was no significant statistical difference [12] between the oral group (46.6%) and the vaginal group [13] which is consistent with the results of the present study.

In another study by Bebbington et al. [13] in 114 patients who were the candidates for pregnancy termination in the second trimester, the patients were placed in two groups of oral misoprostol (65 persons) and vaginal misoprostol (49 persons). The oral group of misoprostol, 200 µg of drug was prescribed every hour until three hours, and then 400 µg of drug was prescribed every four hours, and in the vaginal misoprostol group, 400 µg of drug was prescribed every four hours until 24 hours. Successful termination of pregnancy in the first 24 hours in the vaginal group (85.1%) was significantly higher than the oral group (39.5%) and the interval of pregnancy termination from initiation of treatment in the vaginal group (19.6 ± 17.5 hours) was significantly less than the oral group (34.5 ± 28.2 hours) [13] which was inconsistent with the results of the current study. Since, in the present study the first dose had been prescribed vaginally in both groups and the studied cases were also lower than the study of Bebbington, perhaps the difference of these studies is in the number of samples or the method of prescribing misoprostol. There was no significant difference between the oral group (7 persons) and vaginal group (4 persons) according to the need for curettage [13], which is consistent with the results of the current study.

Conclusion

It appears that the compound method of vaginal misoprostol in a primary dose with the continuation of the oral dose, is not more effective than the vaginal misoprostol method alone.

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Case Reports

Depression and pregnancy-associated death by suicide after spinal cord injury: a case report


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Summary

Purpose of investigation: To report a case of a pregnant woman with traumatic spinal cord injury complicated with a psychiatric disorder. Case Report: A 24-year-old woman at 18 weeks of gestation was transferred to our hospital with a history of having jumped from a third-floor apartment patio. Result: A trauma survey showed no life-threatening hemorrhage, and fetal wellbeing was confirmed. Neurological examination showed complete loss of motor and sensory function in her lower extremities. Termination of pregnancy was advised and was achieved medically. Surgical intervention was performed to achieve stabilization of the spine and decompression of neural elements. After the operation, she was referred to a psychiatrist, and the administration of paroxetine, etizolam and flunitrazepam was begun. Four months after undergoing the abortion, she choked herself to death on her ward bed. Conclusion: Although it is rare, we should pay special attention to the substantial suicide risk of women who face severe spinal cord injury.

Key words: Pregnancy-associated death; Suicide; Psychiatric disorder; Spinal cord injury.

Introduction

The findings of both the “Confidential Enquiries into Maternal Deaths 2000 to 2002. “Why Mothers Die” and the Office of National Statistics linkage study suggest that psychiatric disorder, and suicide in particular, is the leading cause of maternal death [1]. Perinatal psychiatric disorder can be seen to complicate 15% of maternities both during pregnancy and in the postpartum period [2]. A minority of these illnesses are extremely severe risk factors, with relapsing psychosis or untreated pre-existing psychosis in particular constituting a medical emergency. In addition, depressive disorders are the most common form of psychological distress after spinal cord injury (SCI), and SCI-induced suicide is the leading cause of death in SCI patients younger than 55 years [3]. Therefore, physicians should be aware of a case of a suicide attempt by a young pregnant woman that resulted in traumatic SCI. We report here the case of a pregnant woman with traumatic SCI complicated with an untreated psychiatric disorder.

Case Report

A 24-year-old woman, para 4, gravida 1 at 18 weeks / 6 days of gestation, was transferred to our hospital with a history of having jumped from her third-floor apartment patio, following which she developed severe back and pelvic pain. On admission, she was on a backboard with her spine immobilized under oxygen mask with a reservoir bag. In the emergency room, she appeared diaphoretic and restless. Her vital signs were blood pressure 98/60 mmHg, pulse 86 beats/min, respiratory rate 24 breaths/min, body temperature 35.1°C and SpO2 (pulse oximetry) 100% (O2 12 l/min, reservoir bag). The management of such a case was performed to prioritize assessment and stabilization following the ABCDE plus F (fetal assessment) scheme based on the Japan Advanced Trauma Evaluation and Care (JATEC) protocol.

On primary survey, her consciousness level was E3V4M6 (Glasgow Coma Scale). Plain x-rays (chest and pelvic) and ultrasonography (transthoracic and transabdominal) revealed no hemorrhage in the intrathoracic, intraabdominal, retroperitoneal and intrauterine spaces. Fetal wellbeing and viability were confirmed. She had no symptoms such as contractions, vaginal bleeding, or abdominal pain on initial presentation. Her anal sphincter reflex was unclear. On secondary survey, neurological examination showed complete loss of motor and sensory function in her lower extremity. Helical computed tomographic scanning with multiplanar reconstruction (MRP) and 3-dimensional (3D) rendering showed Th12 and L3 burst fractures and spinal code compression at the level of Th12 (Figures 1 and 2). The lab tests showed that her maternal platelet counts and fibrinogen were within normal limits, and her blood type was O, Rh (D)-positive. A urine toxicology screen was negative. Sixty minutes after arrival, the administration of methylprednisolone was begun (30 mg/kg intravenous, followed by 5.4 mg/kg per hour over 23 more hours), and she was admitted to the intensive care unit for continued monitoring. Subsequently her sensory function slightly improved and provided a final diagnosis of Frankel Scale B SCI.

Her past medical history was significant and included several years of untreated depression and suicide attempts (overdose, wrist slashing, and inhaling gas). Four years previously she had married and had a viable first pregnancy. However, when admitted to our hospital, she was divorced and had lost contact with her family. At that time she was a commercial sex worker, and her partner was a minor. On the morning of the day she was transferred to our emergency department, she had visited an...
Depression and pregnancy-associated death by suicide after spinal cord injury: a case report

obstetric hospital complaining of abdominal pain. At that time, her pregnancy (18 weeks and 6 days of gestation) was first proved despite the use of contraception. After a series of consultations among physicians (obstetrician, orthopedist, psychiatrist, anesthesiologist and social worker) and her family (we made immediate contact with her family after written informed consent was obtained), we concluded that the pregnancy was a contributing factor to the parasuicide attempt and a risk factor for possible suicide, in addition to the fact that an untreated psychiatric illness was present. Termination of the pregnancy was advised and was achieved medically with gemeprost (20 weeks and 3 days of gestation). On the 9th postpartum day, surgical intervention was performed to achieve stabilization of the spine, reduction of dislocations and decompression of neural elements. After the operation, she was referred to a psychiatrist for further management and the administration of paroxetine (20 mg/day), etizolam (3 mg/day) and flunitrazepam (4 mg/day) was begun. Concurrently she was admitted to the Recovery and Rehabilitation Service. However, four months after the induced abortion, she was discovered in cardiopulmonary arrest on her ward bed. The resuscitation effort performed in accordance with the Advanced Cardiac Life Support protocol was not successful. She choked herself to death using a tight tie around her neck.

Discussion

In 1986, the Centers for Disease Control and Prevention (CDC, US) and the American Congress of Obstetricians and Gynecologists (ACOG, US) defined "pregnancy-associated death" as the death of a woman from any cause while she is pregnant or within one year of the termination of pregnancy. We here discuss the case of this unpreventable pregnancy-associated death in terms of three aspects.

First, we quickly provided optimal care to the pregnant trauma patient with good communication among a multi-disciplinary group of physicians. As a result, primary treatment was begun within 60 minutes of her arrival. In obstetric emergencies and trauma, the mother's life is always our top priority. Trauma care priorities do not change when the patient is pregnant [4]. Any treatment required to save the mother’s life or treat her critical status should be undertaken, regardless of her pregnancy, including any diagnostic imaging deemed necessary [5].

Second, we recommended the termination of her pregnancy, and the pregnancy was aborted. We believe that there are three prerequisites for continuing the pregnancy in cases of pregnancy complicated with psychiatric disorder: (1) a stable medical condition and regular evaluation by a psychiatrist and obstetrician; (2) close collaboration between the psychiatrist and obstetrical care provider; and (3) involvement of the family and other support networks in preparation for the occasion that the woman will not be able to adequately care for herself or her baby. None of them was present in this case. Soon after the onset of spinal cord injury, her relationship with her partner broke down. It was obvious that due to her poor social background and dysfunctional family her baby’s welfare would not be protected.

Finally, we could not prevent her from committing suicide. Mortality after traumatic SCI, especially in women, has increased despite modern treatment and care. Special attention should be paid to the prevention of suicide and accidental poisoning [6], as these patients are at high risk for suicide and should be monitored closely. As for this case, in addition to paraplegia after traumatic SCI, other potential substantial risks of suicide such as untreated...
ed psychiatric disorder, previous suicide attempts, and induced abortion were present in this patient. The occurrence of a previous suicide attempt has been shown to increase the risk of suicide to 38 times the risk in the general population [7], although increased risk of suicide ideation and later suicide attempts have not yet been assessed for pregnant and postpartum women specifically. Also, much higher rates of both homicide and suicide were found in women who obtained an abortion compared to those who carried their pregnancy to term [8].

In conclusion, we should pay special attention to the substantial suicide risk of women who face severe SCI. The present case has important clinical implications and may provide guidance for physicians in the management of patients who suffer SCI resulting from a suicide attempt in the perinatal period.

References

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Holoprosencephaly in clomiphene-induced pregnancy: a possible association? A case report and literature review

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Summary
Clomiphene is widely used for inducing ovulation. Evidence for congenital abnormalities, in particular central nervous system defects (CNS-D) and in babies born from clomiphene-induced pregnancies is conflicting. The authors report a case of holoprosencephaly (HPE) in a fetus delivered from a mother receiving clomiphene.

Key words: Pregnancy; Malformation; Clomiphene; Holoprosencephaly.

Introduction
Holoprosencephaly (HPE) is a complex brain malformation resulting from incomplete cleavage of the prosencephalon, occurring between the 18th and the 28th day of gestation and affecting both the forebrain and the face. It is estimated to occur in one in 16,000 live births [1]. During early embryonic period, the frequency is one in 250, but progressively declines because of high mortality rates [2]. The term was first used in 1963 to describe a spectrum of malformations which have, as their common finding, failure of the proper formation of midline structures of the forebrain [3]. The range of expression varies from mild forms, where the right and left ventricles are separated, but there is continuity across the frontal cortex, to severe forms, where there is a single brain and no interhemispheric fissure (alobar holoprosencephaly). The severe forms are generally associated with facial deformities such as anophthalmia, cyclopia, and the presence of a proboscis [4].

Case Report
A 29-year-old infertile woman was treated with clomiphene for two consecutive cycles starting on day two of her menstrual cycle (50 mg for five days). After the second cycle of clomiphene, she became pregnant. The initial pregnancy course was normal and no illness or drug consumption were reported. An ultrasound at 20 weeks of gestation gave unclear results for brain malformations; the echographic examination repeated after six weeks showed cerebral malformations. At 32 weeks of gestation, the patient legally terminated the course of pregnancy: she delivered a 1,690 g fetus affected by holoprosencephaly and cleft lip and palate. Genetic consultation revealed a normal fetal karyotype; the familiar history was negative for holoprosencephaly. TORCH infection during the first trimester was excluded. The molecular genetic diagnosis was not pursued due to its high cost and because it was not expected to provide a reliable prognosis for the family.

Discussion
The causative factors of HPE are numerous, of which chromosomal disorders account for no more than 40% to 50% of cases, with a higher prevalence observed in trisomy 13, trisomy 18, and triploidy. Mutations seen in the putative genes account for about 28% of all HPE cases. HPE can also be associated with several multiple malformation syndromes with a normal karyotype, as CHARGE syndrome, Smith-Lemli-Opitz syndrome, and others [5]. The remaining cases of HPE are thought to be related to maternal diseases and/or exposure to teratogens: risk factors include maternal diabetes [6], maternal alcoholism [7], and prenatal exposure to drugs, such as retinoic acid [8], antiepileptic drugs [9] or cholesterol biosynthesis inhibitors [10]. Moreover, cytomegalovirus [11], toxoplasma [12], and rubella [13] have been suspected to be involved in the pathogenesis of the malformation. Other anectodal reports have suggested a possible association between HPE and/or cyclopia and in utero exposure to sulfasalazine [14], salicylates [15], estroprogestins [16] or misoprostol [17].

In the past decades, a causal association between CNS-D and clomiphene has been suggested. In 1973, Dyson and Kohler described two patients who delivered infants with anencephaly and spina bifida following treatment with clomiphene [18]. Since this initial report, several similar observations have been reported [19-21]. To the authors’ knowledge, no cases of HPE associated to clomiphene in utero exposure have been reported.

The association between use of clomiphene and HPE could be considered unlikely if the active substance is not present during the first weeks of embryogenesis. Geier et al. demonstrated the absence of clomiphene and/or its metabolites during organogenesis in the blood of patients previously treated with clomiphene [22]. By contrast, other studies reported that a small amount of clomiphene and its metabolites excreted in the urine and in the feces may be detectable for six weeks after treatment [23]. Moreover, using a mouse model, Dziedzak reported an increased risk of exencephaly in the offsprings of females injected with clomiphene before ovulation in doses similar to those used in humans [24].

Clomiphene is excreted principally through the intestine.
Five days after oral administration, 51% of the administered dose is excreted. However, some clomiphene and its metabolites are detectable for six weeks in biological samples, suggesting an enterohepatic recirculation of the drug and its metabolites. Serum concentrations of zuclophene (cis-isomer of clomiphene) remains at least ten percent of peak levels 28 days after ingestion of a single 50 mg tablet. Therefore, repeated administration of a single 50 mg tablet at 28-day intervals may undergo accumulation and the effects of these doses may be cumulative [25]. For this reason, clomiphene may be more effective in inducing ovulation during the second and later cycles of treatment although the dose administered remains the same. This accumulation justifies the presence of clomiphene even after the "all or nothing" period with possible unwanted effects in some patients.

Studies investigating the association between neural tube defects and clomiphene use do not provide conclusive results. Some epidemiological studies suggested that clomiphene did not appear to substantially contribute to the occurrence of isolated CNS-D [26, 27]. A pooled analysis of all of these studies on clomiphene and CNS-D showed a prevalence ratio of 1.08 (95% CI 0.76 - 1.51) and the authors concluded that an increased risk of CNS-D due to clomiphene could not be ruled out, although any such elevated seemed likely to be less than twofold [28]. A similar result (OR 4.5, 95% CI 0.7 - 26.7) has been reported from other authors after adjustment for confounders, although the initial crude OR was 6.4 (95% CI 1.3 - 31.4) although the dose administered remains the same. This result may not substantially contribute to the occurrence of isolated CNS-D [26, 27]. A pooled analysis of controlled epidemiologic studies and rec-ommendations for future studies”.

Conclusion

In conclusion, there are no current clear elements to establish if clomiphene therapy may be a risk factor for holoprosencephaly. The authors’ experience adds a further possible case of central nervous system defects observed after clomiphene use to those already published. Larger studies are needed to better understand if clomiphene has some teratogenic potential.

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Conservative management of massive hematoperitoneum caused by ovulation in a patient with severe form of von Willebrand disease - a case report

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Summary
Von Willebrand disease (VWD) is the most common inherited bleeding condition that involves extended or excessive bleeding, caused by the deficiency or defect of von Willebrand factor (VWF). Hematoperitoneum as a complication of gynecologic diseases represents an acute condition which is usually caused by the hemorrhagic corpus luteum or a rupture of either ectopic pregnancy or a hemorrhagic ovarian cyst. The authors present a unique case of conservatively managed massive hematoperitoneum caused by ovulation in a patient with severe form of von Willebrand disease who had right adnexectomy due to hemorrhagic corpus luteum four months prior. This conservative management by blood product and factor concentrate support could be a method of choice in selected hemodynamically stable patients. Furthermore, recurrent bleeding episodes following ovulation could be prevented by suppression of ovulation using oral contraceptive pills.

Key words: Hematoperitoneum; Ovulation; Von Willebrand disease; Conservative management.

Introduction
Von Willebrand disease (VWD) is the most common inherited bleeding disorder caused by a deficiency or defect of von Willebrand factor (VWF) [1, 2]. Type 3 of VWD is a very rare form of disease, characterized with a complete deficiency of VWF and secondary severe deficiency of F VIII [2]. Symptoms of VWD are more common in women considering that they are exposed to hemostatic risks during the menstrual period or pregnancy / delivery during their reproductive period [2, 3].

Hematoperitoneum as a complication of gynecologic diseases represents an acute condition which requires operative treatment. It is usually caused by a hemorrhagic corpus luteum or a rupture of either ectopic pregnancy or hemorrhagic ovarian cyst [4]. Hematoperitoneum secondary to ovulation is rare, and in most cases is associated with severe bleeding disorders, such as afibrinogenemia or VWD’s, or in patients undergoing anticoagulation therapy [5, 6].

The authors present a unique case of conservatively treated hematoperitoneum caused by ovulation in a patient with severe (type 3) form of VWD.

Case Report
A 38-year-old woman was admitted to the hospital due to a deteriorated general condition, followed by tenderness in the lower part of the abdomen. The patient suffered from a severe form of VWD since childhood. The patient had two normal vaginal deliveries with life-threatening postpartal hemorrhages, but without any additional data regarding their management. All menstrual periods were hypermenorrhoic. The patient had adnexectomy on the right side due to adnexal tumor formation four months prior. The tumor was histopathologically verified as a hemorrhagic cyst with hydrosalpinx. Both surgery and postoperative period were uneventful, while the patient was on VWF / FVIII complex therapy (Haemate P 2000 IU i.v.).

The patient was pale, generally weak, but with stable blood pressure. During the gynecological examination, an adnexal mass about five cm in size was verified on the left side. The adnexal mass was mobile, elastic, smooth-surfaced, and palpatory tender, but without peritoneal irritation. The laboratory results showed a low hemoglobin level (Hgb - 88 g / L), while parameters for infection (WBC, CRP), and β-HCG were negative. The level of CA-125 was slightly elevated (42.2 IU / L), and other tumor markers (AFP, CA 19.9, CA 15.3, CEA) were within normal range. Value of VWF at that moment was zero percent, and other parameters of hemostasis were as follows: PT 13.2 s, a PTT 28.7 s, INR 1.21, fibrinogen 3.4 g / L, AT 60.5%, D-dimer 2.31 mcg / L. Transvaginal ultrasound (TVUS) examination verified a hypoechoic mass (40 x 30 mm) in the left adnexal region, clearly marked with blood clot on its surface and surrounded with suspected hemorrhagic cyst rupture or state after ovulation. There was a moderate amount of free fluid in Douglas’s pouch with several small blood clots sized up to two cm (Figures 1A and B).

The patient was transferred to the intensive care unit, and therapy with 20 IU of cryoprecipitate was begun. In order to assess the patient’s condition and further therapeutic possibilities, magnetic resonance imaging (MRI) of abdomen and pelvis were performed. An MRI of the abdomen showed enlarged spleen (15 cm in cranio-caudal diameter), as well as a right lobe of the liver. In projection of the left adnexa, there was an oval, clearly marked formation, 4.7 x 4 cm in diameter. There were several follicles on the left ovary. Posterior to this formation and behind the uterus, there was an organized clot formation with

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diameter of 5.8 x 4.0 cm. Another formation (3.8 x 3.5 cm in diameter) with the same MRI characteristics, was located parasagittally on the right side in Douglas’s pouch corresponding to the blood clots. Perihepatic and parasplenic free hemorrhagic fluid was verified as well (Figures 2A, B, and C). These finding confirmed the hematoperitoneum caused by ovulation, which represents the condition that is usually managed surgically.

Since the patient was hemodynamically stable, the decision was made to treat the patient conservatively. After the initial administration of cryoprecipitate (20 IU), therapy was continued with Haemate P 2000 IU / 24 hours i.v. in combination with iron supplements. The laboratory analysis included CBC, PT, PTT, and fibrinogen performed on a daily basis. The fourth day from the beginning of therapy, the VFW was 64%, and F VIII 133%, and the day after VFW was 80%, and F VIII was 114%. On the sixth day, the value of VWF decreased to 32%, and on day eight, it was 16%. The value of hemoglobin increased, and on day 11 it was 125 g / l. Since vital parameters, clinical, and CBC findings were stable, the substitution therapy was suspended. Two days later, the value of VFW was zero percent again. The control ultrasound exam showed that there was no free liquid around the liver and spleen, while the amount of pelvic free fluid was decreased. The ovary and the clot around the ovary were the same size as previously measured. The final ultrasound exam before discharge, showed a significant

![Image 1A](image1a.png) ![Image 1B](image1b.png)

Figure 1. — Ultrasound images during admission to the hospital. A) Free fluid and blood clot in Douglas pouch. B) Left ovary with blood clot.

![Image 2A](image2a.png) ![Image 2B](image2b.png) ![Image 2C](image2c.png)

Figure 2. — MRI images during admission to the hospital. A) Sagittal section of pelvis, left ovary with blood clot. B) Transversal section of pelvis, with pelvic free fluid. C) Perihepatic and perisplenic blood.
improvement (Figures 3A and B). The patient was discharged home with oral contraceptive therapy. The contraceptive therapy was continued from the first day of next menstrual period for another three months. The patient was in good clinical condition during regular monthly follow ups throughout a period of three months.

Discussion

VWD is caused by the abnormality of VWF, which plays an important role in hemostasis. It is the most frequent form of inherited abnormality of hemostasis. The main manifestation of VWD is a mucocutaneous hemorrhagic syndrome. Early diagnosis is very important to avoid hemorrhagic complications, especially if the surgical procedure is planned or inevitable [7]. The degree of the VWF defect determines the severity of spontaneous bleeding [8]. In these patients, prophylactic treatment is required in order to prevent excessive bleeding following surgery [8]. It is usually short-term prophylaxis used to prevent imminent postoperative complications [8]. Patients with severe forms of the VWD may have frequent hemarthroses, especially when a factor VIII (FVIII) levels are below 10 IU/dL, recurrent gastrointestinal (GI) bleeding, and in children who have epistaxis frequently can cause anemia [9]. In these patients, long-term prophylaxis with VWF/FVIII concentrates should be the matter of choice, rather than just treatment of bleeding episodes [9].

Although hematoperitoneum following ovulation is rarely clinically significant, in women with congenital or acquired bleeding disorders, it may lead to life-threatening hemorrhage [6, 10]. It is more common in patients with severe bleeding disorders, such as afibrinogenemia, type 3 of VWD, or in patients undergoing oral anticoagulation therapy [5]. Hemoperitoneum due to a gynecological disease in patients with VWD can be a very acute condition that requires emergency surgery. In cases of massive hematoperitoneum, surgical interventions, such as adnexectomy or oophorectomy, are usually performed [6, 11]. However, surgery may represent the additional risk for these patients, and this was one of the reasons why the authors decided to proceed with conservative treatment.

Conservative treatment in the present case was also determined by the patient’s hemodynamic stability. Initial administration of cryoprecipitate was substituted with Haemate P i.v. (2000 IU/24h). Haemate P is the widely used VWF/FVIII concentrate due to its high VWF:FVIII ratio [12]. Federici et al. showed in a cohort study, an excellent to good clinical response with VWF / FVIII concentrates in 97% of bleeding episodes and in 99% of surgical procedures in patients with VWD [13]. Conservative management with blood product and factor concentrate should be considered when it is possible to avoid surgery [11]. Study of Payne JH, et al. demonstrated that recurrent bleeding episodes following ovulation may be conservatively treated and prevented by ovulation suppression [11]. Although the nature of VWD is heterogeneous, the concentration of zero percent VWF, as the patient had, is very rare and almost accidental. The patient was observed by the hematologist, and during therapy, the maximal value of VFW was 80% and decreased over the following eight days, while hemoglobin levels increased. Single daily doses of Haemate P in this case proved to be sufficient, both as potential surgery prophylaxis and as a therapy. After achieving a stable condition of the patient, treatment was continued with long-term hemorrhagic prophylaxis by using oral contraceptive pills. Oral contraceptives are the treatment of choice in congenital bleeding disorders to control ovulation-related hemoperitoneum [11, 14]. Since the treatment with Haemate P can lead to thromboembolic complications, it is very important to perform a pharmacokinetic study in order to strictly tailor doses of VWF / FVIII concentrates [12, 15].

The present is a unique case of massive hematoperitoneum treated conservatively in a woman with very severe VV disease (0% VWF). The patient was clinically stable all the time, and the treatment was conducted with
single daily dose of 2000 IU i.v. of Haemate P, which proved to be sufficient. Massive hemoperitoneum due to ovulation is a serious complication for women with VWD, and usually leads to surgery. This case report showed that conservative management could be a method of choice even in patients with a severe form of VWD, if they are hemodynamically stable. This can be achieved by using VWF / FVIII concentrates and oral contraceptive pills to prevent recurrent bleeding episodes that might appear after ovulation.

References

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Leiomyomatosis peritonealis disseminata and pregnancy: a case report


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Summary

Leiomyomatosis peritonealis disseminata (LPD) is a benign tumor of smooth muscle tissue. It is rare and characterized by the development of multiple peritoneal nodules mimicking peritoneal carcinomatosis. We report a case of LPD diagnosed in a 35-year-old patient, G4/P1, without any major gynecological history. The patient underwent an elective cesarean section at 42 weeks, during which numerous peritoneal nodules ranging in size from 0.1 to 0.5 cm were found. Microscopic examination showed a proliferation of smooth-muscle cells without mitosis or atypia or necrosis.

Key words: Leiomyomatosis peritonealis disseminata; Leiomyoma.

Introduction

Leiomyomatosis peritonealis disseminata (LPD) is a benign tumor of smooth muscle tissue and is characterized by the proliferation of multiple peritoneal nodules. Nodules of variable size are found throughout the peritoneal surface, on the omental apron simulating a peritoneal carcinomatosis, and often coexist with uterine fibroids [1] although no clear correlation between LPD and uterine fibroids has been established [2]. We present the second reported case in the Ivory Coast since the one published in 2006 [3].

Case Report

A 35-year-old woman (G4/P1) was admitted to the maternity ward of Cocody University Hospital (Abidjan, Ivory Coast) for an elective cesarean section indicated due large fetus size to in October 2009. Her first child had been delivered vaginally. She had irregular cycles between 28 and 32 days and menstrual duration was four to five days. She had never used contraceptives and had no history of uterine fibroids. She also had had two terminations of pregnancy with an uneventful postoperative course. On admission, we noted a good general condition: blood pressure = 11/7; weight = 77 kg; height = 161 cm. Uterine size was estimated at 37 cm. The fetal heart sounds were regular at 150 bpm. The uterus appeared regular and soft to the touch. Speculum examination showed a vagina with no abnormalities. On vaginal examination, the inferior segment of the uterus was small and the cephalic presentation repressed. Other examinations were unremarkable. Obstetric ultrasound revealed a fetal weight superior to 4,400 g. Laboratory tests as part of the preoperative evaluation were normal. Cesarean section allowed an delivery with macrosomia, weight: 4,600 g, Apgar score 8-9 at 1 and 5 min. At cesarean section, multitude nodular formations ranging in size from 0.1 to 0.5 cm scattered throughout the pelvic cavity were revealed. These nodules were visible on the right broad ligament, the bladder-uterine peritoneum, and the pelvic colon on the omentum (Figures 1 to 4). Before closing the abdomen, biopsy was performed for nodular histological examination. The exam highlighted a proliferation of smooth muscle fibers without mitosis, atypia, or necrosis. The postoperative course was uneventful and the patient was releas from hospital on the 7th postoperative day. No special treatment was required in the postoperative course, and the postoperative consultation six weeks after surgery was normal.

Discussion

Frequency

LPD is a rare disease. Since the first case reported by Wilson and Peale in 1952, a broad review of the Anglo-Saxon literature has identified to date 132 cases reported by more than 80 teams, including 113 women in the reproductive group age, seven postmenopausal women, six cases in males and one case in an animal (a horse) [4]. Despite the abundance of literature on LPD, the etiopathogenesis, diagnosis and treatment are still unclear.

Etiopathogenesis

The intimate mechanism of development of LPD is still today a mystery; however the role of estrogen in the genesis of this disease has been discussed in numerous publications [3, 5, 6]. Animal studies have shown that high rates and prolonged elevated levels of estrogen can induce metaplasia of mesenchymal stem cells into fibroblastic, leiomyocytes or endometrial stroma [7]. These animals developed disseminated leiomyomatous peritoneal lesions similar to LPD. High levels of estrogen and progesterone were found on LPD cells suggesting a real potential hormonal responsiveness of these tumors. Finally the high frequency of LPD during genital activity including pregnancy (our observation) validates the idea of involving hormonal activity in the genesis of LPD. Thus the temptation is great to introduce hormonal therapy in the management of LPD.
LPD and uterine fibroids have in common in their genesis a hormonal influence and histologically to develop in smooth muscle. Thus the appearance seems to be the same disease. However, this argument is constantly defeated by the following facts: the occurrence of LPD without intrauterine leiomyomas and the presence of uterine fibroids without LPD, particularly in postmenopausal women [2], and male cases of LPD [8], which led to the idea that LPD could be a new disease entity [4]. The rarity of LPD described in the black African population where there is a higher frequency of uterine fibroids compared to Caucasian women [9], is an additional challenge for the connection of etiopathogenic LPD and uterine fibroids.

Moreover LPD can coexist with a number of pathologies such as Currarino syndrome (in groups of caudal regression syndrome) characterized by multiple congenital abnormalities: anorectic malformation, rectovestibular fistula, ectopic right ureteral orifice, megaureter, hemisacrum [10] or pelvic endometriosis [11].

The hypothesis of peritoneal transplant after laparoscopic myomectomy has been raised. Five cases reported in the literature support this hypothesis. Fragments from the morcellation of myoma during laparoscopic surgery left in the peritoneum would be capable of inducing metaplasia of the peritoneal mesenchymal cells and particularly vulnerable women could develop LPD [4, 12]. According to these authors the need for a good peritoneal toilet after laparoscopic myomectomy, removing the peritoneum of any myoma tissue, could aid in prevention of LPD.

We have already mentioned the coexistence of LPD with Currarino syndrome. Genetic syndromes such as leiomyomatosis of the esophagus (X-linked Alport syndrome [13] or the genitourinary tract (multiple cutaneous and uterine leiomyomatosis) are known [14]. The familial characteristics of LPD have been mentioned by Halama et al. [2]; they describe a case of a white family in which six members were affected by LPD. In addition they noted the association of LPD with Raynaud’s syndrome and nodular prurigo with lichenification of the skin.

Diagnosis

Patients generally exhibit nonspecific abdominal symptoms: abdominal pain or discomfort, or rectal pain, and sometimes bleeding (in the case of an associated uterine fibroid). Clinic examination may reveal abdominal masses with increased abdominal girth. A single case of acute abdomen in relation to bowel obstruction has been described in the literature [15]. In practice, patients are usually asymptomatic and the diagnosis is incidental to the occasion of laparotomy (our case).

The contribution of imaging in the diagnosis is not decisive. Computed tomography and magnetic resonance have shown in some cases images of abdominopelvic diffuse masses [15] suggestive of peritoneal carcinomatosis, which is the main differential diagnosis of LPD. Biopsy and histological study of sampling biopsies are
the keystone of diagnosis. Given the abundant vasculature of peritoneal nodules, the risk of severe hemorrhage can not be excluded at the time of biopsy [2]. For these reasons the procedure should be meticulous and include biopsy. Histological examination had shown a fusiform proliferation of smooth muscle cells without mitosis or necrosis, and without atypia or atypical with low-grade [2, 16]. Hyper-vasculature without evidence of vascular invasion may be noted [2]. Electron microscopy can show an abundance of intracellar contractile fibers, a basement membrane surrounding the cells, mitochondria at the nuclear poles and many pinocytic vesicles on the cell surface [17]. The histological features for some authors are at a stage of traditional development between fibrobasts and mature smooth muscle cells [2]. Immunohistochemical studies have shown that tumor cells co-expressed smooth muscle actin, vimentin, desmin, h-caldesmon, and calretinin [16, 18]. The tumor cells also exhibit positivity for progesterone and estrogen receptors. In our case the changes observed were exclusively represented by a proliferation of smooth muscle cells without mitosis, no atypia or necrosis.

**Treatment**

In terms of therapy, no treatment is accepted by most authors after a review of frozen section samples to determine the histological nature [1, 3]. The risk of malignant transformation is rare. Indeed eight cases of malignancy have been reported in the literature [16]. According to Yamaguchi et al. and Sharma et al. in about 2-5% of cases, progression to malignancy can be observed [8, 19], justifying the need for a codified monitoring well. According to Goldberg cited by Halama et al. [2], the addition of anti-estrogen, removal of exposure to estrogen, and chemical castration by agonists of LH-RH can lead to the regression of tumors. An aromatase inhibitor such as anastrozole was effective for nodules in the women in the study of Takeda et al. [6]. Cases of favorable evolution after surgical removal of nodules have been reported and hormone therapy has been proposed to avoid recurrences, however, no definitive therapeutical concept has evolved thus far [2]. In the case we present, we opted for no treatment with clinical and CT scan monitoring.

**Conclusion**

LPD is a rare disease whose evolution is generally benign, despite the intraoperative findings that frequently lead to peritoneal carcinoma. Although benign, the potential risk of degeneration into leiomyosarcoma imposes clinical and CT scan monitoring.

**References**


Successful pregnancy after uterovaginal anastomosis in patients with congenital atresia of cervix uteri

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Summary

We present a case of successful pregnancy after effective uterovaginal anastomosis in a 26-years-old patient with congenital atresia of the cervix uteri. She spontaneously achieved pregnancy after four years of uterovaginal anastomosis. Gestation was at the eighth lunar month and the delivery was done by cesarean section due to rapidly progressing fetal asphyxia. The patient gave birth to a live healthy male, weighing 1,950 g, with an Apgar score of 5 and 8 at 1 and 5 min, respectively. The postoperative course was uneventful, and leakage of lochia was normal.

Key words: Congenital cervical atresia; Uterovaginal anastomosis; Pregnancy.

Introduction

Congenital cervical atresia is a rare anomaly of the female genital tract. The incidence of Mullerian hypoplasia/agenesis-type I anomalies is approximately 0.1% in the general population, representing approximately 3% of all uterine anomalies [1]. In clinical practice, the aims of treatment of this condition are firstly to relieve the symptoms related to hematometra and retrograde menstruation, and secondly to restore fertility and regular bleeding. Conservative surgical treatment such as cervical canalization, cervical reconstruction and uterovaginal anastomosis of women with these anomalies has remained controversial [2]. Successful pregnancy in a patient with congenital cervical atresia is a great challenge with respect to techniques and reproductive medicine [3]. To our knowledge, reports of successful pregnancies achieved spontaneously after effective uterovaginal anastomosis are rare.

Case Report

The patient, a 21-year-old female, was admitted to the reproductive unit of our clinic with the diagnosis: primary amenorrhea, atresia of the uterine cervix, hematometra, and hematocolpos, with virgo intacta. Based on this history, it was decided to proceed with surgery. In order to build a functional uterovaginal passage the operation was performed using combined transabdominal and transvaginal approaches. LCS scissors (i.e., involving the use of an ultrasound (US) harmonic scalpel) were used to resect the atretic uterine cervix. The resected part of the atretic cervix was sent for histopathological analysis. Anastomosis and sutures were carried out between the isthmic part of the uterus and vagina using single circle monocryl sutures. The uterine cavity was drained by a Foley catheter, which remained in place for seven days. The surgical procedure was without complications. Four years later the patient presented again at the reproductive unit. She received estradiol valerate, levonorgestrel (Cyclo-Proginova 2 mg) tablets 21 days per month for six months each year. She visited the clinic because she was married and wished to become pregnant. Over the previous six months the patient had had regular menstrual cycles lasting 28 days. Repeated measurements of LH, FSH, estradiol, progesterone and prolactin concentrations were three times those measured during the previous menstrual cycle, on the 3rd, 11th and 21st days of the cycle. These results confirmed a normal ovulatory cycle, and her partner’s semen analysis was normal. US examination performed on the 11th day of the menstrual cycle revealed a normal-sized uterus, a three-layer endometrium structure that was 11 mm in diameter, and normal ovaries. A pre-ovulatory follicle that was 25 mm in diameter was seen on the left side. Four months later, she presented at the clinic again because she had missed her menstrual period. US examination of the vaginal wall revealed an intrauterine gestational sac with embryonic echo 6.24 mm in diameter and presence of heartbeats. The age of pregnancy was six weeks and three days, which corresponded to the length of amenorrhea. Serum ß-hCG concentration was 5588 U/l. For luteal support, 600 mg micronized progesterone (Utrogestan capsules, 100 mg) was administered daily, vaginally. Follow-up was scheduled at three-week intervals. On follow-up by clinical examination at 14 weeks of pregnancy, the cervix was fixed, closed and was palpable to a total length of approximately 0.5 cm. We concluded that cervical cerclage was not necessary. As there was a risk of premature delivery, maturational of the fetal lungs was induced using weekly dexamethasone 8 mg (dexametason) IM injections on three successive days and repeated again three weeks later. Then, the 26-year-old patient was admitted to our hospital at eight lunar months of pregnancy, exhibiting symptoms of premature membrane rupture. Upon examination, the uterus corresponded to the length of amenorrhea, with no contraction. Leakage of amniotic fluid and fetal heart tachycardia were present. The fetus was in the breech position. The vagina was 5 cm in length and the cervix was not palpable but was dilated to 1.5 cm. Based on US parameters, the pregnancy corresponded to 33.4 weeks of pregnancy. The patient was admitted to the high-risk pregnancy unit, and because of rapidly progressing fetal asphyxia, cesarean section was performed a few days later. The only difficulty during the operation was that the bladder was lifted high in front of the uterus. A healthy male weighing 1,950 g with an Apgar score of 5 and 8 at 1 and 5 min, respectively, was born. The postoperative course was uneventful, and leakage of lochia was normal.

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Successful pregnancy after uterovaginal anastomosis in patients with congenital atresia of cervix uteri

Discussion
Obstructive uterine anomalies usually present with abdominal pain and a pelvic mass at the time of menarche. The malformation described in our patient, according to the VCUAM classification, belongs to type C 2 a, including all cases of congenital hypoplasia/agenesis of the uterine cervix [4]. The diagnosis of a high barrier by clinical, transabdominal and transrectal US examination, magnetic resonance imaging and laparoscopy is important in the diagnosis of this type of anomaly [5-8].

Patients with cervical agenesis associated with or without vaginal aplasia can have serious health problems, and typically lack reproductive function [9, 10]. The literature contains multiple reports of various conservative surgical techniques that have been used to deal with these malformations. However, consensus regarding an optimal technique is still lacking. Cervical obstruction has been most frequently solved by forced formation of canals, uterovaginal canalization aided by intraoperative US or endoscopically monitored canalization, in order to maintain the connection between the cavity of the uterus and vagina [11-13]. The surgical approach leads to normal menstrual bleeding, resolution of cyclic pelvic pain, and frequently preserved fertility [14]. Preservation of the uterus provides the opportunity to achieve pregnancy spontaneously or by applying artificial reproductive technology techniques [15]. One of the operational techniques of establishing communication between the vagina and uterus is uterovaginal anastomosis. Uterovaginal anastomosis and cervical reconstruction have been proposed and described by several authors [3, 16, 17]. Often, very shortly upon this intervention, stricture of the newly formed canal occurs, and cervical permeability typically fails. Patients generally have severe complications because of infection, adhesions or retrograde menstruation, pelvic pain and endometriosis. Leakage of menstrual blood is rarely observed over the long-term, and spontaneous pregnancy rarely occurs [17]. Given these frequent complications of surgery, many authors agree that, total hysterectomy effectively addresses the issue [18]. In this type of surgery, the problem of sterility in these patients often remains unresolved. To preserve reproductive function, operations for the creation of neovaginal and uterovaginal anastomosis are recommended. Neovagina or uterovaginal anastomosis should be performed as soon as possible after puberty. Uterovaginal anastomosis involves securing the transience and functionality of the external genital tract. Our patient expressed a desire to have corrective surgery performed to preserve her reproductive capacity. In these clinical conditions, given that the length of her vagina was sufficient, we decided to perform uterovaginal anastomosis. This operational approach, and successfully completed pregnancy several years after the project, was our first experience with this condition. In short, the surgical technique consisted of the following: resection of the fibrous supravaginal part of the cervix uterus as well as anastomosis of the isthmic part of the uterus and vagina. Thus, the incised isthmicocervical part of the uterus was pushed through the open vaginal fornix and sutured by single-circle stitches with no tension. The advantage of this procedure is that instead of forced dilation through the fibrous supravaginal part of the cervix, amputation, creates a natural isthmicouterine canal, with no tendency to stricture formation. Thus, a permanent connection between the uterus and vagina is ensured. On follow-up, upon the first menstruation, through the speculum, a circular opening of the isthmicouterine canal was observed that was approximately 5-8 mm in diameter, from which mucous leaked. The patient was advised to take oral contraception in the six months after the operation to protect herself from pregnancy. After that time, the patient was advised to take estradiol valerate, levonorgestrel (Cyclo-Progynova 2 mg) tablets 21 days per month, for six to eight months every year. The patient was advised to attend gynecological, colposcopic and US follow-up every three months. The chance of a spontaneous pregnancy in these patients is reduced, even after a successful reconstruction of the genital tract, due to severe endometriosis, as well as cervical re-obstruction and tubal factors. Many authors have reported success with pregnancies that were spontaneously formed or aided by artificial reproductive technologies [19, 20]. We believe that in our case maintenance of the cervical canal without interrupting production and leakage of cervical mucus prevented infection, retrograde menstruation, and endometriosis. We also believe that the use of estradiol valerate, levonorgestrel (Cyclo Progynova 2 mg) helped to keep the neocervical canal open. Four years after successful uterovaginal anastomosis, our patient spontaneously became pregnant. Cesarean section was performed without any serious difficulties during the operation. The leakage of lochia was normal.

Conclusion
Our results show that the technique described for resection of the fibrous tissue of a supravaginal part of the uterine cervix and uterovaginal anastomosis has been proven effective in the treatment of congenital atresia of the uterine cervix. This technique allows preservation of reproductive ability and provides a chance for a subsequent desirable pregnancy.

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Severe Asherman’s syndrome complicated with placenta increta conceived by intracytoplasmic sperm injection following hysteroscopic surgery

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Summary

Although severe Asherman’s syndrome is a disease that may cause infertility, pregnancy and childbirth are possible by performing hysteroscopic surgery. However, the obstetrical outcome is not always satisfactory. We report a case where severe Asherman’s syndrome occurred following a cesarean section. Hysteroscopic surgery was performed due to secondary infertility, and pregnancy was achieved through a subsequent intracytoplasmic sperm injection. At 23 weeks of gestation, the patient was hospitalized due to the threat of premature labor, and a cesarean section was performed at 29 weeks of gestation after pregnancy-induced hypertension occurred. It was determined to be abnormal adherent placentation such as placenta increta through intraoperative findings, and a cesarean hysterectomy was performed. The pathological diagnosis of the uterus was placenta increta. Due to the risk of complications from placenta increta in pregnancies following hysteroscopic surgery in patients with severe Asherman’s syndrome, it is important to realize the high risk involved in such cases during the pregnancy course, and careful perinatal management should be required.

Key words: Severe Asherman’s syndrome; Hysteroscopic surgery; Intracytoplasmic sperm injection; Cesarean hysterectomy; Placenta increta.

Introduction

Asherman’s syndrome is a disease that presents various symptoms due to the partial or complete obliteration of the uterine cavity caused by endometrial damage. Major clinical symptoms are menstrual abnormalities, infertility, and recurrent pregnancy loss [1]. Although there are reports of cases where clinical symptoms improved through hysteroscopic surgery, thus resulting in pregnancy and childbirth, the reproductive outcome has not been always satisfactory following surgery for severe Asherman’s syndrome [2]. This report describes a case where severe Asherman’s syndrome occurred after a cesarean section, and although pregnancy was achieved through intracytoplasmic sperm injection (ICSI) following hysteroscopic surgery, a cesarean hysterectomy was required due to placenta increta.

Case Report

A 37-year-old female and her 37-year-old husband presented due to secondary infertility of three years duration. The patient had previously conceived spontaneously and delivered a normal mature infant by cesarean section at 39 weeks of gestation due to intrauterine infection at another hospital. Her menstrual cycles were regular. However, she had pronounced hypomenorrhea. Her hormonal testing was normal. The semen analysis was also normal. Ultrasonography showed normal uterus size with thin endometrium. In hysterosalpingography, the uterine cavity was narrowed and both tubes were occluded (Figure 1). Hysteroscopy revealed dense intrauterine adhesions and marked reduction in the size of the uterine cavity. Both tubal ostial areas were occluded. The patient was diagnosed as having Asherman’s syndrome and classified grade 4 according to the European Society of Hysteroscopy classification of intrauterine adhesions [3].

She underwent transcervical resection (TCR) to restore the normal size and the shape of the uterine cavity. TCR was performed under spinal anesthesia with the continuous flow resectoscope; a diameter of 8 mm fitted with a 3 mm of cutting loop electrode (Olympus Corp., Tokyo, Japan). D-sorbitol solution (3%) was used for uterine dilution. Treatment was performed by making four direct myometrial incisions using a 3-mm loop electrode for the longitudinal incisions into the myometrium extending from the uterine fundus to the isthmus (Figure 2). An intrauterine device was inserted immediately after surgery. The patient then received three cycles of Kaufmann therapy (Premarin and Provera; Pfizer Japan Inc., Tokyo, Japan). An intrauterine device was removed three months later. Menstruation improved after the operation. Ultrasonography showed 6.4 mm thickness of endometrium during the preovulatory period.

The patient elected to undergo in vitro fertilization. She received 900 µg of buserein acetate (Suprecur; Mochida Pharmaceutical Co., Ltd., Tokyo, Japan) daily, starting at the midluteal phase of the pretreatment cycle and ending at the time of human chorionic gonadotropin (hCG) injection. The patient then received 150 IU of recombinant human follicle-stimulating hormone (rhFSH) (Follistim; Organon, Osaka, Japan) daily from day 3 of the treatment cycle until the day before the administration of 10,000 IU of hCG (HCG Mochida; Mochida Pharmaceutical Co., Ltd., Tokyo, Japan). HCG was administered when at least two follicles reached a diameter of ≥ 18 mm.

Transvaginal follicular aspiration was performed approximately 34 hr after hCG injection. Seven oocytes were retrieved. Conventional insemination was performed. Four oocytes were fer-
utilized. Embryo transfer was performed on day 5 of culture. Two blastocysts were then transferred. The endometrial thickness was 6 mm at the time of transfer. The patient thereafter conceived. However, massive bleeding occurred at five weeks of gestation. Her serum hemoglobin level decreased to 5.6 g/dl. Emergency operation (dilation and curettage) was carried out for hemostasis.

In the second attempt, the patient received the same controlled ovarian hyperstimulation. Three oocytes were retrieved. Conventional insemination was performed. However, none of the oocytes became fertilized.

In the third attempt, the patient received 900 µg of buserelin acetate daily, starting at day 2 of the menstrual cycle phase and ending at the time of hCG injection. The patient received 225 IU of rhFSH daily from day 3 of the cycle until the day before the administration of 10,000 IU of hCG. Eight oocytes were retrieved. ICSI was performed. Six oocytes were fertilized. Embryo transfer was performed on day 5 of culture. Two blastocysts were then transferred. The endometrial thickness was 6 mm at the time of transfer (Figure 3). The patient successfully conceived. A single pregnancy was thereafter identified in the uterus at six weeks of gestation. The patient was hospitalized for premature labor at 23 weeks of gestation. Tocolysis with a β-sympathomimetic agent and bed rest were thus initiated. Hypertension (systolic pressure ≥ 140 mmHg and diastolic pressure ≥ 90 mmHg) and proteinuria (proteinuria > 300 mg in a 24-hour collection) were observed at 28 weeks of gestation. Therefore, she was diagnosed as having pregnancy-induced hypertension (PIH). The termination of pregnancy was decided due to hypertension and increased proteinuria. Cesarean section was performed at 29 weeks of gestation under spinal anesthesia. At laparotomy, the myometrium attached to the placenta was very thin. Placental cotyledons and engorged blood vessels were visible through the serosa in the same area. Based on these
findings, a diagnosis was made of abnormal placentation such as placenta increta. Cesarean hysterectomy was thus elected. A low transverse cesarean section resulted in the delivery of a 1,083 g infant [Apgar score 6 (1 min) and 9 (5 min)]. Next, total hysterectomy was performed (total blood loss: 2,320 ml; operation time: 1 h and 25 min). The pathological diagnosis of the uterus was placenta increta (Figure 4). The subsequent postoperative course was unremarkable.

Discussion

In the literature, reports of cases where hysteroscopic surgery was performed to handle severe Asherman’s syndrome, subsequently leading to pregnancy and childbirth, are not scarce. Pregnancy rates following surgery have been reported as being 42.8% by Capella-Allouc et al. [4], 42.9% by Protopapas et al. [5], and 32.5% by Yu et al. [6]. However, subsequent pregnancy progress is not always satisfactory. Although Capella-Allouc et al. [4] observed a total of 15 pregnancies in 12 patients, second trimester fetal loss was observed in three cases, and in two of those cases Shirodkar cervical cerclage was reportedly executed following another pregnancy. In addition, as a complication during delivery, it has been reported that placenta accreta was observed in two out of nine cases of acquired newborns.

The effectiveness of the surgical treatment of Asherman’s syndrome is determined by 1) whether the interior cavity of the uterus has returned to a normal anatomy; 2) whether menstruation has returned to normal; and, 3) whether or not pregnancy and a subsequent newborn was acquired in cases with a history of infertility or fetal loss. When considering the pregnancy and neonatal acquisition rate, the expansion of the uterine cavity and the recovery of fibrosed endometrial function are equally very important.

The spontaneous miscarriage rate following Asherman’s syndrome surgery is reported to be approximately 20% [2]. On the other hand, Everett [7] has reported that the spontaneous miscarriage rate in the general population is 12%. Yu et al. [2] describe that although the number of cases must be increased and verified to determine whether the spontaneous miscarriage rate is increased after surgery due to Asherman’s syndrome, it is thought that successful implantation is hampered with the presence of fibrosis of the endometrium. In our case, although pregnancy was achieved on the first in vitro fertilization, excessive bleeding occurred in the five weeks of gestation, and emergency surgery was therefore required to stop the bleeding. A blood transfusion was not done, but severe anemia occurred. This condition would rarely occur in a normal case, and dysfunction of the endometrium due to Asherman’s syndrome is believed to be the cause of the miscarriage and significant blood loss.

In the literature, abnormally adherent placentation such as placenta accreta has been reported in pregnancies following Asherman’s syndrome surgeries [2, 4, 8]. Although we considered this possibility and observed the condition of the placenta with ultrasonography, it did not lead to a diagnosis of abnormal placentation such as placenta accreta, and an examination of the placenta was planned using magnetic resonance imaging. Subsequently, PIH occurred, which led to a cesarean section. Prior to performing a cesarean section, the possibility of abnormal placentation could not be ruled out; therefore, surgery was performed after obtaining approval from the patient and explaining that if abnormal placentation was diagnosed at the time of surgery, a hysterectomy might be required. Placenta increta was suspected from findings during surgery, and a hysterectomy was performed after fetal delivery. A postoperative pathological finding concluded that it was placenta increta. In a macroscopic finding of the resected uterus, a primary focus was observed in the fundus of the uterus. The intrauterine cavity from the fundus of the uterus to the isthmus was enlarged by hysteroscopic surgery, and the fundus, which was the primary focus of the placenta increta, was not removed. It is not clear whether an abnormality of the endometrium due to Asherman’s syndrome itself was the cause of placenta increta, or if it was related to the operation of the hysteroscopic surgery. However, TCR itself may cause abnormal placentation.

We have reported a case where hysteroscopic surgery was performed due to the presence of severe Asherman’s syndrome, and the subsequent treatment led to successful conception. Following conception, a cesarean section was performed due to PIH, and a hysterectomy was required due to placenta increta. Although severe Asherman’s syndrome is a disease where pregnancy is possible by surgery, it is believed that strict management is needed and it should be kept in mind that spontaneous miscarriage or second trimester fetal loss are possible, and additionally, complications of abnormally adherent placentation such as placenta accreta or placenta increta can develop at delivery.

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Ruptured subcapsular liver hematoma and pregnancy: a rare complication of severe preeclampsia: a report of a case discovered fortuitously at the Maternity Teaching Hospital of Cocody

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Summary

We report a case of spontaneous rupture of a subcapsular hematoma of the liver (SHL). It was discovered incidentally at the end of an emergency exploratory laparotomy performed due to unexplained hemoperitoneum with hypovolemic shock which occurred with severe preeclampsia. Diagnosis and therapeutic management are very difficult in sub-Saharan Africa due in part to the limitations and lack of medical equipment. The prognosis is usually marked by the death of the patient, as in our case. Through this clinical observation we wanted to show the interest in performing a liver ultrasound at any level of preeclampsia to detect liver abnormalities as soon as possible.

Key words: Subcapsular hematoma Liver (SHL); Pregnancy; Preeclampsia.

Introduction

Subcapsular hematoma of the liver (SHL) is a very serious but uncommon complication of severe preeclampsia [1]. It is defined as blood collection under the liver capsule and was described for the first time by Abercrombie quoted in the Mahi et al. study [2]. It occurs in an unspecific clinical picture leading to a delayed diagnosis [1, 3] which is often detrimental because it leads to secondary rupture of the liver capsule which is rare and extremely serious [1, 3]. Maternal mortality is in order of 50 to 75%, and that of the fetus of 60 to 80% [3]. This prognosis is more for burden for our sub-Saharan Africa where people are particularly poor and financially deprived. Through this clinical observation we wanted to measure the severity related to the difficulties of diagnosis and management in our developing country.

Case Report

A 34-year-old female, G4/P3, consulted for preeclampsia at 32 gestational weeks with predominant abdominal pain syndrome in the upper right quadrant. The symptoms had evolved for two weeks with headache and vomiting. She received two days of antulcer treatment and diazepam with no improvement. In her history no knowledge of hypertension during previous pregnancies or peptic ulcer was found.

On admission, chronic epigastric pain associated with excessive weight gain was noted. The medical examination highlighted serious epigastric pain associated with extreme agitation. Her blood pressure was 160/110 mm Hg, associated with massive albuminuria. Uterine size was estimated at 29 cm. The fetal heart rate was regular at 144 beats per minute. Rather quickly the clinical signs became serious, with hypovolemic shock and extreme abdominal distension without diffuse loss of normal contours of the uterus. There was no vulvar bleeding so we considered hypovolemic hemorrhagic shock with hemoperitoneum. An emergency exploratory laparotomy was therefore carried out associated with reanimation measures. After aspiration of abundant hemoperitoneum (2 l), a cesarean first allowed the extraction of a dead fetus. The exploration found no uterine lesion. No uterine vascular injury was observed. However the patient continued to have active bleeding from the floor above the mesocolic shelf. The exploration showed the presence of a large hematoma in the capsule of the liver with bleeding in almost all segments of the hepatic hematoma with rupture of segments 4 and 5 (grade 3). Moreover, the liver was soaked with blood giving it a brownish appearance. The spleen and the rest of the mesocol were healthy.

Hemostatic tamponade of the hematoma with abdominal fields was carried out in vain. The hemodynamics could not be rectified because of the unavailability of blood products. The death of the patient occurred on the operating table two hours after the start of surgery.

Discussion

Frequency

SHL is rare outside of pregnancy [2]. The occurrence during pregnancy is mainly seen in association with preeclampsia and/or HELLP syndrome [2]. Its frequency varies according to reports. It is low in developed countries, estimated at 1/40,000 to 1/250,000 pregnancies [4]. This may be related to better detection and better treatment of preeclampsia. This frequency remains undervalued in underdeveloped countries, especially those in sub-Saharan Africa. Indeed, mild forms go unnoticed due to the limited practice of ultrasound (US) or abdominal scanner. Also in severe cases responsible for sudden
death, an autopsy is performed exceptionally to make the diagnosis in our country. Sociocultural and economic beliefs are mentioned in particular to explain this. Previously, however, the lack of diagnosis was related to the poor quality of US in our country.

**Contributing factors**

Apart from preeclampsia, SHL can occur in direct abdominal trauma or pre-existing focal hepatic lesion (hemangioma, adenoma, focal nodular hyperplasia, hepatoma, and perihepatitis) [5] or anticoagulant treatment [2]. Few cases of spontaneous onset of SHL during pregnancy have been described [2].

Hematoma can occur at any age, with a wide choice in multiparous women aged over 30 years old [5]. It occurs in 50% of cases after 36 weeks of gestation and in 85% of the cases it appears before labor during and in 15% of cases during postpartum [1]. Also it more frequently involves the right lobe of the liver (75%), the left lobe in 14% and both lobes in 11% of cases [3]. These facts are identical to those found in our case and thus support the literature data.

**Pathophysiology**

Some authors [2] incriminate the role of microtrauma in the formation of the hematoma, which occurs in a liver already weakened by preeclampsia, such as abdominal extension. After autopsy, in fact, there is extensive necrosis of the ischemic liver, hemorrhagia, and some cases of fibrin deposits in the periporal sinusoids [2]. Disturbances in coagulation have also been implicated [2]. However in most cases, preeclampsia, is for most authors [1, 2, 5] the grounds of this complication, as indicated in our observation.

For Langer *et al.* [1] the mechanism of occurrence of the hematoma could be explained by two complementary theories. One involves acute disseminated microangiopathy causing acute coagulopathy which results in deposition of fibrin in the sinusoids and arterioles in the liver: this causes multifocal hemorrhagic necrosis. The other is utero-placental ischemia which results in the release of vasoactive substances responsible for causing spasms of capillary doors, ischemia and hemorrhagic necrosis of the liver [1, 2].

**Clinical diagnosis**

All authors agree on the difficulty of diagnosis. Indeed, small liver lesions bring about a simple distension of Glisson’s capsule and can explain preeclampsia in some patients; the upper right quadrant pain resolves spontaneously after delivery [2]. In severe forms the diagnosis rarely occurs before surgery [2].

SHL usually involves two successive evolutionary stages spontaneously [3, 6]. The first one corresponds to the formation of an unruptured hematoma with sudden distension of the capsule in preeclampsia, characterized by severe epigastric pain and/or right upper quadrant pain with scapular lumbar or thoracic radiation. It is often accompanied by painful hepatomegaly on palpation [2]. It is resistant to the usual analgesics and may be accompanied by nonspecific signs (headache, nausea or vomiting with faintness) which can delay diagnosis [1]. The pain is the best sign suggestive of a hematoma.

In the second phase intraperitoneal rupture of SHL occurs which causes hemorrhagic shock associated with signs of cardiovascular collapse [2]. Physical examination noted a distended abdomen, painful as a whole [6]. In our case the delay in diagnosis of our patient caused rupture with hemoperitoneum.

**Diagnostic tests**

Clinical and hepatic lesions may precede all changes with the biological value of medical imaging as a diagnostic aid [5]. In an emergency setting, US examination has established itself as essential for the diagnosis [3]. It was difficult to perform for our patient due to the emergency related to the precarious state of the patients and the rapid installation of the clinical picture as was the case for many authors [2, 5]. Abdominal US is required first as suggested by El Youssoufi *et al.* [3] in cases of preeclampsia and/or HELLP syndrome. It can confirm the presence of an already suspected SHL or in case of associated intraperitoneal effusion [2]. US scans evoking a SHL may even precede the onset of clinical signs such as Strauss *et al.*, pointed out [6]. The liver scanner, allows better assessment of a liver injury, showing an oval hypodense image [6]. Mesenteric arteriography also objectifies arteriolar rupture and specifies the topography of the hepatic arterial vasculature to facilitate hemostatic action [6]. These two tests are not common in our practice. Moreover paraclinical explorations should not delay any therapeutic action in these patients.

**Treatment**

The management of SHL depends mainly on the integrity of the liver capsule and follows the rules of conventional liver surgery [1, 6]. Further resuscitation pre-,
per- and postoperative aims to correct high blood pressure, hypovolemia, circulatory collapse and possible alterations in coagulation [9]. Fetal extraction by cesarean section alone can stop the progression of liver damage in cases of preeclampsia and HELLP syndrome according to Langer et al. [1].

In case of integrity of the capsule (unbroken SHL), the authors agree on surgical abstention of the liver. Suffice it to medical treatment (blood transfusion) and an abdominal scan or US scan [7] to monitor the spontaneous regression of the hematoma [1]. Surgical treatment is indicated if there is rupture of the hematoma. Hemostasis is achieved by as conservative means as possible, namely by packing or tamponade hemostatic substances (biological glue, collagen compresses). Upon failure of conservative measures, the use of hepatic artery ligation or one of its branches has been described [1, 8]. Arterial embolization is a nonsurgical method that reduces mortality [6]. A liver transplant should be considered exceptionally because of the many problems, and our patient’s only indication remained acute liver failure after control of bleeding [2]. We opted for conservative treatment because of our limited therapeutic options.

Prognosis

The prognosis of SHL is poor for most authors [1-3]. Maternal mortality is heavy, from 50 to 75% and fetal mortality ranges from 60 to 80% [3]. In one series, El Youssoufi et al. reported five maternal deaths of eight cases and four fetal deaths [3]. In our case maternal death occurred due to vain intraoperative hemostasis attempts. The poor prognosis appears to be related to three key factors for some authors [5, 6]: 1) the delay between SHL and surgery, 2) extent, and 3) especially the characteristic of the ruptured hematoma. In our case these factors were associated. Wicke et al. [8] noted no deaths with unruptured SHL cases that did not undergo surgery. However, maternal mortality was extreme (three times) in unoperated cases when the hematoma was ruptured. In all cases when a cure is obtained, it is without sequelae. The obstetric future does not seem to be compromised and a new pregnancy can be carried out under supervision [2].

Conclusion

SHL is a very serious and rare complication of preeclampsia and HELLP syndrome. The maternal and fetal mortality are heavy. The diagnosis should be considered in any pregnant woman in labor or with right upper quadrant pain and/or epigastrium pain in relation to preeclampsia. Liver US is needed urgently. It should also be part of the monitoring of any severe preeclampsia. Only such an approach will minimize risks. What to do before a SHL depends mainly on the integrity of the liver capsule. Abstention surgery is recommended by most authors.

References


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Pheochromocytoma in ectopic pregnancy: A case report

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Summary
Objective: To study pregnancy characteristics in women with pheochromocytoma and to improve awareness of this comorbidity among obstetricians and gynecologists. Methods: The diagnosis and treatment of a case of ectopic pregnancy with pheochromocytoma is described. Results: The patient was diagnosed with a ruptured left Fallopian tube isthmus due to pregnancy, with comorbid left adrenal pheochromocytoma. Conclusion: Ectopic pregnancy with heavy bleeding and elevated blood pressure is indicative of pheochromocytoma. Measurement of the levels of urinary vanillylmandelic acid and urinary and serum catecholamines, as well as ultrasonography, can help diagnose this comorbidity.

Key words: Pheochromocytoma; Ectopic pregnancy; Case report

Introduction

Pheochromocytoma is a rare tumor originating from the medulla of the adrenal gland and extra-adrenal paraganglia. Pheochromocytoma cells secrete catecholamines and cause hypertension. The incidence of pregnancy with comorbid pheochromocytoma is 2-7 per 100,000 [1, 2]. Pheochromocytoma in pregnancy is very dangerous, posing a serious risk to the lives of both mother and fetus. The reported maternal and fetal mortality of patients with undiagnosed pheochromocytoma is higher than 50% [3]. However, pheochromocytoma in ectopic pregnancy is rarely reported. Therefore, in order to increase the awareness of this condition, we report a case of ectopic pregnancy with comorbid pheochromocytoma.

Case Report

A 24-year-old woman was admitted on December 16, 2010 because of lower abdominal pain of five hours duration after intercourse and menopause for 57 days. Her previous periods were regular, lasting about three days with cycles ranging from 37 to 40 days. After the last menstruation on October 19, 2010, she did not experience symptoms of early pregnancy such as nausea and vomiting. Her urine pregnancy test conducted on December 6, 2010 was positive. Five hours before admission, the patient had lower abdominal pain after sexual intercourse with an accompanying heavy feeling in the anus. Additional symptoms experienced by the patient included dizziness, palpitation, and cold sweating, but vaginal bleeding was absent. On physical examination, her temperature was 36.4°C, pulse was 124 beats/min, respiratory rate was 22/min, and blood pressure was 92/52 mmHg. The gynecological examination showed that the vulva was normally developed. The vagina was patent with a small amount of white secretion. The cervix was smooth and soft with lifting pain. The posterior fornix was plump and tender. The uterus was in the anterior position with normal size, normal uterine motility, and tenderness. The patient had right adnexal tenderness, but without palpable masses, and left adnexal tenderness and thickening. On December 16, 2010, ultrasonography showed a normal-sized uterus with a 103 x 60 mm mixed mass just above the uterus. There was a yolk sac-like echo inside the mass, and 55 mm of fluid in the pelvic cavity. A blood workup conducted immediately after admission found that the white blood cell count was 29.2 x 10^9/l, and hemoglobin was 106 g/l. The patient underwent laparoscopic left salpingectomy under general anesthesia. During the operation, a total of 2,000 ml free blood and blood clot was cleaned from the abdominopelvic cavity. The left Fallopian was thickened, and the isthmus had ruptured. Postoperative blood pressure was 130/90 mmHg, and heart rate was 124 beats/min. The patient was extubated with full consciousness. The patient had a sudden cough with moderate amount of pink frothy sputum 1.5 h after the operation. At this time, her blood oxygen saturation was 70%, blood pressure was 168/90 mmHg, and heart rate was 162 beats/min. After treatment, these values became 100%, 140/80 mmHg, and 130-140 beats/min, respectively. She was then transferred to the intensive care unit, where her renal insufficiency was corrected and a relatively stable cardiac function was maintained for a while. However, the patient’s condition subsequently deteriorated with QRS widening and ST-T variation in the electrocardiogram, significant abnormality of myocardial enzymes, heart wall motion abnormality detected by colored ultrasound images, and cardiogenic shock; the patient died after rescue. The cause of death was determined to be: (1) severe myocarditis, acute left ventricular failure, cardiogenic shock, and acute renal failure and (2) ruptured left Fallopian tube isthmus pregnancy. The autopsy result provided by the Forensic Identification Center of Sun Yat-sen University indicated that there was an 8.0 x 7.5 x 6.0 cm tumor on the left adrenal gland of the patient. Forensic pathological diagnosis (B6624) showed: (1) left adrenal pheochromocytoma, (2) post-resection of the left Fallopian tube, (3) suppurative tonsillitis, (4) congestion and edema of the brain and lung, and (5) congestion of the liver, spleen, kidney, pituitary, ovary, and uterus.

Discussion

Pheochromocytoma is a tumor of the catecholamine-producing chromaffin cells of the adrenal medulla and the extra-adrenal paraganglion system. It secretes large amounts of norepinephrine and epinephrine, prompting a significant increase in blood catecholamine levels. This causes severe systemic small vessel spasms and leads to a series of symptoms, including increased blood pressure, cardiac arrhythmia, and metabolic disorders [4]. The...
onset of the disease often occurs during pregnancy, delivery, or trauma operations and poses a high risk of death if not handled properly.

Various stress factors during pregnancy may exacerbate the disease. Patients may present with heart failure or cardiac arrhythmia because of an overloaded cardiovascular system, as well as cerebral ischemia, hypoxia, or cerebral vascular hemorrhage in the central nervous system. Most pregnant patients die during delivery or several days after delivery because of hypertensive crisis, severe cardiac arrhythmia, and heart failure. The placental tissue may be damaged by hypoperfusion, ischemia, and hypoxia, and in severe cases, even infarction, necrosis, and placental abruption. Pheochromocytoma may result in poor fetal growth, spontaneous abortion, fetal distress, or fetal death; the mortality rate is high for both the mother and fetus. During pregnancy, hypertension may occur as a sudden increase in blood pressure from normal level or as paroxysmal increases on the basis of persistent hypertension. Blood pressure fluctuations are related to sudden changes in posture and sudden increases of intra-abdominal pressure and do not respond to general anti-spasmodic and anti-hypertensive therapies. In this case, the patient had paroxysmal hypertension despite massive loss of blood and a heart rate higher than 120 beats/min. Therefore, the possibility of pheochromocytoma should have been considered in this case. As pregnancy does not change the catecholamine levels in blood and urine, elevated levels of blood and urine catecholamines, norepinephrine, epinephrine, and metanephrine can be indicative of pheochromocytoma. The catecholamine levels in fetal cord blood, however, will be normal despite the increased catecholamine levels in maternal blood [5]. This is a result of monoamine oxidase activity, which degrades catecholamines, in the placenta. B-ultrasound scanning and magnetic resonance imaging can also be used for the diagnosis of pheochromocytoma. These procedures are safe for the fetus, and the accuracy of B-ultrasound scanning can be as high as 89-97% [6, 7]. However, in the case of late pregnancy, the enlarged uterus can often affect the ultrasound scan. Radiological examination in early pregnancy can cause fetal malformations, mental retardation, and abortion and is generally considered undesirable. Examinations using radioactive nuclides like metaiodobenzylguanidine (MIBG) should also be performed carefully. MIBG has a small molecular size and can pass through the placental barrier, making it unsuitable for pregnant patients, unless the patient decides to terminate pregnancy because of suspected extra-adrenal tumors whose location is difficult to determine.

Pregnancy with pheochromocytoma can be easily misdiagnosed as severe gestational hypertension. In cases of pheochromocytoma, the onset of hypertension is accompanied by headache, palpitations, and hyperhidrosis, which are critical for the diagnosis of this disease. The following tips could help discriminate the two diseases: (1) most patients with pheochromocytoma present with a sudden onset of hypertension or a sudden increase in blood pressure on the basis of persistent hypertension, and the symptoms can occur before 20 weeks of pregnancy or even before pregnancy, but most patients with gestational hypertension sustain high blood pressure with fewer fluctuations and the symptoms often occur after 20 weeks of pregnancy; (2) in pheochromocytoma, hypertension is often accompanied with palpitations, hyperhidrosis, and headache, with rare and mild edema and proteinuria, whereas patients with gestational hypertension often present with severe edema and proteinuria, with less palpitations and hyperhidrosis; (3) after the application of magnesium sulfate or the termination of pregnancy, the symptoms of pheochromocytoma are often not relieved, whereas those of gestational hypertension are often relieved or disappear; and, (4) most patients with pheochromocytoma have increased catecholamine levels in the blood and urine and increased vanillylmandelic acid (VMA) levels in 24 h urine, and a lump or lumps could be detected by imaging examinations, whereas patients with gestational hypertension do not show these changes. The patient in this case did not have significant hypertension or other discomfort and as such, the clinicians did not consider the onset of pheochromocytoma. However, the massive loss of blood and paroxysmal hypertension still suggested the possibility of this disease.

In 90% of cases of pregnancy with pheochromocytoma, the tumors are benign. Patients should receive surgery to remove the tumor shortly after diagnosis and should not wait for natural delivery with long-term drug treatment. If a patient is in the first or second trimester, she usually does not have to terminate pregnancy. If she is in the third trimester, it is relatively safe to choose cesarean section. She can choose to remove the tumor during or a few weeks after the cesarean section. Preoperative use of α-adrenergic receptor antagonists improves maternal hemoconcentration, enhances tolerance to the rapidly changing pathological and physiological states before and after the operation and eases spasms of placental arteries and improves blood supply to the placenta. Therefore, α-adrenergic receptor antagonists are conducive to the healthy development of the fetus. During the medication process, clinicians should closely monitor changes in the patient’s blood pressure and heart rate and pay special attention to orthostatic hypotension. The use of α-adrenergic receptor antagonists can reduce fetal mortality from 50% to 30% and maternal mortality from 40% to 17% [1]. Although β-adrenergic receptor antagonists can quickly and effectively control symptoms such as hyperglycemia and rapid heartbeat, this type of drug can potentially retard intrauterine growth. Therefore, it should only be used in combination with α-adrenergic receptor antagonists and with close monitoring of fetal development [8, 9].

In this case, the patient received emergency surgery shortly after hospitalization due to this diagnosis and did not undergo relevant postoperative examinations. Therefore, the disease was not clearly diagnosed, and as a result, appropriate treatment was not provided. As there have been few reports
about ectopic pregnancy with pheochromocytoma, we report this case to suggest that massive blood loss in ectopic pregnancy with increased blood pressure may be an indicator of this disease. Examinations of VMA levels in urine, catecholamine levels in urine and blood, and B-ultrasound scanning should be used for diagnosing this disease. Once diagnosed, the patient should receive surgery and medication as soon as possible.

References

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Defect of methylenetetrahydrofolate reductase in a patient with ten habitual miscarriages: a case report

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Summary
This is a case report of a 47-year-old patient that came to our Clinic due to bleeding during the 23rd week of twin pregnancy after in vitro fertilization-intracervical insemination/embryo transfer (IVF-ICI/ET) treatment. Prior to this pregnancy, this patient had had ten spontaneous miscarriages, eight of which following IVF-ICI/ET, and two following spontaneous conception, all in the eighth week of pregnancy. After several miscarriages, the age of 43, the patient was suggested to be tested for thrombophilia; it was then discovered that she had the methylenetetrahydrofolate reductase (MTHFR) gene defect, in the homozygous Tobiano (TT) form. Thus she was treated with cardiolipin and folic acid before pregnancy, and continued with folic acid after the pregnancy had been diagnosed. Fraxiparine 0.4 ml subcutaneous (s.c.) should be introduced from the second month of pregnancy until one day before delivery. It is a useful treatment for the patients with MTHFR defect, as it prevents miscarriage and promotes successful pregnancy.

Key words: MTHFR defect; Recurrent miscarriage; Treatment.

Introduction
Interest in research of 5,10-MTHFR C677T polymorphism has been constantly increasing worldwide. The enzyme MTHFR has a central role in the folate cycle and metabolism of homocysteine. This enzyme is a catalyst of 5,10-MTHFR to 5-MTHFR, resulting in accumulation of active form of folate which is necessary for remethylation of homocysteine to methionine. It is 5,10-MTHFR that determines whether folate will be used for methylation or for nucleotide synthesis.

The 5,10-MTHFR gene is placed at the end of the short arm of chromosome 1 (1p 36.3) [1]. The C677T allele is characterized by a point mutation at the position 677 of the MTHFR gene, which alters cytosine into thymine. Three genotypes with changed bases have been described: homozygous CC-type, heterozygous CT-type, homozygous TT-type. This mutation of the MTHFR gene that determines whether folate will be used for methylation or for nucleotide synthesis.

Polymorphism of C677T is more frequent in homoyzgosis and heterozygosis, among subjects with spina bifida. This polymorphism is associated with spina bifida in 1.75% of TT-genotype, and in 1.16% of CT-genotype. In Italy, this polymorphism is much more frequent compared to other populations with dominating mutated TT homozygote in 15-25%. In C677T homozygote the risk of neural tube defect is 5.9% in women who have not been taking vitamin and folate supplements (both during periconceptional and pregnancy) and in 1.2% who have been taking supplements. Recommended daily dose of folate during pregnancy is 0.4 mg, while otherwise it is 0.2 mg. In MTHFR 677 TT genotype, average level of homocysteine is significantly higher than in MTHFR 677 CT and MTHFR 677 CC genotype [5]. Increased level of homocysteine and MTHFR 677 TT genotype was established in a research of Korean patients with unexplained recurrent spontaneous miscarriages [5].

Spontaneous miscarriage is defined as a spontaneous termination of two or more consecutive pregnancies before 20th week of pregnancy. In the majority of cases, it is extremely difficult to determine a causative factor, because up to 15-33% recurrent miscarriages are idiopathic. Efficient utero-placental circulation, which may be affected by hemostasis disorders, is necessary for successful outcome of pregnancy.

Maternal thrombophilias (factor V Leiden mutation, MTHFR defect, factor II mutation, protein C or S deficiency) are important disorders in obstetrics [6]. The exact mechanism between hyperhomocysteinemia and pregnancy loss is yet unknown. The studies demonstrated borderline increase of homozygous MTHFR defects in women with fetal loss and increase of relative risk for pregnancy loss in women with this defect. It is still unclear whether folate supplementation with folate decreases the risk of pregnancy loss [7-10].

MTHFR mutation is currently believed to be a risk fac-
tor for habitual miscarriage, although there are some differences in the available studies. The majority of studies imply that the incidence of homozygous form is more frequent in women with three or more repeated miscarriages, while few studies demonstrated no association between loss of fetus and MTHFR mutation [7-10].

The authors found a MTHFR defect in a patient with habitual miscarriage and decided to present it, since there are conflicting data in literature regarding the significance of MTHFR defects in repeated miscarriages.

Case Report

A 47-year-old patient came to our Clinic due to bleeding during the 23st week of gestation (ng) of a twin pregnancy after the result of IVF-ICI/ET treatment. Diagnosis at admission included:  ‘Grav ml V 1/2, St. post IVF-ICI/ET, Gravidita vetusta, Cervix, Ab. Inominus, MTHFR, St. post ab. habitabilis N X.

Status at admission included: cervix was 1.5 cm and there was trace of blood on the examination glove. The last period occurred on March 29, 2010, and the expected date of delivery was January 6, 2011. Complete lab tests were performed and all the results were within normal range, except for hemoglobin level which was decreased, so a treatment with iron and folic acid was introduced. Cervical and vaginal smears were normal, and urine and urine culture had no pathogens. The patient was also examined by a specialist for internal disorders (blood count, coagulation factors, biochemical analysis, electrocardiography, and chest examination) and a good general condition of this patient was confirmed.

Ultrasonic examination detected healthy, twin pregnancy, with sufficient quantity of amniotic fluid in both fetuses, eutrophic growth of both fetuses, and placenta placed on the posterior wall of uterus, with retro-placental hematoma with 19 mm in diameter. D-dimmer was 1.22 mg/L FEU, and CRP = 4.9 mg/L, leukocyte = 10.1, INR = 1.15.

The patient immediately underwent fociolitic intravenous (i.v.) and anticoagulant therapies with heparin, and hematologist prescribed 0.4 ml of Fraxiparine subcutaneously (s.c), once in 24 hours. The D-dimmer was checked at 7-14 days. The hematologist insisted that D-dimmer value should not exceed 2.5 mg/L, otherwise the patient had to be urgently referred back to a hematologist, considering the homozygous TT defect of MTHFR (677 TT).

Only tonsillectomy and appendectomy were referred. At the age of 15, she began her menstruation cycles that continued to be regular. The patient is allergic to Penicillin.

The patient suffered from primary sterility, although the test results of both partners were normal. After these results, an intrauterine insemination preceded by clomiphene stimulation was unsuccessfully performed at the age of 36. A year later another IVF attempt equally failed. Afterwards eight procedures were performed in the following four years, but despite positive results, miscarriages resulted each time. The patient then refused to continue with further treatments. At the age of 43 she consulted with a geneticist and was diagnosed with a 50% genetic mutation of MTHFR (disturbed folate metabolism), i.e. that she was a homozygote TT677 at the gene for MTHFR. The doctor proposed treatment with cardiolipin and folic acid. At the age of 45 and 46 years she got pregnant spontaneously, but the pregnancies were again interrupted at 8 ng by spontaneous miscarriage. Pathohistology showed the genetic error in chorion villi.

At the age of 46 she underwent the ninth attempt of IVF-ICI/ET and two embryos were transferred (two ET), both were accepted, and the pregnancy proceeded. Treatment with folic acid and fraxiparine (0.4 ml s.c at 24 hours) commenced from the second month of pregnancy, with regular monitoring of D-dimmer and INR at 7-14 day intervals. In consideration of her obstetric history, she was hospitalized at 23st ng due to bleeding. The aim was to maintain such a pregnancy as long as possible.

Results

Despite intensive treatment and monitoring, bleeding started at 26th ng and color Doppler imaging showed placentia previa marginalis. The patient was advised strict bed rest with intensive intravenous tocolysis with prolonged hospitalization. From this moment bleeding was alternate until the 29th ng when a strong abdominal pain occurred followed by abundant bleeding, and a cesarean section was urgently performed. The first fetus had placental abruption, while both fetuses had cephalic presentation; the first one was female, weighed 960 grammes (g), with an Apgar score (Ap score) of 4/5. The second fetus was male, weighed 1,050 g, with an Ap score of 6/7.

Both babies were urgently transported to the Institute for Neonatology in Belgrade. The female newborn death occurred during the transfer, notwithstanding two resuscitation attempts. The male fetus survived, and is alive and healthy at the moment (weight 2,500 g).

Discussion

Approximately 15% of pregnancies end in miscarriage, while 0.5-1% couples have recurrent miscarriages. Habitual abortion is defined as a spontaneous miscarriage of two or more consecutive pregnancies, before the 20th week of pregnancy [11].

Causes of habitual abortion in most cases remain unknown. As described by the authors, all miscarriages occurred during the first trimester. The histopathological findings indicated a problem in the development of chorion villi. It is well known that MTHFR is an important enzyme in folate metabolism. MTHFR gene mutation causes a reduction in activity of this enzyme, resulting in increased plasma levels of homocysteine, which is a risk factor for the occurrence of thrombosis. Expressed MTHFR defects with hyperhomocysteinemia and homocysteinuria may result in peripheral neuropathy, mental retardation, thrombosis, and heart attack. Mild MTHFR defects are more prevalent in the general population, and represent a risk for disorders of the arteries.Nelen et al., reported that MTHFR C677T mutation increased plasma homocysteine level, resulting in two- and three-fold increase of recurrent spontaneous miscarriages [12]. The studies indicated a substantial increase of plasma homocysteine in patients with MTHFR C677T homozygote TT type, which was significantly associated with miscarriages, as was the case in the patient presented in this case report (she had had ten consecutive abortions). Data
regarding the association of MTHFR genetic mutation and the recurrent spontaneous miscarriages are still controversial.

Some researchers consider that MTHFR genetic mutation represents a risk factor for idiopathic spontaneous miscarriages. Other researchers demonstrated high influence of homozygous type in recurrent miscarriages (as it was the case with the presented patient), while others did not recognize the connection between MTHFR mutation and fetal loss. Feyzi et al., claim that even heterozygous MTHFR defects might result in spontaneous miscarriage, whether alone or in combination with other factors [13]. In the present case, the patient had homozygous MTHFR defect, TT type, and since both she and her husband were perfectly healthy, ten consecutive abortions might be attributed to MTHFR defect. Treatment with cardiolipin, folic acid, and fraxiparine assisted the patient to carry the pregnancy until 29th week, at which she had to deliver by cesarean section, due to placenta abruption.

Conclusion

In healthy patients, who are not diagnosed with any acute, chronic, or systemic disorder, and who have recurrent idiopathic abortions, it is necessary to test MTHFR gene defect. If they test positive for the defect, treatment should include cardiolipin and folic acid before pregnancy, and continued with folic acid after the pregnancy has been diagnosed. Fraxiparine 0.4 ml s.c. should be introduced from the second month of pregnancy until one day before delivery.

This current case report presents a useful treatment for the patients with MTHFR defect, as it prevents miscarriage and promotes successful pregnancy.

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Endometrial osseous metaplasia and infertility: a case report

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Summary
Endometrial osseous metaplasia is a rare clinical entity. It causes infertility and occurs in more than 80% of cases after an abortion. Various theories have been proposed and the most accepted theory is metaplasia of the stromal cells into osteoblastic cells that produce bone. This disease may be misdiagnosed. However once diagnosed, the complete removal of bone spicules by hysteroscopy allows, in most cases, fertility to be restored. We present the case of a 36-year-old patient nulliparous with a history of abortion for eight years who consulted May 5, 2008 to become pregnant. Detailed examination showed chronic endometritis with bone metaplasia as a possible cause of her infertility. Seven months after complete removal of bone fragments by hysteroscopy, the patient had a spontaneous pregnancy with normal development. She gave birth to a male infant weighing 3,000 g with an Apgar score of 9 at 1 and 5 min. Delivery and postpartum were normal.

Key words: Bone metaplasia; Endometrium; Infertility; Hysteroscopy.

Introduction
Endometrial osseous metaplasia, a rare but not exceptional disease, is characterized by the presence of bone tissue in the endometrium. It is often diagnosed in women with secondary infertility [1, 2] and more than 80% of reported cases occur after an abortion [2-4]. However, there is controversy as to the etiology and pathogenesis of this disease [3] despite the many reports in the literature. We report the first documented case in the Ivory Coast.

Case Report
The patient, 36-year-old, consulted on 05/05/2008 with secondary infertility and the desire to become pregnant. Her gynecological history revealed menarche at age 13 year, a regular cycle 25-28 days, primary dysmenorrhea, and a period of menstruation of five days. An abortion in 2000 at 13 weeks of gestation occurred with a normal evolution. Physical examination and laboratory tests were unremarkable. Analysis of the husband’s semen was normal. Transvaginal ultrasonography revealed a linear hyperechogenic area in the uterine cavity measuring 13 mm (Figure 1). This image persisted over several ultrasound (US) images. Hysterosalpingography displayed an incomplete cervicoisthmic picture due to uterine synechia with bilateral tubal patency maintained. The patient was subjected to diagnostic hysteroscopy. Hysteroscopy was done and revealed an irregular structure at the uterine isthmus with a few spikes that looked whitish and hard after ablation. Histological analysis of parts removed from the uterus showed some fragments of endometrial and osteoid tissue with a small inflammatory lymphoplasmocytic infiltrate due to chronic endometritis with bone metaplasia (Figure 2). A month later, control US and hysteroscopy were normal. Six months later after this control, the patient became pregnant with a normal evolution and delivery by natural means resulting in the birth of a male infant weighing 3000 g with an Apgar score of 9 at 1 and 5 min. The postpartum period was normal.

Discussion
Frequency
Ossification of the endometrium is a rare clinical entity. Although its impact is not fully known, it has been estimated that it represents 0.15% of the cases referred for diagnostic hysteroscopy [3]. The incidence is much lower according to Makris et al. [5]. Despite the many reports in the literature by about 80 medical teams [6, 7], the etiopathogenesis of this disease remains controversial [3].

Etiopathogenesis
In patients with a history of endometrial ossification, over 80% of cases occur after an abortion (our observation), spontaneous or therapeutic [1-3, 6, 7], suggesting the responsibility of embryonic or fetal fragments in osteogenesis. This may be pure fetal skeletal retention [7] which is possible when the abortion is incomplete and the age of the pregnancy is greater than three months of gestation [2, 7, 8]. Nevertheless, a study in the literature shows that most documented cases involve pregnancy less than three months (also our observation). Therefore it appears unlikely that endometrial ossification is of fetal origin, especially as the histological study of biopsies never revealed fetal tissue (our observation, Figure 2) [6]. Some authors described individualized bone structures in the embryo at six weeks of gestation, but those bones did not show the usual appearance of endometrial ossification which is almost always laminar [7]. Others think that fetal...
bone fragments could be reabsorbed and secondarily induce alternative osteogenesis [9]. Finally for some, embryonic cells to osteoblastic potential could be due to curettage in the deep layer unregulated by the endometrium [10, 11]. However these embryo-fetal theories do not allow the explanation of endometrial bone formation in the absence of curettage after spontaneous miscarriage among nulligravida women, or in the postpartum period [7].

Some metabolic disorders have been associated with bone metaplasia, such as hypercalcemia, hypervitaminosis D, hyperphosphatemia and hyperthyroidism [12] without any clear correlation. In the same sense, prolonged estrogenic stimulation of the endometrium has also been questioned [13]. In the largest series [3, 7], none of these factors were associated with bone metaplasia of the uterus, suggesting that the contributions of these pathogenic mechanisms are not effective [14].

Chronic endometritis, chronic endocervicitis, and traumatic injuries have been implicated in the proliferation of mesenchymal cells which are known to have metaplastic power [10, 15]. It has been suggested that chronic post-abortion endometritis may promote superoxide radicals and tumor necrosis factors from the inflammatory cells. The long-term exposure of superoxide radicals and tumor necrosis factor on multipotent stromal cells would lead to the differentiation of endometrium and could change endometrial stromal cell metaplasia into osteoblastic cells [4, 16].

Already in 2009, the study of Cayuela et al. [17] proved the maternal origin of endometrial ossification after a comparative analysis of DNA from the bone and endometrium of the mother. Also another study analyzing the DNA of endometrial bones showed 14 samples (although all patients had a history of abortion); eight cases in which maternal origin of endometrial ossification was proven (95% confidence interval 63-100%, level of evidence III) and six cases in which the origin remained unclear [3]. Thus the maternal origin of endometrial ossification appeared highly likely or almost certain from these two studies.

**Diagnosis**

The only pathognomonic sign of endometrial ossification is the spontaneous expulsion of small bone fragments, which is in fact an exceptional event [7]. Other signs mentioned in the literature are nonspecific and may be associated with other alterations of the endometrium (endometritis and synechiae): bleeding or hypoamenorrhea, pelvic pain, menstrual irregularities, and dyspareunia, vaginal discharge [7, 14, 18]. The most common complaint was menorrhagia (50%), followed by infertility (43%), in the series of Parente et al. [3]. In general, the time between abortion and discovery of the disease varies between eight weeks and 14 years [4], and up to 40 years [3] (eight years in our observation). In practice, the clinical expression of endometrial ossification is generally poor; the desire for pregnancy is the main reason for consultation, as in our case [1-20]. Indeed, in addition to endometrial abnormalities that lead to bone fragments, endometrial ossification acts as a real intrauterine contraceptive device with inflammation preventing any nesting [4, 7, 19], which is why infertility occurs more frequently.

US examination plays a primary role in the diagnosis. Endometrial ossification appears at US as a hyperechogenic image which is often linear (Figure 1) mimicking an intrauterine device or calcifications which constitute the
main differential diagnosis. Hysterosalpingography can view the bone fragments as subtraction images and synechiae (as in our case) or intracavitary fibroids can be suspected. Diagnostic hysteroscopy visualizes bone fragments, takes stock of intracavitary lesions and allows for biopsies. Pathological examination of biopsies will show fragments of endometrial tissue and osseous metaplasia in the stroma (Figure 2) [2].

Treatment

Conventional curettage has been abandoned because of its blind and traumatic character to the uterine mucosa. The removal of bone fragments in the clamp under hysteroscopic control seems much better. Recent studies recommend hysteroscopic removal of the bone under US guidance which helps proper visualization and complete removal of the bony spicules that may be embedded in the myometrium [4, 17, 20]. Antibiotic treatment and anti-inflammatories are required. Sequential estrogen-progesterin treatment is often recommended for the following cycle after curettage. The complete removal of bone spicules of the uterine cavity can restore, in the majority of cases, fertility and spontaneous conception as in our observation [1, 4, 6, 18].

Conclusion

Endometrial ossification is a rare disease whose etiopathogenesis remains unclear, but the maternal origin of the ossification is currently the most accepted. It may be the cause of infertility, but once diagnosed, the complete elimination of bone fragments of the uterine cavity by hysteroscopy allows fertility to be restored in the majority of cases.

References


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Primary umbilical endometriosis:
case report and literature review

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Introduction
Endometriosis is defined as the presence of endometrial tissue, stroma and glands outside the uterine cavity. Common sites of endometriosis are the ovaries, fallopian tube, uterine ligament, pelvic wall, intestine and bladder.

Primary endometriosis of extra pelvic sites is unusual. Endometriosis of the umbilicus [1] and umbilical hernia sac is rare [2], especially if there is no history of abdominal, pelvic surgery or known preexisting endometriosis in other sites. The estimated incidence of umbilical endometriosis is 0.5-1% [3, 4].

Secondary endometriosis, (scar endometriosis) can develop after an umbilical hernia repair [5], an inguinal hernia repair [6] and laparoscopy performed through the umbilicus [7] or abdomen [8].

Cutaneous endometriosis could be an indicator of pre-existing abdominal endometriosis without any previous manifestation [9].

Case report
We present a case of a 26-year-old nulliparous patient without any previous history of abdominal or pelvic surgery. Over the past few years she had dysmenorrhea and was seen by a gynecologist. After an abdominal ultra-sound a cyst of 4.6 x 3.9 cm was found in one of the ovaries and a hemorrhagic corpus luteum cyst was suspected as a diagnosis. The gynecologists prescribed an anti-inflammatory drug, lornoxican, and followed her up over time. The cyst was progressively decreasing in size and finally regressed but the dysmenorrhea remained.

During the past year the patient complained of umbilical pain and noticed a dark purplish nodule on the umbilicus with size changes – growth alternating with decreased size continuously over time.

No bloody secretions were observed.

The patient visited a dermatologist whose diagnosis was inflammation of the umbilicus. A local antibiotic cream was given with no result. After that she visited a surgeon who diagnosed an umbilical hernia and an operation was planned. Upon medical history a correlation was made between the painful nodule and menstrual cycle.

The patient realized that the enlargement together with the pain on the umbilicus was cyclic and was happening only a few days per month.

The operation for the umbilical hernia was performed and the specimen was sent for histopathological evaluation with the indication “umbilical nodule”.

Summary
We present a case of primary endometriosis of the umbilicus in a young nulliparous patient without any previous history of abdominal or pelvic surgery. Primary endometriosis of extra pelvic sites is unusual while umbilical endometriosis is quite rare. Diagnosis of endometriosis is difficult to obtain and sometimes diagnoses can be false-positive or false-negative. Some imaging procedures can be done to rule out other disorders but it is difficult to differentiate them from endometriosis. A definite diagnosis can only be established by histopathological examination. Hematoxylin and eosin (H&E) is the staining of choice. Conservative surgical excision of the lesion and drugs such as oral contraceptives and gonadotropin releasing analogues are the first-line treatment.

Key words: Endometriosis; Umbilical endometriosis; Umbilical inflammation; Hematoxylin and eosin (H&E) staining; CD10 staining; Vimentin staining.

Figure 1. — Hematoxylin and eosin (H&E) staining of endometriotic tissue.
The specimen consisted of an ellipse of skin measuring 1.3 x 1 cm with underlying soft tissues that contained a circumscribed nodule 1 cm in diameter. It was routinely processed in paraffin and was stained by hematoxylin and eosin (H&E) staining (Figure 1).

Microscopically, there was a typical area of endometriosis consisting of endometrial-type glands and stroma. Additional immunohistological stains for vimentin (Figure 2) and CD10 (Figure 3) were performed to support the histological finding of endometriosis.

Discussion

Primary endometriosis of the umbilical hernia sac is rare, especially if no previous abdominal or pelvic surgery has been performed, and only a few cases have been reported over the last decade [10-12].

The pathogenesis of extra pelvic primary endometriosis can be explained by the “retrograde theory”, according to which endometrial tissue can spread through the fallopian tube during menstruation. Retrograde menstruation occurs normally in healthy women but only a very small percent develop primary endometriosis [13].

In contrast to normal endometrial tissue, endometriotic tissue differentiates in the fact that it can produce estrogens by itself through the aromatase cycle [14] in vitro.

Genetic [15, 16], hormonal [17] and autoimmune factors [18] also play an important role in the pathogenesis of endometriosis.

According to the American Society for Reproductive Medicine, endometriosis may be classified based on the number, location and depth of endometriotic tissue and the presence of adherence in four stages [Stage I (minimal), Stage II (mild), Stage III (moderate), Stage IV (severe)].

Imaging procedures such as ultrasonography, computed tomography and magnetic resonance imaging are done to rule out other disorders. Sometimes they are useful for determining the location and the size of endometriosis but cannot differentiate endometriosis from soft tissue tumors [19]. On the other hand they can be useful in monitoring the disorder after it is diagnosed.

Histological examination is the only exam for a certain diagnosis. The diagnosis is usually straight forward with H&E stains, but false-negative results can be produced.

In a few cases immunocytochemistry stains, such as vimentin and CD10, are used to confirm the presence of endometrial type stroma around endometrial type glands [20].

The treatment of choice is conservative surgical excision of the lesion, with sufficient healthy margins to prevent recurrence, and drugs.

Drugs such as oral contraceptives and gonadotropin releasing hormone analogues inhibit the growth and activity of endometriotic tissue by suppressing ovarian function. However endometriosis recurs if the patient stops the drugs.

In conclusion, primary endometriosis is a rare entity and diagnosis can be difficult.

References


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