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CLINICAL AND EXPERIMENTAL OBSTETRICS AND GYNECOLOGY (ISSN 0390-6663) publishes original work, preferably brief reports, in the fields of Gynecology, Obstetrics, Fetal Medicine, Gynecological Endocrinology and related subjects. (Fertility and Sterility, Menopause, Uro-gynecology, Ultrasound in Obstetrics and Gynecology, Sexually Transmitted Diseases, Reproductive Biological Section). The Journal is covered by INDEX MEDICUS, MEDLINE, EMBASE/Excerpta Medica.

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Successful treatment of a female with chronic pseudo-intestinal obstruction with sympathomimetic amines and thyroid hormone replacement
J.H. Check, R. Cohen - Camden, NJ (USA)

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Book Review
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A practical approach to the prevention of miscarriage: part 3 – passive immunotherapy

J.H. Check
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 evaluate the efficacy of passive immunotherapy in preventing miscarriage. Methods: Studies both pro and con concerning intravenous immunoglobulin therapy (IVIG) in preventing miscarriage were evaluated. A new therapy of IV intralipid infusion is also reviewed. Results: Intravenous immunoglobulin therapy may be effective but it is necessary to use it prior to conception and monthly thereafter. Some brands are more potent than others. The data concerning intralipid IV infusion involves only small case series but the results from one study were encouraging though we could not personally substantiate these findings. Conclusions: Intravenous immunoglobulin therapy is very expensive. In the author’s opinion there are no immunological studies that can determine if a woman needs immune suppression. The best way to decide is the history – the more miscarriages without any other identifiable cause the more likely passive immunotherapy may be helpful. If intralipid proves as efficacious as IVIG it will be a lot less expensive.

Key words: Intravenous immunoglobulin; Intralipid infusion; Recurrent pregnancy loss; Natural killer cells.

Passive immunotherapy with intravenous immunoglobulins

We take the Hippocratic oath to do no harm. Though intravenous immunoglobulin (IVIG) because of sterilization procedures is generally considered safe from an infectious standpoint its biggest downfall is its expense. It is expensive to use on a one-time basis and for optimal success the recommendation is to use it every month. Even more “financially” harmful is that it should be used prior to conception for maximum effectiveness and thus IVIG could be wasted for three to eight months before conception occurs assuming that it even has benefit in preventing another miscarriage [1-5].

The theoretical mechanism by which IVIG may prevent miscarriage includes decreasing the killing activity of natural killer (NK) cells [6]. As mentioned in the editorial on active immunotherapy with lymphocytes, the beneficial effect of IVIG in this regard may be from the leakage of CD 200 molecules from lymphocytes. These particles may be responsible for the induction of progesterone receptors on gamma/delta T cells which allows the expression of a 34 kDA protein, the progesterone induced blocking factor (PIBF), which is ultimately responsible for suppression of NK cell activity [7, 8]. The use of IVIG may also prevent miscarriage by increasing the activity of suppressor T cells [6]. Thus if in some cases the problem is more related to increased T cell activity, IVIG could help in this manner.

Thus lymphocyte immunotherapy, as discussed in the first part of “A practical approach to the prevention of miscarriage: Part 2 – active immunotherapy”, is believed to mainly inhibit NK cell mediated fetal damage. However, if the problem is related to activated T cell attack through depressed activity of suppressor T cells, or an increase in thymic helper (TH)-1 cytokines, IVIG may be more effective than lymphocyte immunotherapy. My own bias is that more often the problem is related to NK cell attack and frequently all one needs to do is add extra progesterone [8].

For those women where the use of extra progesterone still allows the miscarriage of a chromosomally normal fetus, I would next try active immunotherapy with lymphocyte immunotherapy instead of IVIG because the mechanism may involve specific localized suppression of NK cell activity at the maternal-fetal interface. In contrast, passive IVIG may cause more of a generalized NK cell suppression rather than local. Nevertheless, if the mechanism in suppressing NK cells does involve the high concentration of CD 200 molecules, then it is possible that it may exert a generalized decrease in cytotoxic T cell activity but work in a similar manner as lymphocyte immunotherapy when it comes to suppressing NK cell activity. The possibility exists that if the IVIG contains these CD200 molecules it could act as an active immunotherapy agent with possible induction of progesterone receptors on gamma/delta T cells to allow better expression of PIBF when there is exposure to adequate progesterone. Thus I believe that studies involving the efficacy of either lymphocyte immunotherapy or IVIG in preventing miscarriage should be performed in the setting of extra progesterone support.
To my knowledge there are no randomized studies comparing the efficacy of lymphocyte immunotherapy to IVIG in preventing miscarriage or increasing IVF success. However, since in my opinion there are no tests at present that can tell who needs immune therapy, or when cytotoxic T cell rather than NK cell suppression will be needed, my preferences would be to use lymphocyte immunotherapy because it is so much less expensive than IVIG therapy. My preference would be to first treat a woman with a history of first trimester miscarriages that were either known to be chromosomally normal or unknown if aneuploidy existed with progesterone in the luteal phase and during the first trimester. If another loss occurred, and if the fetus showed aneuploidy, I would treat again with just progesterone. If the karyotype was normal or not able to be determined I would add lymphocyte immunotherapy to the progesterone therapy. If despite this duo treatment another spontaneous abortion occurred with a normal karyotype I might then consider IVIG. Of course, the possibility of uterine structural abnormalities and coagulation disorders should also be excluded.

Just because IVIG has theoretical benefits to account for hypotheses of possible immunological imbalances that may lead to fetal rejection does not prove its effectiveness. Even worse than using a very expensive therapy when cheaper options may exist (e.g., progesterone therapy) is an expensive therapy that has no benefit at all. Indeed a recent Cochrane Database Systematic Review did not find that the use of IVIG improved pregnancy outcome in women with a history of recurrent pregnancy loss [9].

One should use caution concerning the conclusions from the aforementioned Cochrane meta-analysis however as there are some flaws in the design of this meta-analysis that could have led to an erroneous inclusion [9]. The most important flaw was not limiting the selection of studies included in the review to women with recurrent pregnancy loss who began IVIG prior to conception rather than after pregnancy was confirmed [9]. In fact in six studies not showing any benefit in preventing another miscarriage in women with recurrent pregnancy loss only the study by Stephenson et al. gave IVIG before conception [5, 10-14]. In contrast four of five studies using IVIG preconception found this therapy beneficial [1-5].

Another confounding variable may be the brand of IVIG. Clark et al. pointed out that some brands are as much as eight times more potent than others [15]. Interestingly the majority of the negative studies used the less potent brand [15].

I have used IVIG in my practice but because of its expense I could not perform a randomized study or even have enough cases to warrant a matched controlled study. What I can contribute are anecdotes. The most convincing anecdotal case that I treated was one patient who had 12 consecutive losses and had progesterone therapy in her last three. With IVIG she delivered twins successfully in the next pregnancy and delivered twins successfully again with IVIG in her following pregnancy.

Intravenous immunoglobulin also suppresses B-cell production of autoantibody and has been used in women with a history of miscarriages possibly relating to antiphospholipid antibodies [16]. This will be discussed further in a subsequent editorial on coagulation defects and miscarriage.

A possible much less expensive passive immunotherapy treatment for prevention of miscarriage has been proposed and that is the infusion of intralipid [17-20]. Data were published showing suppression of abnormal NK cell activity in peripheral NK cells from women with recurrent miscarriages [21, 22]. There are various hypotheses of how intralipid works but the exact mechanism is not known. A recent study was presented at the 2008 Pacific Coast Reproductive Society by Acacio et al. There were 11 women with recurrent pregnancy loss treated by an infusion of 2-4 ml of 20% intralipid solution and ten of these 11 (91%) had a successful pregnancy [23].

These data are encouraging but the numbers are small and uncontrolled. We have tried 4 ml of intralipid infusion for women with a predisposition to miscarriage. Unfortunately, we could not confirm the benefit of intralipid in a matched controlled study. These data were presented at the 2009 American Society for Reproductive Medicine (ASRM) Meeting in Atlanta, Georgia, USA. Possibly women ≤ age 35 could benefit. At the 2009 ASRM meeting a properly performed multicenter study failed to find benefit for IVIG for recurrent miscarriage.

References


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Advantages of using a lower vs higher dosage of gonadotropins for follicular maturation including cycles of in vitro fertilization-embryo transfer

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Summary

Purpose: To demonstrate the benefits of using lower dosage FSH stimulation for follicular maturation in in vitro fertilization (IVF) cycles and in non-IVF cycles. Methods: Several studies are evaluated in which either high or lower dosage gonadotropins were used in IVF and non-IVF cycles. The patient population were women either with diminished or normal ovarian egg reserve. Results: Very poor pregnancy rates were found with high dosage gonadotropins when there was diminished egg reserve. In contrast pregnancy results per transfer were comparable to women with normal egg reserve when low dose gonadotropin regimens were used. Conclusions: Low dose gonadotropin regimens have the benefit of reducing costs and risks of ovarian hyperstimulation without reducing efficacy and in some cases actually increasing pregnancy rates.

Key words: Minimal stimulation; FSH; Ovarian reserve; Controlled ovarian hyperstimulation.

Introduction

As a woman ages there becomes a paucity of ovarian follicles [1]. It is well known that women aged 45 and over have markedly reduced fecundity approaching zero [2]. Thus even if women aged 45 or older are clearly ovulatory their egg quality is so poor that even achieving a pregnancy is quite rare, i.e., it is not easy to conceive but even then there is a high rate of miscarriage related to chromosome abnormalities [1].

There is evidence that one of the main reasons why the eggs from women of an older reproductive age do not result in pregnancies is related to a natural selection process where the better eggs are recruited at a younger age leaving eggs for the reproductively older women that have markedly lower quality oocytes [3]. One theory is that a mitochondrial factor that allows follicles to progress to antral stage is also responsible for inhibition of apoptosis of the cells in a given embryo beyond blastocyst stage [3]. Thus the remaining eggs in a woman of advanced reproductive age have less of this apoptosis inhibiting factor because if there had been more of this factor present it would not have taken so many years for these follicles to advance to the antral stage.

When women are of advanced reproductive age they have diminished egg reserve and thus diminished number of antral follicles leading to diminished secretion of inhibin B which allows higher levels of day 3 serum FSH. Therefore if younger women have an increased day 3 serum FSH level frequently one makes the assumption that the ovarian state is similar to women of more advanced reproductive age, i.e., decreased number of follicles and it is also assumed that the eggs have poor quality.

Support for this concept was provided by publications in the late 1980s from some of the top in vitro fertilization (IVF) centers of the world demonstrating low numbers of eggs retrieved and very poor pregnancy rates following embryo transfer (ET) in women with increased day 3 serum FSH levels [4-7]. There has been much improvement in pregnancy prognosis following IVF-ET in the modern IVF era related in part to improved embryo culture media and transfer techniques. However even in the modern era some of the world’s finest IVF centers report extremely poor results [8, 9]. In fact one of these IVF centers reported no live pregnancies following the transfer of the usual number of embryos with good morphology in women with diminished egg reserve [9]. Not only did all these reports use traditional controlled ovarian hyperstimulation, but they even used higher dosages of exogenous FSH to try to develop more dominant follicles [4-9].

Reports from multiple IVF centers around the world (including our own IVF center) to national and international reporting agencies all claim extremely rare successful pregnancies in women age ≥ 45 even those with normal FSH levels. Thus the very poor pregnancy rates reported by these world renowned IVF centers using traditional or even higher dosage controlled ovarian hyperstimulation (COH) regimens would certainly seem to support the concept that younger women with diminished egg reserve have an acceleration of the normal atresia process leaving them with only poor quality oocytes.
However, if this is true it is difficult to explain how a group of women with hypergonadotropic amenorrhea and estrogen deficiency for a minimum of one year achieved a pregnancy rate of 28% (19/68) in those who ovulated and a live rate of 11.7% per ovulation cycle without any assisted reproductive procedure (ART) using a technique of gonadotropin suppression with ethinyl estradiol with low dose gonadotropin therapy in some but not all cases [10]. The concept that these eggs from women with diminished egg reserve are of poor quality was also brought into the question by a study of eustrogenic women age ≤ 39 with a mean serum FSH of 18.9 mIU/ml who without ART achieved a clinical and ongoing six-month pregnancy rate of 46.1% and 34.6%, respectively [11]. Successful pregnancies have not only been achieved without ART in menstruating women with serum FSH levels > 100 mIU/ml [12], but successful pregnancies have been achieved in a woman in apparent menopause with serum FSH levels of 164 mIU/ml [13], and even women in apparent menopause with ovaries appearing as streaked gonads [14, 15]. A successful pregnancy was even achieved by merely lowering the elevated FSH and restoring sensitivity to endogenous FSH in a 40-year-old woman in apparent menopause with several years of amenorrhea and estrogen deficiency with a documented serum FSH of 124 mIU/ml (but a claimed level of 180 mIU/ml) who failed to conceive despite four previous transfers of fresh embryos derived from donor oocytes [16].

One theoretical explanation of how could pregnancies be achieved naturally at reasonable rates in younger women up to age 42 with diminished egg reserve [10-16] but yet not with IVF-ET [4-9] could be that embryos derived from a diminished egg reserve for some reason cannot do without some factor provided to them by traversing the fallopian tubes. However, successful pregnancies have been recorded in women in apparent menopause with tubal factor who did achieve a pregnancy through inducing ovulation by restoring sensitivity of some of the few remaining follicles with lowering of the elevated serum FSH levels [17, 18]. One woman required a low dose of gonadotropins [17] but the other one was completely natural, i.e., without any stimulation with exogenous gonadotropins [18]. Furthermore, one woman with an elevated day 3 serum FSH who needed IVF because of male factor and was still menstruating achieved three live deliveries out of four IVF-ET cycles over an 8-year time span [19].

Even in the old era of IVF when pregnancy rates were not nearly as high as in the modern IVF era a 15% (6 of 40) pregnancy rate per cycle was recorded for women with serum FSH levels > 18 mIU/ml [20]. In the early part of the improved IVF era from 1997 to 1999 a report showed for women aged ≤ 38 with a day 3 serum FSH > 12 mIU/ml a clinical pregnancy rate of 28.6% (4/14) and an ongoing pregnancy rate past the first trimester of 21.4% per transfer [21]. These results were compared to 156 women of the same age group and with serum FSH ≤ 12 mIU/ml and the pregnancy rate was 32.0% (50/156) per cycle and an ongoing pregnancy rate of 27.6% [21].

Recently a study evaluated women who had a markedly decreased egg reserve [22]. The actual purpose of the study was to determine the relative effect of blastomere number and fragmentation indices of day 3 embryos on pregnancy and implantation rates. Thus the study consisted of women who had only one embryo to transfer and thus de-selection was eliminated [22]. Women with embryos with at least six blastomeres (which represented 65% of the transfers) had a clinical pregnancy rate per transfer of approximately 40% with a 3.8% and 9.5% pregnancy rate, respectively, for 4- and 5-cell embryos [22]. The live delivery rate with single embryo transfer of a 6-8 cell embryo on day 3 was 31.7% [22].

The study group mentioned above used as study subjects women with far less egg reserve than the recent study by Roberts et al., in which only those with reasonable response as far as number of mature follicles despite the high serum FSH were included [9, 22]. Many controlled ovarian hyperstimulation regimens for women with normal egg reserve began on day 2 or 3 with at least 225 mIU/ml FSH and frequently 300 mIU/ml. Most IVF centers when attempting to stimulate a woman with diminished egg reserve will increase the starting dosage of FSH hoping to get more follicles. Women with the least egg reserve will usually fail to respond to high dosage gonadotropins and their cycles are cancelled. Thus the reports are generally only in those women with greater egg reserve who demonstrate a response sufficient to obtain possibly a minimum of five oocytes [4-9].

The principal of trying to establish ovulation in a woman in apparent menopause is based on the assumption that there are antral follicles still present but that they have acquired a resistance to exogenous and endogenous gonadotropins because the chronically high level of serum FSH causes down regulation of the FSH receptor. The theory continues that lowering the serum FSH by exogenous estrogen can allow restoration of these down-regulated FSH receptors leading to the development of a dominant follicle by stimulation with endogenous and/or exogenous gonadotropin [13-19].

It could be argued that maybe estrogen directly improves the sensitivity of the follicles to FSH without the need to suppress endogenous FSH. However, against this theory is the fact that ovulation induction in hypergonadotropic amenorrhea can also be achieved by lowering the elevated serum FSH with either gonadotropin releasing hormone (GnRH) agonists or antagonists [10, 23, 24].

If this theory is correct then it would seem possible that by using a high dosage of exogenous FSH with its slow clearance or using clomiphene citrate which would cause an exaggerated rise in endogenous FSH that a paradoxical effect with a lower number of follicles stimulated may be found because the elevated serum FSH could down-regulate FSH receptors in granulosa theca cells. In fact, it has been shown that by causing an exaggerated rise in endogenous FSH by clomiphene citrate in a woman with diminished ovarian reserve a reversible iatrogenic menopausal state could occur [25].
Gonadotropins are expensive. Not only did our center adopt a policy to lower the dosage of gonadotropins to prevent the occasional paradoxical negative response, but the dosage was reduced to save the couple money since experience showed no better response with higher dosages of gonadotropins. The general philosophy was to allow the elevated endogenous gonadotropins to drive follicular maturation and possibly add a small dosage of exogenous FSH once the FSH has been suppressed into the normal range by the rising endogenous estradiol. In cases where the FSH remains elevated no exogenous FSH is given as long as the follicle(s) is (are) progressing. If the serum FSH remains elevated and there is failure of the serum estradiol to rise then ethinyl estradiol (20 μg per day) is started to lower the elevated FSH and hopefully restore sensitivity of follicles. How soon the serum FSH and estradiol is repeated is dependent on whether any antral follicles are seen on ultrasound (US). Thus repeat US could be performed in a few days if an antral follicle was found or possibly not for a couple of weeks if none were seen.

In women with less severity of their degree of diminished oocyte reserve a low dosage of FSH (75-150 IU) may be started as early as day 5-7 to try to attain multiple dominant follicles. Similar to high-dosage protocols a GnRH antagonist could be added when a follicle of about 14 mm is attained. Usually an additional 75 IU of FSH is added when the GnRH antagonist is started. Generally the highest dosage of FSH used on a daily basis is 225 IU, usually when the GnRH antagonist is added.

The low-dose gonadotropin stimulation protocols have been divided into three types: natural (usually for the least egg reserve cases) where no gonadotropins are used, natural with a boost of exogenous FSH where FSH is injected in small dosages usually in the late follicular phase, and minimal FSH stimulation where low dosage FSH is used earlier in the follicular phase and is used for women with less oocyte depletion [22]. Any one of these protocols may be used with ethinyl estradiol, and protocols using gonadotropins may use GnRH antagonists in the late follicular phase.

Sometimes follicular maturation is accelerated because of the elevated serum FSH. There are data showing that a short follicular phase may be associated with lower pregnancy rates [26]. Other data show that lengthening the follicular phase with ethinyl estradiol can improve pregnancy rates [27, 28]. Thus sometimes in women with short follicular phases not only is ethinyl estradiol added from the early follicular phase but natural estradiol is added during the luteal phase to help suppress the FSH levels during the luteal phase. Sometimes leuprolide acetate can be used beginning in mid-luteal phase and then it is stopped after about ten days to try to help lower the day 3 serum FSH and help delay follicular maturation. These techniques can also prevent premature luteinization by inhibiting a premature LH surge [29].

Though the study of the effect of morphology of day 3 embryos on outcome following single embryo transfer in women age < 40 showed the lowest pregnancy rate per retrieval, using the natural protocol it should be noted that this group was the closest or even appeared to be in actual menopause. Only 31.6% of the oocyte retrievals led to embryo transfers but the clinical and live delivered pregnancy rates were 21.1% and 15.8%, respectively [22]. The natural protocol with a boost of FSH resulted in 86.2% of oocyte retrievals leading to embryo transfers and the clinical and live delivered pregnancy rates were 28.8% and 23.7%, respectively [22]. The minimal FSH stimulation protocol found that 50% of the oocyte retrievals resulted in embryo transfer with a clinical and live delivered pregnancy rate of 29.4% and 23.5%, respectively [22].

If one better evaluates responders who could transfer three embryos in younger women aged ≥ 35 despite diminished egg reserve as manifested by day 3 serum FSH ≥ 12 mIU/ml, a clinical pregnancy rate of 66% (33/50) was achieved using low-dose FSH stimulation and a live delivered pregnancy rate of 58% with an implantation rate of 34% (51/150) [30]. It should be recalled that only this type of better responder despite elevated serum FSH was evaluated in the studies concluding atrocious pregnancy rates using traditional or higher dosages of FSH in their COH regimen in women of any age with elevated serum FSH [9].

Thus the data showing such good pregnancy rates with low-dose gonadotropin protocols suggest that the majority of younger women with diminished egg reserve did not go through an acceleration of the natural atresia process, leaving them with fewer and inferior oocytes, but instead favor some destructive process resulting in fewer remaining oocytes but the ones spared have the same quality as their age peers [30]. If this conclusion is correct one may wonder why some of the best IVF centers in the world find such poor pregnancy rates even in the modern IVF era [8, 9].

There is a strong possibility that it is the use of a lower dosage of gonadotropins that is responsible for the much higher pregnancy rates in these women with diminished egg reserve. A minority of women with normal day 3 serum FSH, and thus normal oocyte reserve, will even demonstrate poor pregnancy rates when hyperstimulated with high-dose gonadotropins [31-35].

One woman with polycystic ovaries and amenorrhea failed to conceive after six years of corrected ovulatory cycles with follicle maturing drugs and who also failed to conceive after ten cycles of in vitro fertilization where 92 embryos had been transferred, was successful the first time that a frozen embryo transfer was attempted on estrogen/progesterone replacement without follicle maturing drugs [36]. In fact following delivery she started to ovulate spontaneously and with one cycle of luteal phase progesterone support she conceived again at age 40 and delivered another healthy baby [37]. There are data suggesting that the adverse effect of follicle maturing drugs in women with normal ovarian reserve may be related to an endometrial factor allowing advancement of the implantation window with possible premature trophoblast invasion [33, 34].

It behooves the treating physician to always seek the least risky, least expensive and most effective therapy to treat...
a given illness or condition. Gonadotropins are not only very expensive but the use of high dosage can result in non-
IVF cycles with the dreaded complications of ovarian hyperstimulation syndrome and/or the complications of multi-
ple births both to the mother and to the preterm babies. Furthermore, as mentioned sometimes they can actually cause
iatrogenic infertility [35]. Ovarian hyperstimulation syndrome is also a risk with IVF-ET, and although theoretically
the risk of multiple births could be controlled by limiting the number of embryos transferred, in reality, this does not
happen because the cost is so high the couple wants to risk multiple births so as not to pay high prices also for frozen
embryo transfer. In fact some IVF centers do poorly with frozen embryo transfers and keep pushing for fresh IVF
cycles as illustrated by the women described who was a hyper-responder who went through ten fresh IVF-ET cycles
in another facility before we purposely froze all of her embryos [36]. Also the competition for “clients” and the public
record of statistics motivates the treating physician to frequently recommend the transfer of more embryos to hopefully
keep the pregnancy rates higher.

By starting later in the follicular phase and with a lower dosage of gonadotropins an excess of stimulated follicles
can be prevented. This results in a marked decreased risk of OHSS. By allowing the dominant follicle to emerge before
raising the serum FSH levels one can help allow the goal of monofollicular ovulation or at least to allow less eggs in
certain conditions, e.g., anovulation related to polycystic ovarian syndrome where single follicular recruitment is dif-
cult. This technique markedly reduces the cost of gonadotropins. Furthermore with fewer eggs, and thus fewer
embryos, there should be a decrease in the amount of time that an embryologist has to spend per patient, thus saving
money for the IVF center. This financial saving should be passed onto the infertile couple. In fact, we reduce the charge
for IVF to 50% of the high-dosage COH IVF cycle price for minimal stimulation cycles.

There is constantly a quest to improve the chance of success per IVF-ET cycles. Recent research is directed to finding
immune markers for the best embryo, e.g., HLA-G or metabolic by products (metabolomics) to identify the best
embryos to transfer [38, 39]. Each step used to increase the success of selecting the best embryo, e.g., pre-implanta-
tion genetic diagnosis, will cause an already very expensive procedure to become even more expensive. However, start-
ing the gonadotropins later and by using a smaller dosage of gonadotropins, allows good pregnancy rates with less risk
and cost even in women who could make multiple follicles. A recent report of pregnancy outcome in women with
serum FSH < 12 mIU/ml using lower dose FSH protocols found in women age ≥ 35 (n=149) a clinical pregnancy rate
per transfer of 48.3%, a delivered pregnancy rate of 45.6% and an implantation rate of 31.3% [40]. For women aged
36-39 (n=117) these values were 31.6%, 29.1%, and 22.1% and for women age 40-42 these rates were 21.6%, 14.4%,
and 14.0% [40]. For women ≥ 43 (n = 119) these rates were 5.9%, 3.4%, and 3.9% [40].

Interestingly the pregnancy rates for women aged ≥ 35 with serum FSH > 12 were not much different from those
women with normal serum FSH, i.e., a clinical and live delivered pregnancy rate of 47.4% (45/95) and 41.0%. For
women ages 36-39 these rates were 30.7% and 25.9% [40]. These data not only support the concept that low-dose
gonadotropin stimulation protocols for IVF-ET are effective both for women with and without diminished egg reserve
but support the concept that eggs from women with diminished egg reserve have reasonable potential to result in suc-
cessful pregnancies at least when low dosage gonadotropins are used for controlled ovarian hyperstimulation.

In the aforementioned study of IVF-ET in younger women with elevated serum FSH the clinical pregnancy rates and
delivered pregnancy rates were 43.7% and 39.7% for women with serum FSH ≥ 10 mIU/ml vs 52.2% and 43.5% for
women with serum FSH 11-12 mIU/ml vs 54.5% and 54.5% for ranges 13-14 and 50% and 50% for ranges 15-16
mIU/ml. Only with serum FSH levels ≥ 17 was there a reduction in pregnancy rates (33.3% and 11.1%) [40].

There are two main reasons why women with normal day 3 serum FSH levels choose low dosage gonadotropin pro-
tocols: to save money and because they have failed to conceive despite several high dosage COH regimens. One pos-
sible reason for the failure may have been related to an adverse effect of COH on implantation. In contrast, for the
various reasons stated in this editorial, women with increased serum FSH are advised to use a low-dose gonadotropin
regimen from the start. Thus possibly pregnancy rates per transfer in those with normal FSH levels could be somewhat
biased on the low side because there may be some of them who have failed previous IVF cycles not because of the
adverse effect of COH but possibly other occult tubal, oocyte, sperm, endometrial or uterine factors.

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The slow levonorgestrel-releasing intrauterine system (LNG-IUS) 20 mcg/day: a literature review

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Summary

The aim of the study is to present the mechanisms of action, indications, complications, contraindications and the necessary tests before the insertion of a levonorgestrel-releasing intrauterine system (Mirena). After a literature search in Pubmed, a narrative review in the field is presented.

Key words: Intrauterine devices; Levonorgestrel; Fertility; Metrorrhagia; Fertility; Ectopic pregnancy.

Introduction

The slow levonorgestrel-releasing intrauterine system (LNG-IUS) (Mirena) is a simple Nova T IUD, made of polyethylene, while its vertical stem is saturated with 52 mg levonorgestrel mixed with PDMS (polydimethyl siloxane). The 19-nor progestin (LNG) is released at a pace of 20 mcg/24 h during the first year of use, whereas the latter is reduced to 11 mcg/24 h within the next five years [1-3]. Thus, the mean value of its release is about 14 mcg/24 h for the approved [4] 5-year period of usage [5].

The first slow release intrauterine device contained progesterone; it had a one-year duration of action and was marketed some 30 years ago. However, it was withdrawn from the market because of a relevant increase in the percentage of extrauterine pregnancies, since increase of the ratio between the percentage of ectopic pregnancies and the corresponding one of intrauterine pregnancies, was established in comparison with their ratio in the general population. In the meantime, a device releasing synthetic progestin levonorgestrel was being developed and it has been successfully marketed [6].

Literature review

We searched for relevant publications in the Pubmed database up to March 2009. The key words used included the terms: “Mirena”, “levonorgestrel”, “intrauterine device”, and “levonorgestrel-releasing intrauterine system pelvic floor reconstruction”. In addition, we reviewed the references of the initially retrieved articles to identify additional relevant publications. We focused on articles describing the mechanisms of action, indications, complications, contraindications and necessary tests before the insertion of the slow LNG-IUS (Mirena). We identified 3,787 articles with the computerized search. The information found in 37 articles of this search was used to form our narrative review.
This change of the endometrium is possible to demonstrate with the help of ultrasonographic scans in patients who use the LNG-IUS > 3 months (group A). At the same time, a comparative study can take place between them and women using copper IUDs for an almost equal, on average, period of time (group B), as the study of Zalel et al. characteristically describes. Endometrial width appears to be thin (4.1 mm on average) and it differs from the corresponding one of women who carry the copper IUD (mean value 7.3 mm), while no difference is reported in the resistance index (RI) of the cervical branch of the uterine arteries between these two groups. On the contrary, blood flow in the spiral arteries of group A was extremely reduced in 75% (while this phenomenon was not noticed in group B). Together with the thickening of the arterial walls, the capillary thrombosis and reduction in the endometrial width, this explains the fact that amenorrhea or only slight menstrual bleeding was achieved in 87% of patients in group A, whereas 34% of the patients in group B reported menorrhagia or intermenstrual bleeding [3]. The above showed a different (than expected in the normal menstrual cycle) configuration of the endometrial environment. It seems to reflect the preclusion of the transition into a receptive for the implantation of the fertilized ovum, gene expression in the cells, which may take place on the grounds of several influences of the IUD on the genes that are involved in the preparation, and receptivity of the endometrium. The study of Horcajadas et al. [7] showed that with the presence of an IUD in the endometrial cavity, 147 genes with known identity are dysregulated (78 genes up-regulated, 69 genes down-regulated), 52 of which refer to genes that are related to the creation of the window of implantation. It was obvious that two months after the removal of the IUD, the endometrium continued to present a dysregulated gene expression (in 96% of the genes that were studied), whereas, one year later the latter becomes normal in a large portion (80%), just like it is before the insertion of the device. Of course, this study refers to IUDs at large, while extended research is required to be done for each type of IUD. Additionally, the reduction of the possibility for a woman to get pregnant just after the removal of the IUD can be explained through the above mechanism.

**Fertilization**

By promoting the production of glycodelin A (GdA/PP14), which is a progesterone-dependent glycoprotein with contraceptive action from the endometrial cells, the LNG-IUS inhibits binding of sperm to the zona pellucida. Normally this substance is absent from the endometrium during the proliferative and immediate postovulatory phases of the cycle, permitting the coupling of male and female gametes, but it is produced during the middle (5th-6th day after the ovulation) and late secretory phase of the cycle. According to the study of Madelin et al. [8], with the help of immunohistochemistry, in situ hybridization and statistical analysis, it was established that the endometrium from all women who were carrying the LNG-IUS contained GdA mRNA and protein during the midcycle, despite the duration of IUD usage. In comparison, the concentration of these substances was studied in women wearing Cu-IUDs and it was established that the concentration was less frequent among them than in a population with the LNG-IUS. This “inappropriate” GdA production during the menstrual cycle seems to enhance the contraceptive action of the device.

**Other mechanisms of action**

It has been shown that the cervical mucus becomes reduced [9] and thicker in women with the LNG-IUS [10] and the characteristic fern-like crystallization is absent, making the environment hostile to the passage of spermatozoa through the female genital tract [4]. However, some studies report that the quality of the mucus is good in 69% of women who have the LNG-IUS and have ovulatory cycles. Research has shown that the endometrial device interferes with the development of the ovum and the ovulation, possibly through subtle disturbances in the hypothalamic-pituitary system and, consequently, in the secretion of gonadotrophins [11]. Nevertheless, ovulation is successful in a portion > 75% of women using the LNG-IUS [9].

**Indications**

The LNG-IUS has many advantages in confronting several diseases, covering a wide spectrum of ages, from the very first years of menstruation [the LNG-IUS is better than other IUDs in adolescence because of its better menstrual profile – easier cycles as well as elimination of dysmenorrhoea] [10] until later, after menopause [12].

**Contraception**

It has been established by the research of the last two decades that the risk of IUD failure (which is directly translated into the possibility of an upcoming and undesirable pregnancy) is < 2% in five years for women who use such devices and, more specifically, concerning the LNG-IUS, the risk is < 0.5% (in five years) [13]. In another study, it was reported that the percentage of failure is < 0.2/100 women/years and that in a 7-year period, pregnancies reach 1.1% [14]. The success of the LNG-IUS compared with other IUDs is described in the study of Thonneau et al. [15], in which women using Mirena (as the control population) are defined as having a pregnancy risk = 1, with GyneT380, MLCu375 and Gynelle 375 to have a risk = 2.70, with Sertalia = 8.45, with Nova T = 7.20 and with GyneFix = 24.43. The possibility of IUD failure seems to be related positively with the history of previous expulsion of the device (one out of 20 patients) [10], which reflects the possible adverse conditions for retaining it in the endometrial cavity (small uterus, e.g., in adolescents), anomalies in its morphology and its position/tilting, which results in the device being in an inappropriate position after its insertion and, conse-
quently presenting a default action and effectiveness. Anti-inflammatory drugs, history of polyps, leiomyomas, abortion or previous pregnancy with IUDs have not been determined to affect the effectiveness. As a contraceptive the use of Mirena (according to its license) [4] has been defined to be five years, but it has been shown to provide protection for another two years [10, 16]. As far as emergency contraception is concerned, the LNG-IUS is not shown to be effective [9, 17].

**Menorrhagia**

Excessive blood loss (> 80 ml) during menstruation applies to > 10% of the cases that are referred to gynecologists [18]. The intrauterine system LNG achieves high concentration in the endometrial cavity (470-1500 ng/g of tissue), much higher than achieved with systematic administration of LNG, thus explaining the significant portion of amenorrhea that is observed [12]. In studies, it has been established that the LNG IUS reduces 94% of the blood loss in idiopathic menorrhagia in the first trimester and it is a more satisfying method for the patient in comparison with the per-os treatment (norethisterone 5 mg x 3) [19]. On the other hand, the effectiveness of this less aggressive method is lower than the corresponding one of hysterectomy (about 100%) for the treatment of dysfunctional uterine bleeding. However Clarke *et al.*, found that more than one-third of women, who undergo hysterectomy for episodes of menorrhagia have a normal uterus. This idea together with the fact that the LNG-IUS is a more appealing method for patients with dysfunctional uterine bleeding than hysterectomy (~95% of the women who were asked prefer the device if the success rate of this method in use is > 50%) makes this therapeutical approach to menorrhagia quite attractive [18]. Moreover, it has been concluded that it is a quite effective therapeutic method in women with heavy menses and hemostatic disorders [20].

**Hyperplasia of the endometrium**

It has been estimated that there are approximately 200,000 new cases of endometrial hyperplasia per year in the Western world. Usually, women go to a physician because of irregular uterine bleeding, and hyperplasia is diagnosed after investigation: non atypical (simple, complex) or atypical (simple, complex) hyperplasia. The study of Haimovich *et al.* reported that in patients (peri- or post-menopausal) with simple non atypical hyperplasia of the endometrium and two years of follow-up under the action of the LNG-IUS a 50% reduction of bleeding was noticed at three months and no bleeding at all in 24 months, while at 12 months, atrophic endometrium was seen in 93.3% of the cases (secretory endometrium in 6.7%) and in 24 months the endometrium became atrophic in 100% of the subjects [21]. In perimenopausal women, in whom the function of the ovaries is not stable as expressed by the estradiol levels (E2) in the serum, there is an increased risk of hyperplasia due to insufficient secretion of progesterone. The same happens in women with HRT. The device stops abnormal uterine bleeding (~83-88% after the first 4 months post-insertion) and protects women effectively from endometrial cancer for four years after its insertion [3] by inhibiting, with the action of progestagen, the estrogen-dependent development of the endometrium. It is worth mentioning that women with the LNG-IUS who undergo HRT treatment have the same, as the general population, possibility of developing breast cancer and less morbidity from cardiovascular diseases, especially if HRT commenced from the onset of menopause. At large, if HRT and progestagens that achieve high concentrations in the plasma begin years (and not at the onset) after menopause (> 10 y), then it can be harmful for the cardiovascular system, as the preexisting plaque in the vessel walls may be more likely to rupture. In contrast, with progestagens that achieve low concentrations in the serum like the released levonorgestrel of the LNG-IUS, the above risk is very low [12].

Recently, a study was published [22] in which 105 patients > 40 years old with episodes of abnormal uterine bleeding (menorrhagia/menometrorrhagia that could not be managed with conservative therapy in 37/105 individuals and postmenopausal bleeding and spotting under HRT or tamoxifen in 68/105 individuals) underwent treatment with the LNG-IUS with observation (with histological examination of the endometrium – endometrial Pipelle sampling) at three months and six months post-insertion, and 6-monthly intervals thereafter in all cases. Of the patients, 16/105 had simple non atypical hyperplasia of the endometrium, 80/105 complex non atypical, and 9/105 atypical hyperplasia. The results were: 94/105 had regression of the disease (= several degrees glandular atrophy and metaplasia of the endometrium) in 24 months post LNG-IUS insertion (90/105 in the first year; mean time-period of regression (95% confidence; the first 9 months), with 7/94 reversion of hyperplasia at the 2-year-follow-up. The failure of this method was 18/105. To be more specific, simple non atypical hyperplasia cases regressed (in 24 months) in 15/16, complex non atypical hyperplasia in 73/80 and atypical hyperplasia in 6/9, as can be seen in Table 1.

We noted that the LNG-IUS is quite effective in treating endometrial hyperplasia, despite the histological category [2-year regression rate: 92% (88/96) in non-atypical (simple and complex) hyperplasia, 67% (6/9) in atypical hyperplasia]. It seems that the device will contribute in an effective way in the reduction of hysterectomies in several cases of endometrial hyperplasia, thus dramatically diminishing physical as well as psychological consequences of the operation.

**Adenomyosis**

A gynecological disorder of undefined etiology and is characterized by the presence of heterotopic endometrium (glands, stroma) into the myometrium, with adjacent smooth muscle hyperplasia. Metrorrhagia and dysmenor-
rhea are the prevalent and more common symptoms and are found in about 65% of women with adenomyosis. Diagnosis is based on histological examination and, in many cases, is only made at the time of hysterectomy. The study of Bragheto et al., counting on magnetic resonance imaging (MRI) for an accurate, noninvasive method of diagnosis, with high sensitivity and specificity ranging from 86% to 100% in symptomatic women, describes the advantages of using the LNG-IUS as a therapeutic method in these patients. It has been established that the maximal junctional zone thickness (JZ\text{max}), best demonstrated on T2-weighted images as the hypotense area between the myometrium and the endometrium (women with adenomyosis: JZ\text{max} > 12 mm or 8.0-11.9 in some other cases) is reduced to 24.2% in 89.6% of the patients with the LNG-IUS, who are reexamined at three and six months post insertion. At the same time, a significant improvement of menorrhagia and dysmenorrhoea is observed [23].

**Endometriosis**

A gynecological condition that appears in 7-10% of women in the general population and up to 50% of premenopausal women [10]. In several studies on patients with this syndrome many scientific outcomes have been noted, comparing the use of the LNG-IUS with more conservative treatments in alleviating the chronic pelvic pain (CPP) that is related to endometriosis and improving its staging, like the randomized clinical trial of Carlos et al. [1]. The aim of this trial was to compare the effectiveness in six months between the use of the LNG-IUS and administration of GnRH analogues in the treatment of patients with endometriosis. The results showed that although women with the LNG-IUS present more episodes of vaginal bleeding (which improved after the 3rd month) and breast tension, the effectiveness of the method when confronting CPP and improving the staging of the disease is equal to the administration of GnRH analogues; while hypoestrogenism, which is the latter cause and consequently becomes a reason to stop the treatment, mainly because osteoporosis (they are used only for 6 months; otherwise, hormone therapy should be added), can be avoided (normal serum levels of estradiol -E2- in patients with the LNG-IUS) [24]. The absence of this major side-effect of the device is supported by the study of Bahamondes et al. [24], in which no difference was observed concerning bone mineral density (BMD) of the nondominant forearm between a group of women using Mirena for seven years and a group with TCu380A. Additionally, the BMD measurements were similar to the expected values for women in the same age group as the participants (Z-score) (WHO, 1994). It is concluded that the LNG-IUS can be used safely and for an adequate period of time in the treatment of endometriosis, and thus is a cost-effective solution for the patients [1].

**Leiomyomas of the uterus**

Research is going on to determine a probable beneficial role of the LNG-IUS in patients with leiomyomas. It seems that the device treats episodes of metrorrhagia in patients, but it does not seem to significantly change their size [25, 26]. However, Mirena is not used when there are fibroids that distort the uterine cavity, as is clearly described in the contraindications of the product [4].

**Complications**

**Abnormal vaginal bleeding:** unscheduled breakthrough bleeding (BTB). This is a side-effect of the device which mainly occurs in the first three to six months after insertion. It presents as a spotting vaginal bleeding, which may compel the patient to stop using the IUS, and it was found in about 14% of the women who use it [27]. The possible positive relationship with BTB, (during the first 3 months) of adrenomedullin (AM), a substance that is expressed regularly in the endometrium and, together with vascular endothelial growth factor (VEGF) [28], has angiogenic properties and both seem to be important during the normal menstrual cycle.

In women using the LNG-IUS, AM and VEGF are dys-

### Table 1.

<table>
<thead>
<tr>
<th>Regression of hyperplasia at 24 months</th>
<th>Persisting hyperplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Simple non-atypical hyperplasia</strong></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>1 case turned out to have acquired atypical hyperplasia, after hysterectomy performed (because of patient’s request)</td>
<td>16</td>
</tr>
<tr>
<td><strong>Complex non-atypical hyperplasia</strong></td>
<td></td>
</tr>
<tr>
<td>69</td>
<td>4</td>
</tr>
<tr>
<td>(one case had Stage 1B ovarian cancer)</td>
<td>80</td>
</tr>
<tr>
<td><strong>Atypical hyperplasia</strong></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>4 (one case had endometrial cancer Stage 1A)</td>
<td>9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>7</td>
</tr>
<tr>
<td>87</td>
<td>11</td>
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<tr>
<td>105</td>
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The slow levonorgestrel-releasing intrauterine system (LNG-IUS) 20 mcg/day: a literature review

Regulated (AM: up-regulation, VEGF: down-regulation): this is an alteration that points the way toward researching BTB etiology for these two substances for the first three months after insertion of the device in the uterus. The values of AM in women three years after the insertion of the IUS (Hague et al. 2002) [29], were different (reduced) in comparison with the corresponding ones of the first three months. A factor which justifies this deviation seems to be (apart from the different method that was followed) the duration of its use which is significant [30]. Consequently, we should ask for more mechanisms to explain unexpected hemorrhagia which happens after long-term use of the LNG-IUS; mechanisms that have remained unclear so far.

Although abnormal bleeding is rare after prolonged (> 6 months) use of the LNG-IUS [there is a negative connection of the primitive spotting vaginal bleeding with the duration of IUD use, so that the portion of amenorrhea is increased (about 20%) with long-term use], it is reported that it does happen and may become a reason to discontinue its use. Endometrium exposed to progestagen appears to have some large thin-walled venule-like blood vessels, apart from a decreased number of spiral arterioles and reduced density of normal capillaries. These vessels are considered as the possible cause of hemorrhagia, but their role and cause of their existence must be investigated further. It seems that the reason for the prolonged or relapsed bleeding must be investigated in the disturbance of vascularization or in the alteration of blood vessel function, which is a result of the periodic changes of ovarian steroidal hormones, the local effect of levonorgestrel (reduction in the number of progesterone receptors and, consequently, insufficient support of the endometrium), and some other tissue factors (VEGF-A,B,C and D, receptors VEGFs 1,2,3 and other molecules). The study of Möller et al. focused on several differences in VEGFs and their receptors (R) between women with the LNG-IUS (> 6 months) and abnormal bleeding and women with the LNG-IUS without bleeding [26]. When the endometrium becomes very atrophic by the action of the device, vessel abnormalities cause BTB to subside, showing a possible relation between endometrial atrophy and elimination of the side-effect [12].

In practice, if hemorrhagia persists, then it is useful to check the endometrial cavity (for example US, biopsy) to exclude other conditions [31].

Perforation of the uterus and migration of the IUS is a complication that concerns about 0.9% of insertions of the device in the endometrial cavity. The possibility of uterine perforation from the IUS during this procedure relates positively to the difficulty that gynecologists prefer insertion of Mirena in the uterus and it depends on the experience of the gynecologist, the possible anatomical abnormalities of the cervix, and the cervical canal or the anomalies of the uterus position and morphology, and the history of previous birthgiving [5] as well as on the age of the patient.

It is reported that in adolescents, unlike in adults, the insertion of the IUS is more difficult and painful (86%) [10] something that is also likely to happen in postmenopausal women with an atrophic uterus [12]. However, perforation can happen at any time after the insertion, resulting in migration of the device into the pelvic or peritoneal cavity. Surgical removal of the object from the abdominal cavity is performed to reduce the morbidity and mortality of this complication, which becomes difficult if other diseases co-exist [32]. Migration of an IUD has even been described into the bladder (intravesical) [33].
Pelvic inflammatory disease (PID)

The LNG-IUS is, at large, a safe intrauterine device as regards the risk of inducing PID. In the literature, it is reported that the IUS has a reduced risk for PID in comparison to copper devices due to the production of thick cervical mucus and to atrophy of the endometrium. Additionally, the absolute risk for PID is very low and slightly enhanced during the first 20 days after IUD insertion (9.7%). From the 21st day until the eighth year of use, the risk remains almost constant and the same as for the general population (1.4%). Research has shown that the frequency of PID is 0-2.0% when there is not any present infection in the cervix or the uterus and 0-5% in the other cases [10]. In countries, such as Africa, where the prevalence of sexually transmitted disease (STI), like gonorrhea and chlamydia infections, is very high the frequency of PID is expected to be increased. Apart from STIs, different bacteria can creep into the uterus from the vagina or outer environment during the insertion of the device, particularly if there is not sufficient antisepsis [34].

Pelvic actinomycosis is a serious disease, which is attributed to specific microorganisms, the actinomyces-like organisms (ALOs). The latter are frequently found in Papanicolaou tests in asymptomatic women with IUDs. It was established by examining Papanicolaou-stained smears [35] that the prevalence of ALOs(+) was lower in women with the LNG-IUS than in women with copper IUDs (ML375).

Ectopic pregnancy

IUDs reduce the incidence of intrauterine pregnancy as well as the corresponding one of extrauterine pregnancy. Consequently, women who use IUDs have less risk (0.02/100 women/years) for ectopic pregnancy than women who do not use the device (0.3-0.5/100 women/years) [36]. However, there are studies which support the relevant increase of ectopic preganacy in LNG-IUS users, which means that, although this pregnancy is rare, when it happens the possibility of being extrauterine is quite high [37].

Subfertility

The study of Horchadas et al. [7] reports that return to fertility after IUD removal is reduced for the first three months (depending on the type of IUD), whereas one year later it approaches 90%. This is attributed to the disturbance of cell gene expression by the IUD, which persists (96%) two months after its removal, while it becomes 80% normal (almost like before the use of the device) in the first year.

Other side-effects

Since levonorgestrel exhibits some androgenic properties, some mild side-effects can be observed, mainly in the beginning of IUS usage. The most common ones are change of mood, acne, headache, breast tension, hirsutism and change in body weight [12].
Contraindications
According to the product labeling [4], the LNG-IUS (Mirena) is contraindicated to be used in the following: known or suspected pregnancy; undiagnosed abnormal genital bleeding; congenital or acquired abnormality of the uterus including fibroids if they distort the uterine cavity; current genital infection; current or recurrent pelvic inflammatory disease; postpartum endometritis, infected abortion during the previous three months; cervicitis; cervical dysplasia; uterine or cervical malignancy; past attack of bacterial endocarditis or of severe pelvic infection in a woman with an anatomical lesion of the heart or after any prosthetic valve replacement, active or previous severe arterial disease, such as stroke or myocardial infarction; liver tumor or other acute or severe liver disease; conditions associated with increased susceptibility to infections; acute malignancies affecting the blood, or leukemia except when in remission; recent trophoblastic disease while hCG levels remain elevated; and, hypersensitivity to the constituents of the preparation.

Necessary tests before the insertion of the system
IUDs may be inserted anytime during the menstrual cycle. Documentation of a negative pregnancy test is prudent. Insertion may be performed during menstruation to provide additional reassurance that the woman is not pregnant. If insertion is planned during the luteal phase, another nonhormonal contraceptive should be used until after the next menses. A pregnancy test can be done, but the patient should be made aware that a pregnancy test at this time cannot always rule out early pregnancy. An IUD should not be inserted in a woman with an STD. The American College of Obstetricians and Gynecologists recommends a pelvic examination before insertion to screen for chlamydia and gonorrhea [38]. A Pap test it is also recommended before insertion in order to exclude cervical dysplasia or malignancies [39].

Conclusion
The levonorgestrel-releasing intrauterine system is a relatively new option in the treatment of different gynecologic entities. The indications, complications and contraindications of such a therapeutic system have been reviewed.

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[28] www.researchvegf.com


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A novel method to assess the effect of uterine senescence by comparing pregnancy outcome in younger donors vs older recipients who are sharing a common pool of oocytes

J.H. Check, B. Katsoff, T. Jamison, J.K. Choe, D. Brasile, J. Amui

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Summary

Purpose: To evaluate uterine senescence by comparing pregnancy rates in older recipients vs their younger donors who were actually trying to conceive themselves. Methods: A retrospective analysis comparing clinical and delivered pregnancy rates in all infertile donors ≥ age 35 sharing their eggs with a recipient age ≥ 40 over a 6-year time span. These parameters were also evaluated in the first frozen embryo transfer from these couples (if they had one). Results: The clinical and delivered pregnancy rates were similar in younger donors vs older recipients following fresh embryo transfer. There was a non-significant trend for lower implantation rates in the younger donors. No differences were found when comparing frozen embryo transfers. Conclusions: These data support conclusions that the uterus of women ≥ 40 does not inhibit embryo implantation.

Key words: Uterine senescence; Donor oocytes; Frozen embryos.

Introduction

A study over ten years ago of donor egg recipients found comparable implantation and clinical pregnancy rates in recipients < 40 vs those ≥ 40 [1]. The data from Sauer et al. suggested that uterine senescence does not seem to be a big factor in human conception [1].

This concept was supported by a study of shared donor-oocytes in which despite a common oocyte pool the older recipients had higher clinical, ongoing/delivered, and implantation rates than the donors [2]. These data had been interpreted that there had to be some factor in the donors having an adverse effect on implantation. One of these factors may have been the more likely presence of hydrosalpinges in donors vs recipients. Hydrosalpinges are well known to adversely effect implantation [3-5]. Today most in vitro fertilization (IVF) centers surgically remove the infected tubes or ligate them [6-8].

There was always the chance that the conclusions reached by Sauer et al. could have been related to the fortuitous use of better eggs in the older recipients negating the adverse influence of an aging endometrium. The present study attempted to evaluate uterine senescence by using a common oocyte pool.

Materials and Methods

A retrospective review over a 6-year period was performed for shared-donor oocyte cycles where recipients were ≥ 40. Donors were ≥ 35 years old. In the shared oocyte program an infertile donor shares half of the oocytes collected with a recipient in exchange for the recipient paying for the IVF cycle [9].

To cover the possible confounding variable of an adverse effect of the controlled ovarian hyperstimulation regimen, outcome was also compared on the first frozen embryo transfer. Only cycles where both donors and recipients received an embryo transfer were evaluated.

Results

The mean age for recipients was 41.9 (SD 5.6) and for donors it was 31.4 (SD 3.1). There were no significant differences in clinical or delivered pregnancy rates in the donors or the recipients nor any differences in fresh embryo implantation rates (Table 1). There was also no difference in pregnancy or implantation rates when comparing the first frozen embryo transfer (Table 1). The mean number of embryos transferred (combining fresh and frozen) was 2.9 for donors and 3.2 for recipients.

Discussion

These data clearly show that the uterus from women in their 40s is as receptive as younger women. Though successful pregnancies with donor eggs have also been recorded in women > 50 this age group only represented a very small minority of the recipients [10]. Thus these data do not prove that the uterus is as effective in women ≥ age 50 but do not refute this possibility.

Uterine fibroids are known to increase in frequency in women in this age range and donors or recipients with...
fibroids were not excluded. The percentage of fibroids in younger donors vs older recipients was not evaluated in this study but probably was higher in the recipients. Surgery was only performed for submucous fibroids. These data support but do not prove our previous conclusions that the presence of intramuscular or subserosal fibroids in donor egg recipients does not impair the implantation rates [11].

Besides the presence of hydrosalpinges in the donors the other explanation for the aforementioned study showing higher pregnancy and implantation rates in recipients vs donors in a shared program was the possibility that the controlled ovarian hyperstimulation regimen (COH) had an adverse effect on the uterine environment [2]. There are data supporting the concept that COH may adversely effect implantation [12]. In fact some anecdotal case reports support this concept, e.g., a woman who failed to conceive despite transferring 92 embryos over ten IVF cycles but was successful with her first frozen embryo transfer [13], and even conceived naturally at the age of 40 following her first cycle of luteal phase progesterone supplementation [14].

There are data suggesting that the risk that the controlled ovarian hyperstimulation regimen may adversely affect 20% of the women having IVF-ET in the era of salpingectomy for hydrosalpinx [15]. Though the present study showed no significant difference in pregnancy or implantation rates in the donor vs recipients there still was a 20% higher implantation rate in fresh embryo transfer cycles in the recipients which was not present with frozen embryo transfers. Thus the present data do not refute this concept.

These data thus confirm the study by Sauer et al. showing no evidence that women age ≥ 40 have any adverse uterine factor compared to younger women. In the way the present study was performed (in which eggs were shared between younger and older women) the present study ruled out a possible fortuitous better egg pool that could have been a confounding factor in the aforementioned study by Sauer et al. [1].

References


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Table 1. — Outcome following fresh and frozen embryo transfers in donors and recipients sharing Eggs.

<table>
<thead>
<tr>
<th></th>
<th>Donors</th>
<th>Recipients</th>
<th>Donors 1st frozen ET</th>
<th>Recipients 1st frozen ET</th>
</tr>
</thead>
<tbody>
<tr>
<td># transfers</td>
<td>118</td>
<td>118</td>
<td>32</td>
<td>61</td>
</tr>
<tr>
<td># pregnancies</td>
<td>66</td>
<td>73</td>
<td>11</td>
<td>21</td>
</tr>
<tr>
<td>% pregnant/ transfers</td>
<td>55.9</td>
<td>61.9</td>
<td>34.4</td>
<td>34.4</td>
</tr>
<tr>
<td># clinical pregnancies</td>
<td>59</td>
<td>67</td>
<td>8</td>
<td>19</td>
</tr>
<tr>
<td>% clinical/transfers</td>
<td>60.0</td>
<td>56.8</td>
<td>25.0</td>
<td>31.1</td>
</tr>
<tr>
<td># chemical</td>
<td>5</td>
<td>5</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td># ectopic</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td># live/delivered</td>
<td>54</td>
<td>60</td>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td>% live/delivered</td>
<td>45.8</td>
<td>50.8</td>
<td>21.9</td>
<td>26.2</td>
</tr>
<tr>
<td># miscarriages</td>
<td>7</td>
<td>3</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>% miscarriage/clinical pregnancies</td>
<td>11.9</td>
<td>11.9</td>
<td>37.5</td>
<td>21.1</td>
</tr>
<tr>
<td># embryos transferred</td>
<td>348</td>
<td>374</td>
<td>94</td>
<td>194</td>
</tr>
<tr>
<td>Average # embryos transferred</td>
<td>2.9</td>
<td>3.2</td>
<td>2.9</td>
<td>3.2</td>
</tr>
<tr>
<td># sacs implanted</td>
<td>95</td>
<td>122</td>
<td>13</td>
<td>28</td>
</tr>
<tr>
<td>Implantation rate</td>
<td>27.3</td>
<td>32.6</td>
<td>13.8</td>
<td>14.4</td>
</tr>
</tbody>
</table>

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Cryopreservation of blastocysts using a modification of a simplified freezing protocol with a one step removal of cryoprotectant successfully used previously to freeze 2 pronuclear or multi-cell embryos


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Summary

Purpose: To describe a modification of a simplified freezing protocol for the cryopreservation of blastocysts. Methods: 1.5 M glycerol was substituted as a cryoprotectant instead of propanediol. Results: There was a survival rate of 59.1% (13/22) with three live deliveries in seven transfers (42.9% per transfer). The implantation rate was 28.6% (4/14). Conclusions: This is the first description of a new technique for freezing blastocysts. A larger series is needed to determine if the good pregnancy rates will continue.

Key words: Blastocyst; Cryopreservation; Implantation rates.

Introduction

A minority of in vitro fertilization (IVF) centers use, for the cryopreservation of 2-pronuclear (2PN) or multicell embryos, a simplified freezing protocol with a one-step removal of the cryoprotectant 1,2-propanediol (PrOH) [1]. This simplified technique requires an alcohol-bath freezer rather than a liquid nitrogen (LN2) cooled freezer [1].

The present study describes a modification of the simplified freezing protocol, with a one-step removal of cryoprotectant that can be used to cryopreserve blastocysts.

Materials and Methods

The modification for blastocyst freezing involved substituting 1.5 M glycerol for the 1.5 M 1,2-propanediol (PrOH) [1]. This simplified technique requires an alcohol-bath freezer rather than a liquid nitrogen (LN2) cooled freezer [1].

The present study describes a modification of the simplified freezing protocol, with a one-step removal of cryoprotectant that can be used to cryopreserve blastocysts.

Materials and Methods

The modification for blastocyst freezing involved substituting 1.5 M glycerol for the 1.5 M 1,2-propanediol that is routinely used for 2PN and multicell embryos.

Basically the blastocysts were placed in Hepes-buffered HTF (Sage BioPharma) supplemented with 10% serum protein substitute (SPS, Sage BioPharma) at room temperature for 10 min. Blastocysts were then transferred to 1.5 M glycerol (Sigma-Aldrich) solution for approximately 10 min, loaded into 0.25 ml straws with a separate sucrose column, and heat-sealed at both ends. Straws were placed vertically in the BioCool alcohol-bath freezer (FTS Kinetics) and manually seeded at -6°C with a chilled spatula. The embryos were cooled at -0.4°C/min until -40°C was reached; after a 15 min hold the straws were plunged into LN2 for storage.

All stages of blastocysts were frozen: early, expanded, and hatched. The groups were too small to analyze by growth stage. Thawing involved submersion in a 37°C waterbath and “shaking” the straw to mix the 1.0 M sucrose diluent column with the smaller 1.5 M glycerol column containing the embryo.

Blastocysts were considered to have survived if at least 50% of the inner cell mass and trophectoderm were intact after being placed in culture, even if the blastocyst was collapsed. All blastocysts frozen in this study were the extras not transferred fresh on day 5. In no instance did day 3 fresh embryo transfer occur but the rest of the embryos were allowed to cleave to blastocyst stage.

Results

One couple only froze one embryo and it did not survive the thaw, so this cycle was included in the survival statistics but not the pregnancy rate/transfer data. A total of 22 embryos were thawed and 13 survived (59.1% survival). There were three live delivered pregnancies in seven transfers (42.9% per transfer). The implantation rate was 28.6% (4/14).

Discussion

These data show adequate survival and pregnancy rates with cryopreserved blastocysts with this modification of the one-step freezing procedure. The pregnancy rate and implantation rate both appear to be similar to that of Behr et al. [2] who had a pregnancy rate of 36% and an implantation rate of 16% when using Menezo’s two-step protocol and a planar (LN2) freezer. Thus, those IVF centers having good success with the simplified freezing protocol for 2PN and multicell embryos do not have to purchase a LN2 freezer just to freeze blastocysts or switch to vitrification. Of course determination of the true efficacy of this new modified procedure will require a larger study group.

References


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Serum retinol-binding protein-4 levels in polycystic ovary syndrome patients undergoing controlled ovarian hyperstimulation for in-vitro fertilization cycle


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Summary

Aims: To determine serum retinol-binding rotein 4 (RBP-4) levels in polycystic ovary syndrome (PCOS) patients undergoing controlled ovarian hyperstimulation (COH) for an in vitro fertilization-embryo transfer (IVF-ET) cycle and the possible correlation to COH variables. Patients and Methods: 11 consecutive PCOS patients undergoing our routine IVF flexible multidose gonadotropin-releasing hormone (GnRH)-antagonist protocol. Blood was drawn three times during the COH cycle: (1) day 1 or 2 of menstruation, and prior to gonadotropin administration (Day-S); (2) day of or prior to human chorionic gonadotropin (hCG) administration (Day-hCG); and (3) day of ovum pick-up (Day-OPU). Levels of estradiol and serum RBP-4 were compared among the three time points. Serum RBP-4 was measured with a commercial immunoassay. Results: Results showed significantly lower levels of serum RBP-4 on Day-OPU and Day-hCG than on Day-S. Though significant correlations were observed between serum RBP-4 and body mass index, fasting glucose or glucose to insulin ratio, no correlations were found between serum RBP-4 and IVF treatment variables or pregnancy rate. Conclusion: While serum RBP-4 decreases during COH for IVF, there is apparently no correlation of serum RBP-4 levels with IVF treatment variables or outcome.

Key words: Retinol-binding protein-4; PCOS; Insulin resistance; Ovulation induction; Sex steroids; BMI.
Table 1. — Hormone profile and RBP-4 levels of the study patients.

<table>
<thead>
<tr>
<th></th>
<th>Day-S</th>
<th>Day-hCG</th>
<th>Day-OPU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol (pg/ml)</td>
<td>41.4 ± 13.5</td>
<td>1650 ± 713</td>
<td>1016 ± 503</td>
</tr>
<tr>
<td>RBP-4 (ng/ml)</td>
<td>37260 ± 10063</td>
<td>32459 ± 8311</td>
<td>32719 ± 7488</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>87 ± 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin (IU/ml)</td>
<td>10.3 ± 3.8</td>
<td></td>
<td></td>
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<tr>
<td>Glucose/insulin ratio</td>
<td>9.5 ± 3.4</td>
<td></td>
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</tr>
</tbody>
</table>

*p = 0.001 between the subgroups; † p = 0.03 between the subgroups; ‡ p = 0.02 between the subgroups. All values are mean ± SD.

Day-S = day 1 or 2 of menstruation, and prior to gonadotropin administration; Day-hCG = day of or prior to human chorionic gonadotropin administration; Day-OPU = day of oocyte pick-up.

Table 2. — Correlations between serum RBP-4 levels and other patients variables.

<table>
<thead>
<tr>
<th>Serum Estradiol</th>
<th>Serum RBP-4 on Day-S</th>
<th>Serum RBP-4 on Day-hCG</th>
<th>Serum RBP-4 on Day-OPU</th>
<th>R</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>r</td>
<td>0.73</td>
<td>0.76</td>
<td>0.86</td>
<td>0.01</td>
<td>0.001</td>
</tr>
<tr>
<td>p</td>
<td>&lt; 0.01</td>
<td>&lt; 0.01</td>
<td>&lt; 0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>r</td>
<td>0.74</td>
<td>0.61</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>&lt; 0.01</td>
<td>&lt; 0.045</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting insulin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>r</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Day-S = day 1 or 2 of menstruation, and prior to gonadotropin administration; Day-hCG = day of or prior to hCG administration; Day-OPU = day of oocyte pick-up.

Recently, several studies have measured RBP-4 levels in PCOS patients and their relationship to various endocrine variables, indices of insulin resistance or metabolic syndrome [15-21]. Most of these studies have demonstrated an increase in RBP-4 levels in PCOS patients as compared to healthy controls that correlated with patients BMI and insulin levels. Prompted by these findings, in the present prospective preliminary study, we sought to longitudinally investigate serum RBP-4 levels in PCOS patients undergoing controlled ovarian hyperstimulation (COH) using GnRH-antagonist for IVF, and to examine whether it correlates with serum estradiol or other COH variables.

Patients and Methods

The study population consisted of 11 consecutive PCOS patients attending the in vitro fertilization (IVF) unit of our department for treatment of infertility. All patients met the PCOS criteria of the recent ESHRE/ASRM consensus (1) and underwent COH using the flexible multidose GnRH-antagonist protocol. The study required no modification of our routine IVF protocols. We included only the GnRH-antagonist protocol due to our program policy [22], which offers high responder patients the use of GnRH-antagonist during their first IVF attempt. With this strategy we are able to substitute hCG with GnRH agonist to trigger ovulation, with the consequent elimination of severe OHSS.

For the purpose of the study, in addition to the routine monitoring during the COH cycle, blood samples were drawn to determine the hormonal profile (E2, progesterone) and serum RBP-4 levels at three time points: (1) day 1 or 2 of menstruation, and prior to gonadotropin administration (Day-S); (2) day of or prior to hCG administration (Day-hCG); and (3) day of ovum pick-up (Day-OPU).

Data on patients’ age, BMI and infertility-treatment-related variables were collected from the files. Ovarian stimulation characteristics, number of oocytes retrieved, and number of embryos transferred per cycle were recorded. Clinical pregnancy was defined as visualization of a gestational sac and fetal cardiac activity on transvaginal ultrasound.

For serum RBP-4 determination, blood samples were centrifuged for 10 min at 1000 g, and the plasma was stored in aliquots at −70°C until assayed. Serum RBP-4 was measured in duplicate with a commercial immunoassay which employs the quantitative sandwich enzyme immunoassay technique (R&D Systems, Inc. Minneapolis, USA). All samples were assayed at one time to avoid inter-assay variations. The minimal sensitivity of the assay was 0.224 ng/ml and the intra- and interassay variability were 6.9% and 7.2%, respectively. Blanks and controls were included in all experiments.

Moreover, on Day-OPU and prior to OPU, fasting blood samples were drawn for glucose and insulin levels. While serum glucose was tested by the enzymatic UV test for the quantitative determination of glucose on Olympus analyzers, serum insulin was determined by microparticle enzyme immunoassay technology (AxSym Insulin Abbott, Germany).

Informed consent was obtained from all patients before participation in the study, and the study was approved by the Clinical Research Committee.

The results are expressed as means ± standard deviations or rates. Findings were analyzed statistically with the nonparametric Wilcoxon signed rank test and correlation analysis; p values of 0.05 or less were considered significant.

Results

Mean age of the 11 patients was 30.7 ± 6.3 years, and mean BMI was 28.5 ± 5.6 (range 20.7-35.5). Mean number of gonadotropin ampoules used during the COH cycle was 37 ± 21, mean number of oocytes retrieved 12.1 ± 3.9 and mean number of embryos transferred 2.6 ± 1. Pregnancy rate was 36.3%.

Mean serum E2 and RBP-4 levels on Day-S, Day-hCG and Day-OPU, and glucose and insulin level on Day-OPU are presented in Table 1. As expected, serum E2
levels were significantly higher on Day-hCG than Day-S and Day-OPU ($p < 0.001$ and $p < 0.03$, respectively) and significantly higher on Day-OPU than Day-S ($p < 0.001$).

While serum RBP-4 levels were significantly higher on Day-S than Day-hCG and Day-OPU ($p < 0.001$ and $p < 0.02$, respectively) (Table 1), no statistically significant difference was observed in serum RBP-4 levels between Day-hCG and Day-OPU ($p = 0.8$). The correlations between serum RBP-4 levels and several patient variables are presented in Table 2. Figure 1 presents the E2 and serum RBP-4 levels during the cycle. No significant correlations were observed between serum RBP-4 and E2 levels ($R = 0.14$, $p = 0.4$).

BMI significantly correlated with serum RBP-4 levels on Day-S ($R = 0.73$, $p < 0.01$), Day-hCG ($R = 0.76$, $p < 0.01$), and Day-OPU ($R = 0.86$, $p < 0.001$) (Figure 2).

Moreover, serum RBP-4 levels on Day-OPU significantly correlated with fasting insulin and the fasting glucose/insulin ratio ($R = 0.74$, $p < 0.01$ and $R = 0.61$, $p < 0.045$, respectively) (Figure 3).

There were no significant correlations of serum RBP-4 level with patient age, duration of stimulation, amount of gonadotropins used, number of oocytes retrieved, fertilization rate, or pregnancy rates.

**Discussion**

The present preliminary study shows that RBP-4 level is significantly decreased during COH until peak E2 is reached, with no significant difference after hCG administration. Furthermore, while serum RBP-4 level significantly correlated with patients’ BMI, fasting glucose or glucose to insulin ratio, there was no correlation between serum RBP-4 and patients’ age, IVF treatment variables or pregnancy rate.

The statistically significant correlation between serum RBP-4 and BMI demonstrated in our study, was also reported by others. Graham et al. [14] studied lean and obese, diabetic and non-diabetic subjects and found an association between RBP-4 and components of the metabolic syndrome, including increased BMI. Hahn et al. [19] assessed the correlation between metabolic and endocrine parameters with RBP4 levels in PCOS and...
healthy controls. They found RBP4 levels to positively correlate with BMI, body fat, and waist circumference. Moreover, while Barber et al. [23] observed a positive association between RBP-4 and visceral fat area in PCOS patients, Mohlig et al. [17] and Weiping et al. [20] demonstrated significant correlations between RBP-4 and lean body mass or waist-to-hip ratio (respectively), but not with BMI. Lack of correlation between RBP-4 and BMI in PCOS patients was also observed by Chan et al. [15].

In the present study we also observed significant correlations between RBP-4 levels and fasting insulin or glucose to insulin ratio - the latter reflects and inversely correlates with the degree of insulin resistance. These observations are consistent with previous reports by other groups [14, 17-20] that used several other measures to assess insulin resistance and glucose metabolism, including fasting glucose and area under the curve for glucose, oral or intravenous glucose tolerance test and the euglycemic-hyperinsulinemic clamp test. On the other hand, those who estimated insulin resistance by calculating the total insulin area under the curve on an oral glucose tolerance test [16], or by the homeostasis model assessment of insulin resistance using the formula: [{fasting insulin (mIU/ml) X fasting glucose (mg/dl)/18}/22.5] [15] could not confirm this correlation, and therefore suggested that RBP4 might not be a useful marker of insulin resistance and glucose metabolism.

The lack of association between serum RBP-4 and estradiol levels during ovarian hyperstimulation noted here, is consistent with previous reports by other groups [15, 17]. While Chan et al. [15] investigated the correlation of E2 and T with RBP-4 levels in PCOS patients and found that RBP-4 levels were not directly affected by T and estradiol, Mohlig et al. [17] could not demonstrate any correlation between RBP-4 and free testosterone, DHEAS, androstenedione, and estradiol. On the other hand, Tan et al. [21], while studying RBP4 expression from adipose tissue of overweight PCOS women, observed a significant increase in RBP-4 mRNA and protein expressions following exposure to estradiol. The solution to this discrepancy may lie in the known negative impact of obesity on patient response to COH or pregnancy outcome [24]. That is, the RBP-4 level may act as a confounding factor which positively correlates with obesity, rather than an independent variable affecting ovarian response to COH. We therefore conclude that in PCOS patients, while RBP-4 significantly correlates with BMI and the degree of insulin resistance and decreases during COH, it probably has no direct effect on follicular growth and maturation or ovarian response to COH.

To the best of our knowledge, the present preliminary study is the first to provide information on RBP-4 levels during COH. We observed a significant decrease in RBP-4 levels from Day-S to Day-hCG, with a non-significant increase after hCG administration. This trend is exactly opposite to that shown for serum E2 levels. Moreover, our study yielded no correlation of serum RBP-4 levels with serum estradiol level nor other IVF treatment variables (duration of stimulation, amount of gonadotropins used, number of oocytes retrieved, or fertilization rate) or pregnancy outcome. We therefore conclude that serum RBP-4 might not help in choosing the proper approach to COH nor aid fertility specialists and their PCOS patients in the decision-making process.

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A comparison of pregnancy rates following fresh and frozen embryo transfer according to the use of leuprolide acetate vs ganirelix vs cetrorelix

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Summary

Purpose: To determine if controlled ovarian hyperstimulation (COH) regimens using the gonadotropin releasing hormone (GnRH) agonist leuprolide acetate result in higher pregnancy and implantation rates than COH regimens using the GnRH antagonists cetrorelix or ganirelix following fresh and frozen embryo transfer. Methods: Retrospective analysis was performed evaluating the pregnancy rates with the first fresh and first frozen embryo transfer cycles according to which protocol was used. A haphazard decision was made on which protocol to use. Women were required to be < 40 years of age and have had ≥ 5 eggs retrieved. Results: Significantly lower implantation rates were seen with ganirelix compared to leuprolide acetate or cetrorelix. Conclusions: These data should hopefully encourage interest in a prospective study to determine if conclusions about the inferiority of ganirelix are not merely fortuitous.

Key words: Gonadotropin releasing hormone; Agonist, antagonist; Fresh and frozen embryo transfer.

Introduction

The use of gonadotropin releasing hormone (GnRH) agonists to be combined with gonadotropin stimulation for purposes of in vitro fertilization-embryo transfer (IVF-ET) was first described in 1988 [1]. This technique started the GnRH agonist in the mid luteal phase and become known as the “long protocol” [2]. One of the purposes of adding GnRH agonists was to prevent premature luteinizing hormone (LH) surge [3]. Prior to the use of GnRH agonists approximately 20% of controlled ovarian hyperstimulation cycles for IVF-ET had to be cancelled because of premature luteinization [4, 5].

The long acting GnRH agonists initially stimulate gonadotropins and then by ablating the pulsatility of FSH and LH secretion eventually suppress endogenous gonadotropins. Thus they have to be taken for a long length of time. The duration can be shorter than the three weeks used in the long protocol, but starting in mid-luteal phase when FSH and LH are maximally suppressed, provides the best chance for prevention of premature luteinization.

Development of GnRH antagonists where there is a substitution of two different amino acids in the decapeptide GnRH than the ones substituted for GnRH agonists occurred but they were too toxic to initially be introduced when GnRH agonists were introduced on the market. Eventually toxicity was reduced and these products were able to accomplish almost immediate gonadotropin suppression by blocking the GnRH receptor in a close dependent competitive fashion [6]. The main advantage of the GnRH antagonist over the agonist is the simplicity of the protocol. By starting it in the late follicular phase two cycles are not needed to achieve one controlled ovarian hyperstimulation. Also, elimination of the initial gonadotropin stimulation effects of GnRH agonists would help prevent follicular cysts.

However, one major disadvantage was that there were reports that the use of GnRH antagonist may lower the subsequent pregnancy rates when compared to GnRH agonists [7, 8]. The reason for the 5% difference in pregnancy rates in GnRH agonist vs antagonist protocols is not clear [7]. Various hypotheses for adverse effects of GnRH antagonists on oocytes, embryos, or endometrium have been proposed [8,9]. However some clinical trials found similar pregnancy rates between agonist and antagonist protocols [10-12].

The present study retrospectively evaluated pregnancy and implantation rates in similar types of patients according to whether they used GnRH agonists or antagonists. The GnRH antagonists used were either cetrorelix or ganirelix which are considered equally effective. Nevertheless, the possibility exists that there may be a difference between them as far as subsequent pregnancy or implantation rates. This study, therefore, was somewhat unique in that the pregnancy and implantation rates would be analyzed according to which antagonist was used. Finally the pregnancy and implantation rates would be analyzed following frozen embryo transfer according to the embryo having been formed by either agonist or antagonist and which antagonist was used. If, in fact, higher pregnancy or implantation rates were found with the GnRH agonist (as concluded by the aforementioned meta analysis) and if higher pregnancy rates with frozen...
embryo transfer in the agonist group were also found it would favor the adverse effect of an antagonist being on the oocyte or embryo. In contrast, if the fresh embryo but not frozen embryo pregnancy rates were lower with GnRH antagonists this would support that the adverse effect of GnRH antagonists was on the endometrium.

Materials and Methods

A retrospective cohort analysis of women having their first IVF cycles in our IVF center over a 3-year period was performed. Inclusion criteria were age ≤ 39.9 years and IVF cycles with ≥ 5 eggs retrieved.

The patients were first separated into antagonist and agonist (leuprolide acetate) groups. The antagonist group was further categorized by antagonist identity (ganirelix vs cetrorelix). The antagonists were administered with a 14 mm follicle at a dosage of 250 mcg daily. Leuprolide acetate began mid-luteal phase (10 IU) for ten days, then 5 IU through the follicular phase. Various brands of gonadotropins were utilized.

The decision on which COH regimen to use, i.e., agonist vs antagonist and which antagonist was not pre-determined but up to the choice of the physician. Frequently, the GnRH antagonists were used for timing convenience, i.e., the woman was already past mid-luteal and a whole month would be wasted if trying for an agonist protocol.

Results

Comparison of pregnancy rates following transfer of fresh embryos according to use of ganirelix vs cetrorelix or leuprolide acetate is shown in Table 1. The clinical pregnancy rates were significantly lower ($p < 0.05$) in ganirelix cycles as compared to the cetrorelix and leuprolide acetate cycles combined. There was a trend for lower pregnancy rates ($p = 0.080$) comparing ganirelix to cetrorelix alone. Implantation rates were significantly lower for ganirelix (21.7%, 95/437) versus cetrorelix (26.8%, 131/489) or leuprolide acetate (28.4%, 188/662) ($p < 0.01$).

Table 1. — Live delivered pregnancy and implantation rates according to use of GnRH agonist or antagonist, and which one.

<table>
<thead>
<tr>
<th></th>
<th>Ganirelix</th>
<th>Cetrorelix</th>
<th>Leuprolide acetate</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical pregnancy rate</td>
<td>37.7% (55/146)</td>
<td>48.8% (84/146)</td>
<td>48.1% (117/243)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Live delivered pregnancy rate</td>
<td>35.6% (52/146)</td>
<td>41.9% (72/146)</td>
<td>42.8% (104/243)</td>
<td>.349</td>
</tr>
<tr>
<td>Frozen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical pregnancy rate</td>
<td>30.8% (40/130)</td>
<td>47.2% (51/108)</td>
<td>42.0% (95/226)</td>
<td>.025</td>
</tr>
<tr>
<td>Live delivered pregnancy rate</td>
<td>28.5% (37/130)</td>
<td>36.1% (39/108)</td>
<td>35.4% (80/226)</td>
<td>.338</td>
</tr>
</tbody>
</table>

The table also shows pregnancy rates according to antagonist (and type) and agonist following frozen embryo transfer. A significantly lower clinical pregnancy rate per transfer was seen with ganirelix following frozen ET ($p = .025$).

No significant difference was found when comparing ongoing delivered pregnancy rates in either fresh or frozen ET cycles but the live/delivered pregnancy rates were still 20% lower with ganirelix.

Implantation rates were significantly lower with ganirelix (14.1%, 53/377) versus cetrorelix (24.7%, 73/295) versus leuprolide acetate (20.2%, 24/133) following frozen ET ($p < 0.01, p < 0.01$).

Discussion

For reasons still as yet undetermined, the use of the antagonist ganirelix during COH procedures yields both lower clinical pregnancy and implantation rates as compared to the antagonist cetrorelix and agonist leuprolide acetate. These data suggest that the lower rates may be attributable to adverse effects on the embryo rather than endometrium since the adverse effect was even more evident in frozen ET cycles.

Possibly one of the reasons for conflicting data as to whether antagonists adversely affect the chance of an embryo to implant may be related to which antagonist was studied. One should always be cautious about the conclusion made from a retrospective study, but the data suggests the need for a proper prospective study to better determine if ganirelix does, in fact, adversely effect embryo implantation.

A prospective study was proposed to the Ethics Committee for the Cooper Institute for Reproductive and Hormonal Disorders before requesting permission from the institutional review board of Cooper Hospital University Medical Center. The ethics committee concluded that in view of the data found in the respective study there would be no reason to subject a group of women placing their trust in physicians to provide the best medicine to treat them with a potentially inferior COH protocol that could lead to a lower pregnancy rate. Thus our IVF center will not be conducting the suggested prospective study to make sure that our findings that ganirelix rather than cetrorelix led to inferior pregnancy rates was not merely fortuitous. It is not clear why there should be a difference between the affect of these two antagonists. Possibly these data will encourage another reproductive center to perform this prospective study.

References


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The effect of endometriosis on pregnancy outcome following in vitro fertilization-embryo transfer (IVF-ET) in women with decreased egg reserve

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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 the effect of the presence of endometriosis on the delivered pregnancy rate following in vitro fertilization-embryo transfer. Methods: A retrospective cohort analysis of fresh or frozen embryo transfer in women with diminished egg reserve having IVF-ET and who also had had a laparoscopy. The data was analyzed as to whether endometriosis was present or not. Results: The data demonstrated that women with diminished egg reserve can achieve pregnancies following IVF-ET. The presence of endometriosis did not have any negative effects on pregnancy rates. Conclusions: At least in women with diminished egg reserve the presence of endometriosis did not impair outcome following IVF-ET.

Key words: Diminished egg reserve; Endometriosis; In vitro fertilization-embryo transfer.

Introduction
Endometriosis is one of the most common gynecologic disorders and is significantly more prevalent in the setting of infertility [1, 2]. The prevalence of endometriosis in infertile women ranges from 25-50% compared to 5% in fertile women [2]. There are data suggesting that minimal or mild endometriosis may be associated with decreased fertility potential [3-6].

The majority of women with mild endometriosis have their infertility problem resolved by correcting luteal phase deficiencies and correcting the luteinized unruptured follicle syndrome [7]. However it has been demonstrated that the removal of mild endometriosis in women who have been resistant to treatment can improve pregnancy rates [8, 9].

Some infertile women with endometriosis resistant to conservative therapy conceive following in vitro fertilization-embryo transfer (IVF-ET) without surgically correcting the endometriosis [7]. However in some instances, especially Stage III-IV endometriosis, there are data suggesting reduced fertilization rates with IVF as compared to women with milder endometriosis [10, 11]. Some studies show that removing the endometriosis surgically can improve success rates following IVF-ET including women previously failing with IVF-ET [12-14]. However other studies have failed to find that removal of endometriosis improves IVF-ET outcome [7].

Another area of controversy is whether successful pregnancies are possible in women with elevated serum FSH with IVF-ET. Many early studies found that women with serum FSH on day 3 were not likely to achieve pregnancies even with IVF-ET [15-20]. Even recently a study from one of the world’s most successful IVF centers found that if the serum FSH was > 15 mIU/ml, they had no live pregnancies following the transfer of what appeared to be normal embryos and they strongly suggested that the patient should proceed to donor eggs under these conditions [21].

Not all studies share this negative experience [22, 23]. Pregnancy rates have been as high as 38-42% in women aged 39 and under with 6-8 cell single embryo transfers [23]. The different experience has been attributed to using much less stimulation [24]. There have even been some cases of overt ovarian failure that have had live deliveries following IVF-ET [25, 26].

The present study was initiated to determine if endometriosis exerts any adverse effect on women with diminished egg reserve.

Materials and Methods
A retrospective review was performed during a 4-year time period (2000-2004) of infertile women having had a laparoscopy and who had a day 3 serum FSH > 12 mIU/ml and who were undergoing IVF-ET. The women were stratified according to whether endometriosis was present or not. The women were 38 years of age.

The delivered pregnancy rate was determined for the first transfer. The delivered pregnancy rate was also calculated for the first four transfers (fresh or frozen) unless pregnancy occurred first. There were no restrictions for number of eggs retrieved. Most often minimal or natural protocols were used [23, 24].
Results

For women < age 38 (n = 18), the median age was 36. Endometriosis was present in 77.7% (n = 14).

The median serum FSH was 17 mIU/ml in the group without endometriosis while the median serum FSH was 18 mIU/ml in the group with endometriosis.

The delivered pregnancy rates (first embryo transfer) for women age ≤ 38 without endometriosis was 50% (2/4) and for those with endometriosis – 28.6% (4/14).

The delivered pregnancy rate (up to 4 cycles) without endometriosis was 75% (3/4) and with endometriosis 64.3% (9/14).

Discussion

These data confirm that live delivered pregnancies are possible following IVF-ET despite diminished egg reserve. There was a 33.3% live delivered pregnancy rate (up to 4 cycles) and for those with endometriosis – 28.6% (4/14).

For women < age 38 (n = 18), the median age was 36. Endometriosis was present in 77.7% (n = 14).

The median serum FSH was 17 mIU/ml in the group without endometriosis while the median serum FSH was 18 mIU/ml in the group with endometriosis.

The delivered pregnancy rates (first embryo transfer) for women age ≤ 38 without endometriosis was 50% (2/4) and for those with endometriosis – 28.6% (4/14).

The delivered pregnancy rate (up to 4 cycles) without endometriosis was 75% (3/4) and with endometriosis 64.3% (9/14).

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Association of the change in serum estradiol (E2) levels from the day of to the day after human chorionic gonadotropin (hCG) injection and pregnancy outcome following in vitro fertilization-embryo transfer (IVF-ET) in less than average responders

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Summary

Purpose: To determine if the change in serum estradiol (E2) from the day of human chorionic gonadotropin (hCG) injection to the day after predicts pregnancy and implantation rates following in vitro fertilization-embryo transfer (IVF-ET) in less than average responders. Methods: A retrospective cohort analysis was performed in women with less than average follicular response as defined by a peak serum E2 on the day of hCG of < 1500 pg/ml despite a maximum stimulation gonadotropin protocol. Pregnancy and implantation rates were compared in five groups based on standard deviation (SD) below or above the mean. Results: No differences were found in outcome in any groups including those that were 1-2 SD below the mean or within 1 SD below the mean or up to 2 SD above the mean. The group that was 2 SD above the mean seemingly had higher pregnancy and implantation rates but there were insufficient numbers to allow statistical comparisons. There did not appear to be any confounding variables among these groups. Conclusions: A drop in serum E2 in a group of women that were less than average responders was not associated with a lower chance of conception following IVF-ET.

Key words: In vitro fertilization; Serum estradiol change; Human chorionic gonadotropin injection; Pregnancy outcome.

Introduction

In the early days of in vitro fertilization there was a report that women with tubal disease who exhibited a drop in their serum estradiol (E2) values after exogenous human chorionic gonadotropin (hCG) during in vitro fertilization (IVF) cycles infrequently become pregnant [1]. The authors even suggested cancellation of the retrieval if the serum E2 dropped [1].

However, another study published 13 years later did not find any difference in clinical pregnancies in women whose serum E2 dropped > 10% the day after hCG injection, plateaued or increased > 10% [2].

The women studied in the aforementioned study were generally normal responders [2]. Thus the conclusions reached may not apply to less than average responders. The present study evaluated the effect of the difference in serum E2 on the day of vs the day after the hCG injection in women who were less than average responders.

Materials and Methods

A retrospective study was performed over an 8-year time period to evaluate subpar responders who did not attain a serum E2 of 1500 pg/ml on the day of hCG injection. Only transfers with a minimum of two embryos were evaluated in women age ≤ 39.

The data were not stratified by type of gonadotropin or gonadotropin releasing hormone (GnRH) antagonist or agonist (ganirelix or cetrorelix). The data were stratified according to five groups – two groups where the serum E2 was 1 or 2 standard deviations (SD) below the mean or up to 1 SD below the mean or up to 2 SD above the mean. The group that was 2 SD above the mean seemingly had higher pregnancy and implantation rates but there were insufficient numbers to allow statistical comparisons. There did not appear to be any confounding variables among these groups.

Conclusions: A drop in serum E2 in a group of women that were less than average responders was not associated with a lower chance of conception following IVF-ET.

Results

The mean percent rise in serum E2 on the day after hCG injection was 25% with a SD of 14%. The clinical and live/delivered pregnancy rates and implantation rates according to four groups based on the percentage increase rise of serum E2 the day after hCG injection is shown in Table 1. There were no significant differences in these outcome parameters according to E2 response.

The average age and the serum levels of E2 on the day of and the day after hCG injection is presented in Table 2 as are the average number of mature eggs retrieved.

There were only seven cases with E2 3 SDs above the mean so the data could not be compared. The average age for this group was 32.4. The serum E2 levels the day of and day after hCG were 1001.1 and 4892.3. The average
number of mature eggs was four. Clinical and delivered pregnancy rates were 85.7% and 85.7%, respectively, and the implantation rate was 47.4%. However for the other four groups there did not appear to be any advantage from having a higher serum E2 the day after hCG injection.

Discussion

These data in women with somewhat diminished egg reserve as manifested by generating a maximum serum E2 < 1500 pg/ml on the day of hCG reached the same conclusions as women with normal egg reserve that a drop in the serum E2 level the day after the hCG injection does not predict a lower pregnancy rate [2]. The data was not analyzed as previously, i.e., < 10% within 10% or > 10% which we believed more arbitrary. Instead we thought that from a scientific standpoint an evaluation according to standard deviation was more appropriate.

Table 1. — Clinical and live/delivered pregnancy rates and implantation rates according to four groups based on the percentage increase or decrease in rise of serum E2 the day after hCG injection.

<table>
<thead>
<tr>
<th>Group</th>
<th>1-2 SD below the mean</th>
<th>Within 1 SD below the mean</th>
<th>Within 1 SD above the mean</th>
<th>1-2 SD above the mean</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical pregnancy rate</td>
<td>32.1% (18/56)</td>
<td>42.6% (58/136)</td>
<td>35.5% (49/138)</td>
<td>44.8% (13/29)</td>
<td>.398</td>
</tr>
<tr>
<td>Live/delivered pregnancy</td>
<td>30.4% (17/56)</td>
<td>39.7% (54/136)</td>
<td>31.2% (43/138)</td>
<td>27.6% (8/29)</td>
<td>.343</td>
</tr>
<tr>
<td>rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implantation rates</td>
<td>17.5% (30/171)</td>
<td>21.2% (90/425)</td>
<td>20.2% (80/138)</td>
<td>21.2% (18/85)</td>
<td>.790</td>
</tr>
</tbody>
</table>

Table 2. — Average age and serum levels of E2 on the day of and the day after hCG injection.

<table>
<thead>
<tr>
<th># transfers ≥ 2 embryos</th>
<th>≤ 11%  2 SD below</th>
<th>12-25% 1 SD below</th>
<th>26-40% 1 SD above</th>
<th>41-55% 2 SD above</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age</td>
<td>35.8</td>
<td>35.6</td>
<td>34.6</td>
<td>33.5</td>
<td></td>
</tr>
<tr>
<td>Avg. E2 levels day of hCG (pg/ml)</td>
<td>1049.7</td>
<td>1050.6</td>
<td>976.4</td>
<td>976.1</td>
<td></td>
</tr>
<tr>
<td>Avg. E2 levels post-hCG (pg/ml)</td>
<td>1118.9</td>
<td>1297.2</td>
<td>1435.9</td>
<td>1813.9</td>
<td></td>
</tr>
<tr>
<td>Avg. no. mature eggs retrieved</td>
<td>5.2</td>
<td>5.6</td>
<td>6.2</td>
<td>8.2</td>
<td></td>
</tr>
</tbody>
</table>

References


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**General Section**

**Effects of tamoxifen on tissue nitrite/nitrate levels and plasma lipid peroxidation in female rats**

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¹Department of Obstetrics and Gynecology, Ege University School of Medicine
²Department of Biochemistry, Ege University School of Medicine, Izmir (Turkey)

Summary

**Purpose of investigation:** The effects of tamoxifen on lipid peroxidation and oxidant-antioxidant balance in an animal model were studied. **Methods:** Twelve female adult rats were divided into two groups and DMSO and tamoxifen dissolved in DMSO were administered. Tissues taken from the brain, liver and ovary of rats were dissected. MDA, nitrite, nitrate levels and plasma LDL oxidation in brain, ovary and liver tissues were measured and compared. **Results:** Induced LDL MDA levels were significantly lower in the tamoxifen group (p = 0.009), MDA levels in the liver were significantly lower in the tamoxifen group whereas nitrite levels were found significantly higher (p < 0.05). **Conclusion:** Tissue and serum samples were collected in the experimental surgical laboratory and the tissues were analyzed in the laboratory of the Biochemistry Department. Two groups were formed in accordance with the purpose of the study:

Group 1 (DMSO group) (n = 6): No surgical intervention or medical therapy was performed to female rats included in this group. The rats were administered dimethyl sulphoxide (DMSO) solution which is used as the solvent of tamoxifen.

Group 2 (Tamoxifen group) (n = 6): A dose of 0.2 mg/kg/day tamoxifen dissolved in DMSO was administered intraperitoneally to female rats once daily for 12 days.

After the appropriate anesthesia blood was collected from rats by cardiac injection in both groups two hours after the last dose of treatment. Then laparotomy was performed and tissue samples were collected on ice. The brain, liver and ovary tissues of the decapitated rats were dissected on ice. The tissue samples were kept in a freezer at a temperature of -80°C until the day of biochemical analysis.

Analysis performed on plasma samples

Plasma samples were incubated at room temperature for 30 min with a commercial precipitant reagent (Merck), proposed by Taus et al. [6]. After centrifugation at 1,600 g for 10 min, LDL samples were solubilized by 0.15 M sodium hydroxide. LDL oxidation was assessed by basal and induced malondialdehyde (MDA) in samples containing 200 μg of protein.

Measurement of basal malondialdehyde (MDA) was performed by addition of thiobarbituric acid to the tissue homogenate. This solution was boiled at 100°C for 20 min and centrifuged for 10 min at 2000 rpm. The supernatants were analyzed at a wavelength of 532 nm.

LDL-oxidation was induced by addition of 1 mmol of copper sulfate (CuSO4) and was observed over three hours at 10-min intervals at a wavelength of 234 nm. Peak oxidation was detected at 109.2 ± 9.4 min (n: 10). Then at this point (110th min) MDA measurement was repeated for induced LDL-MDA levels. The results were given in nmol/mg LDL protein. Protein measurements were performed according to Lowry’s method [7].

Key words: Tamoxifen; MDA; Nitrite; Nitrate.

**Introduction**

Tamoxifen is a non-steroid estrogenic agent that displays both estrogen agonist and antagonist activity and it is highly effective in the adjuvant therapy of breast cancer [1, 2]. Tamoxifen has mixed estrogenic agonist and antagonist effects and this may cause protective effects regarding cardiovascular diseases [3].

The potential mechanisms of tamoxifen on breast cancer chemoprophylaxis have not yet been completely understood and probably are beyond simple anti-estrogenic activity. In recent years the major aspect of tamoxifen has been the effect on lipid peroxidation and oxidant-antioxidant balance [4]. Breast cancer cells have been demonstrated to proliferate by decreasing lipid peroxidation and the effects of tamoxifen on lipid peroxidation may help us understand its anticancer activity [5]. The focus of this study was to investigate the effects of tamoxifen on lipid peroxidation and oxidant-antioxidant balance in an animal model. Clarification of the effects of tamoxifen on lipid peroxidation may help to reveal the mechanism of its antineoplastic activity. The present study will also clarify the long-term effects of tamoxifen on lipid metabolism and oxidant-antioxidant balance.

**Materials and Methods**

**Animals and treatments**

Twelve female adult rats were used in the study after permission was given by the Animal Ethics Committee of the Faculty of Medicine, Ege University School of Medicine. Rats were approximately nine to ten weeks old and all were fed with a standard diet (pellet feed) under standard daylight (12 hours of light, 12 hours of darkness) and heat conditions (approximately 20°C). Tissue and serum samples were collected in the experimental surgical laboratory and the tissues were analyzed in the laboratory of the Biochemistry Department.

Two groups were formed in accordance with the purpose of the study:

Group 1 (DMSO group) (n = 6): No surgical intervention or medical therapy was performed to female rats included in this group. The rats were administered dimethyl sulphoxide (DMSO) solution which is used as the solvent of tamoxifen.

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**Conclusion**

Tissue and serum samples were collected in the experimental surgical laboratory and the tissues were analyzed in the laboratory of the Biochemistry Department. Two groups were formed in accordance with the purpose of the study:

Group 1 (DMSO group) (n = 6): No surgical intervention or medical therapy was performed to female rats included in this group. The rats were administered dimethyl sulphoxide (DMSO) solution which is used as the solvent of tamoxifen.

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Results

The levels are expressed in mean ± standard deviation. The Mann-Whitney U-test was used to compare groups.

Statistical Analysis

Statistical analysis was performed using the SPSS 11.0 program. The Mann-Whitney U-test was used to compare groups. The levels are expressed in mean ± standard deviation.

Results

Plasma LDL Oxidation. LDL-MDA levels were assessed in terms of basal and induced levels in both groups. Basal plasma LDL-MDA level was 0.9 ± 0.27 nmol/mg LDL protein (0.55 - 1.20) in the DMSO group whereas it was 0.74 ± 0.22 nmol/mg LDL protein (0.41 - 0.99) in the tamoxifen group (p = 0.283). The induced level of LDL-MDA was 6.14 ± 1.72 nmol/mg LDL protein (1.78 - 9.14) in the DMSO group. Plasma induced LDL-MDA level was 3.2 ± 1.23 nmol/mg LDL protein (1.50 - 5.23) in the tamoxifen group. The induced levels of LDL-MDA were significantly lower in the tamoxifen group (p = 0.009).

Ovarian tissue. Level of MDA was 0.93 ± 0.13 nm/g wet tissue (0.76 - 1.16) in the DMSO group and 0.79 ± 0.27 nm/g wet tissue (0.49 - 1.21) in the tamoxifen group (p = 0.304). Nitrite level was 7.98 ± 6.63 micromole/g wet tissue (4.65 - 21.40) in the DMSO group and 5.58 ± 1.04 micromole/g wet tissue (4.65 - 7.21) in the tamoxifen group (p = 0.401).

Nitrate level was 245 ± 9.43 micromole/g wet tissue (227.30 - 254.63) in the DMSO group; 258 ± 3.58 micromole/g wet tissue (253.99 - 263.95) in the tamoxifen group and a significant difference was detected between nitrate levels in the ovarian tissue (p = 0.004).

Total nitrite-nitrate (NO) level was 253 ± 12.5 micromole/g wet tissue (232.18 - 270.56) in the DMSO group, but total nitrate-nitrate level measured 263 ± 4.26 micromole/g wet tissue (258.64 - 270.23) in the tamoxifen group (p = 0.093) (Table 1).

<table>
<thead>
<tr>
<th></th>
<th>DMSO</th>
<th>Tamoxifen</th>
<th>DMSO</th>
<th>Tamoxifen</th>
<th>DMSO</th>
<th>Tamoxifen</th>
<th>DMSO</th>
<th>Tamoxifen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrite (nmol/mg)</td>
<td>1.49</td>
<td>± 1.74</td>
<td>1.59</td>
<td>± 1.66</td>
<td>7.98</td>
<td>± 5.58</td>
<td>6.63</td>
<td>± 1.04</td>
</tr>
<tr>
<td>Nitrate (nmol/mg)</td>
<td>205.33</td>
<td>± 219.31</td>
<td>256.93</td>
<td>± 257.03</td>
<td>245.51</td>
<td>± 257.73</td>
<td>22.28</td>
<td>± 21.55</td>
</tr>
<tr>
<td>MDA (nmol/mg)</td>
<td>0.76</td>
<td>± 0.63</td>
<td>0.69</td>
<td>± 0.66</td>
<td>0.93</td>
<td>± 0.79</td>
<td>0.65</td>
<td>± 0.13</td>
</tr>
</tbody>
</table>

* p = 0.026; ‡ p = 0.043; † p = 0.004

Discussion

Breast cancer is the most common type of cancer among women and is the second leading malignancy in mortality following lung cancer [8]. Tamoxifen exhibits high activity in adjuvant hormonal chemotherapy and chemoprophylaxis in breast cancer [9]. The prophylactic use of tamoxifen has been recommended for patients even
without residual disease. The generally accepted approach is 5-year adjuvant use of tamoxifen although it increases the risk of developing endometrial pathologies [10] and carries a risk for venous thromboembolism [11, 12].

The mechanisms of tamoxifen action have not yet been well understood; however, they are probably beyond simple anti-estrogenic activity. Tamoxifen binds to estrogen receptors and modulates transcriptional activities in different ways in different target tissues [13].

In our study significant differences between the DMSO and tamoxifen groups with regard to LDL-MDA levels were not determined by the analysis of plasma LDL oxidation. However, induced LDL-MDA levels were significantly lower in the tamoxifen group. These findings support the studies revealing that tamoxifen reduces or prevents LDL oxidation and reporting that tamoxifen influences lipid peroxidation [14].

One of the compounds developing at the terminal stage of lipid peroxidation is MDA which is used for the determination of lipid peroxide levels. In our study MDA levels in ovary, brain and liver tissues were separately examined and the effect of tamoxifen on lipid peroxidation at the tissue level was investigated. No significant difference with respect to MDA levels in ovary and brain tissues was detected between groups; however, MDA levels were significantly lower in liver tissue. MDA, which is formed as a result of tissue lipid peroxidation, is metabolized to the cellular level. The enzymatic destruction of MDA in the liver is caused by aldehyde dehydrogenases and it is metabolized to CO2. MDA is known to have mutagenic features and behaves like a chemical carcinogen [15]. Tamoxifen lowers MDA levels in tissue by its effects on lipid peroxidation and this may contribute to the potential useful effects of tamoxifen in long-term use.

Water, ultrafiltrate and plasma nitric oxide oxidize rapidly to nitrite, the stability of which may take hours. However, nitrite is rapidly converted to nitrate in full blood. Nitrites and nitrates lack biological activity but each one is a good indicator to reveal endogenous nitric oxide production. Nitrite and nitrate levels in the tissues were also analyzed in our study. Nitrite levels did not show significant differences between placebo and tamoxifen groups in ovarian and brain tissues; on the other hand, nitrite levels in the liver tissue of the tamoxifen-administered group were significantly higher. No significant difference was determined between groups in terms of nitrate levels in the liver and brain tissues, but nitrate levels were significantly higher in the ovaries of the tamoxifen group.

Higher levels of nitrate in the liver tissue and nitrate in the ovarian tissue in the tamoxifen group is detected with unclear effects of tamoxifen. Nitric oxide is an autacoid which may display both inflammatory and anti-inflammatory activity. Additionally, it may have antioxidant activity. Nitrite and nitrate levels which were indirect criteria of nitric oxide are effected by the tamoxifen activity.

The long duration of antiestrogenic activity of tamoxifen may negatively affect the function of numerous tissues such as endothelium of the blood vessels [16].

Endothelial function may be adversely affected both by the antiestrogenic effects of tamoxifen and its indirect effect on nitric oxide levels.

In conclusion, the study shows that tamoxifen does not have a negative effect on plasma lipid peroxidation; moreover, it reduces LDL oxidation.

References


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Successful treatment of a female with chronic pseudo-intestinal obstruction with sympathomimetic amines and thyroid hormone replacement

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Introduction

Sympathomimetic amines may be an effective therapy for a wide variety of medical illnesses and conditions, especially found in women, linked by capillary permeability defects as the etiologic factor [1]. Various pain syndromes have been quickly and effectively treated with sympathomimetic amines despite failure to respond to various other therapies [2-4].

Some of the pain syndromes that have shown dramatic improvement with treatment using dextroamphetamine sulfate, despite unresponsiveness to other therapies, include esophageal disorders and gastroparesis [5, 6].

The case report described herein demonstrates the usefulness of sympathomimetic amines for another cause of gastrointestinal pain – pseudo-intestinal obstruction.

Case Report

The patient was diagnosed with chronic pseudo-intestinal obstruction at age 23. As a child she had no problems with growth (was in the 98th percentile at one point) but at five years of age her growth completely stopped for one and a half years.

After extensive testing she was diagnosed by colonoscopy with chronic pseudointestinal obstruction. She responded to sulfasalazine therapy and she was diagnosed with idiopathic orthostatic edema. Treating physicians did not believe that this condition could be solely responsible for the chronic pseudointestinal obstruction. Her family history was important in that her mother, who had typically market because of increased risks of cardiac complications. She pursued an opinion from our office to exclude an endocrinological cause of her problem. Adrenal insufficiency was excluded by a 4:00 p.m. serum cortisol of 21.6 μg/dl (nl 3.1-16.7). The free-thyroid level was slightly low at 0.5 ng/dl (nl 0.7-1.8) with a low thyroid stimulating hormone (TSH) level of < 0.01 (nl .35-5.50). She was thus diagnosed with hypothalamic hypothyroidism. Her serum thyroxin level was also low normal at 2.1 μg/dl (nl 4.5-10.9).

Though she may have had hypothalamic hypothyroidism her treating physicians did not believe that this condition could be solely responsible for the chronic pseudointestinal obstruction. Her family history was important in that her mother, who had to temporarily stop jogging because of pain in her thighs, was diagnosed with idiopathic orthostatic cyclic edema. Treatment with sympathomimetic amines results in dramatic improvement.

Key words: Chronic pseudointestinal obstruction; Sympathomimetic amines; Orthostatic edema; Hypothalamic hypothyroidism.

Summary

Purpose: To determine if a defect in sympathomimetic amines, which is a common cause of various undiagnosed pain syndromes in women could be the cause of chronic pseudointestinal obstruction. Furthermore to determine if this life-threatening illness may similarly respond to sympathomimetic amines as in other pain syndromes, e.g., pelvic pain and interstitial cystitis. Method: A 23-year-old, five foot, female with chronic pseudo-intestinal obstruction, who lost 35 pounds down to 75 pounds, was treated with 15 mg dextroamphetamine sulfate and 50 μg of L-thyroxin (her TSH thyroid hormone level was markedly suppressed in the face of a slightly low free thyroxin level. Results: Her abdominal pain lessened then completely disappeared within a few weeks. Within one year she gained 25 pounds. Conclusions: Chronic pseudo-intestinal obstruction is another way idiopathic orthostatic edema (a condition found predominantly in women) may manifest. Similar to other gastrointestinal pain syndromes and pain in other areas, e.g., pelvis, bladder, head and joints, treatment with sympathomimetic amines results in dramatic improvement.

Key words: Chronic pseudointestinal obstruction; Sympathomimetic amines; Orthostatic edema; Hypothalamic hypothyroidism.
The patient on close questioning had a lot of the classic symptoms of idiopathic orthostatic cyclic edema including abdominal distention, and a ten pound weight gain prior to the gastrointestinal syndrome (which subsequently limited her ability to eat and caused the weight loss), fluid retention, and pain and swelling in the joints [1]. Thus in addition to 50 mcg of levothyroxin for the hypothalamic hypothyroidism she was treated with dextroamphetamine sulfate (15 mg daily).

Her response to therapy was dramatic. Her pain over several weeks disappeared as did her early satiety. Her bowel movements became regular. She gained 25 pounds to attain her present weight at age 25 of 101 pounds. She is able to eat all types of food including milk products.

Despite taking 50 μg of L-thyroxin her serum TSH level has increased into the normal range (1.77 mIU/ml). This suggests that the hypothalamic pituitary hypothyroidism was a consequence of the weight loss and diminished body fuel. Eventually an attempt will be made to stop the L-thyroxin but there is no intention at present to stop the dextroamphetamine sulfate.

**Discussion**

Chronic pseudointestinal obstruction represents a rare and highly morbid syndrome characterized by impaired gastrointestinal propulsion together with symptoms and signs of bowel obstruction in the absence of any lesions occluding the gut lumen [7]. Medical and surgical therapies are often unsatisfactory and long-term outcome turns out to be poor in the vast majority of cases [8].

The dramatic improvement in a short time following treatment with sympathomimetic amine therapy strongly suggests that the improvement was related to the therapy as was demonstrated in other pain syndromes involving possible gastrointestinal motility disorders [5, 6].

Related to the weight loss she developed hypothalamic pituitary type hypothyroidism. This diagnosis was evident by the return of her serum TSH into the normal range despite thyroid hormone replacement once her weight was restored.

It is ironic that a drug considered to be an appetite suppressor used to lose weight would be able to restore the weight of this young lady by improving the intestinal motility defect.

This disorder of sympathomimetic amines, with a 10:1 female/male ratio, frequently manifested by weight gain, edema and nocturia refractory to diet may be associated with a variety of refractory pain disorders. Added to the list should now be chronic pseudointestinal obstruction. This disorder is potentially life-threatening. It may have various etiologies so it is not clear what percentage of patients will respond to treatment. Other questions include whether the improvement is limited to females. There are generally few if any side-effects in dosages up to 30 mg of dextroamphetamine sulfate. The condition of idiopathic edema is a common cause of obscure treatment refractory conditions. Unfortunately it is frequently not considered in the differential diagnosis by the majority of physicians.

**References**


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Emergency obstetric hysterectomy at two tertiary centers: a clinical analysis of 11 years experience

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Summary

This was a retrospective clinical study of emergency hysterectomy performed between 1997 and 2007 at two tertiary hospitals to study incidence, indications and maternal mortality. We included all women who required emergency hysterectomy to control major postpartum hemorrhage after delivery, following a pregnancy of at least 24 weeks’ gestation, regardless of the mode of delivery. There were 12 emergency hysterectomies, with a frequency of 0.0726% among 16,521 deliveries. Indications included uterine atony (4 cases), uterine rupture (3 cases), uterine retroversion (2 cases), abnormal placentalation (2 cases) and amniotic fluid embolization (1 case). The result was two maternal deaths. Although emergency obstetric hysterectomy is a life saving operation, it is associated with high maternal mortality.

Key words: Obstetric hysterectomy; Postpartum hemorrhage; Cesarean hysterectomy.

Introduction

Obstetric hemorrhage can potentially and rapidly become a life-threatening event and is still a major cause of maternal mortality across the world [1]. Over the past decade, the number of cesarean deliveries has increased and also the number of pregnant women with a scarred uterus from prior uterine incision. These patients with a scarred uterus are susceptible to many serious complications, such as uterine rupture, placenta previa and morbidly adherent placenta [2]. Although advances have been made in the development of conservative medical and surgical treatment of major obstetric hemorrhage, emergency peripartum hysterectomy is a life saving procedure, which is usually performed as a last resort for a variety of indications with massive uncontrollable intraoperative or postpartum hemorrhage [1, 3]. Obstetricians should be prepared to perform such operations safely as hysterectomies in those circumstances are different from those performed in gynecological surgery [2].

The purpose of the present study was to estimate the incidence, indications and maternal mortality associated with emergency peripartum hysterectomies performed at two tertiary Greek hospitals.

Material and Methods

In this retrospective clinical study performed between 1997 and 2007 at the maternal units of “Tzaneio” General Hospital, Piraeus and “Chatzikosta” Hospital, Ioannina, Greece we found all the cases of emergency peripartum hysterectomies. All cases were performed as an emergency at the time of cesarean section or in the immediate postpartum period due to life-threatening bleeding unresponsive to conservative measures within 24 hours of a delivery. The conservative treatments involved both surgical and medical interventions, such as fundal massage, bimanual uterine compression, use of blood products, administration of oxytocin and prostaglandins and curettage of the placental bed. All cesarean hysterectomies or hysterectomies after vaginal delivery described were performed after 24 weeks’ gestation.

The result was two maternal deaths. Although emergency obstetric hysterectomy is a life saving operation, it is associated with high maternal mortality.

Results

During the study period there were 16,521 deliveries and 5,360 were by cesarean section. In this period, 12 emergency hysterectomies were performed, with a frequency of 0.0726%; seven emergency hysterectomies were performed after cesarean section and five after normal labor (including vaginal-assisted delivery with the use of a vacuum). Among the seven cases after cesarean section, four were after previous cesarean section; four of the women were primiparas and eight multiparas. Abnormal vaginal bleeding was the reason in all cases. Indications included uterine atony (4 cases), uterine rupture (3 cases), uterine retroversion (2 cases), abnormal placentalation (2 cases) and amniotic fluid embolization (1 case). Total hysterectomies were done for all cases. There were no operative complications such as a bladder injury or ileus and none of the patients had oophorectomy. The result was two maternal deaths and three stillborns. Maternal death was due to consumptive coagulopathy in one case and amniotic fluid embolization in the other.

Discussion

Emergency peripartum hysterectomy (EPH) is not commonly performed and is almost always done in the setting of life threatening hemorrhage during or immediately after abdominal or vaginal deliveries. The incidence of peripartum obstetric hysterectomy in our units is 0.726
per 1,000 mothers delivered and this is in agreement with the incidence reported in the English literature, which varies from 0.2 to 1.3 per 1,000 deliveries [2, 4-7]. In our study, the indications for EPH were uterine atony (4 cases), uterine rupture (3 cases), uterine retroversion (2 cases), abnormal placentaion (2 cases) and amniotic fluid embolization (1 case). Chestnut et al. [8] found that the major indication for the procedure was uterine rupture followed by uterine atony and placenta accreta. Clark et al. [9] reported uterine atony (43%) to be the most common cause of emergency peripartum hysterectomy followed by placenta accreta (30%) from 1978 to 1982. However, Stanco et al. studied the same population from 1985 to 1990 and found that placenta accreta (50%) had become the most frequent cause with uterine atony accounting for 21% of cases [6]. Similarly, Zelop et al. found placenta accreta (64%) and uterine atony (20%) the most common reasons for emergency peripartum hysterectomy [7]. In addition, Kastner et al. found placenta accreta (49%) and uterine atony (30%) the most common indications for emergency peripartum hysterectomy [10]. In the study of Selo-Ojeme et al. hemorrhage due to placenta previa was the main indication for emergency peripartum hysterectomy (47%) [1]. It seems that there were an increased proportion of hysterectomies being done for abnormal placentation and a decreasing proportion for uterine atony compared to those performed in the past. The reasons behind these observed changes are perhaps threefold. Firstly, the medical management of uterine atony has improved since the introduction of agents such as prostaglandin F2α together with concomitant improvement in anesthetic and hematological support [11]. Secondly, a reduction in forceps deliveries in favor of ventouse or cesarean section may have reduced uterine trauma following vaginal delivery [11]. Thirdly, another main reason may be due to an increase in the number of cesarean deliveries over the past decade, as cesarean delivery is a well established risk for the development of placenta previa and accreta [2]. Previous cesarean section is known to increase the risk of placenta accreta occurring from 0.25% in the unscarred uterus to 0.65% following one cesarean section, rising to 10% following four or more cesarean sections. In addition, history of curettage is a risk factor associated with placenta accreta. As regards the prevalence of placenta previa, it increases from 24% following one uterine scar to 67% following four or more cesarean sections [4, 11]. However, an association between placenta previa and previous curettage has not been clearly shown [12-14]. Ananth et al. found a strong association between a history of abortion and the subsequent development of placenta previa [15].

Total hysterectomy is probably the favored procedure for most obstetricians-gynecologists, but does increase the risk of urinary tract injury when compared with the technically simpler subtotal operation [11]. Problems with the cervical stump have been reported in up to 11.4% of cases following subtotal hysterectomy, and usually consist of cyclical vaginal bleeding and discharge. Subsequent cervical stump carcinoma is extremely rare, but evidently continued cytological surveillance is necessary [11]. Conservative surgical measures to preserve the uterus after life threatening hemorrhage during or immediately after abdominal or vaginal deliveries when the reason for the hemorrhage is not placenta accreta include vaginal or uterine packing and the B-Lynch brace suture [11]. Ligation of the internal iliac arteries may be effective, but it remains a very hazardous procedure, even in experienced hands, with risk of trauma to the internal iliac vein [11]. In 1985, Clark et al. reviewed the hospital records of 19 cases of bilateral hypogastric artery ligation for obstetric hemorrhage and found that ligation was only 42% effective at hemostasis, an increase in blood loss and operating time was noted, as well as an increase in the number of complications such as ureteral injury and cardiac arrest. These observations led them to recommend hypogastric artery ligation only for hemodynamically stable patients of low parity [16]. Selective arterial embolization is probably the most effective conservative option in the control of pelvic bleeding, preserving the uterus and hence future fertility, while reducing patient morbidity and length of hospitalization by avoiding further surgery [11].

Emergency postpartum hysterectomy is associated with significant blood loss and need for transfusion. Postoperative complications are common and longer hospitalization inevitable [17]. Overall morbidity was reported in the range of 30-40% [2]. Gonsoulin et al. found that the incidence of transfusion was 68% in emergency cases and 14.6% in elective ones [18]. Urological injuries are usually related to scarring from previous cesarean deliveries encountered when dissecting the bladder from the lower uterine segment [7]. In our study, no bladder lesions occurred, but there were two maternal deaths.

Conclusion

Early intervention and proper technique facilitate good outcome. Experienced obstetricians can accomplish cesarean hysterectomy with speed, moderate blood loss and acceptable morbidity. Therefore, obstetricians should continue to be trained in major pelvic surgery.

References

Emergency obstetric hysterectomy at two tertiary centers: a clinical analysis of 11 years experience


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Comparision of reproductive outcome of the women with hypogonadotrop hypogonadism and tubal factor infertility

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Summary

Objective: To evaluate the outcome of women with hypogonadotrophic hypogonadism (HH) undergoing in-vitro fertilization (IVF). Materials and Methods: Data from 13 cycles of ten hypogonadotrophic patients treated with in vitro fertilization from the period January 2006 to January 2008 were analyzed and compared with treatment results from 20 patients with tubal factor infertility (TI). All patients underwent ovarian hyperstimulation for IVF/ICSI at the same center. HH patients initiated the treatment by receiving daily injections of hMG. The patients in the control group were given the same dosage of recombinant FSH. Results: Demographic characteristics of the patients were comparable. Mean duration of stimulation was 13 days in the HH group and nine days in the TI group; the difference was significant (p < 0.001). Significantly more gonadotropins were used for the stimulation of HH patients (p < 0.05). Peak serum E2 concentration was found to be higher in the TI group. We evaluated the proportion of metaphase II (MII) oocytes to total oocytes retrieved in HH patients and found the number was similar to the TI group. Despite that fertilization and implantation rates were similar in both groups, the cancellation rate was higher in the HH group (23.1% vs 0). However pregnancy and live birth rates were similar. Conclusions: The present study showed that HH women undergoing IVF/ICSI are good responders. The treatment of HH women with IVF/ICSI did not increase multiple pregnancies and OHSS rates over the TI group.

Key words: Hypogonadotropic hypogonadism; In vitro fertilization; Treatment outcome; Tubal factor infertility.

Introduction

There are four groups of patients with suspected anovulatory disorders. These groups are classified as hypogonadotropic, normogonadotropic, hypergonadotropic and hyperprolactinic anovulation. Hypogonadotropic anovulation is called as Class I by the World Health Organization (WHO) [1].

Because of the complexity and patient intolerance of pulsatile GnRH, gonadotrophin therapy is primarily a substitute treatment. Both FSH and LH are required to achieve full maturation of the follicles in women with anovulatory disorders. In spite of recent developments in recombinant technology, a urinary extract containing a fixed combination of LH and FSH, human menopausal gonadotrophin (hMG) has been the most efficient drug for ovulation induction in patients with hypogonagotropic hypogonadism (HH) [2].

In this study, cycle characteristics and assisted reproductive outcomes of HH patients were assessed and compared with women who had undergone IVF/ICSI (in vitro fertilization/intacytoplasmic sperm injection) because of tubal factor infertility.

Materials and Methods

Data from 13 cycles of ten HH patients treated with in vitro fertilization in the period from January 2006 to January 2008 were analyzed and compared with treatment results of 20 patients with tubal factor infertility (TI).

Seven of ten HH patients were referred to us with their confirmed diagnoses elsewhere, but three were diagnosed in our center. All of the HH patients had a history of primary/secondary amenorrhea and no withdrawal bleeding after a progesterone challenge. FSH and LH levels of all the HH patients were under 2 mIU/ml and estradiol was under 20 pg/ml. Their serum thyroid-stimulating hormone (TSH) and prolactin levels were normal. All of the HH patients presented with atrophic endometrium (endometrial thickness < 5 mm). A normal hypophyseal appearance excluded empty sella syndrome.

A control group treated at the same center was comprised of 20 infertile patients who were diagnosed as having tubal factor infertility (TI). Their current hysterosalpingography or latest laparoscopic procedure revealed blocked tubal patency, otherwise their hormonal status and menstrual cycles were normal.

In both groups the patient husband’s sperm parameters were within normal limits (concentration ≥20 million/ml, ≥50% total motility, and ≥30% normal forms (WHO). Patients who had pathological results were eliminated and not included in the study analysis.

hMG (75 IU FSH + 75 IU LH, Menogon-Ferring, Switzerland) was started in all HH patients (225-450 IU/day) and response was assessed with the findings of transvaginal ultrasonography (TVS) and estradiol level. The patients were not given any antagonist medication because a premature LH surge is not usual in these patients. When leading follicles reached 18-20 mm in diameter, 10,000 IU hCG (Pregnyl- Schering Plough/Organon) was administered and TVS-guided oocyte retrieval was performed 36 hours later. ICSI was performed in all oocytes. On days 2-5 after oocyte retrieval, depending on the number of good quality embryos and patient age, two to three embryos were transferred.

Recombiant FSH (Gonal F- Serono/Merck Laboratories) was given to TI patients. The dosage was adjusted according to the patient status (225-450 IU/day) and response was assessed with TVS and estradiol level. When at least one leading follicle

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reached 14 mm in size, a GnRH antagonist of 0.25 mg daily injection (cetrotide- Serono/Merck Laboratories) was added to the treatment and continued up to the day of hCG administration. When leading follicles reached 18-20 mm in diameter, 10,000 IU hCG (Pregnyl-Organon/Shering Plough) was given and TVS-guided oocyte retrieval was performed 36 hours later. ICSI was performed on all oocytes. On days 2-5 after oocyte retrieval, depending on the number of good quality embryos and patient age, two to three embryos were transferred.

The luteal phase was supplemented with 50 mg of progesterone in oil IM (Progonyn- Kocak) daily starting on the day after oocyte retrieval, and was continued until a negative pregnancy test was obtained, or if pregnancy occurred, with 8% vaginal progesterone (Crinone- Serono/Merck Laboratories) daily until week 12 of gestation in both groups. Pregnancy was confirmed by a positive blood test for ß-hCG 12 days after the transfer procedure. Ongoing pregnancy was determined if the pregnancy continued after 12 weeks.

Data were analyzed using the SPSS version 11.5 for Windows (SPSS Inc., USA). The Mann-Whitney U and chi-square tests were used for statistical analysis, where appropriate; \( p \leq 0.05 \) was considered significant.

### Results

The IVF/ICSI cycle outcomes of 13 HH patients were compared to 20 TI patients. All patients underwent treatment cycles for IVF/ICSI at the same center. Demographic characteristics of the patients were comparable (Table 1). In spite of no differences between estradiol levels of the two groups, FSH and LH levels of the HH patients were statistically lower than the others.

**Table 1. — Demographic characteristics of the HH and TI patients.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HH n = 10</th>
<th>TI n = 20</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>31.3 ± 5.6</td>
<td>31.5 ± 4.7</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of infertility (years)</td>
<td>6.8 ± 3.6</td>
<td>6.8 ± 3.2</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61.6 ± 9.6</td>
<td>65.8 ± 8.7</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.3 ± 3.1</td>
<td>25.8 ± 3.1</td>
<td>NS</td>
</tr>
<tr>
<td>FSH (mIU/ml)</td>
<td>0.7 ± 0.6</td>
<td>6.7 ± 1.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LH (mIU/ml)</td>
<td>1.4 ± 2.2</td>
<td>6.7 ± 1.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>E2 (pg/dl)</td>
<td>30.4 ± 8.6</td>
<td>33.4 ± 9.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

BMI: Body mass index; E2: estradiol.

Mean duration of stimulation was 13 days in the HH group and nine days in the TI group and the difference was significant (\( p < 0.001 \)). Total gonadotropin consumption in the HH group was significantly larger than for TI (3630 IU vs 2500 IU). Peak serum estradiol level was significantly lower in the HH group (1044 vs 2500). There were no significant differences from the stand-point of totally retrieved oocyte number and total MII oocyte count (Table 2).

The fertilization rates were 81.9% and 72.9% in the HH and TI groups, respectively, and the difference was not statistically significant. Cleavage and grade 1 embryo rates were not different. Totally transferred embryo numbers were 2.6 and 2.8, respectively. Implantation rate was higher in the TI group but the difference was not significant (52.5% vs 38.3%). Only three cycles were cancelled. All of them belonged to the HH group and two were cancelled due to impaired follicular response, while the other one was cancelled because of failure to achieve an oocyte.

Eight of 13 hypogonadotropic patients (80%) and 14 of 20 tubal factor patients (70%) became pregnant with no significant difference. At the time of this study two pregnancies from the HH group and two pregnancies from the TI group were continuing without any complications. The abortion rate was 25% and 21.4% in the HH and TI groups, respectively. Live birth rate was 50% and 57.1% in the HH and TI groups, respectively.

**Table 2. — Comparison of the ART cycle characteristics of the two groups.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HH n = 13</th>
<th>TI n = 20</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of stimulation (day)</td>
<td>13.0 ± 2.4</td>
<td>9.2 ± 0.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total gonadotropins used (IU)</td>
<td>3630 ± 1685</td>
<td>2501 ± 536</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Peak E2 (pg/ml)</td>
<td>1044 ± 613</td>
<td>2500 ± 245</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total Oocyte (n)</td>
<td>6.5 ± 3.1</td>
<td>7.1 ± 3.6</td>
<td>NS</td>
</tr>
<tr>
<td>MII Oocyte (n)</td>
<td>5.9 ± 2.0</td>
<td>5.4 ± 2.7</td>
<td>NS</td>
</tr>
<tr>
<td>FR (%)</td>
<td>81.9 ± 14.3</td>
<td>72.9 ± 19.5</td>
<td>NS</td>
</tr>
<tr>
<td>Transferred embryo number (n)</td>
<td>2.6 ± 0.8</td>
<td>2.8 ± 0.5</td>
<td>NS</td>
</tr>
<tr>
<td>IR (%)</td>
<td>38.3 (24.8)</td>
<td>52.5 (25.3)</td>
<td>NS</td>
</tr>
<tr>
<td>CR (%)</td>
<td>3 (23.1)</td>
<td>0</td>
<td>0.05</td>
</tr>
<tr>
<td>PR (%)</td>
<td>8 (80)</td>
<td>14 (70)</td>
<td>NS</td>
</tr>
<tr>
<td>Ongoing pregnancy (%)</td>
<td>2 (25)</td>
<td>2 (14.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Missed abortion rate (%)</td>
<td>2 (25)</td>
<td>3 (21.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Ectopic pregnancy (%)</td>
<td>0</td>
<td>1 (7.1)</td>
<td>NS</td>
</tr>
<tr>
<td>LBR (%)</td>
<td>4 (50)</td>
<td>8 (57.1)</td>
<td>NS</td>
</tr>
</tbody>
</table>

E2: Estradiol; MII: Metaphase II; FR: Fertilization rate; IR: Implantation rate; CR: Cancellation rate; PR: Pregnancy rate; LBR: Live birth rate.

### Discussion

This study has confirmed that HH patients undergoing ICSI cycles have comparable outcomes and usually are good responders. We had a small number of HH women and although we are a tertiary center only 13 patients were admitted to our center during two years. Thus, we believe that the cycle outcomes of these women deserved a comparison with other good responders (group TI), considering the rareness.

In spite of a good adjustment between the two groups – according to the general demographic factors – the duration of stimulation was longer and the consumption of gonadotropins was higher in HH patients. It is known that a large amount of gonadotropin usage has a detrimental effect on oocyte and embryo quality. Kumbak et al. pointed out that this high gonadotropin usage did not adversely affect the oocyte yield in HH patients [3]. They compared 27 HH patient cycles with 39 unexplained infertility cases. MII oocyte numbers were the same but the fertilization rate was higher in the HH group. They found no significant difference between the groups with regard to the ratio of grade 1 embryos. High fertilization and implantation rates were found in the HH group. They concluded that the extreme dosages of gonadotropins
used in the HH patients were not detrimental to the oocytes and embryos. “The need of higher gonadotropin usage in regard to silent ovaries, which need to be activated before follicular response is achieved” was their explanation. We agree with their point of view – the need of large doses may be due to the long duration of the hypoestrogenic state.

hMG was used for the stimulation of the HH patients in this study. Ovulation induction for HH patients requires concomitant administration of both FSH and LH to achieve optimal therapeutic results. According to current concepts of the roles of FSH and LH in folliculogenesis, follicular responsiveness to FSH and LH is developmentally regulated [4]. LH is necessary for theca cell androgen synthesis which serves as a substrate for the aromatase enzyme to be converted into estrogen by granulosa cells. Once ovarian follicles reach a diameter of 10-12 mm, their granulosa cells begin to express LH receptors and become receptive to LH stimulation. In other words, while granulosa cells from early antral follicles are only responsive to FSH, granulosa cells from FSH-stimulated follicles are responsive to either FSH or LH. In assisted reproductive therapy (ART) cycles, usually endogenous LH activity is enough for follicular development and only FSH can provide an adequate response. HH patients need both FSH and LH for ovulation induction. The treatment with urinary FSH or recombinant FSH alone may induce follicular development but presents low fertilization rates [5].

The ovulation induction of hypogonadotropic women with urinary FSH or recombinant FSH alone induces follicular development but it causes low oocyte and embryo yield. Because of that we used hMG. In contrast to our treatment, Burgues and the Spanish Collaborative Group on female hypogonadotropic hypogonadism concluded that combined rFSH and rLH treatment induce follicular growth, ovulation and pregnancy in a good proportion of hypogonadotropic hypogonadal patients [6]. hMG was the only source of LH at one time, however today many case reports and case series have suggested that rLH is effective and safe for the treatment of HH patients. We used hMG because of its cost effectiveness. Using rFSH with rLH is more expensive for patients when compared to hMG. The main disadvantage of hMG is its administration route. Unlike recombinant preparations, hMG unfortunately can be used only intramuscularly.

The major drawback to our study was that we compared two different stimulation protocols for two groups. TI women are considered to be ideal controls in an IVF/ICSI setting. We used analogues for these patients but there is no need to add analogues in the treatment of HH patients.

There has been some controversy about pregnancy loss rate in HH patients after ART treatment. Previously some studies showed pregnancy losses of 22% and 27% in HH patients undergoing ovulation induction [7, 8]. Our pregnancy loss rate was 25% in the HH group. In contrast to our results, Ulug et al. reported an 8% pregnancy loss in their series [9].

Multiple pregnancy and ovarian hyperstimulation syndrome (OHSS) are the most common serious complications of ART. None of our patients showed severe or moderate OHSS in either group. Only one triple pregnancy was achieved in TI patients. The twin pregnancy rate was 37.5% and 25% in the HH and TI groups, respectively. Based on our small number of cases we can easily say that multiple pregnancy and OHSS were not major concerns in the treatment of HH. Moreover, the transferred embryo number should not exceed three in HH patients.

In conclusion, the outcomes of ART treatments in HH patients were comparable to women with TI. Ovulation induction for HH patients requires concomitant administration of both FSH and LH to achieve optimal therapeutic results. Multiple pregnancy and OHSS rates were lower than the general population of infertile patients. Optimization of the treatment of infertility in HH patients still needs a large case series and well-randomized controlled trials.

References


Effect of long-time administration of tibolone on vaginal cytology of castrated rats

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Summary
Purpose: To evaluate the estrogenic effect of tibolone administered at high-dose and long-term through cytological examination of vaginal epithelium of castrated rats. Methods: 15 adult Wistar rats were submitted to bilateral oophorectomy 30 days before starting the experiment. The rats were then randomly divided in two groups. Experimental rats (n = 9) orally received 1 mg tibolone/day; control rats (n = 6) just received carboxymethylcellulose. Vaginal smears were collected from all rats on days 0, 1-6, 30, 60, 90 and 120 of the experiment. Results: On day 0, smears from all rats were atrophic, classified as anestrus, and remained this type in the control group until day 120. In the tibolone group, on day 3 all the rats had vaginal cytology similar to estrus and maintained the same aspect till day 90. Conclusion: Tibolone has estrogenic action in the vaginal epithelium which is already evident after the first dose and remains without major changes over time.

Key words: Tibolone; Rats; Menopause.

Introduction

Climacterium is a phase of a woman’s life which is characterized by the transition between the non-reproductive and reproductive period, characterized by gradual reduction of ovarian function [1]. Menopause marks the end of this period, and therefore is defined as the final interruption of menstrual cycles [2]. The decreased secretion of estrogen observed in climacterium is responsible for several symptoms [1, 3]. Among the most common, one can cite vasomotor symptoms (hot flushes) [1, 3-5], osteoporosis [6], menstrual disorders [1,5], nervousness and irritability [1,5], genitourinary atrophy [5], vaginal dryness [4], and decreased libido [4]. Estrogen deficiency can cause atrophic changes within the urogenital tract with marked reduction of vaginal lubrication (vaginal dryness) and dyspareunia due to vaginal atrophy. Alterations in the urinary tract can arise leading to recurrent infection, urinary incontinence or pollakiuria [7].

Tibolone is a synthetic steroid acting in a tissue-specific mode and used in hormone replacement therapy. It is converted into three active metabolites exerting progestagenic, estrogenic and androgenic effects in vivo and in vitro [8]. By its selective effects, it has been recommended as an excellent alternative to long-term hormone therapy to alleviate postmenopausal symptoms [9]. Tibolone leads to many benefits in sexual function, vaginal atrophy, urogenital symptoms and bone loss. It also has a low incidence of vaginal bleeding and breast pain, symptoms common in other hormone replacement treatments [10]. Therefore, the use of tibolone is beneficial to the urogenital system, since in contrast to absence of endometrial stimulation, the genitourinary tract is stimulated in menopausal women by use of this drug [8].

The aim of this study was to determine the estrogenic effect of tibolone administered at high dose and long-term through cytological examination of vaginal epithelium of castrated rats.

Material and Methods

Animals
Fifteen Wistar rats, aged 8 weeks and weighing 250 g were used. All rats were produced and maintained in the Animal Facility of the Laboratory of Experimental Nutrition (LABNE-UFF). Rats were housed in individual plastic cages, with controlled temperature (24 ± 2ºC) and artificial illumination alternated in cycles of 12/12 hours. Filtered water and commercial food (FRI-LAB RATOS II, FRI-RIBE) was supplied ad libitum.

Oophorectomy
Bilateral oophorectomy was performed in all rats 30 days before the beginning of the experiment, following the norms of vivisection of animals recommended by the Brazilian School of Animal Experimentation (COBEA). The work was approved by the Ethics Committee in Research of the College of Medicine/Antonio Pedro, University Hospital/Federal Fluminense University. Anesthesia was intramuscular with ketamine (100 mg/kg) and xylazine (20 mg/kg) [11].

Chemicals
Tibolone used in this study was donated by the manipulation pharmacy OFFICILAB. The drug was diluted at 0.2% in solution of 0.5% carboxymethylcellulose (CMC).

Experimental design
After surgery the rats stayed 30 days without medication, receiving only diet and water ad libitum to reduce sex hormone levels and come into surgical menopause [12]. Rats were randomly distributed in two groups. The experimental group (n = 9) received 0.5 ml/rat of tibolone, giving 1 mg/day/rat. The control group (n = 6) received 0.5 ml/day/rat of CMC. Each
group received their treatment by gavage administration for 120 consecutive days.

Vaginal smears were obtained immediately before the oophorectomy (day -30) to ensure that the rats were in the normal estral cycle. Thirty days after surgery (day 0), a new vaginal cytology was performed to verify the status of menopause. After starting the administration of tibolone and CMC, vaginal swabs were collected on days 1-6, 30, 60, 90 and 120 of the experiment to evaluate the vaginal trophism, which is classified as estrus, proestrus, metestrus and diestrus. Smears in estrus, proestrus and metestrus indicate hormonal influence and anestrus points to lack of hormonal influence by atrophic vaginal cytology [13, 14] (Table 1). Smears were immediately fixed in 95% alcohol and stained by the Papanicolaou method.

Table 1. — Criteria for vaginal cytology classification.

<table>
<thead>
<tr>
<th>Estral cycle phases*</th>
<th>Vaginal cytology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrus</td>
<td>Cornified cells</td>
</tr>
<tr>
<td>Metestrus</td>
<td>Cornified and epithelial nucleated cells (all types), leukocytes and mucus</td>
</tr>
<tr>
<td>Diestrus</td>
<td>Leukocytes, mucus and epithelial round cells</td>
</tr>
<tr>
<td>Proestrus</td>
<td>Cornified and epithelial nucleated cells (all types)</td>
</tr>
<tr>
<td>Acyclic phase**</td>
<td>Leukocytes, mucus and epithelial round cells</td>
</tr>
</tbody>
</table>

*Adapted from Baker, 1979 [13]; **Adapted from Dimarco et al., 2007 [14].

Results

The standard cytology found in both groups until day 3 of the experiment is shown in Table 2. On day 0, i.e., before starting the treatment, all rats showed typical cytology of anestrus in both control and tibolone groups. In the control group (n = 6) this standard cytology lasted until the end of the study. In the tibolone group (n = 9), after administration of one dose, i.e., on day 1, one rat had cytology similar to metestrus and another similar to proestrus. The cytology of the other seven rats remained in anestrus. On day 2, one rat showed standard cytology comparable to the transition from anestrus to proestrus, seven showed cytology similar to proestrus, and one rat already had cytology similar to estrus. On day 3, all rats in the tibolone group had vaginal cytology similar to estrus, which lasted until day 90 of the experiment. On day 120 it was observed that three of nine rats began to show cytology similar to metestrus, two had cytology compatible to the transition from estrus to metestrus and four remained similar to estrus.

Tibolone is a highly effective steroid in postmenopause due to the biological activity dependent on its metabolism to 3α and 3β-OH, which displays an affinity for the estrogen receptor (ER), but not to either the progesterone receptor (PR) or the androgen receptor (AR) [15]. The current results demonstrate that 1 mg/day of tibolone administrated for 120 days has an estrogenic action in the vaginal epithelium at the very beginning evidenced by the change in the pattern of vaginal cytology of castrated rats. Smears of the control group continued to have an atrophic pattern.

Tibolone administered to ovariectomized rats for a short period showed a relative potency of 6% compared to ethynyl-estradiol (EE) after daily oral application. The mean number of positive smears (presence of nucleated or cornified epithelial cells) was evaluated and for a full estrogenic response a dose of 1mg/kg tibolone was needed [16]. We used a higher dose of tibolone, equivalent to 16 mg/kg with similar results. However, in adult ovariectomized monkeys treated with tibolone at 0.05 mg/kg or 0.2 mg/kg for two years, no effect of tibolone at either dose was observed on the vaginal maturation index and keratinization [17].

Randomized studies indicate that tibolone normalizes the vaginal karyopyknotic and maturation indexes and alleviates symptomatic atrophic vaginitis. Thus, women treated with tibolone report significant reduction in vaginal dryness and dyspareunia [18]. In a prospective and non-randomized study to assess the effects of six years of tibolone therapy on the genital tract in postmenopausal women both the vaginal karyopyknotic index and maturation index increased significantly in the tibolone treated group, but not in the control group [19]. This result demonstrates estrogenic effects of tibolone on the vagina, which is in agreement with the findings of this study. The vaginal cytological findings and symptoms evaluated in recently postmenopausal women (n = 50), who used 2.5 mg of tibolone daily for two years, showed a significant increase in the karyopyknotic index and maturation value whereas there was no change in the control group (n = 50). Significant symptomatic improvement occurred in vaginal dryness, dyspareunia, sexual enjoyment and libido. Therefore, tibolone has a significant estrogenic effect on the vagina as demonstrated by vaginal cytology [20]. In accordance with this report, an experiment performed with incubation of vaginal tissue from postmenopausal women and oophorectomized rats using radiolabeled tibolone showed stimulatory effects in both women and rats. This effect was due to action of the 3α-OH-tibolone metabolite [8].

According to the literature, tibolone is a tissue-specific compound with favorable effects on the vagina, climacteric symptoms, mood and sexual well being in postmenopausal women [21]. In this study tibolone showed early estrogenic effects on the vaginal tissue of oophorectomized rats. This fact is evidenced by the presence of vaginal cytology similar to estrus in treated rats, indicating estrogen action.
Effect of long-time administration of tibolone on vaginal cytology of castrated rats

In conclusion, tibolone has estrogenic action in the vaginal epithelium, which is already evident after the first dose and lasts without major changes over time.

Acknowledgment

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References


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Vaginal fluid pH, cervicovaginitis and cervical length in pregnancy

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Summary

Aim: The purpose of this prospective study was to determine the possible association among vaginal fluid pH, cervicovaginitis and cervical length in singleton pregnancies at 16-22 weeks of gestation. Methods: A total of 240 asymptomatic singleton pregnancies at 16-22 weeks of gestation were included to the study. Vaginal fluid pH was determined using pH paper in a sterile speculum examination, and cervical length was examined by transvaginal ultrasonographic measurement. Vaginitis was diagnosed by pH determination and wet mount smear; cervicitis was diagnosed by cervical examination. Patients were followed to delivery and hospital records were reviewed to extract obstetric information. Preterm delivery was defined as delivery at or prior to 36 weeks of gestation. Abnormal pH was defined as a pH of > 5.0. Patients with cervicovaginitis (n = 72) were compared with those without any trace of infection (n = 60).

Results: The mean gestational age was 20.3 ± 1.4. We found an significant association among cervicovaginitis, cervical length and vaginal pH. There was a significant correlation between an elevated vaginal pH (≥ 5.0) and a shortened cervical length (r = -0.59, p < 0.001). Vaginal fluid pH ≥ 5.0 was associated with increased risk of preterm delivery (OR 4.3, 95% CI 2.0, 9.3; p = 0.001) as well as delivering an infant of less than 2,500 g (OR 4.0, 95% CI 1.4, 11.0; p = 0.009). Conclusions: Elevated vaginal fluid pH in women at 16-22 weeks of gestation seems to be associated with a decreased cervical length and increased risk of preterm delivery.

Key words: Vaginal fluid pH; Cervical length; Preterm birth; Cervicovaginitis.

Introduction

Preterm birth remains one of the primary causes of perinatal morbidity and mortality. It is now clear that intrauterine infection plays a major role in the pathogenesis of preterm birth, which itself is responsible for 70% of perinatal deaths and almost one half of long-term neurologic morbidity [1]. It was postulated that vaginal organisms found in bacterial vaginosis (BV) may first ascend into the chorioamniotic space. Preterm labor and delivery are then caused by a maternal and fetal response to choriodecidual bacterial colonization. In some women, bacteria cross the intact chorioamniotic membranes into the amniotic fluid, and some of the fetuses ultimately become infected.

Cervical length is also an independent risk factor in the pathogenesis of preterm labor [2-4]. The risk of preterm delivery appears to be inversely proportional to that of cervical length, increasing significantly with shorter cervical length measurements [5]. Inflammation of the maternal-fetal interface is a common cause of cervical shortening, particularly before 31-32 weeks’ gestation [6]. Such inflammation may not arise solely from either an infectious or a vascular insult but rather from both. With regard to infection, bacterial vaginosis has often been related to cervical shortening and preterm birth [7, 8].

Therefore a simple method of identifying the presence of bacterial vaginosis may be useful in screening for patients at risk for preterm labor. In a prospective study of 107 pregnant women, an increased vaginal pH significantly predicted the presence of bacterial vaginosis [9].

The purpose of this prospective study was to determine the possible association among vaginal fluid pH, cervicovaginitis and cervical length in singleton pregnancies at 16-22 weeks of gestation.

Materials and Methods

A total of 240 asymptomatic singleton pregnancies at 16-22 weeks of gestation were included to the study. The patients were divided into the following groups: group A, negative for vaginitis and cervicitis (no infection group, n = 60; 25%); group B, positive for vaginitis and cervicitis (infection group, n = 72; 30%); group C, possible or negative for vaginitis and positive for cervicitis (n = 51; 21.3%); group D, positive for vaginosis and possible or negative for cervicitis (n = 57; 23.8%). The study was conducted in accordance with the guidelines as described in the Helsinki Declaration (as revised in Tokyo 2004) on human experimentation. Informed consent was obtained from all patients.

Each patient was questioned with regard to last normal menstruation. Gestational age according to last menstruation was compared with gestational age as determined by using ultrasonography (US). Where sonar was performed in the first trimester of pregnancy, we determined the gestational age according to the last menstrual period, with a discrepancy of one week. For the second trimester, the limit was two weeks, and for the third trimester, the limit was three weeks.

Vaginal infection was diagnosed as follows: After the insertion of a vaginal speculum, the vaginal pH was determined by using pH-Universal indicator sticks (E. Merck, Darmstadt, Germany; pH range, 1-14). Vaginal secretion was obtained from...
the lateral vaginal walls by using the blunt end of a wooden spatula and applied to two locations on a glass slide. The whiff test was executed by adding a drop of 10% potassium hydroxide solution to one of these locations. The test result was positive if an unpleasant fishy odor resulted. A drop of 0.9% sodium chloride solution was then added to the second location, and if at least one of the following was present: (1) T vaginalis, (2) positive whiff test result, and (3) clue cells. Cervicitis was diagnosed if at least two or three of the following was present at the inspection of the cervix: (1) red cervix, (2) discharge, (3) ulceration; and white blood cells on the sodium chloride solution side and more leukocytes than epithelial cells on the potassium hydroxide solution side and for the mycelia of Candida albicans on the potassium hydroxide side. Vaginitis, for the purpose of this study, was diagnosed if at least one of the following criteria was present: (1) Trichomonas vaginalis, positive whiff test result, clue cells.

Table 1. — Demographic characteristics of the patients (n = 240).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Average</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>27.4 ± 4.6</td>
<td>18</td>
<td>39</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>20.3 ± 1.4</td>
<td>18</td>
<td>22</td>
</tr>
<tr>
<td>Vaginal pH</td>
<td>4.9 ± 0.8</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Parity</td>
<td>0.6 ± 0.6</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Gravida</td>
<td>1.9 ± 0.9</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Cervical length (mm)</td>
<td>35.8 ± 6.0</td>
<td>23</td>
<td>72</td>
</tr>
</tbody>
</table>

*Infection was diagnosed if at least one of the following criteria was present: Trichomonas vaginalis, positive whiff test result, clue cells.

Table 2. — Wet mount vaginal smear and whiff test results (n = 240).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Döderlein’s bacilli</td>
<td>38.3</td>
</tr>
<tr>
<td>Clue cells</td>
<td>37.5</td>
</tr>
<tr>
<td>Positive whiff test result</td>
<td>12.9</td>
</tr>
<tr>
<td>More leukocytes than epithelial cells</td>
<td>18.8</td>
</tr>
<tr>
<td>Trichomonas vaginalis</td>
<td>17.9</td>
</tr>
<tr>
<td>Vaginal infection*</td>
<td>51.3</td>
</tr>
</tbody>
</table>

*Infection was diagnosed if 2 or 3 of the stipulated variables were present.

Table 3. — Diagnosis of cervicitis in the study group (n = 240).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharge</td>
<td>34.1</td>
</tr>
<tr>
<td>Red cervix</td>
<td>38.7</td>
</tr>
<tr>
<td>Ulceration</td>
<td>39.5</td>
</tr>
<tr>
<td>Cervical infection*</td>
<td>53.8</td>
</tr>
</tbody>
</table>

*Infection was diagnosed if 2 or 3 of the stipulated variables were present.

Table 4. — Comparison between group A (no infection) and group B (infection).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A (n = 60)</th>
<th>Group B (n = 72)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>26.7 ± 4.7</td>
<td>27.2 ± 4.5</td>
<td>0.55</td>
</tr>
<tr>
<td>Gestational age (weeks)*</td>
<td>20.6 ± 1.4</td>
<td>20.3 ± 1.2</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Gravida*</td>
<td>1.8 ± 0.9</td>
<td>1.9 ± 0.9</td>
<td>0.58</td>
</tr>
<tr>
<td>Parité*</td>
<td>0.5 ± 80.61</td>
<td>0.65 ± 0.67</td>
<td>0.54</td>
</tr>
<tr>
<td>Trichomonas vaginalis**</td>
<td>26 (36.1)</td>
<td>26 (36.1)</td>
<td></td>
</tr>
<tr>
<td>Clue cells**</td>
<td>56 (77)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive whiff test result**</td>
<td>21 (29.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Döderlein’s bacilli**</td>
<td>37 (61.7)</td>
<td>13 (18.1)</td>
<td></td>
</tr>
<tr>
<td>More leukocytes than epithelial cells**</td>
<td>26 (36.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal pH*</td>
<td>4.2 ± 0.58</td>
<td>5.6 ± 0.86</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Gestational age at birth (weeks)*</td>
<td>38 ± 0.9</td>
<td>36.9 ± 1.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Birth weight (g)*</td>
<td>3336 ± 320</td>
<td>3053 ± 404</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Preterm birth (weeks)**</td>
<td>1 (1.7)</td>
<td>18 (25)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Values in parantheses are percentages. *Values are mean ± SD, ** Values are the number of patients.

Table 5. — Comparison between the groups of vaginal pH ≤ 5 (n = 172) and pH > 5 (n = 68).

<table>
<thead>
<tr>
<th>Variable</th>
<th>pH ≤ 5 (n = 172)</th>
<th>pH &gt; 5 (n = 68)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>27.3 ± 4.8</td>
<td>27.6 ± 4.05</td>
<td>0.64</td>
</tr>
<tr>
<td>Gestational age (weeks)*</td>
<td>20.4 ± 1.3</td>
<td>20.2 ± 1.2</td>
<td>0.21</td>
</tr>
<tr>
<td>Clue cells**</td>
<td>52 (30.2)</td>
<td>38 (55.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Positive whiff test result**</td>
<td>12 (7)</td>
<td>18 (27.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cervicitis**</td>
<td>68 (39.5)</td>
<td>61 (89.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Vaginitis**</td>
<td>70 (40.7)</td>
<td>53 (77.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cervicovaginitis**</td>
<td>24 (14)</td>
<td>48 (70.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cervical length (mm)**</td>
<td>37.8 ± 5.7</td>
<td>30.9 ± 3.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Gestational age at birth (weeks)**</td>
<td>37.8 ± 1.2</td>
<td>36.6 ± 1.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Birth weight (g)*</td>
<td>3272 ± 356</td>
<td>3005 ± 398</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Preterm birth (weeks)**</td>
<td>14 (8.1)</td>
<td>19 (27.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Birth weight &lt; 2500 g**</td>
<td>7 (4.1)</td>
<td>10 (14.7)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Values in parantheses are percentages. *Values are mean ± SD, ** Values are the number of patients.
Discussion

The cause of preterm birth is multifactorial. Pathophysiologic changes preceding clinical indicators of preterm labor include the presence of inflammatory cytokines in amniotic fluid during the second trimester, fetal fibronectin expression in cervicovaginal mucus, shortening of the cervix on US examination, and an increase in maternal salivary estriol. It is important to note that the clinical presentation is strongly influenced by the dominant factor in the pathogenesis. For example, a short cervix is a particularly important risk factor in patients who deliver their neonates before 26 weeks' gestation [10].

A recent meta-analysis performed by Leitich et al. [11] confirmed that BV was associated significantly with adverse pregnancy outcome and that the risk of preterm delivery at < 37 weeks of gestation, as calculated in the main analysis, was > 2-fold in women with BV.

An elevated vaginal pH level is a well-known characteristic of bacterial vaginosis. In their study, Hauth et al. [12] concluded that women with an early pregnancy vaginal pH, those whose pH was 5.0 or greater had a significantly increased incidence of subsequent preterm birth at < 37, < 35, or < 32 weeks’ gestation. Women whose vaginal pH was 5.0 or less also had significantly fewer subsequent spontaneous preterm births and fewer newborn infants weighing less than 2,500 g or less than 1,500 g.

Our study contributes to this finding because we found a significant correlation between an elevated vaginal pH (> 5.0) and a shortened cervical length (r = -0.59, p < 0.001). Vaginal fluid pH > 5.0 was associated with increased risk of preterm delivery (OR 4.3, 95% CI 2.0, 9.3; p = 0.001) as well as delivering an infant of less than 2,500 g (OR 4.0, 95% CI 1.4, 11.0; p = 0.009). Therefore it seems as if an elevated vaginal pH could be used as a tool in screening for patients at risk for preterm labor.

In conclusion, an elevated vaginal fluid pH in women at 16-22 weeks of gestation seems to be associated with a decreased cervical length and increased risk of preterm delivery. In cases in which US examination is not available, however, an elevated vaginal pH may be a simple and useful predictor.
References


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Perineal ultrasound evaluation of urethral mobility after the TVT-O procedure


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Summary
Aims: The aim of study was to assess, by means of perineal ultrasound (US), women treated with the trans-obturator suburethral sling procedure for urinary stress incontinence (USI). Methods: Twelve women with USI and urethral hypermobility were enrolled. Static and dynamic perineal US of urethral mobility was performed before and after tension-free vaginal tape obturator (TVT-O) procedure: US parameters evaluated were pubis-urethra distance and inclination angle of the urethral axis. Results: The Valsalva stress US evaluation showed a return to normal range of the pubic urethral distance in all cases ($p = 0.0001$); also a correction of the angle of inclination of the urethral axis occurred in all patients ($p < 0.0001$). Conclusions: Our results propose the use of perineal US for patients with USI as an additional diagnostic tool and a means for postsurgical follow-up.

Key words: Perineal ultrasound; Urinary stress incontinence; TVT-O.

Introduction
Urinary stress incontinence (USI), defined by the International Continence Society (ICS) as the complaint of involuntary urinary leakage on effort or exertion, or on sneezing or coughing, is an involuntary leakage of urine during periods of raised intraabdominal pressure, in the absence of a detrusor contraction [1].

In fact, during a woman’s life, the uterus, vagina, bladder neck and urethra undergo various “topographic” modifications caused by pregnancy, childbirth, postmenopausal estrogen deficiency and pelvic surgery, and within these settings particular importance has to be given to urethral mobility, which can be involved in the pathogenesis of USI when the proximal urethra is no longer within the intraabdominal closure pressure zone [2, 3].

The degree of urethral mobility is evaluated essentially by clinical examination, but it is not well defined or standardized: on vaginal examination urethral length, position and mobility are assessed, and hypermobility of the bladder neck may be visualised during a cough or Valsalva as the backward and downward movement of the urethra by the Q-tip cotton bud test.

Ultrasound (US) of the pelvic floor (perineal/vulvar, introital, endovaginal, transanal, endoanal [4, 5]) is currently gaining importance as a diagnostic tool for the evaluation of defects of the pelvis surrounding tissues and continence disorders. It allows the healthcare provider to obtain both anatomical or “static” images and functional or “dynamic” characteristics, during the increase of intraabdominal pressure [6], with important information concerning cervical-urethral mobility [7, 8] and USI [9, 10].

The mainstay of treatment for USI is conservative management with containment devices and physiotherapy, with recourse to surgery where indicated and desired. Advances in surgical techniques have led to the availability of various minimally invasive interventions such as suburethral sling procedures, e.g. tension-free vaginal tape obturator (TVT-O) procedure [11].

We attempted to evaluate and quantify the degree of urethral mobility using perineal US in women with USI treated with the TVT-O procedure [12]. The two US parameters used were pubic-urethral distance, which is the distance between the pubis and midurethra, and inclination angle of the urethral axis, which is the angle between the pubic bone and the internal urethral orifice [13, 14].

Materials and Method
Subjects and surgical procedures
Twelve postmenopausal women with USI and urethral hypermobility referred to our Pelvic Floor Centre were enlisted in the study. The trial obtained approval from an independent Ethics Committee and formal, informed consent from the patients was obtained.

These subjects underwent acquisition of urogynecologic history, urogynecologic clinical examination (urogynecologic objective examination, voiding diary, Q-tip test, stress test, pubococcygeal test), urodynamic assessment (cystomanometry, uroflowmetry, pressure-flux study, and urethral pressure profile), transabdominal and transvaginal pelvic US. Moreover, the patients underwent static and dynamic perineal US to evaluate the degree of urethral mobility.

Inclusion criteria for the study were: postmenopausal age, body mass index (BMI) $\geq 18.5$ kg/m$^2$, history of at least one vaginal childbirth, and moderate/severe USI. Exclusion criteria were: age $> 65$ years, BMI $\geq 30$ kg/m$^2$; urge incontinence with overactive bladder or detrusor instability, pelvic organ prolapse, previous urogenital surgery, or current or previous use of estrogen therapy.

The patients filled out an anonymous questionnaire to ascer-
tain the absence of symptoms of prolapse. In addition only those women who showed absence of objective clinical signs of an altered suspension state of the pelvic organs or who, at the most, showed mild cystocele were enrolled.

Subsequently the patients underwent the TVT-O procedure (TVT-O™, Ethicon) to correct the urethral hypermobility and restore urinary continence. TVT-O was carried out according to the technique described by de Leval [11]: a paraurethral dissection plane is made from a minimal suburethral incision to the obturator foramen; the obturator membrane is punctured, an introducer is passed along the passage made, and a spiral trocar of the TVT-O device is guided along the introducer through the obturator membrane before being rotated out through the groin incision (made at a plane 2 cm above the urethral meatus at a point 2 cm lateral to the labial crural folds); once the trocar is pulled through and the correct tension has been achieved, the plastic cover over the tape is removed and the tape is thus positioned without tension under the junction between the mid and distal urethra (an instrument between the tape and urethra ensures that the mesh remains tension free); lateral vaginal fornices are checked for breaches in the vaginal epithelium at the conclusion of the procedure to avoid paraurethral vaginal mesh erosion.

The patients, after a clinical check within a month from the surgery, completed a post-surgery follow-up at six months, and on this occasion they were tested again clinically and by perineal US. A more precocious US assessment was intentionally left out because we do not consider it very reliable in the immi-
nence of surgery.

The cure was defined as no urine loss during stress. Improvement was defined as significantly fewer leakage episodes during stress than before surgery, with a satisfied patient.

**Ultrasound procedure and measurement parameters**

The US procedure was carried out on patients with a half-full bladder (approx. 250 cc) as it is advisable to avoid excessive bladder filling which could jeopardize later patient collaboration in performing the Valsalva maneuver and alter the measurement of the US parameters [13, 15].

All subjects underwent a perineal US test by the translabial technique using a convex probe of 3.5 MHz longitudinally placed on the vulvar rim and inclined slightly superior with the patient in dorsal lithotomy, with the hips flexed and slightly abducted, after covering the transducer with a glove for hygienic reasons (Voluson® 730 Expert, General Electric). This produced...
a large panoramic view of the anatomical structures in the front section of the pelvic floor. This probe placement also allowed median sagittal scanning of the front perineum [4, 6].

As to the optimal orientation of images in the mid-sagittal plane, some authors [4] prefer an orientation as on conventional transvaginal US (cranioventral aspects to the left, dorsocaudal to the right), while others [6], including the authors, prefer image inversion on the US system [14]. We use an up-down inversion to simplify image interpretation. Therefore, the US beam originates from the bottom of the monitor and the patient’s caudal part is displayed in the lower portion. It could also be useful to hold the probe so that the patient’s front remains on the left and the back on the right of the monitor. This has the practical advantage of allowing full correspondence between the movements of the right hand (doing the scanning) and the movements displayed on the monitor as is seen in all other US examinations. Since any image reproduced in one of the above orientations can be converted to the other by simple rotation through 180°, formal standardization may not be necessary [6].

The pubic bone appears as an oval image surrounded by regular wrapping (curved ligament), on the left of the screen. The transonic longitudinal structure in the middle of the screen is the urethra and above this is the bladder. On the upper part of the bladder the uterus is evident and finally, on the right of the screen and adjacent to the urethra, is the vaginal canal [14].

As the pubic bone is the only fixed structure inside the observation field it was used as a landmark for taking the measurements: the pubic-urethral distance, which is the distance between the rear margin of the pubic bone and the rear wall of the midurethra and the inclination angle of the urethral axis, which is obtained by drawing a line through the major axis of the pubic bone and a line through the longitudinal axis of the urethra [6, 13, 14]. The mid urethral reference point was determined by subjective assessment. Bladder neck position and mobility can also be assessed by perineal US [9, 10]: points of reference are the central axis of the pubic symphysis [2] or its inferoposterior margin [16].

All subjects received both a “static” and “dynamic” evaluation. In the “dynamic” phase the same structures are observed except the abdominal pressure is increased through the Valsalva maneuver. This was achieved by having the subject ‘cough’.

Specifically, the use of cine loop (the ability to store and reproduce the last images) allowed the evaluation of urethral mobility, using the above measurement parameters, at the time of the major abdominal push. US measurements were all obtained by one investigator and a single measurement, however patients had to carry out the Valsalva maneuver several times and the maximum excursion was selected by cine loop for the measurement.

There was no specific standardization of the Valsalva effort and increases in intraabdominal pressure. In fact, attempts at standardising the Valsalva maneuver have not found widespread application since intraabdominal pressure measurement is required, i.e., a rectal balloon catheter.

We estimated as indicative values of normal urethral range on Valsalva in postmenopausal women with at least one vaginal childbirth, between 15 and 18 mm for the pubic-urethral distance and 80-120° for the inclination angle of the urethral axis [14].

**Statistical analysis**

Data were analysed using the paired Student t-test and results were expressed by mean ± standard deviation (SD) and range.

The level of statistical significance was set at \( p < 0.05 \).

### Results

The subjects who enlisted in the study (\( n = 12 \)) were 56.83 ± 6.10 years old (range 47-65), with a BMI of 25.08 ± 3.12 kg/m² (20-30).

In patients affected by USI, the presurgical perineal US values of the pubic-urethral distance on Valsalva were always ≥ 18 mm, except one case with a mean value of 21.52 ± 3.74 mm (range 12-26) (Figure 1); this distance at rest was 18.73 ± 3.64 mm (range 11-24).

Values of the angle of inclination of the urethral axis on Valsalva before the TVT-O procedure were always ≥ 120° with a mean of 123.58 ± 3.94° (range 120-131) (Figure 2); this angle at rest was 103.08 ± 2.57° (range 100-109) (Table 1).

### Table 1. — Baseline characteristics and perineal ultrasound measurements – mean ± S.D (range).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± S.D (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56.83 ± 6.10 (47-65)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.08 ± 3.12 (20-30)</td>
</tr>
<tr>
<td>Pubic-urethral distance - Rest (mm)</td>
<td>18.73 ± 3.64 (11-24)</td>
</tr>
<tr>
<td>Pubic-urethral distance - Valsalva (mm)</td>
<td>21.52 ± 3.74 (12-26)</td>
</tr>
<tr>
<td>Angle of inclination of urethral axis - Rest (°)</td>
<td>103.08 ± 2.57 (100-109)</td>
</tr>
<tr>
<td>Angle of inclination of urethral axis - Valsalva (°)</td>
<td>123.58 ± 3.94 (120-131)</td>
</tr>
</tbody>
</table>

### Table 2. — Pre- and postsurgical (TVT-O) values of distance of the pubic-urethral and inclination angle of the urethral axis at rest and on Valsalva – mean ± S.D.

<table>
<thead>
<tr>
<th></th>
<th>Pre-surgery values</th>
<th>Post-surgery values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pubic-urethral distance (mm)</td>
<td>18.73 ± 3.64</td>
<td>21.52 ± 3.74</td>
</tr>
<tr>
<td>Angle of inclination of urethral axis (°)</td>
<td>103.08 ± 2.57</td>
<td>123.58 ± 3.94</td>
</tr>
</tbody>
</table>

\( p = 0.0003 \) vs presurgery values at rest; \( p < 0.0001 \) vs Pre-surgery values on Valsalva; \( p = 0.0183 \) vs presurgery values at rest; \( p < 0.0001 \) vs presurgery values on Valsalva.

In all cases of patients treated for USI return in the range of normality of the pubic-urethral distance was calculated and registered. For postmenopausal women on Valsalva effort the pubic-urethral distance at rest was 13.17 ± 2.79 mm (range 8-16) at six months from the TVT-O procedure (\( p = 0.0003 \)); the same parameter on Valsalva was 15.33 ± 2.27 mm (range 11-18) after surgery (\( p = 0.0001 \)) (Figure 3).

Moreover the angle of inclination of the urethral axis was corrected in all patients to the normal range for Valsalva values: the angle of inclination of the urethral axis at rest was 99.58 ± 3.60° (range 92-105) at six months from surgical intervention (\( p = 0.0183 \)); the same parameter on Valsalva was 106.42 ± 5.16° (range 102-118) after surgery (\( p < 0.0001 \)) (Figure 4) (Table 2).

Post-surgical follow-up at six months showed significant improvement in the values of US parameters corresponding to a correction of USI, except in one case when there was a recourse to self-catheterism for partial retention; it resolved after five days.
Discussion

Mobility of the female urethra undergoes various modifications due to pregnancy, postmenopausal estrogen deficiency, and pelvic surgery: this urethral hypermobility can be involved in the pathogenesis of USI [2, 3].

The degree of urethral mobility is evaluated essentially by clinical examination, but it is not yet well defined and standardised; perineal US of the pelvic floor is currently gaining importance as a diagnostic tool for the evaluation of pelvic anatomical and functional defects [6] with key information on cervical-urethral mobility [7, 8] and USI [9, 10].

In the present study we evaluated the pubic-urethral distance and the inclination angle of the urethral axis by perineal US to quantify the degree of urethral mobility in women with USI treated with the TVT-O procedure [11, 12]. These two simple and reproducible US measurements, which have been used previously for similar purposes [6, 13, 14], were taken through the perineal technique at rest (static) and under Valsalva stress (dynamic) conditions. We have defined values beyond which urethral mobility under stress can be considered as pathological such as a normal range for postmenopausal women: a pubic-urethral distance between 15 and 18 mm and inclination angle of the urethral axis in the range of 80-120° [14].

In our experience, women affected by USI and treated with the TVT-O procedure had surgical correction in the urethral axis in the range of 80-120° [14].

In the present study we evaluated the pubic-urethral distance and the inclination angle of the urethral axis by perineal US to quantify the degree of urethral mobility in women with USI treated with the TVT-O procedure [11, 12]. These two simple and reproducible US measurements, which have been used previously for similar purposes [6, 13, 14], were taken through the perineal technique at rest (static) and under Valsalva stress (dynamic) conditions. We have defined values beyond which urethral mobility under stress can be considered as pathological such as a normal range for postmenopausal women: a pubic-urethral distance between 15 and 18 mm and inclination angle of the urethral axis in the range of 80-120° [14].

In our experience, women affected by USI and treated with the TVT-O procedure had surgical correction in the urethral axis in the range of 80-120° [14].

The correction of USI in all study group cases implies that urethral modifications produced by the TVT-O sling on pubic-urethral distance and inclination angle of the urethral axis can explain the improvement in urinary continence.

However, the present findings require further validation and clarification, particularly through increased testing with a larger sample cohort. Nonetheless our results, even if in a small study group, suggest a role for perineal functional US in the estimated parameter as an additional diagnostic research fool in postsurgical follow-up of patients with USI.

Urinary incontinence due to stress is frequently associated with urethral hypermobility in women. Establishing a range of normality for urethral mobility through US is extremely useful when examining women suffering from USI. Our experience proposes a simple and reproducible US technique and measurement for diagnosis and postsurgical follow-up in women with USI with urethral hypermobility treated with the TVT-O procedure. The perineal evaluation of this same mobility brings about various possible therapeutic choices. Furthermore, these US recordings can be of great help both in identifying a surgical correction operation and in postoperation follow-up [12].

Perineal US in USI and surgical options can surely have a supplementary function at the objective examination and at the classical urogynecologic diagnostics in evaluating urethral mobility and its possible regression after surgery. Moreover, perineal US is economical and has easy technical availability as well as exam repeatability.

Acknowledgements

This study was supported by a grant from the Second University of Naples.

References

[10] Di Pietto L., Scaff A., Lambiase M., Torella C., Sciorio C., Dato E., Nocerino A., Di Petrillo M.L., Fusco R., Rotondi M. et al.: “Urinary incontinence due to stress is frequently associated with urethral hypermobility in women. Establishing a range of normality for urethral mobility through US is extremely useful when examining women suffering from USI. Our experience proposes a simple and reproducible US technique and measurement for diagnosis and postsurgical follow-up in women with USI with urethral hypermobility treated with the TVT-O procedure. The perineal evaluation of this same mobility brings about various possible therapeutic choices. Furthermore, these US recordings can be of great help both in identifying a surgical correction operation and in postoperation follow-up [12].

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Acknowledgements

This study was supported by a grant from the Second University of Naples.
Is placebo as effective as estrogen regimens on vasomotor symptoms in women with surgical menopause?

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Summary

Objective: To evaluate the short-term effects of two hormone therapy (HT) regimens and placebo on the Greene Climacteric Scale (GCS) of women with surgical menopause following six months of treatment. Methods: This 6-month, prospective, randomized, parallel-group, masked evaluator study compared the efficacy of once daily administration of 0.625 mg conjugated equine estrogen (group I), 3.9 mg transdermal 17β-estradiol patch applied every week (group II) and placebo (group III). Mean GCS before and after six months of treatment in each group was compared. Results: In groups I and II, vasomotor symptoms (p < 0.005, p < 0.05), somatic symptoms (p < 0.05, p < 0.05) and total score (p < 0.005, p < 0.01) significantly reduced from baseline values respectively, while the other subscores revealed no statistically important differences following six months of HT. In group III, vasomotor (p < 0.05), subscore and total score (p < 0.05) decreased significantly while other subscore reductions were not significant. Conclusions: Estrogen regimens and placebo seem to be effective in alleviating vasomotor symptoms. Additional larger prospective randomized studies need to be conducted in an aim to look at not only short-term but also long-term effects on climacteric symptoms, in comparison to both placebo arms and different dose and mode of HT use.

Key words: Surgical menopause; Greene Climacteric Scale; Hormone therapy; Placebo.

Introduction

Many psychological disturbances such as depressed mood, sleep problems, anxiety, irritability, and decreased libido that adversely affect the quality of life are attributed to early signs and symptoms of estrogen deprivation following surgical or natural menopause [1, 2]. We previously reported that intensity and frequency of urogenital symptoms and climacteric complaints based on the Greene Climacteric Scale (GCS) increased during menopausal transition [3].

Studies are quite conclusive as to whether hormone treatment (HT) improves the quality of life of menopausal women [4, 5]. As a measure for climacteric symptoms and complaints, the GCS has been introduced to meet the present accepted standards for psychological, somatic and vasomotor symptoms [6]. Taking the estrogen arm of the WHI study into consideration, although increased risk of stroke and no protective effect against breast and heart, estrogen still remains the most efficient way to alleviate climacteric complaints [7, 8].

The aim of this study was to evaluate the short-term effects of two HT regimens and placebo on the GCS of women with surgical menopause following six months of treatment.

Material and Methods

This 6-month, prospective, randomized, parallel-group, masked evaluator study conducted at the Department of Gynecology and Obstetrics Menopause Unit, Eskisehir Osmangazi University compared the efficacy of once daily administration of 0.625 mg conjugated equine estrogen (CEE), a 3.9 mg trans-
The GCS measured a total of 21 symptoms (Table 1) (6). Each symptom was rated by the woman herself according to its severity using a four-point rating scale: not-at-all (0); a little (1); quite a bit (2); extremely (3). Symptoms 1-11 address psychological symptoms divided in a measure of anxiety (symptoms 1-6) and depression (symptoms 7-11). Somatic symptoms are addressed in symptoms 12-18 and vasomotor symptoms in symptoms 19 and 20. Symptom 21 is a probe for sexual dysfunction. The total GCS is the sum of all 21 scores. Mean GCS before and after six months of treatment in each group was compared. Statistical analysis was performed by using SPSS for Windows, Version 13.0 (SPSS Inc, Chicago, IL, USA). Mean values are expressed as mean ± standard error of mean (SEM). Data were analyzed by the paired Student’s t-test analysis. All tests were two-sided, and statistical significance was set a priori at \( p < 0.05 \).

Table 1. — Items of the Greene Climacteric Scale [6] *.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Group I (n = 83)</th>
<th>Group II (n = 83)</th>
<th>Group III (n = 83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Heart beating quickly or strong</td>
<td>1.1 ± 0.1</td>
<td>1.2 ± 0.1</td>
<td>1.1 ± 0.1</td>
</tr>
<tr>
<td>(2) Feeling tense or nervous</td>
<td>0.9 ± 0.1</td>
<td>0.9 ± 0.1</td>
<td>0.9 ± 0.1</td>
</tr>
<tr>
<td>(3) Difficulty in sleeping</td>
<td>0.8 ± 0.1</td>
<td>0.8 ± 0.1</td>
<td>0.8 ± 0.1</td>
</tr>
<tr>
<td>(4) Panic attacks</td>
<td>0.7 ± 0.1</td>
<td>0.7 ± 0.1</td>
<td>0.7 ± 0.1</td>
</tr>
<tr>
<td>(5) Difficulty in concentrating</td>
<td>0.6 ± 0.1</td>
<td>0.6 ± 0.1</td>
<td>0.6 ± 0.1</td>
</tr>
<tr>
<td>(6) Feeling tired or lacking in energy</td>
<td>0.5 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>0.5 ± 0.1</td>
</tr>
<tr>
<td>(7) Loss of interest in most things</td>
<td>0.4 ± 0.1</td>
<td>0.4 ± 0.1</td>
<td>0.4 ± 0.1</td>
</tr>
<tr>
<td>(8) Feeling unhappy or distressed</td>
<td>0.3 ± 0.1</td>
<td>0.3 ± 0.1</td>
<td>0.3 ± 0.1</td>
</tr>
<tr>
<td>(9) Crying spells</td>
<td>0.2 ± 0.1</td>
<td>0.2 ± 0.1</td>
<td>0.2 ± 0.1</td>
</tr>
<tr>
<td>(10) Irritability</td>
<td>0.1 ± 0.1</td>
<td>0.1 ± 0.1</td>
<td>0.1 ± 0.1</td>
</tr>
<tr>
<td>(11) Feeling dizzy or faint</td>
<td>0.0 ± 0.1</td>
<td>0.0 ± 0.1</td>
<td>0.0 ± 0.1</td>
</tr>
<tr>
<td>(12) Pressure or tightness in head</td>
<td>0.0 ± 0.1</td>
<td>0.0 ± 0.1</td>
<td>0.0 ± 0.1</td>
</tr>
<tr>
<td>(13) Parts of body feel numb</td>
<td>0.0 ± 0.1</td>
<td>0.0 ± 0.1</td>
<td>0.0 ± 0.1</td>
</tr>
<tr>
<td>(14) Headaches</td>
<td>0.0 ± 0.1</td>
<td>0.0 ± 0.1</td>
<td>0.0 ± 0.1</td>
</tr>
<tr>
<td>(15) Muscle and joint pain</td>
<td>0.0 ± 0.1</td>
<td>0.0 ± 0.1</td>
<td>0.0 ± 0.1</td>
</tr>
<tr>
<td>(16) Breathing difficulties</td>
<td>0.0 ± 0.1</td>
<td>0.0 ± 0.1</td>
<td>0.0 ± 0.1</td>
</tr>
<tr>
<td>(17) Hot flushes</td>
<td>0.0 ± 0.1</td>
<td>0.0 ± 0.1</td>
<td>0.0 ± 0.1</td>
</tr>
<tr>
<td>(18) Sweating at night</td>
<td>0.0 ± 0.1</td>
<td>0.0 ± 0.1</td>
<td>0.0 ± 0.1</td>
</tr>
<tr>
<td>(19) Loss of interest in sex</td>
<td>0.0 ± 0.1</td>
<td>0.0 ± 0.1</td>
<td>0.0 ± 0.1</td>
</tr>
</tbody>
</table>


Results

Demographic characteristics of groups I, II and III are shown in Table 2. No statistically significant differences were observed between three groups. Although not depicted in Table 2, the level of education, occupational status, and percentage of women currently on regular exercise did not differ between the groups. Before HT, baseline GCS total score and subscores of both groups prior to HT were similar. As shown in Table 3, in group I and group II, vasomotor symptoms (\( p < 0.001, p < 0.05 \)), somatic symptoms (\( p < 0.05, p < 0.05 \)) and total score (\( p < 0.05, p < 0.005 \)) significantly reduced from baseline values, respectively, while the other subscores revealed no statistically important differences following six months of HT. In group III, the vasomotor (\( p < 0.05 \)) subscore and total score (\( p < 0.05 \)) decreased significantly while other subscore reductions were not significant. Oral estrogen and placebo revealed statistically significant differences when compared with transdermal estrogen and oral estrogen in which reduced GCS subscores and total score statistically were nearly the same as placebo.

Discussion

This prospective, double-blind study has demonstrated that oral transdermal estrogen and placebo significantly improved vasomotor symptoms and total score. Taking all groups into consideration, anxiety, depression and sexual subscores statistically showed no improvement following six months of HT. In the present study oral CEE was found to be the most effective in vasomotor symptoms (\( p < 0.001 \)). Although transdermal 17β-estradiol and placebo are less effective than oral CEE in vasomotor symptoms, they also revealed statistically significant improvement (\( p < 0.05 \)).

This clinical trial compared the short-term effects of 0.625 mg oral CEE, transdermal 17β-estradiol and placebo on GCS scores in women with surgical menopause. The subject of this study was mostly a homogenous group with regard to obesity, occupation, level of education and state of regularly exercising and hysterectomy status. All of those factors have been proven to result in more climacteric symptom-free periods during postmenopause [9].

To confront climacteric complaints different treatment strategies have been established such as physical exercise, hormone therapy, tibolone, alternative remedies like antidepressants and herbal therapy [10-12]. Of them, different forms of HT such as the oral vs transdermal route or a low-dose continuous combination of estrogen+progestrone and tibolone were compared with each other or placebo in several studies [13-18]. Cohen et al. [13] examined the effect of short-term (4 weeks) use of transdermal 17β-estradiol with placebo in 22 peri-postmenopausal women. The authors concluded that perimenopausal women may benefit from short-term use of an estradiol patch but did not obtain conclusive results on women with surgical menopause. Baksu et al. [14] through a randomized, double-blind interventional study has compared the effects of tibolone and transdermal estrogen therapy on climacteric complaints in women with surgical menopause following six months of HT. They concluded that both the transdermal estradiol patch and tibolone showed significant improvements in menopausal symptoms, depression and anxiety scores assessed by Kupperman’s scales compared to the placebo group. Haines et al. [15] conducted a prospective, randomized, placebo-controlled study on the effect of 1 and 2 mg oral estradiol on menopausal symptoms, anxiety and depression symptoms of postmenopausal women (assessed by Kupperman’s scale).
Table 3. — Distribution of total GCS scores and mean subscores ± SEM of women with surgical menopause assigned to 0.625 mg oral CEE (group I), a 3.9 mg weekly transdermal 17β estradiol patch (group II) and placebo (group III) before and six months after the initiation of HT (*paired Student’s t-test).

<table>
<thead>
<tr>
<th>Groups</th>
<th>Anxiety</th>
<th>Depression</th>
<th>Somatic</th>
<th>Vasomotor</th>
<th>Sexual</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>0.93 ± 0.04</td>
<td>0.91 ± 0.05</td>
<td>0.86 ± 0.03</td>
<td>1.42 ± 0.08</td>
<td>1.10 ± 0.11</td>
<td>0.96 ± 0.02</td>
</tr>
<tr>
<td>After</td>
<td>0.94 ± 0.04</td>
<td>0.87 ± 0.04</td>
<td>0.74 ± 0.03</td>
<td>1.00 ± 0.08</td>
<td>1.90 ± 0.11</td>
<td>0.86 ± 0.02</td>
</tr>
<tr>
<td>p*</td>
<td>ns</td>
<td>ns</td>
<td>&lt; 0.05</td>
<td>&lt; 0.005</td>
<td>ns</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>Group II</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>1.04 ± 0.04</td>
<td>0.90 ± 0.05</td>
<td>0.85 ± 0.04</td>
<td>1.54 ± 0.09</td>
<td>1.27 ± 0.11</td>
<td>1.1 ± 0.66</td>
</tr>
<tr>
<td>After</td>
<td>0.95 ± 0.03</td>
<td>0.82 ± 0.03</td>
<td>0.74 ± 0.03</td>
<td>1.31 ± 0.07</td>
<td>1.43 ± 0.09</td>
<td>0.74 ± 0.50</td>
</tr>
<tr>
<td>p*</td>
<td>ns</td>
<td>ns</td>
<td>&lt; 0.05</td>
<td>&lt; 0.05</td>
<td>ns</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Group III</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>0.93 ± 0.04</td>
<td>0.82 ± 0.04</td>
<td>0.80 ± 0.04</td>
<td>1.56 ± 0.09</td>
<td>1.20 ± 0.11</td>
<td>1 ± 0.06</td>
</tr>
<tr>
<td>After</td>
<td>0.94 ± 0.04</td>
<td>0.74 ± 0.04</td>
<td>0.78 ± 0.03</td>
<td>1.36 ± 0.07</td>
<td>0.92 ± 0.10</td>
<td>0.83 ± 0.06</td>
</tr>
<tr>
<td>p*</td>
<td>ns</td>
<td>ns</td>
<td>&lt; 0.05</td>
<td>ns</td>
<td>&lt; 0.05</td>
<td></td>
</tr>
</tbody>
</table>

CEE: conjugate equine estrogen; ns = not significant.

Is placebo as effective as estrogen regimens on vasomotor symptoms in women with surgical menopause?

over a 12-month study period and, finally concluded that there was a significant reduction in menopausal symptom scores in the 2 mg dose but not in the 1 mg dose compared to placebo.

Based on the results of our study, placebo seemed to be as effective as estrogen in alleviating the vasomotor complaints following six months of HT, a contradictory finding to published studies in the literature [13, 14, 16]. Different type of scales used, different ethnic populations and sample size, and various durations of hormone treatment may explain the discrepancies mentioned above. Whether this study has limitations such as sample size and short follow-up period, the different impact of two HT regimens and placebo on Greene Climacteric Scores remains to be elucidated.

To conclude, estrogen regimens and placebo seem to be effective in alleviating vasomotor symptoms. Further prospective randomized studies need to be conducted on a large case series with the aim of looking at not only short-term but long-term effects on climacteric symptoms in comparison to both placebo arms and different dose and mode of HT use.

References


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Tubal ectopic pregnancy in the north of Jordan: presentation and management

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Department of Obstetrics and Gynecology, Jordan University of Science and Technology, Irbid (Jordan)

Summary

Objective: To evaluate and compare the current approach to the management of ectopic pregnancy between the main two civil hospitals in the north of Jordan. Design: A retrospective study. Material and methods: A retrospective review was made of the records of all patients with confirmed ectopic pregnancy admitted to Princess Badea Teaching Hospital (PBTH), and King Abdullah University Hospital (KAUH) between January 1, 2005 and December 31, 2005. The total number of deliveries for the same period was obtained from the labor ward records of hospitals. Information regarding demographic data, presenting symptoms, methods of diagnosis and treatment were extracted from individual patient records. Results: There were 50 cases of confirmed ectopic pregnancy in PBTH compared with 20 cases in KAUH. The total number of deliveries at PBTH was 9,000 (1 ectopic/180 deliveries) while at KAUH, the number of deliveries was 3,000 so the ratio was 1: 150. The majority of patients (82%) had ruptured ectopic pregnancy at presentation. All cases at PBTH were managed by laparotomy. Of the 20 cases at KAUH, five cases were managed laparoscopically and three received medical treatment for their ectopics. There was no maternal mortality from ectopic pregnancy or its management at either hospital. Conclusion: The management of ectopic pregnancy in our community is still suboptimal. We recommend the development of clinical protocols for early diagnosis and referral, training in transvaginal scanning and an increase in the use of laparoscopy for the management of ectopic pregnancy.

Key words: Ectopic pregnancy; Methotrexate; Laparoscopy.

Introduction

Ectopic pregnancy remains an important cause of maternal morbidity and occasionally mortality [1]. The management of ectopic pregnancy has changed considerably over the last few years. The availability of rapid and sensitive tests for β-hCG, improved transvaginal ultrasound (TVS) techniques and development of clinical protocols for diagnosis and treatment have made early and non-invasive diagnosis of ectopic pregnancy possible, and allowed medical therapy of this condition [1-4]. Furthermore, advances in laparoscopic surgery would theoretically allow most ectopic pregnancies to be managed laparoscopically under ideal situations.

Unfortunately, advances in the management of this condition are not available or practical everywhere. Late presentation with massive hemoperitoneum is not uncommon in developing countries, which limits both the use of conservative treatment and contributes to high maternal morbidity and mortality [5].

The aim of this study was to evaluate the current approach to the management of ectopic pregnancy in the main two civil hospitals in north of Jordan.

Material and Methods

A retrospective review was made of the records of all patients with confirmed ectopic pregnancy admitted to Princess Badea Teaching Hospital and King Abdullah University Hospital (KAUH) between January 1, 2005 and December 31, 2005. The total number of deliveries for the same period was obtained from labor ward records.

Information regarding demographic data, presenting symptoms, methods of diagnosis and treatment were extracted from individual patient records.

Results

During the study period, there were 50 cases of confirmed tubal ectopic pregnancies at PBTH and 20 cases at KAUH. The total number of hospital deliveries was 9,000 at PBTH and 3,000 at KAUH. The ratio of tubal ectopic pregnancy to total hospital delivery was 1: 180 at PBTH and 1:150 at KAUH.

The average age of patients was 28.8 years (range 16-40) at PBTH, and 31.7 years (range 23-40) at KAUH. The highest incidence of ectopic pregnancy occurred in multiparous women at both hospitals (Table 1).

Eight patients (16%) from the PBTH group and two (10%) from the KAUH group used intrauterine contraceptive devices, while the majority of patients from both PBTH and KAUH did not use any form of medical contraception (74% and 85%, respectively). Three patients (6%) with tubal ectopic pregnancy from the PBTH group had conceived by IVF while one patient (5%) from the KAUH group conceived by IVF. Twenty patients (40%) from PBTH and nine patients (45%) from KAUH had a previous history of uterine evacuation for retained products of conception. However, only one patient (2%) from PBTH and one patient (5%) from KAUH had a previous history of documented pelvic inflammatory disease.
Abdominal pain was by far the most common presenting symptom (94% for PBTH, 85% for KAUH), followed by an episode of vaginal bleeding (Table 2). Amenorrhea was noted in 60% of the PBTH cases and in 73% of the KAUH cases. Abdominal tenderness was elicited in 90% of the PBTH patients and in 75% of KAUH patients, while an adnexal mass was palpable in seven cases (14%) of PBTH and four (20%) of KAUH cases.

Transabdominal ultrasound was performed in 47 (94%) cases at PBTH, and in all cases at KAUH. The commonest sonographic finding was free fluid in the pouch of Douglas (44% for PBTH and 35% for KAUH), indicating a leaking or ruptured ectopic pregnancy. Ultrasound was not performed in three cases at PBTH because of the state of collapse and clinical picture of intraperitoneal bleeding.

All PBTH cases were managed by laparotomy. In 18 cases (36%), laparoscopy was implemented as a diagnostic tool. Nearly all patients underwent salpingectomy (60% right side, 36% left side). Only nine patients had an unruptured ectopic pregnancy at the time of surgery. However, at KAUH, medical treatment with methotrexate was used in three (15%) cases, laparoscopic surgery was performed in five (25%) cases, and the remaining (60%) had laparatomy.

Two-thirds of patients had their operation within 12 hours of admission. Only three patients had to wait 72 hours or more to undergo surgery (Table 3). Seventeen patients (34%) required intra- or postoperative blood transfusion to correct their anemia at PBTH compared to three patients (15%) at KAUH.

The average hospital stay was 3.5 days. Twenty-eight patients (56%) went home on the fourth postoperative day. There were no maternal mortalities from ectopic pregnancy during the period of study.

Discussion

The rate of ectopic pregnancy varies worldwide. The annual incidence of ectopic pregnancy in the USA is around 2% [6]. In Norway, Sweden and UK, the rates more than doubled between the 1970s and the 1990s, but are now declining [7-10]. In Nigeria, the rate is increasing from 1:287 to 1:44 [11, 5]. In Saudi Arabia, Sobande

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristics.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBTH*</td>
<td>KAUH**</td>
</tr>
<tr>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>16-25</td>
<td>15</td>
</tr>
<tr>
<td>26-35</td>
<td>27</td>
</tr>
<tr>
<td>≥ 36</td>
<td>8</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>1-4</td>
<td>35</td>
</tr>
<tr>
<td>&gt; 4</td>
<td>9</td>
</tr>
<tr>
<td>Contraception</td>
<td></td>
</tr>
<tr>
<td>– Combined pills</td>
<td>1</td>
</tr>
<tr>
<td>– Minipills</td>
<td>4</td>
</tr>
<tr>
<td>– IUCDs ***</td>
<td>8</td>
</tr>
<tr>
<td>– None user</td>
<td>37</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Clinical findings of ectopic pregnancy at PBTH and KAUH.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBTH*</td>
<td>KAUH**</td>
</tr>
<tr>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Symptoms:</td>
<td></td>
</tr>
<tr>
<td>– Amenorrhea</td>
<td>30</td>
</tr>
<tr>
<td>– Abdominal pain</td>
<td>47</td>
</tr>
<tr>
<td>– Vaginal bleeding</td>
<td>36</td>
</tr>
<tr>
<td>– Syncope</td>
<td>3</td>
</tr>
<tr>
<td>– Shoulder pain</td>
<td>4</td>
</tr>
<tr>
<td>Signs:</td>
<td></td>
</tr>
<tr>
<td>– Abdominal tenderness</td>
<td>45</td>
</tr>
<tr>
<td>– Cervical excitation</td>
<td>35</td>
</tr>
<tr>
<td>– Adnexal mass</td>
<td>7</td>
</tr>
<tr>
<td>Ultrasound findings:</td>
<td></td>
</tr>
<tr>
<td>– Extraterine sac or alive fetus</td>
<td>2</td>
</tr>
<tr>
<td>– Fluid in the pouch of Douglas</td>
<td>22</td>
</tr>
<tr>
<td>– Adnexal mass</td>
<td>17</td>
</tr>
<tr>
<td>– Empty uterus</td>
<td>6</td>
</tr>
<tr>
<td>– Not done</td>
<td>3</td>
</tr>
<tr>
<td>Use of laparoscopy:</td>
<td></td>
</tr>
<tr>
<td>– Used</td>
<td>18</td>
</tr>
<tr>
<td>– Not used</td>
<td>32</td>
</tr>
<tr>
<td>– No surgery</td>
<td>0</td>
</tr>
<tr>
<td>State of the tube:</td>
<td></td>
</tr>
<tr>
<td>– Ruptured</td>
<td>41</td>
</tr>
<tr>
<td>– Unruptured</td>
<td>9</td>
</tr>
<tr>
<td>– Not assessed</td>
<td>0</td>
</tr>
</tbody>
</table>

* PBTH: Princess Badea Teaching Hospital; ** KAUH: King Abdullah University Hospital.

* PBTH: Princess Badea Teaching Hospital; ** KAUH: King Abdullah University Hospital.
and Archibong reported an incidence of 0.74 per 100 live births [12].

The rate of ectopic pregnancy was 1:175 in the north of Jordan. This relatively low rate could be explained by the fact that termination of pregnancy and sexually transmitted diseases are uncommon in Jordan. The commonest risk factor found in our study was prior evacuation of the uterus for retained products of conception.

Laparoscopic management of ectopic pregnancy is generally preferred over laparotomy [13, 14], due to lower cost, blood loss and analgesia requirements and shorter postoperative recovery. In this study, however, conventional surgery with salpingectomy was the standard modality of ectopic pregnancy treatment at PBTH. This is explained by late presentation in most cases and lack of training for operative laparoscopy. For the same reasons, medical management of ectopic pregnancy was not implemented at PBTH. At KAUH, a quarter of cases were managed by laparoscopic surgery, 15% of cases were managed by medical treatment (methotrexate), and in only 60% of cases laparotomy was performed. This is due to the availability of trained gynecologists in the use of operative laparoscopy.

Maternal mortality from ectopic pregnancy fell from 35.5 to 3.8 deaths per 10,000 women between 1970 and 1989 in the USA [15], and from 16 to three deaths per 10,000 pregnancies between 1973 and 1993 in the UK [7]. In the developing world, however, mortality remains high [16]. There were no maternal deaths due to ectopic pregnancy during the period of our study. A high index of suspicion of ectopic pregnancy and short decision-intervention interval may explain this [17, 18].

In conclusion, the management of ectopic pregnancy in our community is still suboptimal. We recommend more development of clinical protocols for early diagnosis and referral, and training in transvaginal scanning. Moreover, with the new technological advances in laparoscopic surgery, it is recommended that training in this technology be implemented with the view of conducting less invasive and more conservative procedures.

References

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Umbilical cord prolapse in the southeast region of Turkey: evaluation of 79 cases

Department of Obstetrics and Gynecology, Dicle University School of Medicine (Turkey)

Introduction

Umbilical cord prolapse (UCP) is an obstetric emergency where the umbilical cord descends in advance of the presenting fetal part during labor, increasing perinatal morbidity with high perinatal mortality. The incidence of this undesirable situation is decreasing because of the increased use of elective cesarean section [1, 2]. UCP occurred in 6% of deliveries in 1932, now complicates only approximately 2% of deliveries [3, 4]. There are some well known risk factors for this situation which include abnormal fetal presentation, low birthweight (lower than 2,500 g), prematurity, multiple gestations, multiparity, hydroamnios, and amniotomy [5]. This retrospective study was designed to determine the prevalence and perinatal outcome of deliveries complicated by cord prolapse at Dicle University College Hospital.

Material and Methods

This retrospective study was performed at the Obstetrics and Gynecology Department of Dicle University Faculty of Medicine between January 2000 and December 2008. Seventy-nine (0.36%) of the deliveries were complicated by UCP. We diagnosed umbilical cord prolapse by palpating the umbilical cord in front of the presenting part after rupture of the membranes. Data from the patients included maternal age, obstetrical history (gravidy, parity), age of gestation, presentation of the fetus, birthweight and 1 and 5 min Apgar scores. Risk factors were as follows: lack of prenatal care, multiparity, preterm rupture of the membranes, multiple pregnancies, previous cesarean section, amniotic fluid abnormalities (hydramnios > 24 cm, oligohydramnios < 5 cm). Amniotomy is used in our clinic after the presenting part has descended through the pelvis. We performed amniotomy on 38 (50%) patients.

Results

During the study period 79 cases of UCP occurred. During this period there were 21,487 deliveries; the incidence of umbilical cord prolapse was one in 272 births (0.36%). In that period, totally 8,876 cesarean sections were performed; 0.84% of these cesarean sections were performed for UCP. Umbilical cord prolapse occurred in 52 (65.8%) cases with vertex presentation, 16 (20.2%) cases with breech presentation, six (7.5%) with transverse lie and five (6.3%) with foot presentation. In the control group the number of breech presentations was 18 (18%). Twenty-three (29.1%) of the cases were twin pregnancies, whereas in the control group there was no twin pregnancy. We performed amniotomy in 38 (48.1%) of the cases; 23 (29.1%) of these had UCP. The difference was not statistically significant. The mean age of the study cases was 31.44 ± 5.46 and the control group was 28.98 ± 5.04. The mean gravidy was 4.9 ± 2.72 in the study group and 3.63 ± 2.56 in the control group. The mean parity was 3.46 ± 2.47 in the study group and 2.07 ± 2.12 in the control group. Seventy (88.6%) of the cases were multiparous women. In the control group 68 (68%) women were multiparous. Study cases were 1.3 times more likely to be multiparas than control group cases. Cesarean section was performed in 76 cases (96.2%) and there were nine (11.3%) perinatal deaths. Conclusion: Umbilical cord prolapse is a risk factor of perinatal morbidity and mortality. Fetal weight < 2,500 and abnormal fetal presentation are associated with increased risk of umbilical cord prolapse. Cesarean section resulted in a significantly decreased risk of perinatal mortality.

Summary

Objective: The aim of the study was to determine the risk factors and perinatal outcomes of umbilical cord prolapse (UCP). Material and Methods: This study was performed at Dicle University between January 2000 and December 2008 on 79 cases in which deliveries were complicated by umbilical cord prolapse. Results: 0.36% of all deliveries were complicated by umbilical cord prolapse. The presentation of the fetuses were as follows: vertex, breech and transverse lie and foot presentation. Thirty-four (43%) fetuses with UCP had a fetal weight of 2500 g as compared with nine (9%) for fetuses in the control group (p < 0.05). Mothers in the study group were 1.3 times more likely to be multiparas than the control group (p = 0.16) Cesarean section was performed in 76 cases (96.2%) and there were nine (11.3%) perinatal deaths. Conclusion: Umbilical cord prolapse is a risk factor of perinatal morbidity and mortality. Fetal weight < 2500 g and abnormal fetal presentation are associated with increased risk of umbilical cord prolapse. Cesarean section resulted in a significantly decreased risk of perinatal mortality.

Key words: Umbilical cord prolapse; Cesarean; Perinatal mortality.
Another important risk factor is multiparity; Kahana et al. found that low birthweight does not increase risk of UCP [4]. In our study we found that low birthweight increases the UCP with significant statistical difference (p = 0.09). Another well known risk factor for UCP is hydramnios, especially polyhydramnios. Kahana et al. [10] and Dilbaz et al. [9] found that hydramnios increases the risk of UCP 3.3 times and 21 times. In our study only two cases had polyhydramnios. Lack of prenatal care is another studied factor in the literature [11]. Kahana et al. found that lack of perinatal care is an independent factor of UCP [10]; in our study the 96% of the patients did not take prenatal care. The most important point that affects the perinatal mortality is, the time between the diagnosis of UCP and delivery [12]. When the prolapse is diagnosed as soon as possible the delivery should be performed if the fetus is mature [13], and also Uygun et al., believes that prompt cesarean section should be the treatment of choice when cord prolapse is diagnosed, when the fetus is still alive, and when delivery is not imminent [4]. We performed cesarean section in 76 cases, and our clinical choice for UCP is cesarean. When we look at the literature we can see that perinatal mortality ratio is between 3.9%-16.2% [4, 10], and in another study this ratio is 1/80 [9]. In our study we found perinatal mortality as 11.3%.

To prevent and decrease the perinatal and maternal mortality effective antenatal care, hospital vaginal delivery and prompt cesarean section seems to be the most important points. Moreover healthcare professionals should know the risk factors of UCP very well and should be aware during the follow-up of this cases.

### Discussion

UCP, which occurred in 6% of deliveries in past, now complicates only approximately 2% of deliveries [1, 3]. The reduced incidence probably reflects changes in obstetric practice, especially the increased use of elective cesarean section. The high number of our UCP cases is depends on that our hospital is the biggest and sole reference hospital of southern east region of Turkey. In the literature the incidence of this situation is varies between one in 162 to one in 714 deliveries [3, 4]. In our case series the incidence is one out of 272 births in our study (36%). There are many risk factors of UCP recorded in the literature [6, 7]; we have found risk factors similar to these studies. The most accepted risk factor is non engagement of the presenting part of the fetus [8, 9]. In the previous studies the risk of prolapse is found to be 4-6% in breech presentation and 7-15% in transverse presentation [8]. In our study this risk was 20.2% for breech presentation and 7.6% for transverse presentation. Another important risk factor is multiparity; Kahana et al. reported that 88% of their patients were multipara [4, 8, 10] and Uygur et al. showed that multiparity increases prolapse risk 1.6 times [4]. In our study multiparity was 88.6% of the cases and 68% of the control group with a 1.3 times increased risk for multiparity. However the difference was not statistically significant (p = 0.164). Low birthweight is another risk factor associated with umbilical cord prolapse [6, 7], but Uygur et al. found that low birthweight does not increase risk of UCP [4].

### References


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Prague, Czech Republic, European Union
October 23-26, 2010

mailto: IGCS_2010@mail.vresp.com
Adolescent pregnancies and obstetric outcomes in Southeast Turkey: data from two regional centers

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Summary

Purpose of investigation: To evaluate adolescent pregnancy and obstetric outcomes. Methods: This retrospective cohort study was performed by analysis of patient files and birth records of pregnant women who delivered in two cities in Southeast Anatolia, Turkey. Pregnant women aged 19 years old and younger were included in the study group. Women between 20 and 35 years of age constituted the control group. Results: The incidence of adolescent pregnancy during the study period was 11%. Birth weight and hemoglobin level were significantly higher in the control group (p < 0.05). The majority of the women in the study group delivered vaginally (p < 0.05). The incidence of preterm labor, intrauterine growth retardation, and stillbirth was significantly higher in the study group (p < 0.05). Adolescent mothers were most likely to have low birth weight and very low birth weight babies (p < 0.05). Conclusion: Adolescent pregnancies were associated with adverse pregnancy outcomes in our study population. Possible grounds for such increase warrant further evaluation and discussion.

Key words: Adolescent pregnancy; Obstetric outcomes; Turkish women.

Introduction

Adolescent pregnancy continues to be a challenging public health issue around the world and is considered a high-risk type of pregnancy, involving physiological, psychological, and sociological risks [1]. Despite regional differences adolescent pregnancies constitute 0.9-21% of all pregnancies globally. Especially in developing countries social problems, poor healthcare, and poor socioeconomic status cause an increase in the rate of adolescent pregnancies [2]. The incidence of pregnancy among women aged 15-19 years in various Turkish studies was reported to be 8.7% [3], 7.9% [4], and 11.8% [5].

Adolescent pregnant women suffer substantially higher maternal and perinatal morbidity and mortality than adult women [6-9]. Poor pregnancy outcomes may be aggravated by socioeconomic, cultural, geographic, and racial factors [10-14]. Most studies report that certain physiological risks are higher among adolescent mothers, such as inadequate maternal weight gain during pregnancy, preterm births, low-birth-weight (LBW) infants, cephalopelvic disproportion (CPD), pregnancy-induced hypertension (PIH), abortion, stillbirth, and iron deficiency anemia [8-10, 15]. In contrast, some studies have suggested that adolescent pregnancies are not associated with increased risks of adverse perinatal outcomes compared with adult pregnancies [16-20]. All studies highlight the importance of preventing adolescent pregnancies, or, if that is not possible, close follow-up strategies should be implemented to reduce complications.

The purpose of this study was to compare obstetric and perinatal outcomes in pregnant adolescents with those in pregnant adults who delivered in two cities in Southeast Turkey.

Materials and Methods

This retrospective cohort study was performed by analysis of patient files and birth records of pregnant women who delivered at Kahramanmaraş Sutcuimam University Medical Faculty Hospital, Obstetrics and Gynecology Clinic and Siirt Government Hospital (in two cities in Southeast Anatolia, Turkey), during the period January 2007 to January 2009. Pregnant women aged 19 years old and younger were included in the study group. Women between 20 and 35 years of age constituted the control group. Multiple pregnancies, deliveries before the 24th gestational week, and fetuses lower than 500 g were excluded from the study. Patient data were retrieved from records.

All demographic features such as age, nulliparity, multiparity, and hemoglobin (Hb) levels, and any data from gestation and the neonatal period were recorded. Preterm labor, postmaturity, birth weight, cesarean section (CS), operative delivery (vacuum extraction), preterm rupture of membranes (PPROM), PIH, intrauterine growth retardation (IUGR), breech presentation, and stillbirth rates were examined as outcomes of gestation and perinatal complications. Delivery before 37 weeks was classified as preterm labor. Deliveries after more than 41 weeks were classified as postmature. Preeclampsia was diagnosed with a blood pressure > 140/90 mmHg and ≥ 1+ proteinuria in the urine examination. All intrauterine and intrapartum deaths were considered in a single group, the stillbirth group. Birth weight was divided in three categories: under 1,500 g; very low birth weight (VLBW); 1,500-2,500 g, LBW; and above 4,000 g; macrosomia.

SPSS 15.0 was used for the statistical analysis. Chi-square and Student’s t-tests were performed to identify differences in obstetric and perinatal complications between pregnant adolescents and adult pregnant women.
Results

There were 311 pregnancies in women aged ≤ 19 years [13-19] (study group) compared with 2,525 pregnancies in the 20-35 age group (control group). The incidence of adolescent pregnancy during the study period was 11%. The mean age of pregnant adolescents was 17.1 (range 13-19, SD: ± 0.8). Mean gestational age was similar in the two groups, i.e., 37.6 ± 2.6 vs 38.1 ± 2.5. Mean birth weight and hemoglobin level were significantly higher in the control group, i.e., 3,031.5 ± 575.3 vs 3,177.8 ± 649.4 and 11.5 ± 1.0 vs 11.7 ± 1.3, respectively, (p < 0.05) (Table 1). Some obstetric outcomes compared among the adolescents and adults are shown in Table 2. Two hundred fifty-four (81.7%) of the pregnant adolescents were nulliparous compared to 519 (20.6%) of the pregnant adults (p < 0.05). The majority of the women in the study group delivered vaginally (75.9% vs 59.1%; p < 0.05). The incidence of CS in the study and control groups was 24.1% and 40.1%, respectively, (p < 0.05). There was no difference in the rate of vacuum extraction between the groups (3.5% vs 3.9%). Antenatal complications and problems are listed in Table 3. The incidence of preterm labor, IUGR, breech delivery and stillbirth was significantly higher in the study group, i.e., 19.3% vs 9.1%, 6.8% vs 2.7%, 10.0% vs 6.3% and 7.7% vs 1.8%, respectively, (p < 0.05). There were no significant differences in PIH, PPROM or prolonged pregnancy between the groups. The distribution of birth weights is given in Table 4. Adolescent mothers were more likely to have LBW and VLBW babies, i.e., 17.0% vs 5.5% and 7.1% vs 2.2%, respectively, (p < 0.05).

Discussion

The adolescent pregnancy rate in our study was 11.0%, which was similar to the 11.8% rate reported by Keskinolu et al. [5] and higher than the incidence of 8.7% reported by Aksit et al. [3]. According to the Turkey Demographic and Health Survey (TDHS)-2003 the overall level of teenage childbearing is approximately 8% in Turkey, and the Eastern region has the highest level, with 9.1% [21]. The recently reported TDHS-2008 demonstrates that the age-specific fertility rate of the 15-19 age group declined from 60 births per 1,000 women in 1998 to 46 births per 1,000 women in 2003 and eventually to 35 births per 1,000 women in 2008 [22]. The prevalence of adolescent pregnancies in Turkey is still higher than it is in several Europe countries and the USA; for example, it has been reported to be 20 births per 1,000 women in the Netherlands [23], 42.9 per 1,000 women in 2002 in the USA [24], and 5.6% in Greece [25]. Some developing countries like India [26] and Brazil [27] have higher prevalences, i.e., 14.7% and 29%, respectively. TDHS-2003 emphasized that the level of adolescent fertility is strongly associated with women’s educational level. The proportion of teenage women who are pregnant or who have already given birth decreases from about 15% among women with less than primary education to 3% among women with at least a high school education.
in Turkey. They think that this low rate of contraceptive use is the reason for unintended pregnancies [2]. With increasing education and socioeconomic status the incidence seems to fall, but it remains a problem.

Most of the adolescent mothers in our study were nulliparous and delivered vaginally. The CS rate was significantly higher in the control group. There are contradictory views about this. Some studies report adolescent pregnancy as a risk factor for CS [12, 16, 17, 26], whereas others have disproved this [8, 9, 15, 18, 19, 25, 28, 29]. Our study does not support the belief that adolescent mothers are at increased risk for fetopelvic disproportion as a consequence of incomplete development. Jolly et al. attributed the etiology of high incidence of vaginal delivery in adolescents to the presence of a more functional myometrium, greater connective tissue elasticity, and lower cervical compliance, which allowed for more spontaneous vaginal deliveries [9]. Another possible explanation for this condition could be the high prevalence of LBW babies in the study group, which would be associated with a higher chance of successful vaginal delivery. In addition, the families in this region usually want more than four or five children and they know that this will not be possible if a CS is performed, and so the families compel adolescent pregnant women to deliver vaginally. We think this parental pressure increases the possibility of vaginal delivery among adolescents in our region.

The most common antenatal complication in pregnant adolescents in our study was preterm labor, with a 19.3% rate ($p < 0.05$). The association between young maternal age and preterm labor remains controversial. As reported in several studies, in adolescents poor antenatal care, poor nutrition, anemia, cigarette smoking, and drug addiction during pregnancy may increase the rates of stillbirth, LBW, and preterm delivery [8-10, 12, 14, 15, 17-19, 23], while other studies [16, 20, 28, 29] do not corroborate this. Smoking rates have been found highest among adolescent mothers in the USA [24], but in Turkey adolescents have the lowest rate [21]. In THDS-2003, in order to assess women’s nutritional status, the body mass index (BMI) of women who had given birth in the five-year period was calculated and a BMI less than 18.5 was used to identify cases of chronic malnutrition. The incidence of mothers’ BMI falling below 18.5 in the 15-19 age group was 9.6% and was significantly higher than that in older age groups [21]. Stevens-Simon et al. reported that a low BMI was associated with preterm delivery in adolescents [30]. Another most important factor that increases the risk of preterm labor is low gynecologic age (biological immaturity) [10].

We found a significantly high incidence of LBW and VLBW babies in the study group ($p < 0.05$). This also is debated in various studies. Some studies report a correlation between maternal age and LBW or VLBW [2, 7, 8, 9, 12, 15, 19, 24, 26], while others do not [20, 28, 29]. The incidence of macrosomia was significantly high in the control group ($p < 0.05$). In a study performed in Turkey the most common obstetric complication was LBW, with a rate of 28.7% [2]. The incidence of LBW in our study was 17.0% and it was the second most common obstetric complication. The reasons for these conditions may be poor socioeconomic status, poor nutrition, and high incidence of preterm labor.

Since the 1970s, especially in developed countries, the perinatal consequences of adolescent pregnancies have shown significant improvement due to early and appropriate antenatal care and support. Antenatal care is an important issue for better obstetric outcomes; usually pregnant adolescents receive no or late antenatal care compared to pregnant adults [13]. However, because menstrual irregularities are common in adolescents they tend to have later awareness of their pregnancy, later first prenatal visits, and fewer total prenatal visits than adults. In Turkey, younger, low parity women, women living in urban areas and in the regions other than the East, and women with at least a first primary level education are more likely to have received antenatal care compared to other women. While in the Eastern region of Turkey 57% of pregnant women receive antenatal care from a doctor, this rate rises to 85.8% in the Western region [21]. Oboro et al. found that the risks for younger teenagers were not significantly different from those in older mothers when women with inadequate prenatal care were removed from the analysis [12]. In Turkey, with the change in the medical care system in 2008 every women below 18 age can receive free antenatal care from all hospitals, and social support is readily available from the government whether they have any health insurance or not. This (medical accessibility) condition with the decrease in incidence of adolescent pregnancies in Turkey may enhance the perinatal outcomes of adolescent pregnancies in the future.

In conclusion, there is incongruity about the perinatal outcomes of adolescent pregnancies. As mentioned above, while some reported studies demonstrate high risk some others do not. The studies in the literature usually attempt to establish the reason for these maternal and perinatal risks in pregnant adolescents. Therefore, we asked the same question and tried to find an answer; the incidence of adolescent pregnancies is decreasing, the use of contraception is increasing, most of the pregnant adolescents are married, the current pregnancy is wanted, the families desire another baby within two years, smoking among adolescents is very low, and they can access free antenatal care from all hospitals – then what is the reason for these unfavorable perinatal outcomes in Turkey? We thought that low socioeconomic and low educational status were the main reasons for these consequences. Special attention is required to educate these women to achieve more positive outcomes. Furthermore, timely and appropriate prenatal care must be advised to adolescents to obtain better obstetric outcomes. Every effort should be made to reach out to adolescents to ensure that they receive optimal care and outcomes.
References


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Pregnancy-related acute renal failure in the southeast region of Turkey: analysis of 75 cases

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Summary

Objective: To study the clinical profile, management and outcome of the patients with pregnancy-related acute renal failure (PRARF). Methods: All patients with PRARF admitted between January 2006 and January 2009 were analyzed. Results: The total number of women with PRARF was 75. Age range of women with PRARF was 21 to 46 years and 36% of the cases of PRARF were seen in the postpartum period. PRARF was caused by sepsis in 14.6%, toxemias of pregnancy in 75.2%, and hemorrhage of pregnancy in 12%. Postabortal sepsis was the cause in 14.6%. Dialysis was needed in 33.3%. Maternal mortality rate was 10.6%. Conclusions: Pregnancy-related acute renal failure is a major health problem and carries very high mortality and morbidity. Poor healthcare facilities and lack of antenatal healthcare clinics are major identified causes.

Key words: Troponin I; Homocysteine; Preeclampsia; Pregnancy.

Introduction

Acute renal failure (ARF) may be defined as a sudden decrease in renal function which is usually reversible, over a period of several hours to days, sufficient enough to result in retention of nitrogenous waste products (e.g., blood urea nitrogen [BUN] and creatinine) in the body. In pregnancy it can occur during antenatal or postnatal periods. ARF is a rare but an important complication during pregnancy. There has been a marked decline in the incidence of pregnancy-related acute renal failure (PRARF) over the past 50 years in industrialized countries as a result of improved antenatal care and obstetric practices [1]. PRARF is commonly caused by septic abortion in early pregnancy and by toxemia of pregnancy, hemorrhage during pregnancy (antepartum and postpartum), and ischemic acute tubular necrosis in late pregnancy [2].

The purpose of this study was to highlight the magnitude of the problem leading to high mortality and morbidity. Pregnancy-related acute renal failure is a challenging health problem of women, especially in rural areas. Therefore effective measures are needed to prevent this preventable complication of pregnancy.

Materials and Methods

This study was conducted at the Department of Obstetrics and Nephrology in Dicle University, Diyarbakir, Turkey from January 2006 to January 2009. During this period 75 patients were evaluated for pregnancy-related acute renal failure. PRARF was diagnosed when there was a sudden oliguria (24-hour urine output < 400 ml) or anuria with serum creatinine elevated to > 1.5 mg%.

Dialysis was needed in 25 or 33.33% of the patients; hemodialysis was given to 22 (29.33%), continuous venovenous hemodialysis to one patient (1.3%), and peritoneal dialysis to two (2.6%). Blood and blood sample transfusions were needed 41 (54.6%) of the patients.

The various abnormal laboratory findings are given in Table 2. Anemia was seen in 70.6% and thrombocytopenia in 57.3%. Electrolyte abnormalities were seen in 67.4% and they were hypernatremia in 12%, hyponatremia in 15.5%, hyperkalemia in 17.3% and hypokalemia in 10.6%. Mean creatinine level was 4.2 mg%, proteinuria was detected 53 (70.6%) of the patients.
Maternal mortality was 10.6% (8 patients). HELLP and eclampsia accounted for 50% (4 of the 8 patients). Sepsis was the cause of death in two patients (25%) and two patients (25%) died due to hemorrhage.

Table 2. — Abnormal laboratory findings in pregnancy related acute renal failure (n = 75).

<table>
<thead>
<tr>
<th>Laboratory findings</th>
<th>Number of cases</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>53</td>
<td>70.6</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>43</td>
<td>57.3</td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>14</td>
<td>15.5</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>13</td>
<td>17.3</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>8</td>
<td>10.6</td>
</tr>
<tr>
<td>Abnormal liver function tests</td>
<td>42</td>
<td>56</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>53</td>
<td>70.6</td>
</tr>
</tbody>
</table>

Discussion

ARF is an infrequent but life-threatening complication of pregnancy. The declining trend of PRARF is attributed to the legalization of termination of pregnancies and to better antenatal and postnatal care [1, 3, 4].

The frequency distribution of PRARF is bimodal in relation to the period of gestation. The first peak is seen between seven and 16 weeks, being caused by septic abortion, while toxemia, hemorrhage and puerperal sepsis account for the second peak which is seen between 34 and 36 weeks [2, 3]. In our study, it was observed that a significant proportion of cases occur in the later part of pregnancy and in the puerperium.

Toxemia was the most common cause of PRARF (75.2%) in our study. The next, in order, were postabortal sepsis (14.6%) and hemorrhage of pregnancy (12%). In our study, preeclampsia/eclampsia was the cause of PRARF in 69.2% of cases, while it was reported to be around 50% of cases in some earlier studies [1, 2].

The legalization of abortion was followed by a substantial decrease in the percentage of septic abortion-related acute renal failure in several developing countries [5]. In addition, we have noted that the majority of pregnant women are multigravida. Therefore, the avoidance of an unwanted pregnancy and prevention of septic abortion are keys to eliminating ARF associated with septic abortion in early pregnancy. Aseptic management of labor and abortion would eliminate avoidable ARF. Prompt treatment of any hemorrhage during pregnancy and labor would also reduce ARF significantly.

The reported mortality rate of PRARF was up to 56% in developing countries, whereas it was less than 30% in developed countries [1, 2, 5]. In our study, it was 10.6% (8/75). Kumar et al. recently reported a maternal mortality rate of 24% [6]. This appears to be the result of aseptic delivery and early management of antepartum and postpartum hemorrhage.

Conclusion

ARF is a dangerous complication of pregnancy which carries very high mortality and morbidity which although high in the initial period, has decreased in recent years. This is associated with a declining trend in post-abortal ARF and a reduction in maternal mortality. These changing trends in obstetrical ARF are mainly due to decreases in the number of septic abortions, puerperal sepsis, the legalization of abortion, and improved care of obstetrical complications.

References


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An analysis of hysteroscopy experience over a seven-year period

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Introduction

The development of hysteroscopy has obtained a minimally invasive approach to common gynecologic problems, such as infertility and abnormal uterine bleeding (AUB). During the 1970s, hysteroscopy began to increasingly attract the attention of physicians as a diagnostic and therapeutic alternative due to its greater accuracy in diagnosis and treatment, reduced morbidity, and reduced health care costs [1]. Increased clinician training and smaller diameter hysteroscopes have led to a widespread use of this important technology.

In this study, we present a review of hysteroscopic procedures performed in the Department of Obstetrics and Gynecology, University of Gaziantep, Turkey over a period of 7 years from 2002 to 2009, particularly highlighting the preoperative indications, postoperative diagnoses and complications associated with the procedure.

Materials and Methods

Cases from the database of the Department of Obstetrics and Gynaecology in Gaziantep University pertaining to all patients who underwent hysteroscopy – diagnostic or therapeutic – between January 2002 and July 2009 were analyzed (N = 580). Particular attention was given to the indication for the procedure, postoperative diagnoses, and associated complications.

Therapeutic hysteroscopy was performed after dilation of the cervix to Hegar number 9. A 9-mm rigid Storz resectoscope was inserted into the uterine cavity. Distention of the uterine cavity was achieved using 1.5% glycine with an inflow pressure of 110 mmHg provided by the Storz Hamou Endomat.

Results

Over the 7-year period from January 2002 to July 2009, 580 hysteroscopic procedures were performed at the Department of Obstetrics and Gyneacology in Gaziantep University. All procedures were started as diagnostic hysteroscopies and then we performed therapeutic hysteroscopies on 421 (72.59%) of the 580 patients. The mean age of the patients was 31.1 years (range 18 to 63 years). Of the 580 patients 337 (58.20%) also underwent laparoscopy together with the hysteroscopic operations.

The most common indication for diagnostic hysteroscopy was infertility followed by AUB. The most typical pathologies diagnosed at operative hysteroscopy were uterine septum, endometrial polyps, Asherman’s syndrome, submucous myomas, and other uterine anomalies. The complication rate was 0.86% of the total hysteroscopies. False passage and uterine perforation were the most common acute complications. No late complications occurred.

Discussion

Hysteroscopy is a minimally invasive procedure and has gradually gained worldwide popularity due to its effectiveness, lower costs and simplicity, as we have experienced at our center (Table 2).
In the present study, the most common indication for the procedure was a complaint of infertility. While some authors consider that hysteroscopy is a technique that complements hysterosalpingogram (HSG) [2], others claim that HSG or one of the newer alternative techniques to evaluate tubal patency should supplement the hysteroscopic assessment [3] in infertile patients. In our clinic we usually perform hysteroscopy, a technique that complements HSG for infertility. In this study we performed hysteroscopy on 411 infertile patients who had abnormal HSGs and we observed no obvious intrauterine pathology in 127 (31%) patients. According to this result the sensitivity of HSG at our clinic was 69%. This result is supported by a study by Kessler and Lancet who reported that in about two-thirds of the cases hysteroscopy findings were not correlated with those found on HSG [4].

Our study found septate uterus to be the most common anomaly in the infertile population who had undergone hysteroscopy following HSG. In women with infertility, the role of uterine anomalies, and particularly that of the septate uterus, remains unclear [5-7]. Several case series demonstrated the mean pregnancy rate in previously infertile patients to be 47% and a reduction in the spontaneous abortion rate, from 91% to 17% on average, after hysteroscopic metroplasty [6, 8]. Thus we performed hysteroscopic septum resection and metroplasty on 132 infertile patients and on 15 patients suffering from recurrent miscarriage (RM).

The literature that associates myomas and endometrial polyps with infertility/reproductive loss suggests that pregnancy rates approximating 50% are achieved with myomectomy or polypectomy [6, 8]. We performed hysteroscopic polypectomy on 87 and myomectomy on 16 infertile patients.

The acute complication rate associated with this procedure was a complaint of infertility. While some authors consider that hysteroscopy is a technique that complements hysterosalpingogram (HSG) [2], others claim that HSG or one of the newer alternative techniques to evaluate tubal patency should supplement the hysteroscopic assessment [3] in infertile patients. In our clinic we usually perform hysteroscopy, a technique that complements HSG for infertility. In this study we performed hysteroscopy on 411 infertile patients who had abnormal HSGs and we observed no obvious intrauterine pathology in 127 (31%) patients. According to this result the sensitivity of HSG at our clinic was 69%. This result is supported by a study by Kessler and Lancet who reported that in about two-thirds of the cases hysteroscopy findings were not correlated with those found on HSG [4].

Table 1 — Patien complaints and postoperative hysteroscopic diagnoses.

<table>
<thead>
<tr>
<th>Complaint</th>
<th>n (%)</th>
<th>Septate uterus</th>
<th>Uterine polyps</th>
<th>Uterine synchieae</th>
<th>Myomata</th>
<th>Other uterine anomalies</th>
<th>Normal cavity n</th>
<th>IUD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infertility</td>
<td>411</td>
<td>132</td>
<td>87</td>
<td>39</td>
<td>16</td>
<td>10</td>
<td>127</td>
<td></td>
</tr>
<tr>
<td>AUB</td>
<td>99</td>
<td>17</td>
<td>52</td>
<td>5</td>
<td>27</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RM</td>
<td>23</td>
<td>(4)</td>
<td>15</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>47</td>
<td>(8)</td>
<td>3</td>
<td>8</td>
<td>17</td>
<td>2</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>580</td>
<td>150 (26)</td>
<td>150 (26)</td>
<td>63 (11)</td>
<td>46 (8)</td>
<td>12 (2)</td>
<td>159 (27)</td>
<td></td>
</tr>
</tbody>
</table>

AUB: Abnormal uterine bleeding; RM: Recurrent miscarriage; IUD: Intrauterine contraceptive device.

Table 2 — Distribution of cases and postoperative diagnoses on a yearly basis.

<table>
<thead>
<tr>
<th>Years</th>
<th>n (%)</th>
<th>Septate uterus</th>
<th>Uterine polyps</th>
<th>Uterine synchieae</th>
<th>Myomata</th>
<th>Other uterine anomalies</th>
<th>Normal cavity n</th>
<th>IUD</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>86</td>
<td>17</td>
<td>22</td>
<td>10</td>
<td>3</td>
<td>2</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>88</td>
<td>18</td>
<td>23</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>103</td>
<td>18</td>
<td>25</td>
<td>9</td>
<td>8</td>
<td>1</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>114</td>
<td>19</td>
<td>30</td>
<td>8</td>
<td>13</td>
<td>2</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>580</td>
<td>150 (26)</td>
<td>150 (26)</td>
<td>63 (11)</td>
<td>46 (8)</td>
<td>12 (2)</td>
<td>159 (27)</td>
<td></td>
</tr>
</tbody>
</table>

In conclusion, our data is consistent with reports from other studies supporting that hysteroscopy is a safe and effective minimally invasive procedure with a low rate of complications with certain surgical principles.

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Is insulin-dependent diabetes and obesity a predisposition for endometrial and pancreatic carcinoma?

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Summary
Among 178 patients operated for endometrial carcinoma during a five-year period, 17 were re-operated at the Institute of Surgery (9.5%) because of pancreatic head carcinoma. The frequency of insulin-dependent diabetes was pointed out in patients – 28% of those who were first diagnosed with endometrial carcinoma. Moreover in the same group diagnosed with endometrial carcinoma, we found 17 to have pancreatic carcinoma, and among those there were 12 cases that had diabetes (70.58%).

Key words: Endometrial carcinoma; Pancreatic carcinoma; Diabetes; Obesity.

Introduction
Keeping in mind that diabetes and obesity are entities with a growing incidence today, it is necessary to consider this problem among the multiple fields of medicine. Diabetes can be correlated with a pathologically increased body mass index (BMI) [1]. A genetic predisposition for diabetes is well known and could be correlated to pathologically increased BMI, thus increased estrogen production [2, 3]. At the same time, the increased estrogen production may lead to a mutation in the endometrial cells and formation of carcinoma in these cells [4, 5]. A diagnosis of pancreatic carcinoma is easier with the appearance of new diagnostic procedures such as ultrasound (US), computed tomography (CT) scan and magnetic resonance imaging (MRI) imaging [6]. With advanced findings in the genetic changes in pancreatic carcinoma, future research could include the identification of those events in the early stages of the disease which could, together with advanced technology, lead to earlier detection of pancreatic cancer when curability can still be achieved [7].

Materials and Methods
During a five-year study, we retrospectively analyzed 178 patients with established endometrial carcinoma. In some of the cases the diagnosis was established after fractional curettage, and confirmed the diagnosis after surgery. In 80% of the cases, a common factor was increased BMI. Together with this risk factor, out of the 178 patients, 49 patients (28%) had insulin-dependent diabetes. In 17 cases (9.5%) pancreatic head carcinoma was also present. Out of all patients undergoing pancreatic head surgery, insulin-dependent diabetes was present in 12 cases of obese women. Some of the cases were observed first in the surgical ward, while some patients were primarily admitted to the gynecology ward. The age of our patients ranged between 55 and 71 (mean age 55). The mean time of observation was 24 months (range: 2 to 111 months). All the patients had curative resection. The patients with different histological diagnoses (such as neuroendocrine tumors, mucous and serous cystic tumors, and adenosquamous carcinoma), where duodenum pancreatectomy was performed, were not a part of this study.

Results and Discussion
We analyzed 178 patients with endometrial carcinoma. We carried out a five-year retrospective study. Summarizing the patient data from the surgery and gynecology department records, complete laboratory results, patient history and surgical and histopathological findings, we obtained interesting data. Out of the 178 women with carcinoma, 17 cases (9.5%) had pancreatic head surgery. It prompted us to search for a common factor in these cases. In 80% of the endometrial carcinoma cases, a common factor was increased BMI. Together with this risk factor, of the 178 patients, 49 patients (28%) had insulin-dependent diabetes and 17 patients (9.5%) had pancreatic head carcinoma. Out of all patients with pancreatic carcinoma, insulin-dependent diabetes was present in 12 cases (70.58%). Some of the cases were first observed in the surgical ward, while some patients were primarily admitted to the gynecology ward. The mean time of observation was 24 months and all the patients had curative resection.

In the group of patients who were subjected to surgery for ductal pancreatic adenocarcinoma, total five-year survival rate was 11%, while the literature data show a five-year survival range between 6.8% and 25% [6]. If patients had endometrial carcinoma together with ductal pancreatic adenocarcinoma, the survival rate was much
Is insulin-dependent diabetes and obesity a predisposition for endometrial and pancreatic carcinoma?

lower - less than 2.3%. We do not believe this was connected with endometrial carcinoma cases, as the highest stage of invasion was IC. Nonetheless, complete immunological collapse in chronic metabolic disturbances should be kept in mind.

The survival rate of endometrial carcinoma cases alone in our 5-year-analysis (without coexisting pancreatic cancer) was: Stage I more than 95%; Stage II 75-85%, Stage III less than 12%, and Stage IV less than 2% [2, 4].

In relation to their influence to survival rate, besides pancreatic carcinoma, several prognostic factors were analyzed. It was established that age and preoperative symptoms had no significant influence on survival in our study, or in papers published so far [5, 8].

Likewise, there has been no positive relation between the stage of endometrial carcinoma and the stage of pancreatic carcinoma reported [6].

In our group of patients that had both types of tumors together, the lowest survival rate was in the group of patients with a pancreatic tumor diameter more than 5 cm. Fortner et al. [8] have also indicated tumor size as a significant prognostic factor, thus indicating a good basis for selection of patients who should be subjected to surgery.

Tumor differentiation is also a good prognostic factor. In our study, all the patients with poorly differentiated tumors died within a five-year period (average survival 11 months), while the literature shows an average five-year survival of 16.5 months (14.1%) in patients with well and moderately differentiated tumors and 13.2 months (8.2%) in patients with poorly differentiated tumors [6].

The lymph nodes were positive in 73% of our cases, and 78% of those patients did not survive. There was no significant statistical difference between patients with positive lymph nodes and those with negative ones.

Conclusion

The relation between endometrial carcinoma, obesity and insulin-dependent diabetes in women prompts the necessity of timely screening (primarily laboratory), for possible pancreatic carcinoma. Even a 9% relation between pancreatic carcinoma and endometrial carcinoma in insulin-dependent women necessitates proper screening.

Pancreatic carcinoma is a systemic disease, at least at the time of diagnosis, with existent diagnostic possibilities.

Most patients who survive a five-year period (a very small number of patients) die later from the consequences of the primary disease; endometrial carcinoma alone has a greater survival rate than when combined with pancreatic carcinoma.

Extensive surgery is needed in patients who have smaller tumors due to a high incidence of local carcinoma cell spread; thus the existence of lymphogenous dissemination (86%), positive lymph nodes (30%) and intra (extra) pancreatic neural infiltration (70%), i.e., 50% of the cases.

Endometrial carcinoma in the given group did not show a tendency to spread in relation to laboratory findings of pancreatic cancer deterioration.

The results of these, as well as other studies, show that early screening is crucial in obtaining timely, and for the time being primary, surgical therapy.

References


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Peripartum cardiomyopathy and Klippel-Trenaunay syndrome

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Department of Obstetrics and Gynecology, University of L’Aquila (Italy)

Summary

Klippel-Trenaunay syndrome (KTS) is a rare congenital disorder of unknown etiology characterized by venous malformations or varicose veins, cutaneous capillary malformations, and hypertrophy of soft tissues with limb (usually asymmetric lower extremity) involvement. Peripartum cardiomyopathy (PPCM) is characterized by rapid onset heart failure during the final month of pregnancy or within five months of delivery, in the absence of identifiable risk factors or previous heart disease. The aim of this study was to illustrate the correlation between the KTS and the onset of PPCM in women with twin pregnancies. Our case is a 35-year-old woman, gravida II para I, with KTS, twin pregnancy and PPCM. We can assume that, as the heart of a women with KTS usually works with a low preload reserve due to the widespread venous varicosities, if a significant increase in preload occurs, it may lead to the onset of cardiac dilatation and thus PPCM.

Key words : Peripartum cardiomyopathy; Klippel-Trenaunay Syndrome; Twin pregnancy.

Introduction

Klippel-Trenaunay syndrome (KTS) is a rare congenital disorder characterized by a specific symptom triad: cutaneous capillary malformations, venous malformations or varicose veins, hypertrophy of soft tissues [1-4] with limb (usually asymmetric lower extremity) involvement. The first description of this syndrome was reported in 1900 [5] but the molecular mechanism remains unknown and realistically multiple genetic factors are involved [6]. KTS is uncommon and no consensus yet exists on the correct approach to its investigation and treatment. The syndrome may present local and systemic complications (Table 1). A tendency of KTS to recurrent thromboembolic events is well known with a reported incidence of up to 22% [7]. Peripartum or postpartum cardiomyopathy (PPCM) is characterized by rapid onset heart failure during the final month of pregnancy or within five months of delivery in the absence of identifiable risk factors or previous heart disease [8]. The diagnosis of PPCM is made according to criteria provided by the World Health Organization/International Society and Federation of Cardiology [9], the Guidelines of the National Heart, Lung, and Blood Institute Workshop on the "Prevalence and the Etiology of Idiopathic Dilated Cardiomyopathies" [10] and the more recent Guidelines for the "Study of Familial Dilated Cardiomyopathies" [11], designed to improve the sensitivity and specificity of the old classification criteria (Table 2). Early signs and symptoms of heart failure can be obscured by pregnancy, because often the patient considers them to be normal. The incidence of peripartum cardiomyopathy ranges from one in 1,300 to one in 15,000 pregnancies. The mortality rate of peripartum cardiomyopathy is 30-60% and death may be caused by severe pulmonary congestion [12]. Etiology of PPCM is unknown [13-15] and several hypotheses have been proposed: myocarditis, viral infection, autoimmune factors, inflammatory cytokines, and abnormal hemodynamic response to physiological changes in pregnancy. Common reported risk factors for PPCM are advanced maternal age, multiparity, multiple gestations, black race, obesity, malnutrition, gestational hypertension, preeclampsia, poor antenatal care, breast feeding, cesarean section, alcohol, cocaine and tobacco abuse, low socio-economic conditions and family history [15, 16]. No strong hereditary association has been identified [16].

Case Report

The patient was a 35-year-old woman, gravida 2 para 1, with KTS syndrome, twin pregnancy and peripartum cardiomyopathy. No prenatal or obstetric complications occurred during her prior pregnancy and delivery. There was no history of heart disease, excessive alcohol consumption, recent viral infection, hypertension, diabetes mellitus, or preeclampsia. The patient came to our observation at the 34th week of gestation with early labor contractions. She had elephantiasis of the lower left limb (Figure 1), cutaneous capillary hemangioma (Figure 2) spread all over the body surface and vulval varicosities (Figure 3). Dyspnea and asthenia (NYHA class II) occurred at the 32nd week of gestation. A prompt vascular examination was carried out and a compression bandage was applied to the lower limbs. Administration of subcutaneous heparin (Clexane 4000 UI) for prophylaxis of deep vein thrombosis (TVP) was initiated. Due to the vulval varicosities, the elephantiasis of the lower right limb and the unfavorable cervix a cesarean section was performed. The operation was carried out without complications and the fetal outcome was good. Both twins’ Apgar scores were 8-9. Two hours later the patient showed symptoms of increasing dyspnea and chest pain. ECG, chest X-ray, total body computed tomography (CT), with and without contrast agent, and...
Echocardiogram were performed, assuming the onset of an acute pulmonary embolism. The electrocardiogram showed sinus rhythm with short P-R and nonspecific ST-T abnormalities. The chest X-ray showed pulmonary edema and cardiomegaly. A filling defect in the areas of the main and peripheral pulmonary arteries was reported by CT with bilateral pleural effusion, more marked on the right, and thickened areas in the lower lung most probably referring to acute pulmonary edema. Echocardiography demonstrated a 35-40% left ventricular ejection fraction, a 25.4% fractional shortening and a 5.9 cm/m² left ventricular end-diastolic dimension with signs of congestive heart failure (CHF). A mild mitral regurgitation also occurred. Data were consistent with peripartum cardiomyopathy. As a result, the patient was transferred to the Intensive Care Unit. On admission to the emergency department the patient presented with mild respiratory distress, with oxygen saturation of 84% on room air, heart rate of 84 bpm and blood pressure 100/50 mmHg. Her laboratory evaluation, including a complete blood count and chemistries, were remarkable only for an elevated white blood cell count of 19.4. D-dimer was elevated (5052). She was treated with furosemide, angiotensin converting enzyme (ACE) inhibitor (ramipril), low molecular weight heparin 4000 UI and potassium canrenoate. Seven days later the echocardiogram showed an improvement of the pathology. Left ejection fraction was 59%, fractional shortening 46% and left ventricular end-diastolic dimension 5.0 cm/m². The patient did well for the following six months and returned to active employment. Subsequent investigations showed a normal echocardiographic pattern.

**Discussion**

Pregnancy has rarely been reported in patients with KTS and since 1989 there have been only 13 cases of pregnant women with KTS reported in the literature [17]. Maternal and fetal risks associated with pregnancy in women with KTS are proportional to the severity of the disease, which can be exacerbated by pregnancy. An association between KTS and fetal growth restriction has been reported, maybe due to placental insufficiency caused by angiomatosis related to the syndrome [18]. Complications that may arise in pregnancy in patients with KTS include bleeding, DIC, thromboembolic events and pain. The occurrence of pulmonary embolism has also been reported [19] so careful monitoring of coagulopathic disorders is advisable [20]. However, literature data do not report an increased risk of peripartum cardiomyopathy in patients with KTS. We can assume that, as the heart of a women with KTS usually works with a low preload reserve due to the widespread venous varicosities, if a significant increase in preload occurs, this may lead to the onset of cardiac dilatation and thus peripartum cardiomyopathy. In our case the twin pregnancy may have played a determinant role.

**Table 1. — KTS: complications.**

<table>
<thead>
<tr>
<th>KTS: complications local</th>
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</thead>
<tbody>
<tr>
<td>- Pain</td>
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<tr>
<td>- Cellulitis</td>
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<tr>
<td>- Ulceration</td>
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<tr>
<td>- Thrombophlebitis</td>
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<tr>
<td>- Gangrene</td>
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<tr>
<td>Involvement of internal organs</td>
</tr>
<tr>
<td>- Neurovascular anomalies</td>
</tr>
<tr>
<td>- Pulmonary vein varicosities</td>
</tr>
<tr>
<td>- Pleuro-pericardial effusions</td>
</tr>
<tr>
<td>- Pulmonary embolism</td>
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<tr>
<td>- Colorectal and urinary tract</td>
</tr>
<tr>
<td>- Hemorrhage</td>
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</table>

**Systemic**

- Consumptive coagulopathy high-output cardiac failure

**Table 2. — PPCM: diagnostic criteria.**

<table>
<thead>
<tr>
<th>Demonstrable echocardiographic criteria of left ventricular dysfunction</th>
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<tbody>
<tr>
<td>- Ejection fraction &lt; 45%</td>
</tr>
<tr>
<td>- Left ventricular fractional shortening &lt; 30%</td>
</tr>
<tr>
<td>- Left ventricular end-diastolic dimension &gt; 2.7 cm/m² body surface area</td>
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</table>
Conclusion

Although the KTS was previously considered a contraindication to pregnancy, close monitoring can greatly improve the maternal and fetal outcome. Regardless of adequate preconception counselling, systematic clinical and instrumental monitoring is recommended and a close collaboration between the obstetrician and the cardiologist is mandatory to reduce morbidity and mortality related to the onset of peripartum cardiomyopathy.

References


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Novel therapeutic strategy for uterine arteriovenous fistulas: case report

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Introduction

Uterine arteriovenous fistulas are rare causes of uterine bleeding, but are known as lesions with a risk of unexpected massive vaginal bleeding [1-5]. The degree often leads to a shock state, and there can be the need for blood transfusion [3]. Uterine vascular lesions involve arteriovenous malformations, true aneurysms, pseudoaneurysms, and chorioangioma of the placenta [1]. In a broad sense, arteriovenous malformations have been variably described as cirsoid aneurysm, arteriovenous aneurysm, arteriovenous fistula, pulsating angioma and cavernous hemangioma [2, 5]. In a narrow sense, arteriovenous malformations are considered to be mainly congenital. On the other hand, arteriovenous fistulas are considered to usually be acquired [1, 4]. Most reported acquired cases were complicated by a history of cesarean section or uterine endometrial curettage, or the usage of intrauterine contraceptive devices [2-6]. Hormonal dysfunction and an inadequate healing process from previous damage are believed to play some role in the pathogenesis [4]. In addition, uterine arteriovenous fistulas are found in women who have menstruation and can become pregnant [4, 6].

In this case, color Doppler ultrasonography (US), dynamic computer tomography (CT), and conventional angiography were able to define the extent of uterine arteriovenous fistulas, and a novel therapeutic strategy for uterine arteriovenous fistulas was developed: hysterectomy after blood flow decrease by bilateral uterine artery embolization.

Summary

Background: The major presenting symptom of uterine arteriovenous fistulas is massive, torrential vaginal bleeding, the degree of which often leads to a shock state. Case: A 35-year-old woman, gravida 3, para 2 presented with massive vaginal hemorrhage at the first menstruation six months after delivery. Uterine arteriovenous fistulas were diagnosed by color Doppler ultrasonography (US), dynamic computer tomography (CT), and conventional angiography. The patient underwent hysterectomy after bloodstream decrease by bilateral uterine artery embolization. Conclusion: The extent of uterine arteriovenous fistulas was diagnosed by color Doppler US, CT, and pelvic angiography, and this precise evaluation led to an adequate therapeutic strategy for uterine arteriovenous fistulas.

Key words: Uterine arteriovenous fistulas; Bilateral uterine artery embolization; Color Doppler ultrasonography; Dynamic computer tomography; Conventional angiography.

Case Report

A 35-year-old woman, gravida 3, para 2 had a history of hydatidiform mole at 22 years old. She presented with massive vaginal hemorrhage at the first menstruation six months after the delivery of her second child. Her blood pressure deteriorated, and the peripheral blood hemoglobin was 4.9 g/dl. Coagulation study results were within the normal range. Color Doppler US showed multiple hypervascular flows in the uterine myometrium (Figure 1). The bleeding was controlled by combination treatment with estrogen and progestin. The peripheral blood hemoglobin recovered up to 9.7 g/dl with oral and parenteral iron without any blood transfusion in about one month. Human chorionic gonadotropin in serum was negative.

To evaluate whether uterine arteriovenous malformations were the cause of the massive uterine bleeding, contrasting CT was taken. The CT revealed a bilateral vascular lump throughout the myometrium to the pelvic and uterine cavities (Figure 2). Most of the vascular lump consisted of expanded veins, but the lump might have involved some arteries according to the early stage of contrasting just after the start of the contrasting procedure.

Figure 1. — Multiple anechoic spaces and color signals in a mosaic pattern shown by color Doppler US.
agent drip infusion (Figure 3). The vascular lump was diagnosed as uterine arteriovenous fistulas. The patient selected hysterectomy because she had already had two children, and wanted to avoid the recurrence of massive uterine bleeding after artery embolization. Pelvic angiography demonstrated hypervascular masses supplied predominantly by bilateral uterine arteries but also by other internal iliac arteries (Figures 4 and 5). To avoid massive bleeding at hysterectomy, preoperative artery embolization was performed for blood flow decrease of the saturated internal organs detected by contrasting CT (Figure 2).

The post-embolism angiogram showed that the blood flow decreased approximately 90% in the right side and 40% in the left (Figure 6). No immediate complications such as pain and fever occurred after the embolization. The patient underwent hysterectomy with 220 g of bleeding, and afterwards the pelvic vascular lump almost completely disappeared because the uterine arteriovenous fistula, recognized as the nidus, was removed by hysterectomy. Neither symptoms nor abnormal signs, checked by contrasting CT one month after surgery, occurred.

Discussion

The major presenting symptom of uterine arteriovenous fistulas is intermittent and torrential vaginal bleeding, especially torrential bleeding that is believed to occur from the arteries [2, 3]. US is the most common investigation tool, and especially color Doppler US with spectral wave analysis is valuable [1-3, 7]. To evaluate the extent of uterine arteriovenous fistulas, CT is less invasive than pelvic angiography, which can be useful for diagnosis with artery embolization treatment [4]. Reports of good outcomes and successful pregnancies after artery embolization have gradually increased recently, but the long-term success rate of embolization was still reported to be from 79% to 90% [4-6]. Although the degree of uterine bleeding and number of enriched collateral vessels are critical in treating uterine arteriovenous fistulas, the management in patients with symptomatic uterine arteriovenous fistulas depends on the desire for pregnancy [4, 5]. As our patient had no desire to preserve her fertility, but desired a radical cure, she underwent hysterectomy after artery embolization to avoid massive bleeding at hysterectomy.

Conclusion

The extent of the uterine arteriovenous fistulas was diagnosed by color Doppler US, CT, and pelvic angiography, and this precise evaluation led to an adequate therapeutic strategy.
References


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**Book Review**

**HANDBOOK OF WOMEN'S HEALTH**
edited by Jo Ann Rosenfeld.

“Women’s health” is in its second edition.

The importance of this book lies firstly in pointing out how medical scientific research has always aimed at studying and evaluating middle-aged men. These results have then been applied to women of any age – ranging from childhood to old age – often leading to a distorted interpretation of results.

Women have a different biological role than men and many psychophysical situations do not exist in men or cannot be compared to those in women.

Underlining the need to use methods that specifically aim at assessing women’s health – as described in chapter 1 – allows research and medicine to take a major step forwards and also to deal with diagnosis errors and incorrect approaches to interpreting female clinical features.

As detailed in the list of contents, the book embraces the entire sphere of female physiology and pathology, at the same time bearing in mind psychological aspects and the importance of social context.

The chapters are all written very clearly, allowing anyone – from the student to the expert – to fully benefit from consultation of the manual.

The full range of issues covered provides an all-embracing knowledge about women’s health.

The chapters are written with expertise and always provide useful in-depth information which makes it easier to understand the contents.

The issue examined in chapter 5, section I, is particularly valuable: the study of psychosocial health in women throughout their life. Usually, this topic is not considered by doctors when assessing symptoms in their patients for purposes of correct diagnosis, which should – in turn – be the starting point for correct treatment.

If the patient’s past experiences are not taken into account, symptoms are often misinterpreted and, as a result, therapy may be inadequate. For this reason, the issue treated in this chapter is significant, especially if linked to chapters 21 and 22 of section V.

To conclude, we believe this text brings a significant progress in understanding the female universe as regards women’s physical and psychic health.

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