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an International Journal

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Editorial Office (M. Critelli):
Galleria Storione, 2/A - 35123 Padua (Italy) - Tel. +39-049-8756900 - Fax +39-049-8752018
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CLINICAL AND EXPERIMENTAL OBSTETRICS AND GYNECOLOGY is issued bimonthly in one volume per year by 7847050 CANADA Inc. Montréal. Printed in Italy by “Centro Servizi Editoriali S.r.l.” - Grisignano di Zocco - 36040 Vicenza (Italy).
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DHEA pre-treated patients, poor responders to a first IVF (ICSI) cycle: clinical results

Gynaecology-Obstetrics Clinic. Department of Health of Women and Children, University of Padua, Padua (Italy)

Summary

Purpose: To evaluate the effect of the premedication with dehydroepiandrosterone (DHEA) on the results of the in vitro fertilization (IVF) treatments in a group of women with evidence of diminished ovarian reserve. Materials and Methods: This experimental, prospective, pre-post study enrolled 29 patients with evidence of diminished ovarian reserve and poor-responders to a previous treatment. They received 75 mg/die of DHEA for a minimum of eight weeks; from the 18th day of the cycle before the stimulation with follicle stimulating hormone (FSH), they took trans-dermal estradiol (E2) (50 mcg every other day). The protocol of the stimulation consisted of a short cycle with follicle stimulating hormone receptor-human menopausal gonadotropin (FSHr-HMG) and low doses of gonadotropin releasing hormone agonist (GnRH-a) (0.05 mg/die). The study was carried out comparing the results obtained respectively with the pre-DHEA and the post-DHEA treatments. Results: The comparative analysis of the results showed a significant increase in the number of the retrieved oocytes (p < 0.01), of the oocyte quality (p = 0.02) and a reduction of cancelled cycles (p = 0.03). Moreover, after the treatment with DHEA, there was an increase, though non-significant, in the number of embryos, in the fertilization rate, and in the number of pregnancies. Conclusions: This study confirms the beneficial effects of DHEA in patients who resulted poor responders to IVF treatments. Therefore, DHEA appears to be an effective treatment for age related sub-fertility.

Key words: Dehydroepiandrosterone (DHEA); Diminished ovarian reserve (DOR); FIVET/ICSI cycle; Non responders (OFF)<; Poor ovarian response (POR).

Introduction

With the trend in increased rates of infertility, connected to the aging of the Western population, the problem of low response to infertility treatment is becoming more and more frequent. With the advancing of the women’s age, in fact, there is a reduction in the quantity and quality of the oocytes with increased rates of embryo aneuploidy and, consequently, reduced pregnancy rate and increased miscarriage rate [1].

In general, the majority of women reach menopause around 50 years. In the Venetian region, after the Resolution n. 822, 06/14/2011, the access to treatment (1st/2nd level) for infertility in women it was extended up to the age of 50 years at the expense of the NIH. The biological infertility, however, dramatically increases already 10-15 years before menopause [2].

The majority of these patients, in fact, due to the scarcity of the ovarian level of residual follicular pool, tend to be poor-responders to fertility treatment. It is estimated that the 5% - 18% of the treatments with in vitro fertilization (IVF) fail because of a low ovarian response to pharmacological stimulation [3]. The definition of poor ovarian response (POR), which was subjective and variable according to different researchers, was internationally standardized by European Society of Human Reproduction and Embryology (ESHRE) in 2011, according to the Bologna criteria [4]. As a result of this consensus conference, the definition of low ovarian response to treatments of IVF requires the presence of at least two of the following characteristics: 1) advanced maternal age (> 40 years) or the presence of other risk factors for low ovarian response; 2) a previous finding of poor-response (< three oocytes following a conventional stimulation protocol); 3) a test of the abnormal ovarian reserve (antral follicle count [AFC] < five to seven follicles in the two ovaries or anti-Müllerian hormone [AMH] < 0.5 to 1.1 ng /ml).

Various stimulation protocols were proposed, in the literature, for the treatment of poor-responders patients [5-8]. Casson et al. [9] were the first to highlight the beneficial effects of DHEA on the ovarian function. Barad and Gleicher in 2005 [10], demonstrated an increased production of follicles after a treatment with DHEA, and in the following year the same group underlined the beneficial effect of the hormone on various parameters of IVF (the peak of estradiol [E2], the number and quality of oocytes and embryos) in women with evidence of diminished ovarian reserve [11]. In 2007 [12], the same authors reported other positive effects such as increased pregnancy rate and a reduction in its “waiting time”, related to DHEA intaking for at least six weeks before the ovarian stimulation. Wiser et al. in 2010...
[3], in the only prospective randomized study on this subject, affirmed that there is a direct proportional relationship between embryo’s quality and the duration of treatment, showing also an increasing rate of live births as a result of a pre-treatment with DHEA. Gleicher, in 2010 [13], noted, finally, that the supplementation with DHEA induces a reduction in the number and percentage of aneuploid embryos. The studies in literature, therefore, seem to consider DHEA as a good candidate in the treatment of poor-responder patients with a low age-related ovarian reserve.

The purpose of this study was to evaluate prospectively the effects of supplementation with DHEA in the same patients, who were poor responders to a first conventional treatment of ovarian stimulation.

Materials and Methods

Selected patients

The study enrolled 29 patients with clinical evidence of diminished ovarian reserve, which were poor responders, according to the Bologna criteria, to the previous treatment with IVF. The criteria for the exclusion from the study were: older than 45 years, FSH> 30 mIU/ml, AMH < 0.5 ng/ml, body mass index (BMI) > 30.

After an adequate explanation and the signing of the informed consent, the recruited patients were subjected to the following therapeutic treatment:

a) Pre-treatment, of at least eight weeks, with DHEA with a dosage of 25 mg x3/die per os.

b) Application of E2, using 50 mcg trans-dermal patches every other day, from the 18th day of the cycle before the menstruation of the cycle of stimulation.

Both A and B were interrupted on the day of menstruation, day 0.

c) Short cycle of stimulation with low doses of gonadotropin releasing hormone agonist (GnRH-a) (0.05 mg/die s. and follicle stimulating hormone receptor (FSHr) gonadotropin (300 IU/ die s. c.) and human menopausal gonadotropin (hMG) (150 IU/ die s. c.).

The criteria used for the definition of patients not responding to stimulation (OFF) were: an ultrasound checked number of ovarian growing follicles < two and/or E2 < 500 pg/ml.

Once obtained two or more follicles of dimensions ranging between 17 and 19 mm, ovulation was induced through the injection of 250 mg of human chorionic gonadotropin receptor (HCGr) s. c.

Thirty-six hours after induction, an oocyte pick-up (OPU) was carried out in sedation.

The oocytes collected were classified according to the degree of maturity in: germinal vesicles, metaphase I, and metaphase II. From the pool of the collected oocytes, those ones in metaphase II were isolated and used for fertilization with fertilization with intracytoplasmic sperm injection (ICSI).

Forty-eight hours after OPU, the embryo-transfer (ET) was executed.

The luteal support consisted in the use of micronized progesterone, per os or vaginally, (200 mg twice/die) and progesterone i. m. (50 mg/die) until at the least the 14th day from the ET (beta-HCG dosage).

Study plan and statistical analysis

The study plan was experimental pre-post, it was performed enrolling patients initially subjected to a conventional treatment, and in succession to a short cycle with low doses of GnRH-a associated with pre-treatment with DHEA, lasting at least eight weeks. The authors then proceeded to the comparison of the results obtained with the two protocols, taking into account the following variables: number of retrieved oocytes, number of oocytes placed in fertilization (oocytes in metaphase II), number of fertilized oocytes, fertilization rate, percentage of patients not responding to treatment (OFF), beta-HCG positivity, and evolution of pregnancy.

The McNemar test was used for the statistical elaboration of the qualitative dichotomous variables (OFF and positivity of the beta-HCG). In case of qualitative multivariables and in the evolution of pregnancy, the Bowker test of symmetry was applied.

Quantitative variables, such as the number of retrieved oocytes, the number of oocytes placed in fertilization, the number of fertilized oocytes, and fertilization rate were analysed with the Wilcoxon signed ranks test, bringing the median (the value/modality assumed by the combined statistics that are in the middle of the distribution of a quantitative or qualitative sortable character) and maximum and minimum extremes.

All the tests used were performed at two code, considering as statistically significant a value of $p < 0.05$.

Results

The study was conducted from January 2011 to September 2012. In this period 29 patients were recruited. They were poor-responders to previous conventional treatment (called pre-DHEA) and then subjected to the protocol proposed by us using pre-medication with DHEA (defined post-DHEA).

The results, obtained using comparative analysis, are summarized in Table 1.

The proportion of patients not responding to treatment, defined as OFF, was found to be 9/29 (31%) in case of stimulation with conventional protocols (pre-DHEA), while only 2/29 (7%) with DHEA.

The differences proved to be statistically significant ($p = 0.03$), with evidence of increased response to hormonal stimulation cycle thanks to the pre-treatment with DHEA. During data processing it was showed that in a total of 27 women responding to the DHEA protocol, 19/27 completed treatment with both regimens, while 8/27 were non-responders with the classic protocols. Finally, only an enrolled patient was unresponsive to the medication with DHEA but responding to the previous cycle, and in one case there was no response (Table 2).

In the total number of treated patients (29 = 100%), therefore, 65.5% resulted responding to both treatments, 3.5% responded to conventional treatment but not to the DHEA protocol. Another 3.5% resulted non-responder in both protocols, 27% responded to the DHEA protocol, while it was cancelled from the previous cycle of stimulation.

A total of 27 patients, therefore, had access to the stage of oocyte sampling and to the possible IVF, thanks to the treatment with the new stimulation protocol with DHEA. By analysing the amount of retrieved oocytes, the median with conventional treatments resulted one oocyte, with a maximum of four and a minimum of zero and a total of
Table 1. — Comparison of the results obtained with pre- and post-DHEA treatment.

<table>
<thead>
<tr>
<th></th>
<th>Pre-DHEA</th>
<th>Post-DHEA</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>29</td>
<td>29</td>
<td>-</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>39.03 ± 1.2</td>
<td>39.7 ± 1.25</td>
<td>-</td>
</tr>
<tr>
<td>OFF</td>
<td>9/29 (31%)</td>
<td>2/29 (7%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Median Retrieved oocytes (max - min)</td>
<td>1 (4-0)</td>
<td>2 (5-0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Tot = 35</td>
<td>Tot = 66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median oocytes in fertilization (max - min)</td>
<td>1 (4-0)</td>
<td>2 (5-0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Tot = 32</td>
<td>Tot = 53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median fertilized oocytes</td>
<td>0 (3-0)</td>
<td>1 (4-0)</td>
<td>0.05 (n.s.)</td>
</tr>
<tr>
<td>Tot = 20</td>
<td>Tot = 33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median fertilization rate (max - min)</td>
<td>0 (1-0)</td>
<td>0.5 (1-0)</td>
<td>0.10 (n.s.)</td>
</tr>
<tr>
<td>Beta-hCG positivity (%)</td>
<td>0/29 (0%)</td>
<td>4/29 (13.8%)</td>
<td>0.12 (n.s.)</td>
</tr>
<tr>
<td>Evolutive pregnancies</td>
<td>0/29 (0%)</td>
<td>2/29 (6.9%)</td>
<td>0.26 (n.s.)</td>
</tr>
</tbody>
</table>

35, while it was two oocytes resulted with the protocol DHEA, with a maximum of five and minimum of zero and a total of 66. Applying the test function, the difference between the oocytes found in the two treatments was statistically significant (p < 0.01), with an evident greater number obtained using the DHEA protocol. Pre-treatment with DHEA, therefore, increased the amount of oocytes recruited, while increasing the chances of a successful fertilization.

This protocol demonstrated to increase not only the number of oocytes, but also the mature oocytes suitable for insemination, reducing the proportion of immature (germ vesicle, metaphase I) and degenerate cells. With the conventional treatment, in fact, the median of the oocytes placed in fertilization was found to be one, with a maximum of four and a minimum of zero and a total of 32, while DHEA resulted in a median of two, with a maximum of five and a minimum of zero oocytes and the total of 33, with a maximum of four and a minimum of zero and a total of 66, with the post-DHEA protocol. The differences, however, were nearly but not statistically significant (p = 0.05). With regards to the fertilization rate, a median of zero was obtained by the first treatment, with a maximum of one and a minimum of zero, while the second one obtained a median of 0.5, with a maximum of one and a minimum of zero. Even in this case, however, the difference was not found to be statistically significant (p = 0.10). The lack of statistical significance was most likely caused by the low number of recruited patients and the small scale of the total embryos obtained, respectively 16 with conventional protocols and 31 with DHEA. However, the results indicate that DHEA has a tendency to increase the chance of fertilization and, therefore, the indication is to use it to enhance the chances of success of the IVF techniques. Thanks to the regimen of pre-medication with DHEA, a total of four pregnancies (13.8%) were obtained. Only two of them evolved: an early abortion occurred in the other two cases. However the difference between the two treatments, with regards to the number of pregnancies and their progression, did not reach statistical significance (p = 0.12 and p = 0.26, respectively), because of the low number of patients enrolled in the study and the few obtained pregnancies.

Table 2. — McNemar Test: distribution of responding patients with conventional treatment (Pre-DHEA) and DHEA protocol (post-DHEA).

<table>
<thead>
<tr>
<th></th>
<th>Pre-DHEA</th>
<th>Post-DHEA</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>ON</td>
<td>19 (65.5%)</td>
<td>8 (27.5%)</td>
<td>27 (93%)</td>
</tr>
<tr>
<td>OFF</td>
<td>1 (3.5%)</td>
<td>1 (3.5%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>20 (69.0%)</td>
<td>9 (31.0%)</td>
<td>29 (100%)</td>
</tr>
</tbody>
</table>

The median of fertilized oocytes was found to be zero, with a maximum of three and a minimum of zero and a total of 20, with the pre-DHEA protocols, while it was one, with a maximum of four and a minimum of zero and a total of 33, with the post-DHEA protocol. The differences, however, were nearly but not statistically significant (p = 0.05). With regards to the fertilization rate, a median of zero was obtained by the first treatment, with a maximum of one and a minimum of zero, while the second one obtained a median of 0.5, with a maximum of one and a minimum of zero. Even in this case, however, the difference was not found to be statistically significant (p = 0.10). The lack of statistical significance was most likely caused by the low number of recruited patients and the small scale of the total embryos obtained, respectively 16 with conventional protocols and 31 with DHEA. However, the results indicate that DHEA has a tendency to increase the chance of fertilization and, therefore, the indication is to use it to enhance the chances of success of the IVF techniques. Thanks to the regimen of pre-medication with DHEA, a total of four pregnancies (13.8%) were obtained. Only two of them evolved: an early abortion occurred in the other two cases. However the difference between the two treatments, with regards to the number of pregnancies and their progression, did not reach statistical significance (p = 0.12 and p = 0.26, respectively), because of the low number of patients enrolled in the study and the few obtained pregnancies.

Discussion

This study confirms that pre-medication with DHEA, associated with a short cycle with low doses of GnRH-a, increases the overall probability of success in poor-responder patients with clinical evidence of diminished ovarian reserve (DOR). Therefore this clinical trial showed that the protocol with DHEA increases the response rate to stimulation treatments (in situations of poor response to ovarian stimulation), reducing the percentage of cancelled cycles. Besides increasing statistically the number of patients who reach the end of the treatment, DHEA significantly increases the number of retrieved oocytes and the pool of mature cells suitable for insemination, reducing the percentages of immaturity and degeneration. Therefore benefits of DHEA in improving the ovarian function in poor responders are confirmed, as reported by several studies in the literature [11-13].

Thanks to this regimen, a propensity to an increased success rates of stimulation treatments is also shown, as judged by the number of embryos and pregnancies obtained, though without reaching statistical significance, as highlighted in other trials [12].

The mechanism by which DHEA induces all the effects reported in the literature and partially demonstrated in this study, still remains unknown. One hypothesis is that DHEA has a synergistic effect with gonadotropins and exerts, therefore, a selective control in the early stages of follicular maturation [14]. Besides the synergy with the gonadotropins
(chiefly FSH), a direct role of DHEA on ovarian function is hypothesized. The notion derives from the observation of the evolution of the concentration levels of endogenous DHEA: the peak is reached when a woman is between 20 and 30 years of age, followed by a progressive decline of about two percent annually [15].

DHEA is not only the precursor of androstenedione, testosterone, and E2 but it can also influence the follicular growth acting as a ligand for the androgen receptors and/or through alternative non-receptorial ways [16]. Another possible mechanism was described by Casson et al. [17]. They experienced a transient increase of IGF-1 in patients undergoing induction with exogenous gonadotropins after pre-treatment with DHEA, and they related it to the parallel increase in androgens.

Barad and Gleicher [11] postulated that the effects of DHEA can be due to the creation of a polycystic ovarian syndrome (PCOS) -like situation in elderly ovaries. In fact polycystic ovaries were described as a deposit of primordial follicles in transition to primary ones, by the action of GF, LH, and ovarian androgens, whose levels are increased in this pathology. The ovarian theca cells of the pre-antral follicles produce normally androstenedione, testosterone and DHEA: women with PCOS have higher levels of testosterone, androstenedione and DHEA in serum and in ovarian veins [18]. Therefore the prolonged exogenous androgens administration could induce the changes (histologically and sonographically seen) in the ovaries similar to those ones of women with PCOS (18). Therefore the creation of a PCOS-like environment, could explain the cumulative effect of DHEA on antral follicles, observed by Barad and Gleicher [11].

DHEA is a weak androgen that is administered in the U.S.A. as a dietary supplement, without the need for a prescription. The potential side-effects include: acne, hirsutism, alopecia, and oily skin. However, these androgenic effects are minimal at the therapeutic doses of 75 mg/day [19] and they did not occur in any patient in this study. Moreover, considering that different physiological situations of women, such as pregnancy, are themselves characterized by a high level of DHEA, low doses of DHEA are safe, without causing any health injury [20].

Doubts were raised regarding the safety of the treatment because DHEA, as a precursor of androgens and estrogens, could increase the risk of androgen or estrogen-dependent cancers [21]. However because of the low dose and short duration of administration of DHEA in the proposed protocol treatment, these risks cannot exist.

The most obvious limitation of this study is the lack of randomization that, in some way, might have influenced the results because of a possible effect of variables that were not considered in the study and not randomly distributed.

Moreover, strength of the study is the evaluation of the same patients who underwent both types of treatments, since this procedure eliminates the inter-personal variability from an ethnic, social, and pathologic point of view that could affect observations.

The fact that the same women were subjected to successive cycles of stimulation might suggest that the good results obtained with the proposed protocol are influenced by cumulatively previous stimulation. However, since the stimulations performed in the present centre are spaced by at least four months, to restore a condition of ovarian “rest”, each treatment should be free from influences of the previous cycle.

The few samples (29 patients) are certainly a limitation of the study. However, the present work is one of the few perspective studies carried out on this topic. The only randomized perspective study on the effects of DHEA, for example, includes only 17 cases and 16 controls [3]. Moreover the sample quantity makes it difficult to achieve statistical significance regarding the analysis of probability in which the percentage of positivity is further reduced. In fact, given the limited probability of success related to the low ovarian reserve condition to ovarian aging, the number of pregnancies and their development, are quantitatively small and are therefore inadequate to extend the sample assessments to population.

Conclusions

The limitations of this study are mainly two: a few samples (moreso, the same women were perspective evaluated in two successive cycles), the diversity of the protocols and the doses of gonadotropins used in the two cycles (furthermore the short protocol with high doses of FSH in the first cycle were also predominantly used). After these clarifications it is not an exaggeration to state that pre-medication with DHEA appears to be a valid approach in the treatment of subfertility caused by age related reduced ovarian reserve because of its efficacy and the lack of side-effects.

Further studies with larger, prospective, and randomized trials are necessary to confirm the evidence discovered until now.

References

DHEA pre-treated patients, poor responders to a first IVF (ICSI) cycle: clinical results


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**General Section**

Labor induction using modified metreurynters plus oxytocin at an institution in Japan: a retrospective study

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3Department of Obstetrics and Gynecology, Saitama Medical Center, Saitama Medical University, Saitama (Japan)

Summary

Objective: The authors evaluated the effectiveness and safety of “neo-metoro” or “mini-metoro” metreurynters plus oxytocin for labor induction and assessed differences in parturition outcomes, according to the metreurynter used at induction initiation. Materials and Methods: The authors retrospectively reviewed 146 consecutive women with live singleton pregnancies, and who underwent induction. Parturition outcomes were vaginal delivery achieved within the planned schedule (VDPS), vaginal delivery finally achieved (VDF), and induction-to-delivery interval (IDI). Women were divided into neo-metoro, mini-metoro, and without metreurynter groups based on metreurynter use at induction initiation. The authors examined the relationships of metreurynter groups with factors, parturition outcomes, and adverse events. In 113 women who underwent two-day induction, the authors calculated IDI and adjusted odds ratio (AOR) for achieving delivery per unit time. Results: VDPS rates were 65% in nulliparous and 81% in multiparous women. VDF rates were 78% in nulliparous and 90% in multiparous women. AORs for VDPS were 0.30 in nulliparous women and 0.18 in Bishop score (BS) 1–3 class. AORs for VDF were 0.04 in BS1–3 class and 0.14 in BS4–5 class. In 113 women undergoing two-day induction, AORs for achieving delivery per unit time were 0.45 in nulliparous women and 0.46 in obese women, and 0.48 in BS1–3 class. Neo-metoro use at induction initiation tended to reduce IDI. Conclusions: Labor induction using these metreurynters plus oxytocin is safe and effective. The advantages of neo-metoro over mini-metoro use at induction initiation remain unclear; neo-metoro use at induction initiation may reduce IDI.

Key words: Bishop score; Cervical ripening; Cesarean delivery; Foley balloon catheter; Premature rupture of membranes.

Introduction

Labor induction (LI) is one of the most commonly practiced obstetric intervention worldwide. LI comprises of cervical ripening and uterine augmentation. Transvaginal dinoprostone (prostaglandin E2) or misoprostol (prostaglandin E1) is often used to mature the unfavorable cervix for inducing uterine contractions [1]. Sometimes insufficient contractions necessitate uterine augmentation, which is often achieved by intravenous drip administration of oxytocin.

However, transvaginal prostaglandins are not licensed for LI in Japan where mechanical methods are mainly used to mature the unfavorable cervix. Transcervical Foley balloon catheters are used for a mechanical method worldwide. Furthermore, their use often necessitates subsequent oxytocin administration because these catheters induce active labor less effectively than prostaglandins [2]. In Japan, several types of metreurynters are commercially available and widely used for balloon catheterization on LI.

Recently, the Japanese Society of Obstetrics and Gynecology (JSOG) issued a guideline for LI [3, 4]. Nevertheless, clinical studies on LI in Japan, especially those on LI with metreurynter use, are scarce [5, 6]. Each institution has its own LI protocols based on experience and basic clinical policy. At the present institution, Fukaya Red Cross Hospital, Saitama, Japan, the authors use the discoid “neo-metoro” and spherical “mini-metoro” metreurynters. Both are transcervical balloon catheters, designed specifically for LI, made of silicon gum. Neo-metoro forms an approximately six to seven by four-cm disc when inflated with 80–100 ml sterilized water, while mini-metoro forms an approximately four-cm sphere when inflated with 40 ml of sterilized water. Both devices have a moderately hard shaft, making them easier to insert into the cervix than a Foley catheter. The shaft of mini-metoro is slightly thinner than that of neo-metoro. Both metreurynters are inserted through the cervix and placed between the internal cervical os and amniotic membrane or fetal head. Because of the dimensions of these types of metreurynters, neo-metoro is difficult to use when cervical dilatation is less than one cm or more than four cm and mini-metoro is difficult to use when cervical dilatation is less than 0.5 cm or more than three cm. The authors use osmotic dilators if insertion of any me-
treuter into the closed and firm cervix proves impossible, but this did not occur during the study period. Active labor is often not obtained after metreuter use, and in such cases, the authors administer oxytocin via an intravenous drip for uterine augmentation. Here the authors evaluated the effectiveness and safety of methods using neo-metoro or mini-metoro in combination with oxytocin for LI. They also assessed the differences in parturition outcomes according to metreuter type used at induction initiation.

<p>| Table 1.—| Relationship of the metreuter groups with characteristic factors, parturition outcomes, and adverse events in the 146 women. |</p>
<table>
<thead>
<tr>
<th>Factors, parturition outcomes, adverse events</th>
<th>Total n = 146</th>
<th>Without metreuters n = 12 (8%)</th>
<th>Neo-metoro n = 99 (68%)</th>
<th>Mini-metoro n = 35 (24%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>31.4 ± 4.7</td>
<td>33.2 ± 4.9</td>
<td>31.4 ± 4.6</td>
<td>30.7 ± 4.7</td>
<td>0.29</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>93</td>
<td>64%</td>
<td>33%</td>
<td>61%</td>
<td>83%</td>
</tr>
<tr>
<td>Multiparous</td>
<td>53</td>
<td>36%</td>
<td>67%</td>
<td>39%</td>
<td>17%</td>
</tr>
<tr>
<td>Maternal weight (kg)</td>
<td>65.7 ± 10.1</td>
<td>65.2 ± 10.7</td>
<td>66.2 ± 10.3</td>
<td>64.3 ± 9.7</td>
<td>0.65</td>
</tr>
<tr>
<td>Maternal BMI (kg/m²)</td>
<td>25.9 ± 3.8</td>
<td>26.3 ± 3.6</td>
<td>26.1 ± 3.9</td>
<td>25.3 ± 3.7</td>
<td>0.50</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>40.1 (35.0-41.4)</td>
<td>39.2 (35.0-41.0)</td>
<td>40.1 (36.0-42.4)</td>
<td>40.9 (36.1-42.1)</td>
<td>0.016*</td>
</tr>
<tr>
<td>Indication for labor induction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-term PROM</td>
<td>58</td>
<td>40%</td>
<td>0%</td>
<td>39%</td>
<td>54%</td>
</tr>
<tr>
<td>PRH</td>
<td>45</td>
<td>31%</td>
<td>42%</td>
<td>31%</td>
<td>26%</td>
</tr>
<tr>
<td>Complications of a precipitate labor</td>
<td>10</td>
<td>7%</td>
<td>17%</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>Others</td>
<td>12</td>
<td>8%</td>
<td>8%</td>
<td>7%</td>
<td>11%</td>
</tr>
<tr>
<td>Maternal complications (including PRH or GDM)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>80</td>
<td>55%</td>
<td>42%</td>
<td>51%</td>
<td>71%</td>
</tr>
<tr>
<td>Yes</td>
<td>66</td>
<td>45%</td>
<td>58%</td>
<td>49%</td>
<td>29%</td>
</tr>
<tr>
<td>Bishop score at induction initiation</td>
<td>5.3 ± 1.7</td>
<td>7.8 ± 1.6</td>
<td>5.3 ± 1.5</td>
<td>4.4 ± 1.6</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Achieving vaginal delivery without oxytocin</td>
<td>28</td>
<td>19%</td>
<td>–</td>
<td>21%</td>
<td>20%</td>
</tr>
<tr>
<td>Oxytocin administration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>111</td>
<td>76%</td>
<td>100%</td>
<td>73%</td>
<td>77%</td>
</tr>
<tr>
<td>Maximum dose (mu/min)</td>
<td>6.9 ± 3.0</td>
<td>6.7 ± 3.6</td>
<td>6.7 ± 3.0</td>
<td>7.5 ± 2.4</td>
<td>0.44</td>
</tr>
<tr>
<td>Planned schedule</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Two-day induction</td>
<td>125</td>
<td>86%</td>
<td>0%</td>
<td>91%</td>
<td>100%</td>
</tr>
<tr>
<td>One-day induction</td>
<td>21</td>
<td>14%</td>
<td>100%</td>
<td>9%</td>
<td>0%</td>
</tr>
<tr>
<td>Induction-to-delivery interval (h)</td>
<td>21.7 ± 13.6</td>
<td>8.7 ± 11.4</td>
<td>21.3 ± 12.7</td>
<td>27.5 ± 13.8</td>
<td>0.016*</td>
</tr>
<tr>
<td>Mode of delivery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>106</td>
<td>73%</td>
<td>67%</td>
<td>77%</td>
<td>63%</td>
</tr>
<tr>
<td>Vacuum or forceps</td>
<td>18</td>
<td>12%</td>
<td>17%</td>
<td>11%</td>
<td>14%</td>
</tr>
<tr>
<td>Cesarean</td>
<td>22</td>
<td>15%</td>
<td>17%</td>
<td>12%</td>
<td>23%</td>
</tr>
<tr>
<td>Indication for cesarean delivery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arrest of labor NRFS</td>
<td>13</td>
<td>9%</td>
<td>100%</td>
<td>42%</td>
<td>75%</td>
</tr>
<tr>
<td>Others</td>
<td>3</td>
<td>2%</td>
<td>0%</td>
<td>25%</td>
<td>0%</td>
</tr>
<tr>
<td>Vaginal delivery achieved during the planned schedule</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal delivery finally achieved</td>
<td>103</td>
<td>71%</td>
<td>67%</td>
<td>77%</td>
<td>54%</td>
</tr>
<tr>
<td>Neonatal birth weight (g)</td>
<td>3,090 ± 434</td>
<td>3,294 ± 603</td>
<td>3,091 ± 428</td>
<td>3,017 ± 376</td>
<td>0.31</td>
</tr>
<tr>
<td>Low Apgar score (≤ 7 at 1 or 5 min)</td>
<td>11</td>
<td>8%</td>
<td>8%</td>
<td>8%</td>
<td>6%</td>
</tr>
<tr>
<td>NICU admission</td>
<td>2</td>
<td>1%</td>
<td>8%</td>
<td>1%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Data are presented as number, mean ± standard deviation, or percentage (in each metreuter grouping) unless otherwise indicated.

BMI: body mass index; GDM: gestational diabetes mellitus; NICU: neonatal intensive care unit; NRFS: non-reassuring fetal status; PRH: pregnancy-related hypertension; PROM: premature rupture of membranes.

*Statistically significant. †Median (range). ‡Comparison of the neo-metoro group with the mini-metoro group (because all cases in the without metreuter group were administered oxytocin and induced by the one-day schedule).

Materials and Methods

Indications and informed consent

Major indications for LI are premature rupture of membranes (PROM) and post-term pregnancy. Other indications include pregnancy-related hypertension, complications, prevention of precipitate labor, oligohydramnios, fetal abnormality, and societal indications. Anesthesia for labor and delivery (planned or occasional) is not performed at the present institution. In addition, the authors do not handle breech vaginal delivery, twin vaginal delivery, or vaginal delivery after prior cesareans. LI is indicated when spontaneous labor onset does not occur within...
Table 2. — Adjusted odds ratios calculated by multivariate logistic regression analysis assessing the relationship between each factor and VDPS and VDF parturition outcomes.

<table>
<thead>
<tr>
<th>Factors</th>
<th>VDPS AOR</th>
<th>95% CI</th>
<th>p</th>
<th>VDF AOR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Five-year elevating</td>
<td>0.64</td>
<td>0.07–5.2</td>
<td>0.68</td>
<td>1.3</td>
<td>0.69–2.6</td>
</tr>
<tr>
<td>Parity</td>
<td>Nulliparous</td>
<td>0.30</td>
<td>0.10–0.85</td>
<td>0.024*</td>
<td>N/A†</td>
<td></td>
</tr>
<tr>
<td>Maternal BMI (kg/m²)</td>
<td>&lt; 22</td>
<td>1.2</td>
<td>0.34–4.9</td>
<td>0.76</td>
<td>0.87</td>
<td>0.11–7.4</td>
</tr>
<tr>
<td></td>
<td>≥ 29</td>
<td>0.87</td>
<td>0.23–3.5</td>
<td>0.85</td>
<td>0.76</td>
<td>0.11–5.7</td>
</tr>
<tr>
<td>Indication for labor induction</td>
<td>Post-term</td>
<td>1.8</td>
<td>0.65–5.5</td>
<td>0.25</td>
<td>1.00</td>
<td>0.26–3.9</td>
</tr>
<tr>
<td></td>
<td>PROM</td>
<td>0.73</td>
<td>0.22–2.4</td>
<td>0.60</td>
<td>1.1</td>
<td>0.19–7.7</td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td>0.74</td>
<td>0.28–2.0</td>
<td>0.54</td>
<td>0.45</td>
<td>0.12–1.6</td>
</tr>
<tr>
<td>Complications</td>
<td>Yes</td>
<td>0.53</td>
<td>0.16–1.7</td>
<td>0.26</td>
<td>0.33</td>
<td>0.06–1.6</td>
</tr>
<tr>
<td></td>
<td>1–3</td>
<td>0.46</td>
<td>0.21–0.92</td>
<td>0.027*</td>
<td>N/A‡</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4–5</td>
<td>0.79</td>
<td>0.14–5.1</td>
<td>0.80</td>
<td>N/A†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6–7</td>
<td>0.87</td>
<td>0.23–3.5</td>
<td>0.85</td>
<td>0.76</td>
<td>0.11–5.7</td>
</tr>
<tr>
<td></td>
<td>8–10</td>
<td>0.94</td>
<td>0.11–7.7</td>
<td>0.96</td>
<td>0.21</td>
<td>0.004–9.6</td>
</tr>
<tr>
<td>Metreurynter groups</td>
<td>Mini-metro</td>
<td>1.2</td>
<td>0.85–5.8</td>
<td>0.11</td>
<td>1.5</td>
<td>0.40–5.8</td>
</tr>
<tr>
<td></td>
<td>Neo-metro</td>
<td>0.94</td>
<td>0.11–7.7</td>
<td>0.96</td>
<td>0.21</td>
<td>0.004–9.6</td>
</tr>
</tbody>
</table>

AOR: adjusted odds ratio; BMI: body mass index; CI: confidence interval; N/A: not available; PROM: premature rupture of membranes; VDF: vaginal delivery finally achieved; VDPS: vaginal delivery achieved during the planned schedule.

*Statistically significant. †The VDF rate in the multiparous women was too high to analyze the relation to parity, so the factor of parity was extracted in the multivariate analysis. ‡The VDF rate in the BS8–10 class (which was 100%) was too high to analyze.

Table 3. — Multivariate Cox proportional hazards model assessing the effect of each factor on induction-to-delivery interval in 113 women who underwent LI via Schedule A of the two-day induction.

<table>
<thead>
<tr>
<th>Factors</th>
<th>AOR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Five-year elevating</td>
<td>0.82</td>
<td>0.63–1.07</td>
</tr>
<tr>
<td>Parity</td>
<td>Nulliparous</td>
<td>0.45</td>
<td>0.25–0.80</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>&lt; 22</td>
<td>0.64</td>
<td>0.31–1.3</td>
</tr>
<tr>
<td></td>
<td>≥ 29</td>
<td>0.46</td>
<td>0.21–0.92</td>
</tr>
<tr>
<td>Indication for labor induction</td>
<td>Post-term</td>
<td>1.4</td>
<td>0.81–2.4</td>
</tr>
<tr>
<td></td>
<td>PROM</td>
<td>0.94</td>
<td>0.47–1.8</td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td>0.69</td>
<td>0.39–1.2</td>
</tr>
<tr>
<td>Complications</td>
<td>Yes</td>
<td>0.57</td>
<td>0.30–1.03</td>
</tr>
<tr>
<td>Neonatal birth weight</td>
<td>≤ 3,500 g</td>
<td>0.48</td>
<td>0.22–0.96</td>
</tr>
<tr>
<td>Bishop score</td>
<td>1–3</td>
<td>0.76</td>
<td>0.46–1.3</td>
</tr>
<tr>
<td></td>
<td>4–5</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>6–7</td>
<td>0.56</td>
<td>0.12–1.7</td>
</tr>
<tr>
<td>Metreurynter inserted</td>
<td>Mini-metro</td>
<td>1.5</td>
<td>0.89–2.6</td>
</tr>
</tbody>
</table>

AOR: adjusted odds ratio; BMI: body mass index; CI: confidence interval; PROM: premature rupture of membranes.

*Statistically significant.

24 hours of PROM. For safety, cesarean is prioritized over LI in cases with severe complications or in cases wherein vaginal delivery seems to be hard to achieve. Induction initiation occurs after careful consideration of maternal condition and provision of informed consent.

Standard schedules

The basic procedure for LI is metreurynter insertion in combination with subsequent oxytocin administration. Standard schedules of LI comprise two-day and one-day inductions. Schedule selection depends on cervical maturity at induction initiation. In the two-day induction, in principle, metreurynters are inserted in the afternoon (three to five pm) of the day before the target delivery day (Schedule A); sometimes in the morning of the day before the target delivery day (Schedule B). Moreover, the two-day induction is divided into mini-metro insertion and neo-metro insertion at induction initiation. The one-day induction is selected when a woman has a comparatively favorable cervix. Moreover, a neo-metro insertion is administered prior to oxytocin if possible (Schedule C). If the cervix is sufficiently favorable (Schedule D). Inserted metreurynters are removed when extruded through the cervix into the vagina.

If contractions are insufficient in the morning of the target delivery day, oxytocin is administered to obtain active labor. The initial oxytocin dose is two millilits (mu)/min (12 ml/h of five units oxytocin in 500 ml solution), followed by 3.3 mu/min (20 ml/h of oxytocin solution) 30 min later, with a dose increment of 1.7 mu/min (10 ml/h of oxytocin solution) at least every 30 min; the maximum dose administered is 20 mu/min (120 ml/h oxytocin solution).

Manual cervical dilatation, manual membrane stripping, and artificial amniotomy are administered with discretion. Artificial amniotomy will only be performed when delivery (vaginal or cesarean) will likely be achieved within several hours. If delivery is not foreseen to be achieved by five to seven pm based on labor progress during the afternoon of the target delivery day, oxytocin administration is stopped. At this time, without indications for cesarean delivery and if mother and fetus are considered fit to tolerate further attempts, the authors advise rest before attempting LI the following day.

To monitor fetal heart rate and uterine contractions, the authors use cardiotocography with external transducers at least 20 min before and after metreurynter insertion, intermittently during early labor, and continuously during active labor or oxytocin administration. Recently, the authors continuously monitor fetal heart rate in cases with neo-metro insertion, in accordance
with JSOG recommendations when using a transcervical balloon catheter inflated to 41 ml or more [4].

In addition, antibiotics are administered when metreurynters are inserted, PROM occurs, Group B streptococcus has been detected, and prevention of infection is indicated. Broad-spectrum penicillins such as piperacillin sodium are often administered intravenously at the present institution.

Methods
The authors retrospectively reviewed 146 consecutive women with live singleton pregnancies, cephalic presentation, no prior cesarean sections, and who underwent LI at the present institution. They obtained characteristic factors, parturition outcomes, and adverse events from the obstetric database and the medical records.

To estimate LI efficacy, the authors defined parturition outcomes as vaginal delivery achieved within the planned schedule (VDPS), vaginal delivery finally achieved (VDF), and induction-to-delivery interval (IDI). VDPS included women who achieved vaginal delivery, including vacuum-assisted or forceps deliveries, by six pm of the target delivery day. VDF included women who eventually achieved vaginal delivery, including vacuum-assisted or forceps deliveries, however excluding cesarean section. Cesarean delivery was considered as failed induction. IDI was defined as the interval in hours from induction initiation to delivery, including cesarean delivery. Induction initiation was defined as the time of metreurynter insertion or oxytocin administration in women where metreurynters were not used. Women were divided into the following three groups according to metreurynter use at induction initiation: the neo-metoro group, the mini-metoro group, and the “without metreurynters” (WOM) group.

Bishop score (BS), measured upon metreurynter insertion or oxytocin initiation, was used to judge cervical maturity at induction initiation. Women were divided into BS1–3, BS4–5, BS6–7, and BS8–10 classes for analysis and interpretation of results. The following three adverse events were assessed: low Apgar score (≤ 7 at one or five min), admission to a neonatal intensive care unit, and maternal fever during induction (≥ 38°C).

The relationship of metreurynter groups with characteristic factors, parturition outcomes, and adverse events were assessed using the Chi-square ($\chi^2$), Student’s $t$-test, and Mann–Whitney U test. To assess the effect of each factor on VDPS and VDF, the authors used multivariate logistic regression analysis.

IDI was assessed in 113 women who underwent LI via Schedule A. The authors constructed Kaplan–Meier survival curves and analyzed using univariate log-rank tests separately for nulliparous and multiparous women. Moreover, they used the multivariate Cox proportional hazards model to assess the effect of each factor on IDI. Calculated hazard ratios were regarded as odds ratios for achieving delivery per unit time, with higher hazard ratio indicating earlier delivery.

Statistical analyses were performed using JMP 8 and all tests were two-tailed. A $p < 0.05$ was considered statistically significant.

Results
LI was conducted by the two-day induction in 86% (125/146) women and by the one-day induction in 14% (21/146). Furthermore, 77% (113/146) underwent LI via Schedule A [56% (82/146) with neo-metoro, 21% (31/146) with mini-metoro], 8% (12/146) via Schedule B, 6% (9/146) via Schedule C, and 8% (12/146) via Schedule D. Therefore, some metreurynter was used for LI in 92% (134/146).

Table 1 shows the relationship of metreurynter groups with characteristic factors, parturition outcomes, and adverse events in the 146 women. With regards to characteristic factors, nulliparity, late gestational age, and post-term pregnancy were higher and PROM and BS were lower in the mini-metoro group than other two groups. Completely opposite characteristics were evident in the WOM group, while intermediate characteristics were observed in the neo-metoro group. With regards to parturition outcomes, IDI in the mini-metoro group was longer than that in the neo-
metoro group. The VDPS rate was highest in the neo-metoro group, followed by that in the WOM and mini-metoro groups. The VDF rate in the mini-metoro group was lower than that in the other two groups, but the difference was not significant. Adverse events were observed in each group but the differences were not significant. Severe incidents, such as severe neonatal asphyxia, neonatal death, uterine rupture, or umbilical cord prolapse, were not observed in this study.

Figure 1 illustrates the relationship of BS classification with parturition outcomes and characteristic factors in the 146 women. As BS increased, average IDI decreased ($p = 0.011$) and the VDF rate increased ($p = 0.003$). Metreurynter use was lowest in women belonging to the BS8–10 class ($p < 0.001$), and the most of the women in the mini-metoro group belonged to the BS1–3 class ($p = 0.037$).

There is an obvious relationship between parturition outcome and parity. The overall VDPS rate was 71% (103/146) and was higher in multiparous than in nulliparous women [81% (43/53) vs 65% (60/93); $p = 0.035$]. Furthermore, the overall VDF rate was 85% (124/146) and was higher in multiparous than in nulliparous women [96% (51/53) vs 78% (73/93); $p = 0.004$].

Table 2 shows the results of multivariate logistic regression analysis used to assess the relationship between factors, VDPS, and VDF. The VDF rate in multiparous women was too high to analyze its relationship with parity, and hence, parity was excluded from multivariate analysis. The significant adjusted odds ratio (AOR) for VDPS was 0.30 in nulliparous women and 0.18 in women belonging to the BS1–3 class. AOR for VDPS in the neo-metoro group was 2.2, indicating an insignificant positive tendency. The significant AOR for VDF was 0.04 in women belonging to the BS1–3 class and 0.14 in women belonging to the BS4–5 class. With regards to VDF, no advantage of neo-metoro use was evident.

IDI was assessed in 113 women who underwent LI via Schedule A. Kaplan–Meier curves for multiparous women ($n = 39$, Figure 2A) were identical between the neo-metoro and mini-metoro groups. In contrast, Kaplan–Meier curves for nulliparous women ($n = 74$, Figure 2B) showed that the proportion of women who did not achieve delivery within 24 hours of induction initiation differed between the neo-metoro and mini-metoro groups (68% vs 49%), but this difference demonstrated not to be significant by log-rank test. To assess the effect of each factor on IDI, AOR for achieving delivery per unit time was calculated by Cox proportional hazards model (Table 3). Significant AOR was 0.45 in nulliparous women, 0.46 in obese women (whose body mass index at induction initiation was $\geq 29$ kg/m$^2$), and 0.48 in women belonging to the BS1–3 class. The AOR of the neo-metoro group was 1.5, indicating insignificant advantage of neo-metoro use for reducing IDI.

In the 113 women who underwent LI via Schedule A,
VDPS and VDF rates were 73% (83/113) and 88% (100/113), respectively. The VDPS rates were 69% and 82% in nulliparous and multiparous women ($p = 0.18$); 47%, 75%, 87%, and 75% in women belonging to the BS1–3, BS4–5, BS6–7, BS8–10 classes ($p = 0.025$); and 78% and 61% in the neo-metro and mini-meteru groups, respectively ($p = 0.095$). The VDF rates were 82% and 100% in nulliparous and multiparous women ($p = 0.004$); 74%, 87%, 100%, and 100% in women belonging to the BS1–3, BS4–5, BS6–7, BS8–10 classes ($p = 0.034$); and 90% and 84% in the neo-metro and mini-meteru groups, respectively ($p = 0.34$).

**Discussion**

In the present study, the authors evaluated and showed the effectiveness and safety of methods using neo-meteru or mini-meteru metreurynters in combination with subsequent oxytocin for LI. They also assessed the differences in parturition outcomes according to metreurynter type used at induction initiation; neo-meteru use at induction initiation might shorten IDI relative to mini-meteru use.

The overall VDF rates were 78% and 96% in nulliparous and multiparous women, respectively. In a previous study at this institution ($n = 315$) [7], vaginal delivery rates in women with spontaneous labor onset were 91% and 97% in nulliparous and multiparous women, respectively. Therefore, in nulliparous women who underwent LI, vaginal delivery rate was lower than in women who experienced spontaneous labor onset ($p < 0.01$). In contrast, there was no difference in vaginal delivery rates between multiparous women who underwent LI and those who experienced spontaneous labor onset. These results indicate that nulliparous women attempting LI have an approximately a two-fold higher risk of cesarean delivery, consistent with other studies [8, 9].

Among the 113 women who underwent LI via Schedule A of the two-day induction using neo-meteru or mini-meteru prior to oxytocin, the VDF rates were 82% and 100% in nulliparous and multiparous women, respectively. Levy et al. [10] reported LI using a Foley balloon catheter prior to oxytocin ($n = 203$) similarly to the present method. In their study, vaginal delivery rates were 78% and 99% in nulliparous and multiparous women, respectively. The authors of this study believe that their results showed similar efficacy of the Levy’s method.

With regards to parturition outcomes, the advantages of each metreurynter used at induction initiation were unclear. However, both the overall AOR for VDPS and the AOR for achieving delivery per unit time in the 113 women via Schedule A of the two-day induction showed the tendency that the neo-meteru group tended to achieve earlier delivery than the mini-meteru group. Kaplan-Meier analysis of nulliparous women via Schedule A showed the same tendency. Therefore, for achieving early delivery, neo-meteru use might confer an advantage to mini-meteru use in induction initiation. On the other hand, regarding VDF, no advantage of neo-meteru use over mini-meteru use was evident. In their randomized controlled study, Levy et al. [10] compared the efficacy of 30 and 80 ml balloons for cervical ripening during LI. In their study, no difference in cesarean rate was evident between the two volumes. However in their subgroup analysis, in nulliparous women, delivery rate within 24 hours was higher and IDI was shorter in the 80 ml than in the 30 ml group. Such tendencies were not observed in multiparous women of their study. Therefore, the present authors consider that neo-meteru (which has a larger balloon than mini-meteru) use at induction initiation will not affect cesarean rate; however, neo-meteru use at induction initiation, especially in nulliparous women, may shorten IDI relative to mini-meteru use.

In the present study, lower BS at induction initiation was associated with lower VDPS and VDF rates and longer IDI. Failed induction is recognized to occur more often in women with an unfavorable cervix. In their prospective study ($n = 134$), Reis et al. [11] suggested that unfavorable cervical maturity (gauged by abbreviated BS) at admission for LI correlates with not achieving delivery within 24 hours in nulliparous and multiparous women. In the present study, the authors showed that IDI in women with a BS ≤ 3 is longer than in women with a BS ≥ 6 (Table 3). In their prospective study of 1,389 nulliparous women who underwent spontaneous labor onset or LI, Vrouenraets et al. [8] suggested that a BS of ≤ 5 was a risk factor for cesarean delivery (AOR 2.3) compared with a BS of ≥ 6. In the present study, the authors showed that in nulliparous women who underwent LI, a BS of ≤ 5 was a risk factor for failed induction (cesarean delivery), and that a BS of ≤ 3 greatly increased this risk (Table 2).

No differences were apparent in adverse events rates between the metreurynter groups. Moreover, severe adverse incidents were not observed in this study. Concerning methods of cervical ripening and LI, it is recognized that transcervical Foley balloon catheters have a lower risk of uterine hyperstimulation but a slower effect on labor than vaginal prostaglandins [2, 12]. The authors did not directly examine rates of uterine hyperstimulation and non-reassuring fetal status in this study. Moreover, this study might be too small to evaluate the adverse events that would occur during labor and delivery. However, overall rates of the three adverse events which were assessed in this study were acceptably low and no differences in adverse events rates with metreurynter usage were evident. Therefore, the authors do not believe that metreurynter use will raise the risks of adverse events. Actually, in their experience of LI, severe incidents were rarely observed. In contrast, many Japanese obstetricians recognize that metreurynter usage can cause umbilical cord prolapse [4]. In a retrospective observational study of 766 term women with cephalic presentation who underwent LI, Hirashima et al. [5] showed that a spherical metreurynter inflated with 200 ml or more caused
umbilical cord prolapse more often than 150 ml or less. In their case-controlled study including 370 women with LI using neo-metoro plus oxytocin, Maruyama et al. [6] reported a case with umbilical cord prolapse and subsequent neonatal death in the LI group. However, no well-designed studies address whether transcervical balloon catheters cause umbilical cord prolapse. The present authors believe that balloon catheters, especially neo-metoro and mini-metoro metreurynters which are used for balloons inflated with 100 ml or less, are sufficiently safe to mature the cervix and induce labor.

In this study, the authors presented an example of the methods for LI using modified metreurynters and oxytocin in Japan. They hope this paper will form the basis of further studies to solve the controversial and unsolved problems of LI in Japan.

Acknowledgment

A summary of this study was presented at the 122nd Academic Conference of the Kanto Society of Obstetrics and Gynecology, Yokohama City, Kanagawa, Japan, 2011.

References


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Effects of long-term fasting on female hormone levels: Ramadan model

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Summary

Background: Ramadan fasting is a special model of hunger and particularly affects metabolic processes, including carbohydrate and lipid levels. Endocrine changes induced by Ramadan fasting are not well known. Objective: The aim of this article was to evaluate the changes in hormone levels in women before and after the special Muslim fasting period of Ramadan. Materials and Methods: This study was performed in 30 healthy women in Obstetrics and Gynecology department during the Ramadan month of 2011. Patients during and after the first menstrual period had menstrual cycles fasting blood samples taken on the same days. Luteinizing hormone (LH), follicle stimulating hormone (FSH), estradiol (E₂), testosterone, and prolactin (PRL) levels were determined. Results: Before and during fasting LH, FSH, E₂, testosterone and PRL levels were not statistically different. Conclusion: Despite the limited available studies on these subjects in women, effect of Ramadan fasting on hormone levels were found to be within the normal limits.

Key words: Ramadan; Female hormones; Fasting.

Introduction

During Ramadan, the ninth month of the Islamic lunar calendar, healthy adult Muslims are obliged to refrain from taking any food, beverages, or oral drugs, as well as from sexual intercourse between dawn and sunset [1,2]. It is assumed that hundreds of millions of people observe the Ramadan fasting period each year [3]. Individuals typically consume only two main meals a day; the first meal is usually consumed prior to the beginning of the day’s fasting, between 04:30 to 05:30 (i.e., Sahur meal), and the other at the break of the day’s fasting, at 19:00 (i.e., Iftar meal). Hence Ramadan fasting is not complete and there is no restriction to the amount of food or fluid that can be consumed during the permissible period [4]. Fasting is not obligatory for menstruating women and the sick and the children are also exonerated [5]. Since this is a lunar calendar, the timing of this month of fast changes each year and the duration of restricted food and beverage intake can vary from between 12 to 16 hours [6]. In addition, a change in sleeping and waking patterns may cause changes in the physiology, metabolic responses, and functioning of the body’s hormonal system [7,8]. Metabolic and physiological modifications induced by the spontaneous inversion of eating habits during a whole month of Ramadan, as well as its impacts on women’s ovulatory hormones have been partially evaluated before [9-11]. Nutrient ingested in an equal quantity, but at an unusual time is known to induce different metabolic effects [10]. The aim of the present work was to investigate the effects of Ramadan on female hormone levels: follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E₂), progesterone, and testosterone around follicular phase in healthy women living in Yozgat province, Turkey.

Materials and Methods

This randomized, prospective study was conducted in the Obstetrics and Gynecology Department of Bozok University Hospital between August 1st and September 11th, 2011, (during the month of Ramadan). Thirty healthy females (without any acute or chronic disease and with regular menstruation) Muslim participants who were fasting during Ramadan and were not taking any regular medications, cigarette or alcohol, participated in the study after giving their informed consent. The study was approved by local ethical committee of Bozok University. Women with irregular menstruation, who were pregnant, smokers, those with severe hirsutism and galactorrhea, hyperandrogenism, thyroidism, drug consumers (two month before study and within two months of study entry), severe psychological disorders, athletes, primary or secondary amenorrhea, and females who could not fast were excluded from the study. The average fasting period was 14.5 hours; the beginning and ending hours of the fasting were approximately from 5:30 a.m. and 8:00 p.m. The study protocol was approved by the local institutional ethics committee.

The study was performed in two stages: firstly one or two months before the Ramadan, blood was withdrawn from study participants on their 9th to 11th day of menstrual periods (LMP) and secondly, during Ramadan, the same patients’ blood was withdrawn on the same LMP days which were around the 22-24th days of Ramadan during fasting. Thus, the total duration of fasting was 21-24 days with an interruption of at least six to nine days.

Since most of the fasting participants consumed food just before dawn, the authors withdrew their blood samples between 13:00 and 14:00 to make sure they were fasting for around eight hours. Venous blood (20 ml) was separated by centrifugation, and serums

Revised manuscript accepted for publication November 29, 2012

Clin. Exp. Obst. & Gyn. - issn: 0390-6663
XLI, n. 1, 2014
doi: 10.12891/c.omg15722014
sena were stored at –80°C for subsequent determinations in the laboratory of Clinical Biochemistry.

The serum levels of free T₃, free T₄, thyroid stimulating hormone (TSH), testosterone, PRL, FSH, LH, and E₂ were measured on an analyzer, using an electrochemiluminescent immunoassay (ECLIA) kit.

All data are expressed as means ± SDs. The statistical significance of changes in hormone levels was determined using a Wilcoxon signed rank test on values obtained before and during Ramadan. All values were defined to be statistically significant at p < 0.05. Data were analysed using the computer program SPSS for Windows (version 16.0).

Results

Minimum and maximum ages of studied participants were between 21 and 41 years. The average duration of menstrual cycle days were 28.2 ± 2.17 and average menstruation days were 6.86 ± 2.10. There was no correlation between the duration of fasting time and the levels of LH, FSH, E₂, TSH, testosterone and PRL. Serum LH, FSH, E₂, TSH, testosterone, and prolactin levels were not statistically different before and during Ramadan (p > 0.05, Table 1).

Discussion

Ramadan provides a unique model to study the effects of altered eating circadian to a very large meal in a day. It has been previously shown in animals and in humans that time distribution of food intake alters metabolism [11]. Yet, there is limited knowledge about the effect of Ramadan fasting on many biochemical parameter changes [12].

It has been shown that Ramadan can result in a delayed bedtime and shortened sleep, with partial sleep deprivation [13]. The effects of altered sleep patterns and eating habits on female hormone levels have been assumed to be altered but Shahabi et al reported that FSH, LH and Estradiol levels were not altered around ovulation period due to fasting [10]. In this present time period, the authors also did not observe a difference in FSH, LH, and E₂ levels during Ramadan. They therefore suggest that the level of these hormones is not altered in Ramadan and follicular period might not be related to the changes in sleeping hours or caloric intake.

Testosterone levels were not altered by Ramadan fasting in this study group. Although the authors could not find any study addressing the changes in female testosterone levels during Ramadan, it was made clear that the levels of sex hormones and gonadotropins, as well as other hormones, vary in healthy single males during the Islamic fasting month of Ramadan [8]. Mesbahzadeh et al. [8] reported a significant decrease in testosterone on the 20th and 28th days of Ramadan (compared with before Ramadan) that occurs simultaneously with significant increases in FSH levels. The authors contributed this result to the negative feedback system that controls testosterone secretion: following a decrease in testosterone secretion from the testes, the secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus increases and this hormone enters the anterior pituitary through the blood of the hypothalamus–pituitary portal system, thus stimulating the secretion of FSH and LH from the anterior pituitary [8].

Various conflicting results are present regarding different age and sex groups who studied the FSH, LH, testosterone and E₂ levels in different days of Ramadan [3,6,8]. Ramadan is based upon a lunar calendar, and therefore, the beginning of Ramadan may occur at any time in the year, and hence, the duration of the daily fasting span undergoes large variations in relation to the season and latitude [14]. The Ramadan fasting of 2011 was in summer and was longer than the Ramadans of winter. The differences in the present results might be related with seasonal variations in the studied variables: different data may be observed according to the year these studies are performed.

Chennoufi et al. [15] did not observe any difference in testosterone and PRL levels before, during, and one week after Ramadan in eight middle-distance athletes. Fasting first induces estrogen receptor expression at the beginning of the fasting and estrogen binds to these receptors to activate the neural pathway mediating fasting effect on LH secretion [16]. After 48-hour fasting, depending on the action of E₂ on the paraventricular nucleus of the hypothalamus, pulsatile LH is suppressed [17]. While a negative correlation was present between E₂ and LH levels in the present study group, the authors did not observe difference in E₂ levels. In monkeys, Chen et al. [18] observed reduced LH secretion which was associated with inhibition of GnRH pulse during hypoglycemic stress.

The present data confirms the results of Shahabi et al. [10] who reported that, Islamic fasting does not cause significant variation in the secretion of hormones around ovulation nor does it influence the occurrence of ovulation. Although this theory is plausible, the data of the present results belong to the follicular period.

In summary, the present study showed that Ramadan fasting did not affect female hormones during the third week of Ramadan; otherwise, there was no significant effect on folliculation, which kept the same circadian pattern during Ramadan.

Table 1. — Hormone levels

<table>
<thead>
<tr>
<th>Hormones</th>
<th>Fasting</th>
<th>Nonfasting</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH (mIU/ml)</td>
<td>5.99±1.82</td>
<td>5.45±1.61</td>
<td>n.s.</td>
</tr>
<tr>
<td>LH (mIU/ml)</td>
<td>3.67±0.74</td>
<td>3.07±1.84</td>
<td>n.s.</td>
</tr>
<tr>
<td>ESTRADIOL (pg/ml)</td>
<td>87.0±60.0</td>
<td>91.7±64.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>TESTOSTERONE (ng/ml)</td>
<td>0.51±0.20</td>
<td>0.47±0.19</td>
<td>n.s.</td>
</tr>
<tr>
<td>PROLACTIN (ng/ml)</td>
<td>9.18±3.45</td>
<td>9.18±2.55</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

levels.
References


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Difference in post-surgical reproductive prognosis between transcervical resection and transcervical incision of the septum

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Summary

Objective: This study aims to determine the difference between transcervical resection of septum (TCRS) and transcervical incision of septum (TCIS) in the improvement of reproductive prognosis. Study Design: Women with uterine septum in the Affiliated Hospital of Ningxia Medical University were retrospectively analyzed. A statistical method was used according to operative time, postoperative menstruation, postoperative pregnancy rate, postoperative term delivery rate, and so on. Results: Compared with TCRS, the TCIS method decreased operative time, blood loss, and consumption of uterus distension medium. No statistical difference was observed in operative complications between the two methods. After TCIS, the incidence of uterine adhesion was low and the degree of endometrial epithelialisation was high by hysteroscopy review. No statistical difference was observed in residual septum after the operation. The total pregnancy rate after TCIS was higher than that of TCRS. However, no statistical difference was observed in early and late pregnancy loss rates, preterm birth rate, and term birth rate. Conclusion: TCIS exhibits advantages of decreasing operative time, blood loss, and consumption of uterus distension medium. TCIS can reduce the incidence of uterine adhesion and can promote endometrial epithelialisation, which are the key factors to increase pregnancy rate after operation.

Key words: TCRS; TCIS; Uterine septum; Reproductive prognosis.

Introduction

Uterine septum is a common type of congenital malformation of the uterus [1], which is the result of failure of Müllerian duct fusion or of inadequate resorption of fusion. Through large-scale hysteroscopic fallopian tube sterilisation, the authors determined that the estimated incidence rate among fertile population was one percent [2]. These abnormalities seem to have a negative effect on reproductive performance [3]. Women with combined uterine septum have higher spontaneous abortion rate (21% to 27%) and premature birth rate (12% to 33%) with low pregnancy rate (40% to 43%) [4]. The result of pregnancy is related to the implanting location of the embryo [5]. Uterine septum has few endometrial glands as well as insufficient estrogen progesterone receptors and vascular endothelial growth factors. However, the uterine septum has different ultrastructures in implantation compared with the endometrium and other parts of the uterus. This difference in ultrastructures is one of the factors that decrease embryo implantation [6, 7]. Increasing the proportion between septum volume and uterus volume results in the increased probability of embryo implantation on the septum, which accounts for embryo loss during pregnancy [8]. Without surgical interventions, these defects cannot be changed through reproductive technology [9]. Not all women with this congenital malformation have experienced repeated spontaneous abortion and premature birth [10]. However, advising women with a history of long-term infertility or repeat embryo loss to perform metroplasty is necessary [11]. The method of uterine septum metroplasty evolved from uterine septum correction through the abdomen from about sixty years ago to the method of hysteroscopy procedures. For the past twenty years, transcervical resection of septum (TCRS) has become a standard approach. TCRS replaced transabdominal or transvaginal uterus septa metroplasty [12]. TCRS takes into account endometrial injuries under surgical electricity. In recent years, transcervical incision of septum (TCIS) was proposed as a new approach. TCIS involves an incision into the septum, but not a massive resection. Theoretically, this approach decreases the damage of the basalis layer of the endometrium after a massive resection of tissue, which makes local endometrial epithelialisation and septum adhesion formation after operation difficult. However, whether or not a barrier exists in epithelialisation of septum tissue, which remains in uterus after incision; how this barrier affects nidation of fertilized ovum and whether or not improving the operation approach is more superior in improving microinvasive and reproductive prognosis have not been reported.

Women with incomplete uterine septum were randomly divided into two groups, namely, TCRS and TCIS. The following aspects were recorded: operative time, blood loss, consumption of uterus distension medium, uterine adhesion, and endometrial epithelialisation after operation. A follow-up of pregnancy outcome after operation was performed.

Revised manuscript accepted for publication January 3, 2013
comparative analysis was conducted to determine which approach was superior in improving reproductive prognosis.

**Materials and Methods**

**Cases**

A retrospective analysis was conducted on women who were treated in Hysteroscopy Centre in Department of Gynecology in Affiliated Hospital of Ningxia Medical University. These women were diagnosed with incomplete uterine septum. Combining uterine septum and previous miscarriages, and excluding other kinds of infertility, the cases were divided into TCRS and TCIS groups. The surgical procedure was explained in detail to all the women. All women suffered from operation in the follicular phase. This study was conducted in accordance with the Declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Affiliated Hospital of Ningxia Medical University. Written informed consent was obtained from all participants.

**Operation**

Laminaria was used to soften the cervix the night before operation. The women were administered with lumbar anaesthesia in the lithotomy position. After the laminaria was removed, the perineum and vagina were routinely disinfected. The cervix was dilated to Hagar ten cm. The septum length was recorded by a B-mode ultrasonic diagnostic equipment and a graduated pipe with lens. A mirror was placed to observe the uterine shape and to confirm the width of the septum basement. TCRS was performed with symmetrical incision on two sides of the septum by annular electrode. The septum tissue was removed until the bilateral oviduct opening was in the same visual field. TCIS was performed by making a direct incision along the septum midpoint from the lateropulsion of uterus by a needle electrode. The septum tissue was not removed until the normal uterus was recovered. After incision, a T intrauterine device (IUD) was inserted.

**Measurement**

The measurement of the septum length included two methods: 1) a graduated probe assisted the mirror to measure the uterine depth. The uterine depth on top of the septum is the septum length; 2) the transaction of the septum was scanned by B-mode ultrasonic equipment to measure the septum length.

Measurement of uterus distension medium: the uterus distension medium was collected in the bag beside the women and was measured by a graduated bag. The volume of use minus the recycled volume is the absorbed volume.

The incision standards included the following: the monitor of the B-mode ultrasonic equipment was used, and the incision reached the uterine basement (one cm to 1.5 cm). Without the monitor, the uterine basement was in the same horizontal line as the uterine corner on both sides, or the incision on both sides reached the fallopian opening (one cm), until the uterine shape recovered to normal [13].

The research parameters included the septum length before operation, operative time, intraoperative blood loss, consumption of uterus distension medium, as well as incidence and types of intraoperative complications.

**Postoperative re-examination**

The re-examination method involved hysteroscopic review on the third day to the seventh day after postoperative menstruation was cleaned.

The research parameters included residual septum (more than one cm), IUD drops, incidence of uterine adhesion, type of uterine adhesion, and endometrial epithelialisation (endometrial overlay, endometrial thickness on the incision site surface was similar to others, equal opening of the visible crypt and the capillary blood. The presence of all these factors resulted in complete epithelialisation, otherwise, incomplete epithelialisation occurred).

**Postoperative follow-up**

Follow-up period went from August 2009 to August 2011 (24 months). Research parameters included: pregnancy, abortion, premature birth, and term birth after operation.

**Statistical analysis**

SPSS11.5 was used for the measurement data. When the condition was not enough, $\chi^2$ calibration test was adopted. A $p < 0.05$ was considered a significant statistical difference.

**Results**

**General data**

Among 76 cases with incomplete uterine septum, 70 cases volunteered to join this research and signed consent forms. The TCRS group comprised of 33 cases, whereas the TCIS group comprised of 37 cases. No significant statistical difference was observed in age and septum length between the two groups. Two cases in TCIS dropped out because of IUD drop, abdominal pain, and vaginal bleeding.

The general conditions between both groups are shown in Table 1. Two cases in TCRS group with complications during the operation are reported. By contrast, no complications were observed in TCIS group. No significant statistical difference was observed between both groups (calibration $\chi^2 = 0.641, p = 0.423$).

**Postoperative review**

The review after operation is shown in Table 2. A high incidence of residual septum was observed in TCRS group. A significant statistical difference was observed between TCRS and TCIS groups. The incidence of uterine adhesion in TCIS group was lower than that in TCRS group. The degree of epithelialisation in TCIS group was higher than that in TCRS group, which indicates a significant statistical difference.

**Follow-up of reproductive prognosis**

The follow-up of reproductive prognosis is shown in Table 3. During the follow-up period, two cases of pregnancy were reported in TCRS group, of which one case was more than 28 weeks pregnant and one case was in early gestation.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Age (years)</th>
<th>Length of septum (cm)</th>
<th>Operative time (min)</th>
<th>Blood loss (ml)</th>
<th>Uterus distension medium (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCRS</td>
<td>33</td>
<td>28.23 ± 7.15</td>
<td>3.90 ± 0.70</td>
<td>17.23 ± 4.14</td>
<td>15.20 ± 2.12</td>
<td>4820 ± 840</td>
</tr>
<tr>
<td>TCIS</td>
<td>37</td>
<td>29.61 ± 4.28</td>
<td>4.00 ± 0.50</td>
<td>14.75 ± 2.56</td>
<td>7.23 ± 3.45</td>
<td>3910 ± 760</td>
</tr>
</tbody>
</table>

$t$ value: 0.992, $p$ value: 0.325

$t$ value: 0.693, $p$ value: 0.491

$t$ value: 3.050, $p$ value: 0.003

$t$ value: 11.474, $p$ value: 0.000

$t$ value: 4.759, $p$ value: 0.000
The total pregnancy rate in the TCIS group was higher than that in TCRS group. However, no statistical significance was observed in abortion rate of early pregnancy, premature birth, and term birth. Eight cases in pregnancy state were reported. The results are unknown and incomparable because of different pregnancy durations.

**Discussion**

The reproductive prognosis of surgical treatment on the uterine septum, which is required for reproduction, requires improvement especially when a case has had repeated spontaneous abortion and premature labour [14]. Abdominal metroplasty in the early period was conducted by removing the parts including the septum. This method involves making a wedge-shaped incision of the uterine fundus. However, this approach has disadvantages of high adhesion rate and smaller uterine volume. Bret improved this approach by dividing the uterine body and septum in half from the uterine fundus. At this point, both halves of septum were incised, but the septal tissue was not removed. After surgery, the uterine body and endometrial cavity maintained their original volume and reproductive potential [15]. This approach is widely adopted for long-term effects. With the invention of hysteroscopy, TCRS became a classic surgical procedure for uterine septum metroplasty [16]. TCIS borrows the idea of Bret, which does not require the removal of septum tissue, but only making an incision. In practice, once the septum tissue is incised, the fibromuscular part that constitutes the septum immediately retracts to match that of the endometrium. The tissue does not exit the endometrium. The fibromuscular part that constitutes the septum is almost absent of blood vessels. Thus, the occurrence of bleeding indicates that the mesometrium is cut. Compared with TCRS, TCIS has better control of incision and indications for stopping incision. By contrast, each removal of tissue in TCRS requires the hysterectoscopic body to be placed into the uterine cavity for tissue removal. The re-entry into the uterine cavity requires time to achieve a clear visual field, which prolongs the operation time (Table 2). The increasing absorption of perfusion fluid and blood loss decreases, a constant local pressure at the cervical channel is maintained and consequently, complications during the operation are decreased (in this study, no statistical significance was observed because of insufficient cases of complications). This easy, fast, and microinvasive incision can be achieved as a pattern of “dry cut” with its advantages.

The satisfaction of postoperative uterine adhesion and uterine epithelialisation is an evaluation index, which is used to compare the influence on fertility and potency of these two operation approaches. Uterine adhesion correlates with endometrial epithelialisation obstacle [18]. When the stratum basale of the endometrial tissue is damaged, the fibrinogen and fibrinolysin released by the fibroblast in the trauma parts are in the state of dynamic balance. Under the formative fibrillar network structure, stromal cells undergo endogenous repair through cell cycle to reach epithelialisation, which restores its superficial smooth and endometrial function. The fibrous tissues then undergo degradation. If the endometrial fundus is seriously damaged in the endometrial epithelialisation obstacle combined with uterine immune environmental abnormal condition, an abnormal healing mechanism is formed. Fibrin degradation ability decreases, and a substrate layer and fibration is formed. These two aspects prevent endometrial epithelialisation. Therefore, the principle of operation should aim to diminish the damage of endometrial stratum basale [19]. This aim is advantageous for epithelialisation, and can restore its functionality including endometrial receptivity to fertilised ovum. First, compared with TCRS, TCIS does not involve

### Table 2. — Review and result of “second look hysteroscopy” after operation between two groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Drop of intraretroplasty devices</th>
<th>Septum after operation</th>
<th>Membrane</th>
<th>Uterine adhesion</th>
<th>Connective tissue</th>
<th>Degree of epithelisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCRS</td>
<td>33</td>
<td>0</td>
<td>21.21 (7/33)</td>
<td>9.1 (3/33)</td>
<td>3.0 (1/33)</td>
<td>6.1 (2/33)</td>
<td>39.4 (13/33)</td>
</tr>
<tr>
<td>TCIS</td>
<td>37</td>
<td>5.4 (2/37)</td>
<td>2.7 (1/37)</td>
<td>5.4 (2/37)</td>
<td>2.7 (1/37)</td>
<td>0</td>
<td>64.9 (24/37)</td>
</tr>
<tr>
<td>χ²</td>
<td></td>
<td>4.05</td>
<td>42.17</td>
<td>0.809</td>
<td>4.541</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td></td>
<td>0.524</td>
<td>0.040</td>
<td></td>
<td>0.369</td>
<td></td>
<td>0.033</td>
</tr>
</tbody>
</table>

### Table 3. — Follow-up of reproductive prognosis between two groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Pregnancy rate of pre-pregnancy</th>
<th>Premature birth rate</th>
<th>Full-term birth rate</th>
<th>Pregnancy state</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCRS</td>
<td>33</td>
<td>39.4 (13/33)</td>
<td>15.2 (5/33)</td>
<td>21.2 (7/33)</td>
<td></td>
</tr>
<tr>
<td>TCIS</td>
<td>37</td>
<td>64.9 (24/37)</td>
<td>10.8 (4/37)</td>
<td>35.1 (13/37)</td>
<td>2.7 (1/37)</td>
</tr>
</tbody>
</table>
tissue resection, and has less damage to the endometrial stratum basale. Second, compared with ring electrodes used in TCRS, the needle electrodes used in TCIS have less contact area with endometrium. The dot-mode incision can make the incision present in one line. The crosswise incision can reduce the degree of thermal endometrial and myometrial damage, as well as reduce the risk of postoperative endometrial epithelialisation obstacle and uterine adhesion. However, giving specific quantification to this risk is difficult. Compared with the result of second-look hysterectomy of TCRS one month after operation, the incidence of adhesion is low in the TCIS group, and most adhesions are films and easy to separate. The process of epithelialisation is accomplished during second-look one month after operation. Several women who need to have another examination two months after operation exhibit unchanged degree of epithelialisation compared with the first month.

Through the follow-up visits to pregnancy status, the postoperative pregnancy rate of women in the TCIS group was higher than that in TCRS group. Both groups exhibited differences in improving reproductive prognosis, but early pregnancy abortion rate, premature delivery rate, and full-term pregnancy rate demonstrated no statistical differences. The present results suggest that the mechanism of TCIS to improve reproductive prognosis can reduce uterine adhesion and promote myometrial epithelialisation at an early stage.

Regardless of the operational approach and medical instruments used, the ultimate purpose is to improve reproductive prognosis in women. However, a positive reproductive prognosis also includes long-term complications associated with surgery, such as placental adherence, placenta accreta, pregnancy-related uterine rupture, and so on. Although few reports have been made on long-term complications [20], these complications can cause disastrous consequences. The incidence of these complications is related to the degree of myometrial damage by the operation and is theoretically presumed. The characteristics of TCIS incision show that this approach can reduce the stopping time during incision compared with that of TCRS operation approach. However, this aspect needs further analysis. In summary, obstetricians should be particularly alert to this potential risk when managing women with past uterine deformity metroplasty.

Acknowledgments

This work was supported by Ningxia Natural Science Foundation of China to Dan Liu (NZ10123), and the National Natural Science Foundation of China (81160078 and 30872739).

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The cost-effectiveness analysis of laparoscopic treatment of ectopic pregnancy: a single-center review of a five-year experience

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²School of Management, Fudan University, Shanghai; ³Shanghai Jiao Tong University, Shanghai (China)

Summary

Purpose: The aim of this study was to investigate the cost-effectiveness of laparoscopic treatment for ectopic pregnancy by comparing the medical expenses and time of hospitalization of laparoscopic and open surgery for ectopic pregnancy in partial area of Shanghai, China. Materials and Methods: Clinical data of 762 cases with ectopic pregnancy undergoing surgical treatment (307 cases for laparoscopic surgery and 455 cases for open surgery) were analyzed retrospectively. The clinical information including the medical expenses and time of hospitalization was compared. The patients were divided into three groups according to the treatments of different lesions (lesions resection, conservative laparotomy, and exploration group) and were analyzed. Results: The total hospitalization expenses and the top three single costs including surgery, exams, and medicine expenses were higher in laparoscopic group than in open surgery group. There was no significant difference between the two groups on the total time of hospitalization. The hospital days of preoperation were higher but the postoperative hospital days were lower in laparoscopic group than in open surgery group. Compared with the open surgery treatment, the hospitalization expenses of laparoscopic treatment for ectopic pregnancy increased. There was no significant difference on the total hospitalization days. Conclusion: The preoperative waiting period of inpatients increased and the post-operative hospital days reduced in laparoscopic group.

Key words: Cost; Ectopic pregnancy; Hospitalization days; Laparoscopy.

Introduction

Laparoscopy is widely applied in the field of obstetrics and gynecology because of minor damage, less pain, rapid recovery, and other advantages. Main gynecological surgery such as salpingo-oophorectomy and hysterectomy can be performed by laparoscopically assisted surgery. In recent years, laparoscopy-assisted diagnosis and surgical treatment of gynaecological malignant tumors has been carried out. For example, laparoscopic surgery for cervical cancer (CC) study and treatment is one of the main achievements [1]. The impact and use of laparoscopy for benign adnexal tumours have markedly increased [2]. Diagnostic laparoscopy can also be used for evaluating patients with advanced ovarian cancer who qualify for primary cytoreduction [3]. Therefore, gynaecological open surgery has a great tendency to be gradually replaced by laparoscopically assisted surgery. With the clinical application and popularity of laparoscopy, its health economics has becoming the new research focus. Previous studies of laparoscopic gynecologic surgery on the reducing hospitalization days and expenses have been reported, so as to provide basis for its clinical application [4-6]. At present, laparoscopy has been applied widely in a variety of surgical interventions in China [7-9]. Compared with other countries, because of health system and different cultures, the laparoscopic technique in reducing length of hospitalization stay and expenses has had a certain difference in China.

In the present study, in order to investigate the health economics of laparoscopic treatment for ectopic pregnancy, retrospective research was conducted by comparing the medical expenses and time of hospitalization of laparoscopic and open surgery for ectopic pregnancy in the Sixth People’s Hospital, Shanghai Jiaotong University, Shanghai, China. On this basis, the authors explored the value and strategy of laparoscopy on the rational utilization of health resources and reduction of hospitalization expenses, which can provide evidence for the ongoing health care reform.

Materials and Methods

The data used in this study included the related hospital records of the present hospital information system (HIS) from January 2003 to December 2007. All diseases were classified according to the International Classification of Diseases 10th Revision (Clinical modification, ICD10-CM). The search codes included: abdominal pregnancy 000.001, tubal pregnancy 000.101, tubal abortion 000.102, ruptured tubal pregnancy 000.103, ovarian pregnancy 000.201, ruptured ovarian pregnancy 000.202, and ectopic pregnancy 000.901. The surgical records of cases were reviewed by professional doctor and the cases which met the diagnosis of ectopic pregnancy were included in this study. Exclusion criteria included: 1) Two special types of ectopic pregnancy: cornual pregnancy 000.801 and cervical pregnancy 000.802; 2) Cases with complications and/or complications of other diseases that underwent examination and treatment. 3) Patients with ectopic pregnancy that underwent conservative treatment. Information of all retrieved cases also included the patient’s basic information, diagnosis, various fees, hospitalization days, and surgery date. The data were divided into two groups according to the treatment methods:

Revised manuscript accepted for publication September 26, 2013
laparoscopic surgery group and open surgery group. Their medical expenses and time of hospitalization were compared and analyzed. The patients were divided into three groups according to the treatments of different lesions (lesions resection, conservative surgery, and exploration group) and were analyzed.

A database was built through transformation of HIS data into EXCEL format and a retrospective cohort study was conducted. SPSS Version 11.5 was used for data analysis. All values are expressed as means ± SD. The significance of differences between two groups was determined by Student’s-t test and one-way analysis of variance. Chi-square test of two frequencies with completely randomization was used to analyse three types of frequency distributions. A p value of < 0.05 was considered as statistically significant.

**Results**

There were 917 cases of ectopic pregnancy according to the diagnosis criteria of ICD10-CM, accounting for 6.94% of the total number of deliveries over the same period (917/13214). Among the 917 cases, the following cases were excluded in this study: three cases of cornual pregnancy, six cases of cervical pregnancy, 141 cases of patients examined or treated due to reasons other than ectopic pregnancy during hospitalization (including 33 cases of patients with complications of other organs requiring examination and treatment, 61 cases of patients complicated with ovarian or tubal disorders that underwent surgical treatment simultaneously, 32 cases of patients complicated with uterine diseases and that underwent surgical treatment simultaneously, 20 cases of patients with ectopic pregnancy that underwent conservative treatment).

The 762 cases included in this study were divided into two groups: 307 cases in the laparoscopic surgery group including 230 cases of laparoscopic lesions resection, 69 cases of laparoscopic conservative surgery, and eight cases of exploratory laparoscopy; 455 cases in the open surgery group including 384 cases of transabdominal surgery for focus resection, 66 cases of conservative laparotomy, and five cases of exploratory laparotomy. There was a difference in the treatments of lesions: the rate of transabdominal surgery for focus resection in the open surgery group was higher than that of laparoscopic lesions resection in the laparoscopic surgery group (Table 1).

Among the 762 cases, the incidence of emergency surgery was 44.75%. There were 105 cases of emergency laparoscopic surgery, accounting for 34.2% of laparoscopic surgery, which was significantly lower than that of open surgery (Table 2).

Rate of ectopic pregnancy diagnosed and treated by laparoscopy: during 2003-2007 the rate of ectopic pregnancy diagnosed and treated by laparoscopy was 36.2%-46.2% of the total cases. As shown in Figure 1, there was no rising tendency for application of laparoscopy on diagnosis and treatment of ectopic pregnancy in recent years.

Regarding the proportion of fees in two groups of treatment methods: as shown in Table 3, each of the fees had basically the same proportion. The top three fees (operation, inspection, and drug fees) were further compared. The results showed that the total and the top three fees in the laparoscopic surgery group were all higher than the open surgery group. The difference was statistically significant (Table 4). According to the lesions treatments, the fees of two groups were compared. The results showed that the total fees and the top three types of fees (operation, inspection, and drug fees) of treatments by laparoscopic lesions resection and laparoscopic conservative surgery in the laparoscopic surgery group were respectively higher than...
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those of treatments by transabdominal surgery for focus resection and conservative laparotomy in the open surgery group. The differences were statistically significant (Tables 5, 6). The fees of treatment by exploration including costs of hospitalization and operation in the laparoscopic surgery group were higher than the open surgery group (Table 7).

Table 6 — Fees comparison of treatment by conservative surgery in two groups.

<table>
<thead>
<tr>
<th>Fees (Currency: Yuan)</th>
<th>Laparoscopic surgery group (n = 69)</th>
<th>Open surgery group (n = 66)</th>
<th>t value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization cost</td>
<td>8969.82 ± 1234.93</td>
<td>6425.14 ± 2260.62</td>
<td>8.066</td>
<td>0.000</td>
</tr>
<tr>
<td>Operation cost</td>
<td>5119.47 ± 897.88</td>
<td>2984.80 ± 1721.33</td>
<td>8.974</td>
<td>0.000</td>
</tr>
<tr>
<td>Inspection fee</td>
<td>1511.82 ± 855.06</td>
<td>1156.67 ± 376.00</td>
<td>3.099</td>
<td>0.002</td>
</tr>
<tr>
<td>Drug cost</td>
<td>930.45 ± 533.45</td>
<td>666.17 ± 350.35</td>
<td>3.386</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table 7 — Fees comparison of treatment by exploration in two groups.

<table>
<thead>
<tr>
<th>Fees (Currency: Yuan)</th>
<th>Laparoscopic surgery group (n = 69)</th>
<th>Open surgery group (n = 66)</th>
<th>t value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization cost</td>
<td>8517.31 ± 2290.47</td>
<td>5047.68 ± 1732.48</td>
<td>2.892</td>
<td>0.015</td>
</tr>
<tr>
<td>Operation cost</td>
<td>4526.14 ± 1797.88</td>
<td>2206.95 ± 539.48</td>
<td>2.766</td>
<td>0.018</td>
</tr>
<tr>
<td>Inspection fee</td>
<td>2053.75 ± 1026.86</td>
<td>1317.00 ± 517.41</td>
<td>1.711</td>
<td>0.116</td>
</tr>
<tr>
<td>Drug cost</td>
<td>850.51 ± 476.58</td>
<td>792.33 ± 686.97</td>
<td>0.181</td>
<td>0.860</td>
</tr>
</tbody>
</table>

Table 8 — Comparison of hospitalization days between two groups.

<table>
<thead>
<tr>
<th>Days</th>
<th>Laparoscopic surgery group (n = 380)</th>
<th>Open surgery group (n = 455)</th>
<th>t value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization</td>
<td>8.05 ± 3.39</td>
<td>8.21 ± 2.33</td>
<td>-0.787</td>
<td>0.431</td>
</tr>
<tr>
<td>Preoperation</td>
<td>1.64 ± 2.32</td>
<td>0.80 ± 1.70</td>
<td>5.448</td>
<td>0.000</td>
</tr>
<tr>
<td>Postoperation</td>
<td>6.41 ± 2.61</td>
<td>7.41 ± 1.82</td>
<td>-5.53</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Table 9 — Comparison of preoperative hospital days of treatment by lesions resection between two groups.

<table>
<thead>
<tr>
<th>Days</th>
<th>Laparoscopic surgery group (n = 384)</th>
<th>Open surgery group (n = 384)</th>
<th>t value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization</td>
<td>7.91 ± 3.38</td>
<td>8.03 ± 2.16</td>
<td>-0.548</td>
<td>0.584</td>
</tr>
<tr>
<td>Preoperation</td>
<td>1.59 ± 2.30</td>
<td>0.75 ± 1.64</td>
<td>4.829</td>
<td>0.000</td>
</tr>
<tr>
<td>Postoperation</td>
<td>6.32 ± 2.51</td>
<td>7.28 ± 1.73</td>
<td>-5.120</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Table 10 — Comparison of preoperative hospital days of treatment by conservative surgery between two groups.

<table>
<thead>
<tr>
<th>Days</th>
<th>Laparoscopic surgery group (n = 69)</th>
<th>Open surgery group (n = 66)</th>
<th>t value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization</td>
<td>8.30 ± 3.46</td>
<td>9.26 ± 2.95</td>
<td>-1.724</td>
<td>0.087</td>
</tr>
<tr>
<td>Preoperation</td>
<td>1.78 ± 2.27</td>
<td>1.09 ± 2.07</td>
<td>1.854</td>
<td>0.066</td>
</tr>
<tr>
<td>Postoperation</td>
<td>6.52 ± 2.79</td>
<td>8.17 ± 2.10</td>
<td>-3.880</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Table 11 — Comparison of preoperative hospital days of treatment by exploration between two groups.

<table>
<thead>
<tr>
<th>Days</th>
<th>Laparoscopic surgery group (n = 8)</th>
<th>Open surgery group (n = 5)</th>
<th>t value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization</td>
<td>9.75 ± 3.01</td>
<td>8.00 ± 2.55</td>
<td>1.122</td>
<td>0.289</td>
</tr>
<tr>
<td>Preoperation</td>
<td>1.88 ± 3.23</td>
<td>0.60 ± 0.55</td>
<td>1.093</td>
<td>0.308</td>
</tr>
<tr>
<td>Postoperation</td>
<td>7.88 ± 3.56</td>
<td>7.40 ± 2.70</td>
<td>0.272</td>
<td>0.791</td>
</tr>
</tbody>
</table>

Discussion

Operative laparoscopy as the mainstay in management of ectopic pregnancy is the safest and most effective method [10-13]. However, the degree of popularity of operative laparoscopy in management of ectopic pregnancy can be affected by health policy, medical technology, and other factors in different countries. The primary reason of using open surgery for treatment of ectopic pregnancy is no experience in management of ectopic pregnancy by laparoscopy [12]. In addition, one of the reasons for the application of laparoscopic technique is more likely due to the use of open abdominal surgery in emergency. The use of laparoscopy increased with the improvement of early diagnosis of ectopic pregnancy and decrease of requirement for an emergency open surgery intervention in emergency [13]. The percentage of laparoscopic approach for ectopic pregnancy between 2000 and 2006 in Romania has grown from 23.5 to 58.6% [14]. In France, only open surgery is required unless there are contraindications in the use of laparoscopic treatment [15]. The percentage of laparoscopic treatment of ectopic pregnancy in America is up to 70% [16]. Laparoscopy has been...
applied in all surgical areas in China at a higher rate after laparoscopy due to the impact and promotion of the international community since the eighties-nineties of last century [17, 18]. Currently, laparoscopic technique has been mastered by Chinese doctors, especially by those in larger institutions, but its application is not completely universal. In the present study, application of laparoscopic treatment of ectopic pregnancy in a large hospital in Shanghai, China was analyzed. The data indicated that application rate of laparoscopic treatment of ectopic pregnancy during 2003-2007 was 36.2-46.2%. The highest rate was in 2004 and it shows a downward trend in recent years. The main reason may be related to the introduction and promotion of the new technology by the former doctors. With mastery of technology, doctors no longer require promotions and ectopic pregnancy may be diagnosed and treated by lower-seniority doctors. Therefore, open surgery was usually chosen for treatment of by lower-seniority doctors due to lack of experience in laparoscopic diagnosis and treatment, hence leading to a decreasing trend in the number of laparoscopic treatments.

Compared with open surgery, there were different reports on laparoscopy regarding reducing healthcare costs in the management of patients with ectopic pregnancy. Some believe that the total cost can be reduced [18]. It also believed in some reports that there was no difference in costs between laparoscopic surgery and traditional open surgery, and that it could be even higher than open surgery [6, 19, 20]. The reason may be related to different healthcare systems and to varying costs in different countries. In the present study, the data from Shanghai, China showed that the main costs in the management of patients with ectopic pregnancy were fees related to surgery, inspection, and medication. The percentage of hospitalization costs was only three to five percent of the total costs. The cost was higher than that of traditional open surgery and the reason was mainly related to the economic level at the times when charging standards of new technology were established by the Chinese government. Increase of inspection fees may be related to the preparation before laparoscopic surgery. Therefore, because of these factors the total medical fees of laparoscopic surgery in the management of patients with ectopic pregnancy is increased.

Because laparoscopy is less painful and does not increase intra- or postoperative complications, it has a shorter length of hospital stay and quicker return to work than traditional open surgery [5]. Due to different cultural backgrounds, the patients in China are willing to stay in the hospital until fully recovery, so the hospital stay is often longer than many developed countries. The results in this study indicated that compared with traditional open surgery, there was no significant improvement of the total hospitalization days in diagnosis and treatment of ectopic pregnancy by laparoscopy. Because laparoscopy is usually used for non-emergency surgery, the preoperative hospital days were longer in the laparoscopic group than in the open surgery group and the postoperative length of hospital stay is improved due to faster recovery, especially in the cases of ectopic pregnancy by lesions resection. In conclusion, it is feasible to reduce hospital stay of laparoscopic treatment of ectopic pregnancy in China but its effect on reducing costs is not significant.

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**Significance of prenatal joint detection of ABO antibody titers and irregular antibodies in pregnant women with type O blood**

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**Summary**

**Objective:** To investigate the effects of blood transfusion and number of pregnancies on ABO antibody titers and irregular antibodies in pregnant women with type O blood. **Materials and Methods:** The study included 4,200 pregnant women with type O blood (their husbands were with non-O type blood) that were divided into transfusion group and non-transfusion group, according to whether they had a history of blood transfusion. The both groups were respectively divided into three subgroups (the number of pregnancies was one, two, and ≥ three). The ABO antibody titers and irregular antibodies were detected at the same time. The effects of ABO antibody titers and irregular antibodies on hemolytic disease of the newborn (HDN) were discussed. **Results:** There was no consistency of ABO antibody titers and existence of irregular antibody. The positive rates of irregular antibody of transfusion group and of the subgroup (number of pregnancies ≥ three) were far higher than that of non-transfusion group and of the subgroups (number of pregnancies < three), respectively. All pregnant women with positive irregular antibody in non-transfusion group were with HDN. **Conclusions:** For pregnant women with number of pregnancies ≥ three or with history of blood transfusion, the prenatal joint detection of ABO antibody titers and irregular antibodies is helpful for accurately reflecting the in vivo antibody type and level.

**Key words:** Antibody titers; Irregular antibodies; Hemolytic disease of the newborn; Blood transfusion; Indirect antiglobulin test.

**Introduction**

Hemolytic disease of the newborn (HDN) results from the blood group incompatibility between mother and fetus [1]. Maternal IgG antibodies are produced in response to the antigens derived from fetal red cells, cross the placenta, and are responsible for hemolysis and anemia. Severe degrees of fetal hemolysis result in fetal hydrops [2]. ABO-incompatibility occurs in 15-25% of all pregnancies, while the development of HDN in offsprings has a rate of one to four percent, depending on the ethnic constellation of the population [3]. The HDN due to ABO-incompatibility leads to early onset hyperbilirubinemia (within 72 hours of age), and is a high-risk condition because it may present with acute and rapid rise in total serum bilirubin (TSB) values [3, 4]. A strong association between the level of maternal IgG antibody titers and the need for invasive treatment for hyperbilirubinemia in ABO-incompatible neonates has been confirmed. The routine test for maternal IgG anti-A or -B titers in blood group O-mothers may therefore be considered as an additional step in risk assessment of neonates and be useful in the evaluation of the likely response to therapy [5].

Maternal alloimmunization to other red cell antigens remains as the cause of fetal disease since no prophylactic immunoglobulins are available to prevent the formation of these antibodies [6]. The mild to severe cases of fetal hemolytic disease have been reported, when anti-c, C, e, E, or Kell, Kidd, Duffy, MNS, Lutheran, Diego, Xg, P antibodies, as well as other private and public blood group systems are found in the sera of mothers [7].

So was it necessary that all pregnant women tested irregular antibodies? Most developed countries have guidelines for screening all pregnant women for irregular erythrocyte antibodies. According to the guidelines of the British Committee for Standards in Haematology, all pregnant women should be ABO and D antigen typed and screened for the presence of red cell antibodies early in pregnancy and at the 28th week of gestation [8]. According to guidelines in The Netherlands, it has been mandatory since 1998 to screen all pregnant women for the presence of irregular antibodies in the first trimester of pregnancy [9]. However, no such guidelines are followed in developing countries like China. Lee et al. [10] suggest that the routine antenatal antibody screening for Chinese women may not be worthwhile except in D antigen-negative subjects or those with a prior history of hemolytic disease of the newborn. Their views are supported by Wu et al. [11]. However, several cases of hemolytic disease of the newborn due to anti-c or other irregular antibodies have been published in a retrospective diagnosis, their mothers were D antigen-positive and without a prior history of hemolytic disease of the newborn [12-17]. Distinctly, only the routine antenatal antibody screening for Chinese women in D antigen-negative subjects or those with a prior history of hemolytic disease of the newborn was far insufficient.
In this study, the ABO antibody titers and irregular antibodies were detected in 4,200 pregnant women with type O blood. The effects of blood transfusion and number of pregnancies on ABO antibody titers and irregular antibodies were investigated, and the significance of prenatal joint detection of ABO antibody titers and irregular antibodies was analyzed for those who had transfused and were pregnant more than three times.

**Materials and Methods**

**Subjects**

The study included 4,200 pregnant women with type O blood (RhD positive) who were given perinatal care in the present hospital from January 2008 to December 2011. This study was conducted in accordance with the declaration of Helsinki and with approval from the Ethics Committee of People’s Hospital of Henan Province. Written informed consent was obtained from all participants. Their husbands were with non-O type blood. They were divided into transfusion group and non-transfusion group, according to whether they had a history of blood transfusion. The non-transfusion group was divided into three subgroups (the number of pregnancies was one, two, and ≥ three, respectively).

**Methods**

The detection of ABO antibody titers and irregular antibodies was conducted on the screened red blood cells (RBCs) and husband’s RBCs using incomplete antibody test card (indirect antiglobulin test, IAT), according to the standard protocol. The maternal serum was treated with 0.2 M 2-mercaptoethanol. The antibody titers were presented with the reciprocal of dilution factor, using titers ≥ 64 as positive result. The result of irregular antibody test was presented with negative or positive antibody. For positive antibody, its type was initially determined according to the reactivity pattern of screened cells, and then verified with panel cells. The detection and determination were continued until the birth of fetus, and then the ABO-HDN was identified and diagnosed.

The diagnosis of ABO-HDN hemolytic disease in this neonate was based on the parameters as follows: onset of hyperbilirubinemia within 24 hours of birth, fetomaternal ABO incompatibility, laboratory evidence of erythrocyte sensitization, i.e., positive direct coomb’s test (DCT) and exclusion of other causes of early onset of jaundice namely G-6-P-D deficiency and Rhisoimmunization [18].

**Results**

**General data**

In 4,200 pregnant women, 356 cases (8.49%) of which the newborns were diagnosed with HDN, two cases that had positive irregular antibody in non-transfusion group were with HDN, four cases with positive irregular antibody in transfusion group, and three cases were with HDN.

**Antibody titers**

Results of ABO antibody titers and irregular antibodies detection in 4200 pregnant women are shown in Table 1. The total positive rate of irregular antibodies was 0.14% (6/4200). The positive rate of irregular antibodies in transfusion group was 0.49%, which was far higher than that in non-transfusion group (0.059%). The detection results in 3,382 pregnant women without blood transfusion are shown in Table 2. Two cases with positive irregular antibody were the pregnant women of whom the number of pregnancies was ≥ three.

As seen in Tables 1 and 2, the positive rate of ABO antibody titer ≥ 64 was 30%-40%. There were cases with positive irregular antibody (titers < 64 and ≥ 64) in pregnant women both in transfusion group and in non-transfusion group. This suggested that there was no consistency of ABO antibody titers and existence of irregular antibodies. In six cases with positive irregular antibody, five cases had anti-E and (or) anti-C antibody and one case had anti-C antibody.

**Discussion**

Fetal blood type genes are generated 50% from father and 50% from the mother and regulate the production of antigen with different blood types. All blood type antigens in mother cannot stimulate the body to produce antibodies. Only the blood type antigens from father which the mother lacks can stimulate antibody production. Bakkeheim et al. [5] have demonstrated the association between the level of maternal IgG antibody titers and the incidence of hyperbilirubinemia in ABO-incompatible neonates. The presence of these IgG antibodies supports the diagnosis of ABO-HDN [18], and antibody titre levels below 512 identify a reduced risk for severe hyperbilirubinemia and subsequent kernicterus, whereas for higher titre levels, the risk is markedly increased. [5].

In this study, the positive rate of ABO antibody titers ≥ 64 is 30%-40%, but the incidence of HDN is only 8.49%,
which is slightly different with 20.41% in reported data [5]. It can be found that, for pregnant women with ABO-incompatibility, most of their newborns have no HDN, even the ABO antibody titer is $\geq 64$ in late pregnancy. This may be related to the existence of ABO antibody subgroups. In addition, for pregnant women with ABO antibody titers $<64$, the HDN also occurs. The cause may be associated with the presence of irregular antibodies or IgG subclasses. High maternal antibody concentrations with prevailing IgG2 subclass (which does not induce monocyte-driven cell destruction) have been reported to cause slight hemolytic conditions. On the other hand, when the antibody levels are lower, but the IgG1 and IgG3 are predominant, moderate or severe hemolytic disease is also developed [19].

The detection of ABO antibody titers in pregnant women is mainly applicable for determining the IgG antibody for ABO blood types, but not for other antibodies. It is suggested to use husband’s RBCs to detect the ABO antibody titers. The reason is that, the RBCs can furthest reflect all the antibodies responding to husband’s antigens in pregnant women, but not the simple ABO antibodies. The irregular antibody screening is mainly used to confirm the presence of IgG antibodies outside the ABO system. In this study, the positive rate of irregular antibodies in 4,200 pregnant women is 0.14%. This is in accordance with the findings of Lurie et al. [20] and Adeniji et al. [21], who have reported the alloimmunization rates among Rh-positive women of 0.2% and 0.15%, respectively. The positive rate of irregular antibodies in transfusion group is 0.49%, far higher than that in non-transfusion group (0.059%). Two cases with positive irregular antibody were the pregnant women of whom the number of pregnancies is $\geq 3$. Though these results may be affected by specimen volume, or associated with the pregnant women status (there are more than half of pregnant women have over three times of pregnancy), the change trend of irregular antibody production can at least be seen.

As the other antigens outside ABO system are weak, the produced antibodies cannot change the trend of ABO antibody titers in pregnant women. This results in the inconsistency of ABO antibody titers and existence of irregular antibody. The positive irregular antibody exists in pregnant women with negative ABO antibody. However, the majority of irregular antibodies are generated from the immune system, which makes the screening of positive irregular antibodies more clinically significant. Shilpa et al. [12] report that, the dilution titer of 1:4 is associated with fetal hydrops, and no other irregular antibody or any other cause of non-immune hydrops can be attributed to. As reported by Hackney et al. [14], the critical titer of 1:32 without supplementation with ultrasound and the critical titre of 1:16 supplemented with ultrasonographic features of hydrops are considered significant.

For pregnant women without history of blood transfusion, the irregular antibodies are produced by the stimulation of antigens from husband’s RBCs. If the effects of previous pregnancy are excluded (they are firstly pregnant or the corresponding antigens are negative in previous pregnancy), the incidence of HDN is 100%. However the severity of HDN is closely related with the antibody titers and affinity. For pregnant women with history of blood transfusion, the type of positive irregular antibody should be firstly confirmed, and then the antigens in husband’s RBCs are detected using the standard serum. If the corresponding RBC antigen is negative, the effect of antibody on fetus can be ignored. More attention should be highly paid to the case in which the corresponding RBC antigen is positive. In this study, five cases of six pregnant women with positive irregular antibody have anti-E and (or) anti-C antibody, and one case had anti-C antibody. These are consistent with the report of Wu et al. [22].

For pregnant women with number of pregnancies $\geq 3$ or with history of blood transfusion, the prenatal joint detection of ABO antibody titers and irregular antibodies is helpful for accurately reflecting the in vivo antibody type and level. It has an important significance in diagnosing and treating HDN, and should be used as a routine test in perinatal period.

References


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Evaluation of the effects of maternal anxiety on the duration of vaginal labour delivery

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Summary

Objective: In the present study, the authors aim to investigate the effect of anxiety during late pregnancy periods and during labour on the duration of delivery in patients giving birth vaginally. Materials and Methods: In the study we included 50 nulliparous and 35 multiparous patients who were at or above the 28th gestational age and followed-up and admitted for birth at the present hospital. During the admission at the outpatient clinic at third trimester and at the beginning of labour, anxiety levels of patients were detected by performing the Spielberger State-Trait Anxiety Inventory. The duration of the labour stages of pregnant women were recorded and these durations and maternal state-trait anxiety levels were compared. Results: The trait anxiety of patients both during the third trimester and labour was similar, while during labour state anxiety was seen to be increased. Statistically, the levels of the trait anxiety of multiparous patients were significantly higher. There was a statistically significant correlation between state anxiety for both periods in multiparous patients and latent and active phases, the first and the second stages, and total duration of the labour. In addition, there was a significant relationship between trait anxiety levels for both period and total duration of the labour. For multiparous patients, only positive significant correlation was detected with the level of state anxiety during labour. Conclusion: It has been seen that the anxiety occurring at the last trimester of pregnancy and labour, and especially acute state anxiety have negative effects on the duration of the phases of labour. It has been considered that the physical care provided for patients at the last trimester and during labour also evaluation in terms of anxiety and provision of emotional support may cause positive outcomes for the duration of labour.

Key words: Spielberger State-Trait Anxiety Inventory; Maternal anxiety; Duration of labour; Normal vaginal birth.

Introduction

Anxiety, which can be expressed in words such as worry, boredom, an uncomfortable feeling of uneasiness and fear experienced due to danger or possibility of danger caused by internal or external stimuli or any situation viewed and perceived as dangerous by the person. When these feelings - which are healthy within normal limits are surpassed - appear in order to cope with negative situations become severe and prolonged, they can adversely affect lifestyle, activities, social life, and interpersonal relationships of the person. Anxiety after this line appears to create mental problems for the person [1].

Women may face many factors that can cause stress and anxiety during pregnancy, specific physical changes of pregnancy, hormonal factors especially with sudden changes in mood and childbirth, and possible additional stress factors, such as fear of being unable to give birth to a healthy child and pain during labour [2]. Beyond this, factors such as young age, low socio-economic status and education levels, sexual abuse, unwanted pregnancies, inadequate preparation for pregnancy or birth, plus depressive symptoms, and a previous history of psychiatric illness can adversely affect the mental health of pregnant women [3].

Pregnancy is the process of change and adaptation in terms of both psychological and physiological aspects. Biological and psychological differences may occur in different ways for each pregnant woman. In some women, pregnancy does not result in any psychological risk, but in others can create an emotionally vulnerable environment. Anxiety during pregnancy can cause adverse effects on the maternal obstetric status and neonatal health. The last terms of pregnancy and the painful process of labour are periods associated with increased anxiety in the mother [4].

In the present study, the authors plan to investigate whether the duration of labour is affected by anxiety emerging late at the term of pregnancy of the mother and during labour.

Materials and Methods

The present study was planned as a prospective cohort, case-controlled study in patients with 28th gestational week or more admitted to this hospital. Eighty-five women with single gestation, without cephalopelvic discrepancy in the examination, without bleeding diathesis or vaginal infection, with reagent Non Stress Test and occiput anterior presentation, were included in the study. Fifty of these pregnant women were primigravid, 35 of them were multigravid.

Before the study, all patients were informed about the study; their approvals were obtained by giving detailed information
about the forms that they would complete and the normal vaginal delivery.

First age, height, weight, gestational age, number of pregnancies and births of the patients evaluated in the outpatient clinic were identified and recorded. Then, before the normal obstetric examination, patients were requested to complete the State-Trait Anxiety Inventory developed by Spielberger in order to detect and prevent anxiety in adults and young people aged 14 or more. The degree of frequency of feelings and behaviour suggested by the questions in this inventory were expressed by patients by marking one of the options: (1) almost none, (2) sometimes (3) most of the time, and (4) all of the time. In the inventory, the anxiety levels of individuals were detected as a result of calculations made by using two different types of expression in the form of direct and reversed expressions. Once the inventory had been completed, routine obstetric examinations of the patients were performed.

Spielberger State-Trait Anxiety Inventory was applied again at the admission of the patients and during the active stage of labour. Thus patients during the period of labour were determined and recorded. Patients were included in the routine monitoring of labour and duration of labour stages was calculated.

The beginning of the first phase was accepted as the hour that the patients regularly felt pain. First stage was divided into two parts as latent stage; before three-cm dilatation and active stage; after three-cm dilatation.

The elongation disorder was considered for the nulliparous patients due to less than 1.2 cm / h dilatation, and for the multiparous patients due to less than 1.5 cm / h dilatation. The diagnosis of stand still disorder was considered for patients without progression of dilatation at the end of a two-hour period or level at the end of a one-hour period. Re-evaluation was performed on these patients and the diagnosis of fetopelvic non-compliance was excluded. When hypotonic dysfunction was detected, oxytocin support was performed in order to provide 50 mm Hg or more contractions, coming once every three to four minutes and occurring with active or regular intervals.

The amniotic membranes of all patients were opened artificially in the period of four to eight cm dilatation at the follow up period of labour; bladders were emptied, and except for the period of external fetal monitoring and active straining, the patients were allowed to be in their desired positions.

The first stage of labour was accepted as complete when cervical dilatation of ten cm and effacement became 100% and the durations were recorded. Following the completion of the first phase, the second phase was accepted as the period passing until birth, and the third phase was accepted as the period of birth and the placenta and attachments were discarded and the durations were recorded.

Continuous data were presented as mean ± standard deviation. In data analysis, the dependent and independent samples t-test, Spearman's correlation analysis, and partial correlation analysis were performed. Significance at p < 0.05 was accepted.

Results

The present research was carried out on 85 pregnant women including 50 nulliparous and 35 multiparous women. The definitive characteristics of the patients are given in Table 1.

In the comparison of multiparous and nulliparous patients, there was no statistically significant difference in terms of the state anxiety. The trait labour anxiety scores were significantly higher in multiparous patients both during the last trimester as well as labour (p < 0.05) (Table 2).

The State Anxiety Scores for labour were statistically significantly higher than the State Anxiety Scores for the third trimester before labour (p < 0.05) (Table 2).

There was no statistically significant difference between the Trait Anxiety Scores during the admission and the Trait Anxiety Scores during the labour compared with p < 0.001; Spearman's correlation analysis.

The State Anxiety Scores during the admission and the State Anxiety Scores during the labour compared with p > 0.05, Spearman's correlation analysis.

Table 1. — The definitive characteristics of the patients.

<table>
<thead>
<tr>
<th>Descriptive features</th>
<th>Nulliparous (Mean ± SD)</th>
<th>Multiparous (Mean ± SD)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>22.9 ± 3.5</td>
<td>29.1 ± 5.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>161.8 ± 5.3</td>
<td>163.4 ± 3.9</td>
<td>0.1</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>67.1 ± 8.4</td>
<td>76.4 ± 10.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BMI (kg/cm²)</td>
<td>25.7 ± 3.2</td>
<td>28.2 ± 3.6</td>
<td>0.01</td>
</tr>
<tr>
<td>Weight gaining during pregnancy (kg)</td>
<td>12.2 ± 3.9</td>
<td>13.8 ± 5.4</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Table 2. — State Anxiety Scores of the patients.

<table>
<thead>
<tr>
<th>Anxiety scores during admission</th>
<th>Nulliparous (Mean ± SD)</th>
<th>Multiparous (Mean ± SD)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>State</td>
<td>41.51 ± 42.16 ± 40.61 ± 0.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trait</td>
<td>11.01 ± 10.69 ± 11.52 ± 0.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety scores during labor</td>
<td>46.03 ± 44.32 ± 48.48 ± 0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>State</td>
<td>53.67 ± 55.02 ± 51.74 ± 0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trait</td>
<td>9.37 ± 9.35 ± 9.20 ± 0.01</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. — The duration of labor of the patients.

| Latent phase (first phase)      | 1-24 | 9.6 ± 7.20 | 1-24 | 6.18 ± 5.80 |
| Active phase                    |      |           |      |            |
| Active phase (first phase)      | 1-15 | 6.70 ± 3.40 | 2-20 | 6.3 ± 3.88 |
| Second phase                    | 0.16-3 | 0.58 ± 0.49 | 0.08-2 | 0.4 ± 0.42 |
| Third phase                     | 0.08-0.50 | 0.15 ± 0.07 | 0.08-0.50 | 0.18 ± 0.11 |

Min-Max: Minimum-Maximum; Mean ± standard deviation.
6.3 ± 3.8 hours, respectively. Percentile limits of active phase for nulliparous patients were identified as 95% and there were three patients with the duration of active phase of more than 12 hours.

Second phase of labour was detected as the average of 0.5 ± 0.47 hours between five minutes and three hours. For the nulliparous patients who had not received anesthesia, the limit of prolonged second phase was accepted as two hours and there was one patient observed with prolonged second phase. For the multiparous patients who had not received anesthesia, the limit of prolonged second phase was accepted as one hour and there were two patients observed with prolonged second phase.

The mean third phase of labour was 0.16 ± 0.09 hours and patients with prolonged third stage were not detected.

In the correlation analysis performed for all patients, a significant positive correlation between the duration of the latent phase and the State-Trait Anxiety Scores on admission and the State-Trait Anxiety Scores during labour was observed (p < 0.05) (Table 4). For nulliparous patients, a significant positive correlation between the duration of the latent phase and the State-Trait Anxiety Scores on admission and the State-Trait Anxiety Scores during labour was observed. For multiparous patients, significant positive correlation between the anxiety scores and the duration of latent phase of labour was not detected (p < 0.05) (Table 4).

When the effects of maternal BMI, maternal age, the total weight gained during pregnancy, fetal weight, and fetal head circumference that are able to change the duration of labour were controlled, statistically significant positive correlations were observed between the levels of state anxiety at third trimester and during labour, and the duration of active phase of labour in all patients and nulliparous patients (p < 0.05). In multiparous patients, statistically significant correlation was not observed p > 0.05).

After controlling the effects of the factors statistically which would be able to affect the duration of the active phase and the second phase of labour, statistically significant positive correlations were observed between the levels of state anxiety for two phases and the total duration of labour in all patients and nulliparous patients (p < 0.05). In multiparous patients, only statistically significant positive correlations were observed between the trait anxiety scores of the third trimester and the total duration of labour.

After allowing for the effect of all patients and in patients in both nulliparous periods, the total duration of labour between state anxiety levels and a statistically significant positive correlations were observed only in the third trimester of continuity score in patients with multiparous labour significant correlation was found between the total duration.

The third stage of labour is the period between immediately after the birth of the baby and the time that placenta and its annexes are expelled. In this study, patients with prolonged third stage were not detected. Active management at third stage was performed in all patients. In this study, the correlation between the state anxiety during labour and the duration of the third stage of labour was observed.
On the total duration of labour, it has been seen that the state-trait anxiety of both third trimester and during labour had an effect on the total duration of labour. It has been detected that this effect was caused by nulliparous women and it continued after controlling of the other maternal and fetal factors that could have an effect on the duration of labour. In multiparous patients, only the trait anxiety of third trimester and total duration of labour were observed as correlated.

Discussion

The effect of the mental health of pregnant patients on the pregnancy results is an important but often neglected area of research. It has been seen that with the consideration of the stress factors associated with pregnancy, the conduct of studies for anxiety during pregnancy becomes more important. A variety of mechanisms have been proposed for adverse perinatal outcomes caused by anxiety. Some patients with anxiety have negative habits such as smoking, alcohol intake, or not undergoing prenatal examinations. The direct effects of stress-dependent hormones and psychoimmunological factors are considered as other important mechanisms [5]. The level of trait anxiety determines the severity and frequency of state anxiety that the person will experience in dangerous situations in future. Accordingly, it is expected that, under pressure, individuals with high trait anxiety levels show state anxiety reactions quickly and more frequently than individuals with low trait anxiety levels [6]. In the present study, in support of these hypotheses, levels of trait anxiety during labour (trait two point) were found to be high and numerically close to each other in patients with high levels of trait anxiety in the last trimester (trait one point). The state anxiety of patients showed a significant increase during labour. In addition, it was seen that the levels of state anxiety of the patients with high levels of trait anxiety were also higher.

When the anxiety levels between nulliparous and multiparous women were analysed, the mean State Anxiety Scores for both phases were higher in nulliparous women but there were no statistically significant differences. The trait anxiety was higher in multiparous pregnant. The reason for this was considered to be advanced age and additional tensions due to previous children and life events. The mean age and the number of living children in multiparous patients were significantly higher than nulliparous patients. Similar to this data, in a study performed by Albert et al., it was observed that trait anxiety was associated with duration of marriage, number of children and maternal age [7].

In studies that have been made to determine the level of anxiety during pregnancy, it has been observed that a variety of gestational periods were included. Some authors claimed that the anxiety levels in pregnancy increased from the first trimester to the last trimester. On the other hand, in some publications, it has been reported that anxiety levels were higher in first and third trimester, but had a downward tendency in the second trimester [8]. Little et al., have not detected differences in the anxiety levels during pregnancy [9].

During labour, catecholamine-mediated maternal stress response emerges. For pain and stress, catecholamines, especially epinephrine are secreted. Stress hormones bind to the β-adrenergic receptors in the myometrial smooth muscle cells and it has been thought that this impairs the development of regular uterine contractions [10]. In a study performed by Lederman et al. with primigravid patients, the anxiety levels of the patients in labour and plasma epinephrine levels were evaluated. As a result of this, it has been detected that reduction in uterine activity and prolonged active phase of labour have been identified with the high levels of epinephrine in active phase of labour in primigravid patients [11]. In the present study, it has been observed that state-trait anxiety at the third trimester and state anxiety during labour lengthened the duration of latent phase in all patients. In nulliparous patients, there was statistically significant correlation between state anxiety for both periods and both latent and active phases of labour; the first and the second stages and the total duration of labour. In addition, every two period trait anxiety levels were significantly correlated with the total duration of labour. With multiparous patients, only the levels of state anxiety during labour were significant and positively correlated.

In some studies, the levels of maternal endogenous epinephrine were observed to be associated with pain and anxiety. In fact, in a study by Neumark et al. into the progress of labour, an increase in plasma catecholamine and cortisol levels was detected [12]. In another study, plasma catecholamine levels measured at the second stage of labour were higher than the initial levels [13]. It has been detected that administration of epidural analgesia during labour reduced the level of plasma epinephrine, provided the inactivation of sympathetic system and shortened the duration of labour by reducing pain [12, 14]. Maltau et al. have suggested that an increase in sympathetic activity causes irregular uterus contractions and epidural analgesia, by reducing sympathetic activity, may promote more regular uterine activity and cervical dilatation and shorten the duration of labour [15].

As a result of the present statistical analysis, an important correlation was observed with state anxiety of both periods of second phase of labour in nulliparous patients. In multiparous patients, it has been detected that state anxiety during labour had an effect on the second stage of labour. Some increases detected for state anxiety during labour have been thought to be the result of uncoordinated movements of the mother and an inability to provide effective straining. The relation between the second stage duration and state anxiety was more in nulliparous patients where straining had a more important role. This would appear to support our opinions.
A study performed by Grimm with 95 nulliparous and 142 multiparous patients investigated the effects of psychological tension on first and second phases of labour and delivery complications [16]. Grimm detected that the tension was not associated with the first phase of labour and delivery complications, but had an effect on the second phase of labour. It has been claimed that ineffectiveness on the first phase was surprising and the reason for reaching such a conclusion might have been that the initial time of labour was determined based on the patient’s own words. In a study by Mei et al. with 180 primigravid patients, it has been detected that, first and second stages of labour were longer in patients with high anxiety and depression scores [17].

In two different studies performed by Sosa et al. and Langer et al., it has been detected that the companionship of caregivers who gave patients special psychological support during labour, and provided information, physical and emotional support shortened the duration of labour and caused positive effects on the mothers’ breastfeeding [18, 19]. As well as these studies, Scott et al. have reported that continuous emotional and physical support during labour reduced the continuous state anxiety, shortened the duration of labour and prevented the request of birth by caesarean section [20].

In this study, as a result of all of this data and the assessments, the authors observed that the anxiety during the third trimester and labour caused elongation of all stages of labour, especially in nulliparous patients. The authors concluded that this situation may be related to the secretion of stress hormones and insufficient active straining due to patient noncompliance. They thought that the psychological support provided for patients during pregnancy and labour and application of epidural analgesia for developing anxiety due to fear of pain may positively affect the duration of labour.

Conclusion
It has been seen that the anxiety occurring during the last trimester of pregnancy and labour, and especially acute state anxiety have negative effects on the duration of the phases of labour. It has been considered that the physical care provided for patients during the last trimester and during labour and an evaluation in terms of the anxiety and provision of emotional support may cause positive outcomes for the duration of labour.

References

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A study comparing three different laser-assisted hatching techniques

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Summary
Purpose of investigation: Laser-assisted hatching (LAH) is recognized as a useful technology to improve clinical pregnancy rates and implantation rates. This study reports the differences between a new LAH method and two conventional LAH techniques. Materials and Methods: The authors studied 151 patients with repeated implantation failure, who were divided into three groups. Results: In group 1, the zona pellucida (ZP) was opened using LAH (n = 52). In group 2, laser-assisted thinning was performed to dissolve the outer layer of the ZP (n = 49). In group 3, laser-assisted thinning was performed to dissolve the inner layer of the ZP (n = 50). The clinical pregnancy rates and implantation rates among the groups were compared. The results demonstrate that there are significant differences in the clinical pregnancy rates and implantation rates between group 3 and the other two groups. Conclusion: Performing laser-assisted thinning to dissolve the inner layer of the ZP markedly increases the pregnancy rates and implantation rates of patients with repeated implantation failure.

Key words: Laser-assisted hatching; Recurrent implantation failure; Clinical pregnancy rates; Implantation rates.

Introduction
Assisted hatching (AH) has been shown to effectively increase implantation and pregnancy rates, especially in patients with advanced ages [1-5], high follicle stimulating hormone (FSH) levels [6, 7], recurrent implantation failure [8-13], or cryopreservation [14-18]. AH methods include mechanical partial zona dissection, chemical zona drilling, and laser techniques. Studies comparing these methods have reported that laser-assisted hatching (LAH) is more beneficial to the embryo than other AH techniques [19, 20] and that LAH is a safe and rapid method [21, 22].

The zona pellucida (ZP) of human embryos is bilayered; the outer layer is thick and easily dissolved, whereas the inner layer is more compact, resilient, and difficult to dissolve [23]. Physiologically, upon reaching the blastocyst stage, the human embryo hatches from the ZP and has a full communication with the endometrium. Precipitous communication between the cleaved embryo and endometrium may be disadvantageous to the embryo. Conventional ZP thinning of a day-3 embryo may not dissolve the inner layer, which is the main barrier to hatching. Advances in laser technology make it possible to remove the inner layer of the ZP. According to the ZILOS-tk manual [24] and physics, it is impossible to create a hole through the entire zona with the new ZP thinning method, which removes the inner layer of the ZP.

The objective of the present study was to evaluate the outcomes of fresh day-3 embryo transfer after AH with three types of LAH: ZP opening, conventional ZP thinning, and new ZP thinning (removing the inner layer of the ZP), in women with recurrent assisted reproductive technology (ART) treatment failures.

Materials and Methods
Study period and patients
A total of 151 LAH patients took part in the study from November 2009 to August 2010 at the Reproductive Center of the Shenzhen Police Hospital, a public hospital in Shenzhen. All patients gave a written informed consent to participate in this study, and the study design was approved by the local institutional ethics committee. All eligible patients had at least three previous implantation failures in fresh day-3 embryo transfers. Furthermore, in order to minimize the contribution of age as the risk factor for implantation failure, the patients included in the study were 37-years-old and younger. AH was explained to all of the patients who took part in the study before the embryo transfer. On the day of embryo transfer, the patients were randomly selected, beginning with the ZP opening group (group 1, 52 patients), the conventional ZP thinning group (group 2, 49 patients), and the new ZP thinning group (group 3, 50 patients). This protocol was repeated every other day throughout the study. In group 1, 40 µm defect was made in ZP.

Patient treatment
The women were treated with the gonadotropin-releasing hormone analogue triptorelin acetate from either the preceding mid-luteal phase in a long treatment protocol or the second day of the cycle in a short treatment protocol. Ovarian stimulation was carried out with human menopausal gonadotropin (hMG) or recombinant human FSH. Follicular development was monitored with serial vaginal ultrasound examinations and serum estradiol (E2) measurements. Human chorionic gonadotropin (hCG; 10000 IU) was administered intramuscularly (i.m.) when the dominant follicles reached 18 mm in diameter and at least

Revised manuscript accepted for publication February 7, 2013
two follicles were ≥ 17 mm in diameter. Oocytes were retrieved with transvaginal ultrasonographic guidance 35 h after injection of hCG. The luteal support was initiated on day 1 after oocyte retrieval with 60 mg/day of progesterone (Xianju, Taizhou, China), which was administered until the measurement of serum beta-hCG on day 14 and prolonged until 12 weeks in cases of pregnancy. In group 1, 29 patients had three cycles, 12 patients had four cycles, eight patients had five cycles, and three patients had six cycles of their in vitro fertilization (IVF) embryo transfers. In group 2, 30 patients had three cycles, 13 patients had four cycles, four patients had five cycles, one patient had six cycles, and one patient had seven cycles of their IVF embryo transfers. In group 3, 33 patients had three cycles, ten patients had four cycles, five patients had five cycles, and two patients had six cycles of their IVF embryo transfers.

In vitro fertilization procedure
After retrieval, all oocytes were incubated in 0.6 ml Quinn’s Advantage Fertilization Medium in four-well multidish with three to four oocytes per well. The oocytes were incubated in an atmosphere of six percent CO2 at 37°C. Insemination was performed by introducing 500,000 motile sperm into each well, which contained the oocytes in medium under tissue culture oil. The multidish was then incubated overnight.

Intracytoplasmic sperm injection (ICSI) procedure
After being denuded of the surrounding cumulus cells, the oocytes were incubated in a 50-mm plastic dish under tissue culture oil until the ICSI. ICSI was carried out only on oocytes that had extruded their first polar bodies.

Embryo culture and scoring
After checking for fertilization, each pronuclear stage zygote was cultured in a microdrop (30 µl) of Quinn’s Advantage Cleavage Medium containing 10% Quinn’s Advantage Serum Protein Substitute (SPS) in a 30-mm plastic dish until the third day. The day-3 embryos were assigned a numerical grade using the following scale: grade 1, fragmentation less than five percent with equally sized homogenous blastomeres; grade 2, five to 20% fragmentation with equally sized homogenous blastomeres; grade 3, 20%-50% fragmentation with unequally sized blastomeres; grade 4, over 50% fragmentation with unequally sized blastomeres. No more than three embryos in high quality (grades 1 or 2) were transferred to each patient. The remaining high-quality embryos were cryopreserved. Embryos unsuitable for cryopreservation (grades 3 or 4) were discarded.

AH procedures
AH was performed directly on the day-3 cleavage-stage embryos in the 30-mm dish. The embryos were kept in their original culture medium, and all the selected embryos were hatched using the ZILOS-tk laser (1.48-µm diode laser). To perform the procedure, the 30-mm dish was first placed on the stage of the microscope. Then under the 40 x laser-grade objective lens, the embryo was positioned so that a portion of the zona was in the path of the laser beam. The laser beam was activated using a pulse duration of 600 µs and 300 mW of power, and the laser was fired to create a hole in the zona.

In group 1, the embryos underwent laser zona ablation using several pulses, depending on the thickness of the zona pellucida. The final size of the hole made in the zona was measured to be 40 µm (Figure 1a). In the conventional ZP thinning group, multiple irradiations along the convex periphery of the ZP from outward to inward were used to thin 60%-80% of the ZP, and create a defect involving approximately 25% of the ZP circumference (Figure 1b). In group 3, the laser was used to remove the inner layer of the ZP. This procedure was performed from inward to outward, and approximately 40% of ZP thickness was ablated, creating a defect that involved approximately one sixth to one fifth of the ZP circumference (Figure 1c).

Statistical analysis
The Mann-Whitney test, unpaired Student’s t test, and the Fisher’s exact test were used as appropriate to determine the statistical differences among the groups. A p value of < 0.05 was considered significant.

Results
Table 1 compares the data of the three study groups. There were no significant differences in the number of cycle attempts, zona thickness, mean age of the patients, duration of infertility, and the number of embryos transferred among the three groups. The implantation rate (IR) in group 3 was significantly higher than in group 1 (group 3 vs group 1: 17.6% vs 10.4%, p = 0.022) and group 2 (group 3 vs group 2: 17.6% vs 11.2%, p = 0.026). There were significant differences in the clinical pregnancy rates (PR) among the groups (group 3 vs group 1: 30% vs 21.2%, p = 0.02; group 3 vs group 2: 30% vs 24.5%, p = 0.027). Significant differences were found in the multiple gestation rate (group 3 vs group 1: 20% vs 11.5%, p = 0.023; group 3 vs group 2: 20% vs 12.2%, p = 0.03).

Discussion
The possible reasons for repeated implantation failure in infertile patients include zona hardening, asynchrony between the embryo and the endometrial implantation window after ovarian stimulation, and deficiency in the cellular energy required for hatching [25]. Retrospective studies have suggested that AH is beneficial for patients with repeated previous implantation failures [11-13]. LAH is considered less traumatic than chemical- or mechanical-assisted hatching [26-28]. A previous study

<table>
<thead>
<tr>
<th>Table 1. — Pathologic findings.</th>
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<tbody>
<tr>
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<tr>
<td>Patient age (years)</td>
</tr>
<tr>
<td>No. of embryo transfer cycles</td>
</tr>
<tr>
<td>No. of previous attempts</td>
</tr>
<tr>
<td>Zona thickness (µm)</td>
</tr>
<tr>
<td>Duration of infertility (years)</td>
</tr>
<tr>
<td>No. of retrieved oocytes</td>
</tr>
<tr>
<td>No. of two pronucleate (2PN)</td>
</tr>
<tr>
<td>No. of embryos transferred</td>
</tr>
<tr>
<td>No. of blastomeres</td>
</tr>
<tr>
<td>in ET embryos</td>
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<tr>
<td>Implantation rate</td>
</tr>
<tr>
<td>Multiple gestation rate</td>
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<tr>
<td>a(3-1) p = 0.023</td>
</tr>
<tr>
<td>b(3-1) vs b(3-2) p = 0.026</td>
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<tr>
<td>c(3-1) vs c(3-2) p = 0.027</td>
</tr>
<tr>
<td>a(3-2) vs b(3-2) p = 0.03</td>
</tr>
</tbody>
</table>

Pathologic findings.

Group 1 Group 2 Group 3
No. of embryos transferred 2.1 ± 0.5 2.2 ± 0.2 2.4 ± 0.3
No. of blastomeres in ET embryos 7.5 ± 0.6 7.7 ± 0.5 7.6 ± 0.5
Implantation rate 10.4% 11.2% 17.6%
Multiple gestation rate 11.5% 12.2% 20%

a(3-1) p = 0.022; a(3-2) vs a(3-1) p = 0.026; b(3-1) vs b(3-2) p = 0.027; c(3-1) vs c(3-2) p = 0.03.

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A study comparing three different laser-assisted hatching techniques

showed that AH does not increase the abortion rate or the number of biochemical pregnancies [29]. Furthermore, no increases in the major congenital malformation rate or the rate of chromosomal aberrations in children born after LAH [30, 31], confirmed the safety of this technique. Moreover, LAH is a rapid and convenient technique that can be completed in minutes.

Studies have also reported disadvantages of ZP opening and thinning. One study showed that ZP thinning alone was not effective in promoting implantation, due to the intact, hard, inner layer of the ZP [23]. ZP opening may increase the risk of bacterial infection of the embryo, as well as other harmful interactions with the environment. Moreover, the blastomeres could be more likely to separate during the cleavage of the embryo. Some researchers have reported that ZP opening could be more effective in AH of embryos than the ZP thinning [32, 33]. However, there is no consensus regarding the possible advantage of breaching or thinning the ZP in order to increase the IR and PR.

In light of the current debate and previous inconsistent study results, the new ZP thinning technology might provide the most effective way to aid embryo hatching from the ZP. This new method dissolves the inner layer of the ZP, which is regarded as the main barrier of hatching. Meanwhile, the outer layer is easily dissolved, and it still surrounds the blastomeres and protects the embryo from harmful interactions with the environment. The results of the present study demonstrate this point. The IR and PR of group 3 were significant higher than those measured in groups 1 and 2. Since the patients selected were randomized, patient age, ZP thickness, duration of infertility, embryo quality, and other factors did not affect the final results.

In the ZP opening group, the present IR results were similar to those in a previous study by Valojerdi et al. [34]; however, the PR was lower (21.2% vs 27.1%). One possible reason for this difference might be the difference in the target patients. In the present study, the patients included in the study had at least three previous implantation failures, and Valojerdi et al. defined recurrent implantation failures as ≥ two previous cycles. In the conventional ZP thinning group, the present results were similar to previous findings [12].

For a small percentage (6.4%) of embryos, the entire internal surface is close to the blastomeres with no gap between the internal surface and the blastomeres. In these cases, the new ZP thinning method may cause more thermal damage to the blastomeres than other LAH techniques, since the dissolving points are very close to the blastomeres. A further long-term study will be needed to determine whether this damage is serious. The authors found no similar study reported by other researchers.

It should be noted that this study is limited by its small sample size (power = 0.6). Hence, it is very possible that biologically significant differences would not have emerged as statistically significant due to inadequate power. Despite this limitation, the authors obtained good results with this new LAH method in group 3. A follow-up study with more subjects should be pursued to confirm the present pattern of results.

In conclusion, the authors report the successful use of a new LAH technique for ART treatment. The data indicated that the new ZP thinning technology is the most effective method to benefit patients with repeated implantation failures (≥ three previous implantation failures).

References


Figure 1. — Photomicrograph of a day-3 human embryo after zona opening with the laser. a) The opening in the zona pellucida is indicated by an arrow (magnification: × 400). b) The thinned area of the outer layer of the zona pellucida is indicated by an arrow (magnification: × 400). c) The thinned area of the inner layer of the zona pellucida is indicated by an arrow (magnification: × 400).


Clinical analysis of 65 cases of laparoscopic treatments on tubal infertility caused by tubal distortion

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2Department of Gynecology and Obstetrics, Zhengzhou Maternal and Child health hospital, Zhengzhou (China)

Summary
Objective: This study aims to investigate the clinical value of laparoscopic treatment on tubal infertility caused by tubal distortion. Materials and Methods: A total of 65 cases of patients with tubal infertility were divided into three groups based on tubal distortion degree, i.e., 21 cases had a minimum angle of tubal distortion <45° (A group), 39 cases had a distortion angle between 45° and 90° (B group), and five cases had a distortion angle between 90° and 145° (C group). The pregnancy outcome and the impact of tubal distortion degree on pregnancy outcome were analyzed 6 to 24 months after operation. Results: The total pregnancy rate of these 256 cases were 43.75% with an intrauterine pregnancy rate of 40.23% and an ectopic pregnancy rate of 3.52%. In the simple distortion tubal infertility cases, the total pregnancy rate was 44.62%. In Group A, five cases became pregnant after operation (33.33%); in Group B, 19 cases (48.72%); and in Group C, three cases (60%). The differences in pregnancy rate between Groups A and B and Groups A and C were statistically significant (p < 0.05), whereas that between Groups B and C was not (p > 0.05). Conclusion: Tubal plastic surgery via laparoscopy is an effective way to treat infertility caused by tubal distortion by restoring the normal shape of oviducts, especially in cases when the minimum angle of tubal distortion is greater than 45°.

Key words: Laparoscopy; Tubal distortion; Infertility.

Introduction
Infertility is a common condition that affects 15% of couples trying to conceive a baby [1]. The evaluation of infertility includes an assessment of both female and male partners to determine the factors that contribute to the difficulty in conception. Female factors account for approximately 40% of infertility occurrences [2].

Tubal infertility, which has shown an increasing trend, is the leading cause of female infertility [3]. The tubal distortion caused by chronic tubal inflammation or abnormal development of the oviduct changes the normal tubal function, reduces its peristalsis, and affects ovum movement by carrying the ovum to the ampullary portion, thereby ultimately leading to infertility.

This paper aims to study the diagnosis and treatment of tubal distortion. The study included 65 cases of infertility caused by tubal distortion that have undergone laparoscopic operation. This study aims to assess the clinical value of laparoscopic operation in the treatment of tubal infertility and to provide guidance to the treatment of infertility caused by fallopian tube distortion by analyzing the clinical outcomes of 265 cases.

Materials and Methods
General data
From February 2008 to October 2010 in the First Affiliated Hospital of Zhengzhou University, 256 females suffering from tubal infertility were treated by laparoscopic fallopian tube cosmetic surgery. Their sexual life was normal, and immune factors and male infertility factors, such as spermatogenic obstacles and insemination disorder, were eliminated. Moreover, patients associated with ovulation disorders, uterine factors, endometriosis, or pelvic tuberculosis were also excluded. Before the operation, hysterosalpingography was conducted, which suggests tubal abnormality. Other routine laboratory tests were normal, and no operative contraindications were observed. Based on the intraoperative situation, the authors ruled out cases with hydrosalpinx, pelvic adhesions, and adopted cases in which the fallopian tube was soft and whose fimbriated extremity and Douglas lacuna were normal in the follow-up group. The authors were able to determine if pregnancy occurred by telephone follow-ups over the next six to 24 months. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University. Written informed consent was also obtained from all participants.

Surgical technique
Three to seven days after menstruation, the patients underwent laparoscopic fallopian tube cosmetic surgeries under general anesthesia operated by the same doctor. The situation of the Fallopian tubes was assessed using optical lens and surgery was then conducted following intraoperative findings. For simple distorted tubal cases, the fallopian tube was pulled to return to its normal form. Images were obtained using a digital camera, and the fallopian tubes twist angles were measured. The minimum twist angle of the fallopian tubes of each patient was recorded. These 65 patients were divided into three groups based on the measured minimum angle. A total of 21 cases had a minimum angle of tubal distortion that was smaller than 45° (A...
group), 39 cases had a minimum angle between 45° and 90° (B group), and five cases had a minimum angle between 90° and 145° (C group). The twist serosa was initially separated with a monopolar electrocautery hook (Figure 1), and hysteroscopy was then performed to detect the uterine cavity. Ultimately, hydrotubation was conducted, and the meilan liquid flowed out from the fimbria extremity of the operated patients. The pelvic area was thoroughly rinsed after surgery, and drugs (sodium hyaluronate injection) were applied to the wound to prevent adhesion. Antibiotics were taken for three days after surgery. Sexual intercourse and tub baths were contraindicated for one month and contraception was also recommended for one month prior to pregnancy attempts.

### Table 1. — Findings of postoperative pregnancy.

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>No. of intrauterine pregnancies</th>
<th>No. of ectopic pregnancies</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ~ 6</td>
<td>20</td>
<td>1</td>
<td>21</td>
</tr>
<tr>
<td>7 ~ 12</td>
<td>5</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>13 ~ 24</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td>3</td>
<td>29</td>
</tr>
</tbody>
</table>

### Table 2. — Relevance of the minimum angle of tubal distortion and postoperative pregnancy rate.

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Pregnancy rate No. (%)</th>
<th>Intrauterine pregnancy rate No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>21</td>
<td>7 (33.33%)</td>
<td>5 (23.81%)</td>
</tr>
<tr>
<td>B</td>
<td>39</td>
<td>19 (48.72%)</td>
<td>18 (48.72%)</td>
</tr>
<tr>
<td>C</td>
<td>5</td>
<td>3 (60.00%)</td>
<td>3 (60.00%)</td>
</tr>
<tr>
<td>Total</td>
<td>65</td>
<td>29 (44.62%)</td>
<td>26 (40.00%)</td>
</tr>
</tbody>
</table>

### Statistical analysis

The data was analyzed with the SPSS13.0 software, and the Chi-square ($\chi^2$) significance test was conducted. When $p < 0.05$, the difference indicated statistical significance.

### Results

**Postoperative Pregnancy**

A total of 112 (43.75%) patients became pregnant, which comprised 103 (40.23%) intrauterine pregnancies and nine (3.52%) ectopic pregnancies. This result was obtained via telephone follow-ups six to 24 months after surgery. Among them, 65 patients suffered from simple tubal distortion, 29 from postoperative pregnancies, and 27 from intrauterine pregnancies. Postoperative pregnancy within six months was observed in 20 cases, which was 68.97% of the total pregnant patients (Table 1).

**Relevance analysis between the angle of tubal distortion and pregnancy rate**

Relevance analysis results between the angle of tubal distortion and pregnancy rate are as follows (Table 2): seven cases (33.33%) were pregnant and whose minimum angle of tubal distortion was smaller than 45° (Group A); 19 (48.72%) were those whose distorted angle was between 45° and 90° (Group B); three (60%) were those whose angle of tubal distortion was between 90° and 145° (Group C). The pregnancy rate differences among Groups A and B and Groups A and C were statistically significant ($p < 0.05$), whereas that between Groups B and C was not ($p > 0.05$).

### Discussion

According to statistics, among the various reasons for infertility, female factors accounted for approximately 40% [4], of which the oviduct is the primary factor. The obstruction of the fallopian tube accounts for 30%-40% of
tubal infertility [5]. Subtle variations may cause infertility [6]. The fallopian tube is a pair of elongated muscular tubes, and the contraction of the muscles helps move the ovum and transport the oosperm. The transport of the ovum in the fallopian tube relies on the contraction of the smooth muscles, which removes the fimbriated extremity to the ovary during ovulation. The subatmospheric pressure caused by the contraction of the smooth muscles and the wiggle of the infundibulum portion induct the ovum into the fallopian tube. After the ovum enters the fallopian tube, the normal transportation of the ovum relies on the contraction of the tubal muscle. In addition, tubal peristalsis can promote sperm movement from the uterine cornu to the ampulla portion and the oosperm to the uterus cavity. Hence, tubal peristalsis contributes to fertilization and transportation of the oosperm. Chronic tubal inflammation, the sequelae of pelvic inflammation, and tubal growth abnormalities can cause the contraction of the tubal serosa and disorder of the fallopian tube [7]. In serious cases, the obstruction of the tube not only depressed the peristalsis of the tubes but also affected fallopian tubal fluid flow, which ultimately resulted in infertility [8]. The inflammation can also cause the tissues to release prostaglandins, leukocyte chemotactic factor, and other inflammatory mediators, which affect fertilization, embryo implantation, and cleavage. Thus, embryonic development is hindered [9]. Meanwhile, an inflammation of approximately 30% caused by microbial factors is subclinical asymptomatic [10].

Laparoscopic operation is not only helpful in diagnosing the etiology of infertility, but also creates appropriate conditions for the release of the twisted oviduct [11]. Laparoscopy has an amplification effect; thus, the exposed vision is clearer and more open, which increase the accuracy of the operation [12]. However, a non-significant reduction in pregnancy rate occurred with increasing magnification [13]. Compared with traditional operation, laparoscopic operation is performed in confined environments. Thus, the abdominal tissue is not exposed to air. This condition reduces tissue drying and contamination, thereby reducing interference to other organs and tissues in the abdomen. Pelvic electrocoagulation completes the incision and hemostasis, which reduces the likelihood of foreign bodies to enter the surgical site [14, 15]. Furthermore, the use of saline to thoroughly rinse the pelvic and abdominal cavity, either intraoperatively and postoperatively, can improve the abdominopelvic microenvironment and reduce the incidence of adhesions after the operation. Thus, suffering is largely relieved and patients can regain their normal functions in the early postoperative days. Moreover, their gastrointestinal functions also recover quickly. This practice can also reduce the adhesion after operation. The use of laparoscopic fallopian tube cosmetic surgery can release the twisted serosa, recover its normal form and peristalsis function, guarantee the transportation of the ovum and the oosperm, and ultimately improve pregnancy rate. However, several data indicate a non-significant difference in pregnancy rates between open and laparoscopic techniques for lesser degrees of tubal damage [16], which must be further investigated. Based on follow-up results, in the first six postoperative months, the pregnancy rate after operation was highest. After six months, pregnancy rates increased with the passing of time, but the total constituent ratio declined. Therefore, patients should attempt pregnancy as early as possible after one month of contraception. The data shows that when the minimum angles of tubal distortion are < 45°, 45° to 90°, and 90° to 145°, the intrauterine pregnancy rates are 23.81%, 48.72%, and 60.00%, respectively. Pregnancy rates after laparoscopic treatment are different in relation to tubal status [17]. Thus, when the minimum angle is less than 90°, the fallopian tube distortion degree is lower, and the pregnancy rate after operation is higher. However, when the angle is over 90°, the postoperative pregnancy rate does not significantly increase. These results are in agreement with those of Maranas’ study on tubo-peritoneal infertility [18].

For infertilities caused by fallopian tube distortion, especially patients whose minimum angle of the twisted tube is larger than 45°, satisfactory results were always obtained when laparoscopic operation was performed [19]. In addition, compared with the assisted reproductive technology, laparoscopic operation is simple, convenient, and inexpensive. Studies have considered the use of laparoscopy as an alternative to IVF [18]. Moreover, natural pregnancy after operation can reduce the psychological burden of patients and their families, which indicates its significant clinical value.

References


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Introduction

Minimally invasive surgery, like modern laparoscopic surgery, is commonly used throughout the world because it is more advantageous than open procedures. The incidence of major and minor complications from laparoscopic procedures ranges from 0.1%-10% [1-5]. The rapid increase in the number of procedures being performed, the introduction of new equipment, and variability in the training of surgeons all contribute to the complication rate. It is well known that there is a strong correlation between the complication rate and the surgeon’s level of experience. The more experience a surgeon has, the lower the complication rate.

The aim of this study was to describe the prevalence and types of gynecological laparoscopic complications based on the 441 diagnostic and operative laparoscopies that were performed.

Materials and Methods

Medical records of patients undergoing laparoscopies were reviewed in a retrospective study between the dates of October 1, 2010 and February 29, 2012. The setting was a tertiary regional teaching hospital with 606 beds. The laparoscopic procedures were divided into the following: minor procedures (sterilization, minimal adhesiolysis, and minimal endometriosis), major procedures (drainage of abscesses, uterine and colposuspension, ectopic pregnancies, and severe endometriosis) and advanced laparoscopic surgery (hysterectomy, myomectomy, tubal reanastomosis, and pelvic/para-aortic lymphadenectomies). All of these procedures were usually performed by the same senior resident/resident surgical team.

Operative techniques

Patients were placed in the lithotomy position and underwent general anesthesia. A manipulator was placed into the uterine cavity when appropriate and necessary and a urinary catheter was routinely inserted. Direct entry technique was used in all procedures. The video recorder began to record prior to trocar placement for all laparoscopic procedures. If the patient had a history of prior abdominal surgery, a ten-mm trocar was placed in the left upper quadrant or just below the epigastric region after orogastric tube placement was performed. Intraperitoneal insufflation was performed with an intraabdominal pressure of < 15 mmHg. Two additional five-mm satellite trocars were placed in each ilioinguinal area, and if necessary a third satellite trocar was placed in the left upper quadrant. Hemostasis was established with both monopolar/bipolar cautery, clips or sutures. Intraabdominal suturing was the modality of choice for hemostasis in the area of the vaginal cuff during a hysterectomy, for ovarian detorsion sutures or myomectomies. The duration of hospital stay was determined by the type of procedure and the patient’s rate of recovery.

Chi Square testing was used to determine the relationship between nominal variables and gynecological laparoscopic complications; p < 0.05 was considered statistically significant.

Results

A total of 441 gynecologic laparoscopic procedures were enrolled in the study. The median age was 34 years (range, 14-71) and Body mass index (BMI) 26 kg/m² (range, 17-40). The procedures included 74 (16.8%) diagnostic and 367 (83.2%) operative laparoscopies. The overall complication rate was 7.7% (34 cases). Conversion to laparotomy occurred in 16 cases (3.6%). Conclusions: The complication rate was found to be slightly higher than the rates quoted in the literature. This rate of 7.7% is still an acceptable one.
tract injuries 1.6% (seven cases), epigastric vessel injury 1.1% (five cases), postoperative infection 1.1% (five cases), uterine rupture 0.9% (four cases), intraabdominal hemorrhage 0.7% (three cases), subcutaneous emphysema 0.5% (two cases), and postoperative hypoxia 0.2% (one case). The laparoscopic complications occurred in four of the diagnostic cases (0.9%) and 30 (6.8%) of the major/advanced cases.

When reviewing the relationship between the complication rate and type of operation, complications associated with hysterectomy were the most common (eight out of 41 cases, 19.5%), followed by ovarian cystectomies (11 out of 134 cases, 8.2%), and adhesiolysis (three out of 54 cases, 5.6%).

Conversion to laparotomy occurred in 16 out of 441 cases, 3.6% (Figure 3). The most common reason for conversion to laparotomy was dense adhesions (seven out of 16 cases, 43.8%) and uncontrolled intraabdominal hemorrhage (six out of 16 cases, 37.5%).

Discussion

Despite advanced technology and experience, laparoscopic complications remain a major cause of morbidity. The complication rate is directly proportional to the complexities of the surgical procedures and the surgeon’s experience level [6]. According to the present 1.5 year data, the complication rate for gynecological laparoscopies performed in this regional teaching hospital in southern Turkey was comparable to that reported in the literature. The present authors found a complication rate of 7.7%, with no deaths. This rate is slightly higher than that quoted in the literature. However, it is still associated with a respectable mortality rate.

Intestinal injuries were the most common major complications in this series. This incidence was reported between 0.06% to 0.65%. In other large studies, bowel injuries accounted for approximately 20% of all complications and almost half of all major complications by laparoscopy [7-9]. In this study, intestinal complications were seen in seven cases, 1.6% of the time. Two of these complications were repaired by laparotomy and four of them during laparoscopic surgery. On the other hand, a bowel injury was noticed two days after surgery and in this patient, a colostomy was performed.

The reported incidence of bladder and ureteral complications varies from 0.03% to 0.13% in all gynecologic laparoscopies [7-9]. Higher rates of urologic injuries are seen...
during complex operative procedures with an incidence ranging from 0.2% to 1.6%. Bladder injuries are two to three times more common than ureteral injuries [7,10]. In the authors’ experience, there were four bladder injuries and three ureteral injuries. All of the bladder injuries were repaired laparoscopically and one ureteral injury was converted to laparotomy for repair. All others were repaired laparoscopically with a double J catheter.

The inferior epigastric vessels are the most commonly injured vessels often injured at the time of lateral trocar placement. These vessels should be identified laparoscopically and their course should be observed from the inguinal canal up along the anterior abdominal wall [11]. In the authors’ experience, there was one deep epigastric and four inferior epigastric vessels injury. Two balloon tamponade is performed by inflation of a Foley catheter inside the trochar site. After two hours, the balloon is deflated and hemostasis is observed. In three patients with vascular injury, subcutaneous emphysema occurred in five patients and all patients recovered with antibiotic treatment only.

The most dangerous hemorrhagic complications of entry are from injury to the great vessels, they occurred with a reported incidence ranging from 0.01% to 0.64% [12]. The trauma most often occurs secondary to insertion of an insufflation needle, but catastrophic results may result from the tip of a sharp trochar inserted with closed entry technique. In this study, there was no major vascular injury. Three laparoscopic hysterectomies had to be converted to laparotomies secondary to uncontrolled intraabdominal hemorrhage.

Subcutaneous emphysema most commonly resulted from preperitoneal placement of an insufflation needle or trochar. Subcutaneous emphysema is identified when a patient is found to have crepitus under the skin. Subcutaneous emphysema will usually spontaneously regress within two days [2]. In the authors’ experience, subcutaneous emphysema occurred in two patients and patients recovered after one day.

Among the potential complications of general anesthesia are hypoventilation, esophageal intubation, gastrointestinal reflux, bronchospasm, hypotension, narcotic overdose, cardiac arrhythmias, and cardiac arrest. The head down (Trendelenburg’s) position, in combination with the increased intraperitoneal pressure provided by pneumoperitoneum increase the incidence of complications related to general anesthesia [3]. In this study there was a postoperative hypoxia and this patient awoke with no problems.

In a review of the literature, the overall rate of conversion to laparotomy was 2.1%. The two most common reasons for conversion to laparotomy were major vascular and intestinal injuries [13, 14]. In the authors’ experience, conversion to laparotomy rate was 3.6% and most common reasons were dense adhesions and uncontrolled intraabdominal hemorrhage.

Conclusions

The popularity of minimally invasive surgery is increasing as the amount of laparoscopic procedures being performed daily is increasing. During the 1.5 years of this study, the complexity of procedures being performed also increased. The evaluation of the incidence and the type of complications in this series should be beneficial for developing proper skills as laparoscopic surgeons for future procedures performed.

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Age of menarche as a risk factor for gynecological cancer in Iranian women and review of the literature

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Summary

Background: This study analyzed the age of menarche in different regions of Iran with a review of previous studies and examined the changes of menarche age over the past years. Materials and Methods: A descriptive and cross-sectional study which was conducted in 11 different provinces of Iran with a sample size of 26,831. The year of birth and age of menarche in the population obtained through health records which were available in the health centers collected and also questioning the subjects under investigation. Results: The highest average age of 14.6 years obtained from Kermanshah province and the lowest was from Kerman with 12.98 years. The lowest average was observed with age group under 30 (13.22) and the highest age of menarche (13.53) belonged to the 30 to 40 year age group. The average age of menarche in this study was 13.24 years. Discussion: A declining trend of about two to four months for each ten years has been observed in girls born in 1920s to 1940s and then an upward trend of about nine months for ten years in subjects born in 1950s and 1960s. The stressful condition of war and poor economic and social conditions of Iranian people can justify this upward leap. However in women under 30 years of age, the menarche age showed a rapid declining trend to 13.22 years. Conclusion: Obtaining accurate information and knowing all the factors affecting this issue can be very useful in planning the public health in women and health educational programs.

Key words: Age of menarche; Risk factors; Gynecological cancer.

Introduction

Menarche is an important phenomenon of puberty which represents the successful development of this event and is the beginning of the ability to reproduce. Puberty is a transition period from childhood to the teenage girls that is associated with the developmental process. Menstrual bleeding is a very first sign of the onset of puberty [1].

This is a research topic in many academic centers around the world since attention to the evolution of puberty and menstruation is a very important point in the primary care of adolescent girls and mothers and is also important in terms of the economic and social future.

The importance of age of menarche has existed for years before and its first scientific record has been found about 150 years ago [2].

Pubertal timing mechanism is not yet fully understood and to predict the pubertal age all cases that can have an impact on this process will have to be considered [3]. These can be the mechanisms of physiological, genetic, behavioural, and environmental factors that can each have an impact on pubertal process. Since the process of increasing and decreasing age of menarche can have serious reproductive and health outcomes for women, extensive studies on this issue have been conducted in many countries [4-12]. However, in Iran, a comprehensive study to determine the age of menarche has not yet been done. Most of the available studies investigated the age of menarche in a particular area with evaluation of the effect of the other factors on menarche age.

This study analyzed the age of menarche in different regions of Iran with a review of previous studies and examined the changes of menarche age over the past years.

Materials and Methods

This is a descriptive and cross-sectional study which was conducted in 11 different provinces of Iran with a sample size of 26,831. Collected information included the years of birth and the age of menarche in the population obtained through health records which were available in the health centers and also questioning the subjects under investigation. All these information were in reference with full review of other studies regarding the age of menarche in Iran through searching articles in all the databases of Iranian such as SID web site with searching keywords of age of menarche, menstruation, and puberty. In this initial search, 16 articles in Persian were obtained. The full text of all information and articles obtained were analyzed using statistical software SPSS, version 15.

Results

In this study, the authors evaluated 26,831 women born from 1984 to 2001 that were included from eleven different Iranian provinces. The average age of menarche in this study was 13.24 years. The age of menarche according to various Iranian provinces is shown in Table 1.
The highest average age of 14.6 years was obtained from Kermanshah province and the lowest was from Kerman with 12.98. Table 2 shows the average age of menarche in different age groups with ten-year separation. The lowest average was observed with age group under 30 (13.22) and the highest age of menarche (13.53) belonged to the 30 to 40 year age group.

Other information regarding the age of menarche according to geographic area in other Iranian and international articles using data from previous studies is shown in Table 3. The authors compared their result and discovered the following: the highest average age of 14.6 years was obtained from Kermanshah province and the lowest was from Kerman with 12.98 years. The lowest average was observed with age group under 30 (13.22) and the highest age of menarche (13.53) belonged to the 30 to 40 year age group. The average age of menarche in this study was 13.24 years. A declining trend of about two to four months for each ten years has been observed in subjects born in 1920s to 1940s and then an upward trend of about nine months for ten years in subjects born in 1950s and 1960s. The stressful condition of war and poor economic and social conditions of Iranian people can justify this upward leap. However in the present study, women under 30 years of age showed a rapid declining trend of menarche age to 13.22 years.

Discussion

Menarche is the first menstrual bleeding in adolescent girls and has a major role in psycho-social welfare as well as future health of women [1-4]. This study analyzed the age of menarche in different parts of Iran with a review of past studies and an evaluation of changes which has been made over the years. The average age of menarche in this study was 13.24 years. A declining trend of about two to four months for each ten years has been observed in subjects born in 1920s to 1940s and then an upward trend of about nine months for ten years in subjects born in 1950s and 1960s. The stressful condition of war and poor economic and social conditions of Iranian people can justify this upward leap. However in the present study, women under 30 years of age showed a rapid declining trend of menarche age to 13.22 years.

The first recorded age of menarche has been reported 150 years ago in mid 19th century in which they found that the age of menarche in girls in that decade was 16-17 years [3-10]. However in recent decades, many studies worldwide have shown that age of menarche in different countries has declined [10]. Studies where age of menarche has been determined in 67 countries, showed that in the 1960s and 1990s, the age of menarche has reached approximately 13.53 years. In other words, age of menarche has dropped three to four months per decade. Studies in other countries as in the USA and Canada also confirmed this finding [10-13]. An American study showed that the age of menarche reached 12.75 years in 1960s and 12.3 years in 2000 [13].

In India, age of menarche has declined about three to four months per decade and shows a more rapid reduction...
in comparison to the countries in North America and Europe. This could be due to improved diet and growing trend in India’s economic and social conditions in recent years [13-14].

The study conducted in Italy in 2010 showed that the age of menarche in Italian girls in the past decade has been established to be 12.46 years. This was contrary to studies in other countries that still show a decreasing trend. Other factors that were examined in this Italian study were overcrowded families and high maternal age at menarche which increased the age of menarche and having a high body mass index and living with parents which decreased the age of menarche. This study also showed that the age of menarche in girls was about a quarter below the age of menarche in their mothers [14]. Improved economic and social conditions and better nutrition causes increased weight and height during childhood which itself created a downward trend of menarche age from 16 to 13 years throughout the world. The rate of this reduction differs according to country [15].

Early sexual activity and other social and psychological problems are other complications of early menarche age. Based on studies, one of the main causes of early menarche in people with no certain diseases is obesity [16-18]. Children with early puberty, due to the rapid closure of the epiphysial connections in the bones are at risk of decreased height in adulthood [19]. Given the fact that girls achieve their maximum height before the age of menarche and after that the potential for height growth is limited, it is concluded that high age of menarche could have a positive effect on average height.

The effect of maternal education on age of menarche in girls in a Dutch study showed that mothers with higher education level, have girls with lower age of menarche [17]. However, the opposite was seen in a Tehranian study [5]: a reverse relationship was found between the educational level of mothers and the age of menarche in girls.

In another review, it was observed that weight loss delayed the age of menarche by about 15 weeks while increased weight brought the age of menarche forward by 13 to 19 weeks [20].

In a Canadian study it was shown that among all social and economic indicators, only income had significant effect on age of menarche. The result of this study was unlike previous studies [10]. This study demonstrated that high-income is associated with lower age of menarche and vice-versa. This could be explained by the fact that better economic and social conditions and improved nutritional status cause lower age of menarche. Other explanations are that better socio-economic status was associated with a high level of stress that causes the lower age of menarche or associated obesity that could also lower the age of menarche.

Life without parents is strongly associated with early age of menarche. This result was obtained in European countries. In Iran, due to the strong family foundation and not separating the children from the family until legal age has not yet been investigated. Bogaert et al. showed that absence of father in the family can create the possibility of 62.2 that age of menarche in girls occurs under 12 years [21]. Hypothesis raised that psychological and physical stress can cause metabolic changes in the body of teenagers which these changes can be seen in the menstrual cycle and continues beyond that [22]. Breast cancer [23], metabolic syndrome and osteoporosis [15], metabolic diseases [24], Alzheimer’s [15], and overweight and obesity [25-26] increasing incidence of cardiovascular disease [27], community health problems because of early sexual activity, eating disorders, and poor performance are all examples of problems leading to lower age of menarche.

Improved economic and social conditions and better nutrition lead to increased weight and height during childhood which creates a downward trend of age of menarche from 16 to 13 years in countries throughout the world [15-18]. In the present study, the downward trend in the age of menarche has also been shown in Iran, except during the decades in which Iran was at war and eventually has been suggested that in Iran like in other advanced countries, the age of menarche in adolescents aged between 10 to 17 years [3-8, 19]. It is obvious that having accurate information and knowing all the factors affecting this issue can be very useful in planning public health in women and health educational programs which ultimately affect the health of the entire community [20-26]. In executive educational and health programs, the information should be given to the mothers and adolescents at the same time as it can be much more useful and more practical [26-29].

The American College of Obstetrics and Gynecology recommends that the first visit of a specialist should be for evaluation, screening, and preventive services and to provide a health guide for people aged 13-16 years [30]. This medical visit could be a training manual for teenage girls and their mothers regarding the physical development of adolescents based on maturity parameters and normal menarche indicators. Perhaps if this process is executed in the secondary schools during enrollment, parents would be more persistent and would become a widespread practice in the country [16-19].

**Conclusion**

Obtaining accurate information and knowing all the factors affecting menarche can be very useful in planning public health in women and health educational programs which would ultimately affect the health of the entire community. In executive educational and health programs, the information should be given to the mothers and adolescents at the same time as it can be much more useful and more practical.
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Epidemiological investigation of physique situation for birth high-risk children aged 9-15 years in Chengdu, Southwest China

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Summary

Background: As the intrauterine environment can effect children’s growth and development, this study aimed to explore the relationship between birth high-risk and physique situation of 9 to 15-year-old children by cross-sectional investigation, and to provide clues for the monitoring, prevention, and treatment of growth deviation in children. Materials and Methods: This study recruited 7,194 students aged 9 to 15 years in primary and junior schools. Their parents were asked to complete the birth situation questionnaire. Measurements included height, weight, and body mass index (BMI). Birth high-risk infant was defined according to the gestational age and birth weight. Growth deviation was classified as underweight, short stature, overweight, and obesity. Results: The prevalence of all kinds of growth deviations in preterm, full-term, and post-term birth groups were similar, the same as the physique situation at school age among both sexes. The incidence of small for gestational age (SGA) was 6.23%, when at school age, part of SGA had catch-up growth. However, the prevalence of underweight and short stature for SGA was highest in three groups. The weight and height at school age in SGA group was less than that in appropriate for gestational age (AGA) and large for gestational age (LGA) groups. The prevalence of overweight and obesity for LGA and macrosomia were highest in three groups. At school age, the weight in macrosomia and LGA groups was higher than that in the other groups. Conclusions: Longitudinal height and weight development and growth of children with birth high-risk are different from normal children. In order to improve healthy situation, more attention should be paid to height and weight development of those children with birth high-risk at school age, even in pre-school age. Prevention may already begin during pregnancy.

Key words: Birth high-risk; Puberty; Overweight; Obesity; Short stature.

Introduction

With the improvement of socio-economy and medical technology in developing countries, the percent of live offspring at birth with high risk became high, such as preterm, small for gestational age (SGA), large for gestational age (LGA), low birth weight, macrosomia, etc. It is estimated that depending on geographical region, between eight and 26 percent of all infants born worldwide are low birth weight [1]. The prevalence of SGA is about 7.50% ~13.4% in the general population; furthermore, it has also witnessed an increasing trend of macrosomia. Studies reported that macrosomia increased from five to eight percent in several urban areas in China. With the increase of high risk infants, this will bring great challenges to children's health.

Baker et al. supposed the environment of intrauterine and postnatal growth during critical periods of human development may have long-term implications for adult health [2-4]. It has been hypothesized that under-nutrition or other unhealthy factors during pregnancy induce alterations in metabolism, hormonal output, and distribution of cardiac output, which result in central obesity, diabetes, and cardiovascular disease in middle age [5]. Both high and low birth weight, premature and post-mature birth, as well as SGA, have been described as risk factors for later obesity.

The fetal origin of adult disease, or prenatal programming, has been the subject of much study during the past two decades. A large number of epidemiological studies have demonstrated a direct relationship between birth weight and body mass index (BMI) attained later in life [5, 6]. Birth weight can be easily measured, has reference norms, is part of the routine medical record, and may be available historically. Variation in weight at birth serves as a surrogate to reflect underlying mechanisms influencing growth. Moreover, overweight and obesity have become increasingly prevalent worldwide, even among children in developing countries. Some researchers found over-nutrition during pregnancy and high birth weight might cause obesity and related disorders in adulthood. A large national representative study found the association between fetal macrosomia and obesity in childhood, adolescence, and adulthood [7], but for those born SGA, most go on to achieve appropriate catch-up growth by two years of age, approximately 15% do not have a catch-up growth, and most of these children continue to experience poor growth...
Materials and Methods

A multistage random cluster sampling method was used to select the school children aged nine to 15 years. Approximately 10,000 children were selected from nine elementary and secondary schools in three districts of Chengdu. The survey was conducted from January to March 2011. All of the parents agreed to take part in the survey. Standardized health survey questionnaires of school children from project section of the national 11th Five-Year Plan were distributed and completed by parents or guardians, which generally compromised such content: (1) baseline of children: population, gender, birth date; (2) birth outcomes: expected date of confinement, gestational age, and birth weight. Furthermore, weight and height of children were strictly measured by specially-trained researchers. Weight and height were separately assessed to the nearest 100 g and 0.1 cm according to a standard measuring method. BMI was calculated as weight in kg divided by the square of height in meters. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committees of West China Second University Hospital, Sichuan University. Written informed consent was also obtained from all participants.

Birth outcomes including birth weight and gestational age were analyzed to identify the abnormal birth, in which preterm birth as gestation < 37 weeks, full-term birth as gestation ≥ 37 weeks, and < 42 weeks, post-term birth as gestation ≥ 42 weeks; SGA as birth weight below the 10th percentile for each gestational age, AGA as birth weight between the 10th and 90th percentile for each gestational age, LGA as birth weight above the 90th percentile for each gestational age by standards of national surveys of newborns in China; low birth weight as birth weight < 2,500g, normal birth weight as birth weight between 2,500 g and 4,000 g, macrosomia as birth weight > 4,000 g. Birth outcomes were further divided into nine categories according to gestational age (preterm, full term, and post-term), birth weight (low birth weight, normal birth weight, and macrosomia) and birth weight for gestational age (SGA, AGA, and LGA).

The authors chose the weight and height’s standard of Chinese children aged zero to 18 years (2005) as the reference. Growth deviation included underweight, short stature, overweight, and obesity. Underweight and short stature were defined as the weight and height below -2SD for age and gender. Overweight and obesity were defined by the age- and sex-specific BMI reference developed by China for children aged five to 19 years [14].

The SPSS statistical package, version 16.0 was applied to the statistic analyses. Quantitative data are presented as means ±SD. Prevalence data are expressed as percentages and are compared by using chi-squared tests. The physique situation differences between groups were tested by Student’s t-test. A p value of less than 0.05 was considered statistically significant.

Results

Ten thousand questionnaires were distributed, 7,291 (72.9%) were recollected and 7,194 (effective rate 98.67%) that completed approved questionnaires and passed anthropometric measurements were recruited in the evaluation of physique situation. The age of subjects was between nine and 15 years. Among them, 3,494 (48.6%) were boys, whereas, 3,700 (51.4%) were girls.

The overall prevalence of preterm, full-term, and post-term birth was 3.14%, 95.59%, and 1.26%, respectively. The prevalences of underweight, short stature, overweight, and obesity at different gestational ages are shown in Table 1. The prevalences of all kinds of growth deviation in preterm, full-term, and post-term birth group were similar (p > 0.05). The different gestational age’s anthropometric measures by gender and the age groups are shown in Table 2. As shown in Table 2, only in male children aged 13 years, BMI for preterm birth was less than that for full-term birth. The height of full-term group was shorter than that of post-term group for female at 11 years of age. In addition, the weight, height, and BMI were similar across the different gestational age groups.

The overall prevalences of SGA, AGA, and LGA was 6.23%, 75.72%, and 18.06%, respectively. The prevalences of underweight, short stature, overweight, and obesity at different gestational ages and birth weights are shown in Table 3. The prevalences of underweight and short stature for SGA were highest in three groups (χ² = 6.954, 16.134, 18.206, 19.190, p < 0.05). However, the prevalences of overweight and obesity for LGA were highest in three groups (χ² = 34.812, 17.505, p < 0.05). As shown in Table 4, in male children aged nine to 15 years, the weight and height for LGA were higher than that for SGA and AGA, as well as in the female children.

The overall prevalences of low birth weight, normal birth weight, and macrosomia were 2.40%, 93.84%, and 3.75%, respectively. The prevalences of underweight, short stature, overweight, and obesity at different birth weight are shown in Table 5. The prevalences of overweight for low birth weight group was less than that for normal birth weight and macrosomia (χ² = 4.188, 11.954, p < 0.05). The prevalences

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Preterm (n = 226, 3.14%)</th>
<th>Full term (n = 6877, 95.59%)</th>
<th>Post term (n = 91, 1.26%)</th>
<th>Total</th>
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</thead>
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<tr>
<td>Underweight</td>
<td>8 (3.54%)</td>
<td>182 (2.65%)</td>
<td>1 (1.0%)</td>
<td>191 (2.65%)</td>
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<tr>
<td>Short stature</td>
<td>0 (0%)</td>
<td>130 (1.89%)</td>
<td>3 (3.30%)</td>
<td>133 (1.85%)</td>
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<tr>
<td>Overweight</td>
<td>24 (10.62%)</td>
<td>631 (9.18%)</td>
<td>11 (12.09%)</td>
<td>666 (9.26%)</td>
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<tr>
<td>Obesity</td>
<td>5 (2.21%)</td>
<td>188 (2.73%)</td>
<td>2 (2.20%)</td>
<td>195 (2.71%)</td>
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</table>
Table 2. — The weight, height, and BMI for the age groups at different gestational ages.

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<td>52</td>
<td>53</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Pre-term compared with full-term, p < 0.05; † SGA compared with LGA, p < 0.05; ‡ full-term compared with post-term, p < 0.05.

Table 3. — Prevalence of underweight, short stature, overweight, and obesity at different gestational ages and birth weights.

<table>
<thead>
<tr>
<th>Case</th>
<th>SGA (n = 448, 6.23%)</th>
<th>AGA (n = 5447, 75.72%)</th>
<th>LGA (n = 1299, 18.06%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>W</td>
<td>22 (4.91%)</td>
<td>149 (2.64%)</td>
<td>191 (2.65%)</td>
<td>192</td>
</tr>
<tr>
<td>H</td>
<td>21 (4.69%)</td>
<td>96 (1.76%)</td>
<td>133 (1.85%)</td>
<td>250</td>
</tr>
<tr>
<td>BMI</td>
<td>27 (6.03%)</td>
<td>460 (8.57%)</td>
<td>666 (9.26%)</td>
<td>1357</td>
</tr>
<tr>
<td>W</td>
<td>13 (2.90%)</td>
<td>125 (2.29%)</td>
<td>195 (2.71%)</td>
<td>333</td>
</tr>
<tr>
<td>H</td>
<td>12 (2.63%)</td>
<td>149 (2.74%)</td>
<td>201 (2.74%)</td>
<td>360</td>
</tr>
</tbody>
</table>

Table 4. — The weight, height, and BMI for the age groups at different gestational ages and birth weights.

<table>
<thead>
<tr>
<th>Case</th>
<th>SGA</th>
<th>AGA</th>
<th>LGA</th>
<th>SGA</th>
<th>AGA</th>
<th>LGA</th>
<th>SGA</th>
<th>AGA</th>
<th>LGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>W</td>
<td>14</td>
<td>205</td>
<td>37</td>
<td>26</td>
<td>286</td>
<td>30</td>
<td>60</td>
<td>31</td>
<td>54</td>
</tr>
<tr>
<td>H</td>
<td>18</td>
<td>234</td>
<td>262</td>
<td>35</td>
<td>334</td>
<td>38</td>
<td>59</td>
<td>32</td>
<td>53</td>
</tr>
<tr>
<td>BMI</td>
<td>27</td>
<td>303</td>
<td>337</td>
<td>49</td>
<td>439</td>
<td>52</td>
<td>70</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>W</td>
<td>31</td>
<td>354</td>
<td>382</td>
<td>51</td>
<td>548</td>
<td>56</td>
<td>80</td>
<td>50</td>
<td>70</td>
</tr>
<tr>
<td>H</td>
<td>34</td>
<td>406</td>
<td>436</td>
<td>54</td>
<td>590</td>
<td>58</td>
<td>84</td>
<td>53</td>
<td>73</td>
</tr>
<tr>
<td>BMI</td>
<td>37</td>
<td>412</td>
<td>441</td>
<td>57</td>
<td>631</td>
<td>61</td>
<td>90</td>
<td>56</td>
<td>80</td>
</tr>
</tbody>
</table>

Discussion
Although there is high incidence of all kinds of growth deviations in developing countries, such as underweight, of overweight and obesity for macrosomia were higher than that in normal birth weight group (χ² = 11.172, 6.339, p < 0.05). As shown in Table 6, for male children, the weight and height in macrosomia group were higher than those in average weight group and normal birth weight group, as well as for the female children.
short stature, overweight, and obesity, the latter two have become a worldwide epidemic, however little is still known regarding the exact cause of this trend or how best to stop it. For children’s health, prevention may be a better approach than treatment. According to the theory of “programming”, prevention efforts should begin very early in life. Birth weight and gestational age can reflect the condition of growth and development in utero to a certain extent. Some evidence suggests an association between birth weight with adolescent obesity, adult obesity, and other growth deviations [15]. By using a population-based approach, the present study analyzed the gestational age and birth weight impacting on physique situation of school children aged nine to 15 years in Chengdu, which is one of the youngest cities in Southwest China.

The prevalences of underweight, short stature, overweight, and obesity at different birth weights.

Table 5. — Prevalence of underweight, short stature, overweight, and obesity at different birth weights.

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Low birth weight</th>
<th>Normal birth weight</th>
<th>Macrosomia</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 173, 2.40%)</td>
<td>(n = 6751, 93.84%)</td>
<td>(n = 270, 3.75%)</td>
<td></td>
</tr>
<tr>
<td>Underweight</td>
<td>8 (4.62%)</td>
<td>180 (2.67%)</td>
<td>3 (1.11%)</td>
<td>191 (2.65%)</td>
</tr>
<tr>
<td>Short stature</td>
<td>4 (2.31%)</td>
<td>128 (1.90%)</td>
<td>1 (0.37%)</td>
<td>133 (1.85%)</td>
</tr>
<tr>
<td>Overweight</td>
<td>8 (4.62%)</td>
<td>617 (9.14%)</td>
<td>41 (15.19%)</td>
<td>666 (9.26%)</td>
</tr>
<tr>
<td>Obesity</td>
<td>3 (1.73%)</td>
<td>178 (2.64%)</td>
<td>14 (5.19%)</td>
<td>195 (2.71%)</td>
</tr>
</tbody>
</table>

* low birth weight compared with normal birthweight, p < 0.05
* low birth weight compared with macrosomia, p < 0.05
* normal birthweight compared with macrosomia, p < 0.05

Obesity is a growing concern worldwide. The prevalence of obesity has risen dramatically in developed countries over the past two to three decades [18, 19]. In developing countries, the transition from rural agrarian to urban economies has accelerated the appearance of obesity [20]. This study had shown that the tendency of obesity was more likely in LGA and macrosomia group, which was in keeping with the widely reported increase in the incidence of obesity in young children, and was undoubtedly nutritionally related [19, 21, 22]. The weights in macrosomia and LGA group for male children were higher than that in other group, as well as the female children. The result was consistent with Loaiza et al. [23]. A positive relationship between macrosomia, LGA, and obesity at first grade was found. Macrosomia children were more likely to be obese at first grade after assessing the effects of confounding prenatal variables. When weight gain between birth and first grade was > 120% of reference value, the obesity risk was 20 times higher. Wang Y et al. found that adolescent obesity rates

Table 6. — The weight, height, and BMI for the age groups at different birth weights.

<table>
<thead>
<tr>
<th></th>
<th>Low birth weight</th>
<th>Normal birth weight</th>
<th>Macrosomia</th>
<th></th>
<th>Low birth weight</th>
<th>Normal birth weight</th>
<th>Macrosomia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>X ± SD</td>
<td>X ± SD</td>
<td>X ± SD</td>
<td></td>
<td>X ± SD</td>
<td>X ± SD</td>
<td>X ± SD</td>
</tr>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9~</td>
<td>W 10</td>
<td>28.85 ± 4.18</td>
<td>276</td>
<td>34.60 ± 7.36</td>
<td>17</td>
<td>36.89 ± 7.65&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>H 136.20 ± 4.21</td>
<td>140.23 ± 6.21</td>
<td>142.47 ± 7.63&lt;sup&gt;b&lt;/sup&gt;</td>
<td>137.40 ± 5.89</td>
<td>138.75 ± 6.91</td>
<td>140.40 ± 4.65</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BMI 15.50 ± 1.80</td>
<td>17.53 ± 3.14</td>
<td>18.17 ± 3.55&lt;sup&gt;b&lt;/sup&gt;</td>
<td>15.53 ± 1.77</td>
<td>16.07 ± 2.62</td>
<td>16.35 ± 1.42</td>
<td></td>
</tr>
<tr>
<td>10~</td>
<td>W 12</td>
<td>55.08 ± 5.72</td>
<td>624</td>
<td>35.72 ± 7.38</td>
<td>34</td>
<td>38.68 ± 6.96&lt;sup&gt;b&lt;/sup&gt;</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>H 141.71 ± 6.41</td>
<td>143.42 ± 6.28</td>
<td>145.76 ± 7.39&lt;sup&gt;b&lt;/sup&gt;</td>
<td>141.05 ± 8.04</td>
<td>143.70 ± 6.91</td>
<td>147.00 ± 6.44&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BMI 17.48 ± 2.77</td>
<td>17.29 ± 2.92</td>
<td>18.12 ± 2.45</td>
<td>16.67 ± 2.14</td>
<td>16.39 ± 2.46</td>
<td>17.06 ± 2.61</td>
<td></td>
</tr>
<tr>
<td>11~</td>
<td>W 15</td>
<td>33.17 ± 6.81</td>
<td>571</td>
<td>39.64 ± 8.09</td>
<td>31</td>
<td>44.40 ± 13.11&lt;sup&gt;b&lt;/sup&gt;</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>H 145.53 ± 6.92</td>
<td>148.23 ± 7.48</td>
<td>149.37 ± 7.07</td>
<td>146.53 ± 7.30</td>
<td>149.43 ± 7.14</td>
<td>150.74 ± 5.62</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BMI 15.62 ± 2.83</td>
<td>17.97 ± 3.26</td>
<td>19.71 ± 4.36&lt;sup&gt;b&lt;/sup&gt;</td>
<td>16.16 ± 1.90</td>
<td>16.82 ± 2.51</td>
<td>18.04 ± 2.50&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>12~</td>
<td>W 8</td>
<td>43.56 ± 7.09</td>
<td>642</td>
<td>45.08 ± 9.42</td>
<td>36</td>
<td>49.15 ± 9.31&lt;sup&gt;c&lt;/sup&gt;</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>H 156.88 ± 8.46</td>
<td>155.42 ± 8.15</td>
<td>158.58 ± 9.61&lt;sup&gt;c&lt;/sup&gt;</td>
<td>155.28 ± 4.11</td>
<td>155.21 ± 6.22</td>
<td>156.44 ± 5.95</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BMI 17.64 ± 1.93</td>
<td>18.55 ± 2.98</td>
<td>19.40 ± 2.36</td>
<td>17.24 ± 1.92</td>
<td>17.51 ± 2.43</td>
<td>19.11 ± 2.44&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>13~</td>
<td>W 19</td>
<td>43.89 ± 10.17</td>
<td>750</td>
<td>49.15 ± 9.88</td>
<td>29</td>
<td>52.03 ± 10.79&lt;sup&gt;b&lt;/sup&gt;</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>H 159.89 ± 6.26</td>
<td>161.08 ± 8.07</td>
<td>165.28 ± 8.65&lt;sup&gt;a&lt;/sup&gt;</td>
<td>156.19 ± 6.88</td>
<td>157.97 ± 5.60</td>
<td>160.15 ± 5.17&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BMI 17.09 ± 3.46</td>
<td>18.83 ± 2.88</td>
<td>18.91 ± 2.98&lt;sup&gt;b&lt;/sup&gt;</td>
<td>19.91 ± 4.33</td>
<td>18.06 ± 2.49</td>
<td>17.91 ± 2.80&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>14~</td>
<td>W 10</td>
<td>49.58 ± 11.13</td>
<td>393</td>
<td>52.36 ± 10.59</td>
<td>12</td>
<td>61.62 ± 13.55&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>H 163.30 ± 8.30</td>
<td>165.30 ± 7.85</td>
<td>167.33 ± 7.54</td>
<td>158.71 ± 3.64</td>
<td>159.40 ± 5.61</td>
<td>160.56 ± 3.47</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BMI 18.41 ± 2.63</td>
<td>19.08 ± 3.23</td>
<td>21.78 ± 3.29&lt;sup&gt;a&lt;/sup&gt;</td>
<td>16.62 ± 2.57</td>
<td>18.59 ± 2.50</td>
<td>17.89 ± 1.50&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

* low birth weight compared with normal birth weight, p < 0.05; * low birth weight compared with macrosomia, p < 0.05; * normal birth weight compared with macrosomia, p < 0.05.
raised with birth weight [24]. A U-shaped relationship between birth weight and risk of type 2 diabetes was found in the schoolchildren aged six to 18 years in Taiwan [24]. High birth weight also has an association with maternal nutritional situation. Overweight and obese women have a higher risk of macrosomia and LGA. Fetal lipid is deposited quite rapidly during the last trimester of pregnancy. While lean body mass is lower by 22% in SGA, and 20% higher in LGA compared to AGA newborns, there is 51% less fat mass in SGA and 128% more fat mass in LGA newborns [25]. A study of 140,000 American children found that when the birth weight of full-term increases by one kg, the overweight risk in adult increases by 50% (26). In the present study, the prevalence of overweight for low birth weight group was lowest in three groups. When physique situation was analyzed, the weight and height in low birth weight group were less than that in normal birth weight and macrosomia groups, especially in nine-, 11-, and 13-year-old male children. However, for female children, low birth weight group did not differ significantly in weight, height, and BMI with normal birth weight. The result was consistent with Mau- reen’s discovery. Study of the long-term growth of very low birth weight (VLBW) found that the females with VLBW demonstrated greater catch-up in growth than their male counterparts, such that by 20 years of age, they did not differ significantly in weight, height, or BMI when compared with their normal birth weight peers (27). In contrast, the VLBW males remained shorter and weighed less than their normal birth weight controls. Some authors have demonstrated a relationship between low birth weight and increased upper body fat distribution in children and adults, which seems to have more important health consequences in adult life than overall fatness [15].

It is commonly thought that catch-up growth was a phenomenon seen in infants born with SGA or low birth weight and/or low birth length. Catch-up growth is considered to be achieved when the child’s weight or height is below the mean -2SD. In the present study, the incidence of SGA was 6.23%, when at school age, part of SGA had catch-up growth. However, the prevalence of underweight and short stature for SGA were highest in three groups. In spite of only part significant difference, the weight and height for SGA were less than that for AGA. The results were similar as that of a large study of 40,000 American children between 1988 and 1994. Despite catch up growth, the study found that infants born SGA tend to remain shorter and lighter with smaller head circumferences through early childhood compared with infants born AGA [28]. After assessing socio-economy status, Westwood et al. showed a significant deficit in height in SGA non-asphyxiated children aged 13-19 years [15]. It was also estimated that about 15% to 20% of infants with growth restriction had short stature at the age of four years and 7.9% were still short at 18 years of age [29]. In Albertsson-Wikland and Karlberg’s studies, infants who had a short stature at two years were much more likely to also have a short stature at adult age and 8% of SGA were short at five years - a percentage that remained unchanged at least until the age of 18 years [30-32]. Other investigators found growth-restricted infants did not fully catch up with control group of infants in height, weight or body stature by the age of nine years and as a result, were substantially smaller and lighter and might very well remain as such throughout life.

The present study did not find that the incidence of overweight and obesity was higher in SGA group than in other group, that were not consistent with most research.

Since it was designed in a cross-sectional and retrospective study, the retrospective bias was unavoidable. Hence the authors had already been tracking the detailed birth information of these enrolled children according to their birth certificate, meanwhile more information about environment and life styles, as well as diet structure, family history, and some laboratory index would be further analyzed in later work.

In conclusion, the present study confirms that birth situation has an impact on the growth and development at school age. So great are the influences of intrauterine conditions on the developing fetus that they are not easily reversed when normal nutrition is restored. Further follow-up studies are needed in order to determine physique situation in a population of birth high-risk children and what percentage of subjects has a growth deviation. Preventive efforts should be performed during pregnancy. Such information is useful for the management of birth high-risk children and may be valuable for professionals working in follow-up clinics and dealing with parents of children at risk.

Acknowledgements

This study was supported by the national “11th Five-Year Plan” to support science and technology project grants, Ministry of Sciences and Technology, China (2009BAI80B00). The authors thank Prof. Z.Y. Zhao and other teammates of Children’s Hospital of Zhejiang University for providing research guidance. They also gratefully acknowledge the assistance of Educational Bureau of Chengdu.

XF participated in the design of the study, data collection and management, data processing and statistic analysis, and the manuscript writing. YF participated in the study design, coordinated the study personnel, trained the four researchers, and participated in data processing and analysis, and the manuscript writing. LP and HTZ participated in the data collection and data processing. MM conceived the study and participated in its design and supervision, and helped to draft the manuscript and review it. All authors read and approved the final manuscript.
References


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Effect of HbA1C detection on the diagnostic screening for glucose metabolic disorders in polycystic ovary syndrome

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Summary

Purpose: This study aimed to assess the effect of hemoglobin A1C (HbA1C) detection on the diagnostic screening for glucose metabolic disorders in women with polycystic ovary syndrome (PCOS). Materials and Methods: A total of 161 patients with PCOS (mean age = 23.68 ± 4.23 years) were subjected to an oral glucose tolerance test (OGTT). The receiver operating characteristic (ROC) curve was plotted to evaluate the fasting plasma glucose (FPG), and HbA1C was used to probe the sensitivity and specificity of abnormal glucose tolerance. Results: Based on the traditional standards of blood sugar, the prevalence of type 2 diabetes was 5.6%, and the pre-diabetes prevalence was 7.5%. Based on the HbA1C standards, 4.3% of patients were diagnosed with type 2 diabetes, and 10.6% of the diabetic patients can be considered as high-risk populations. Based on the combined standards of OGTT and HbA1C, the prevalence of type 2 diabetes was 6.2%, and the pre-diabetes prevalence was 12.4%. OGTT is considered the gold standard for identifying abnormal glucose tolerance, and HbA1C detection is considered to be stronger than FPG. The areas under the ROC curves of HbA1C and FPG were 0.968 and 0.905, respectively (p < 0.01). The American Diabetes Association (ADA) recommends the cut-off value of HbA1c ≥ 5.7% and FPG ≥ 5.6 mmol/l for identifying abnormal glucose tolerance. The sensitivity and specificity were 76.7% and 89.5% for HbA1c, as well as 40.5% and 94.3% for FPG, respectively. The positive and negative likelihood ratios were 7.1 and 0.63 for FPG, respectively. Conclusion: HbA1C detection can be used as a method for diagnosis and screening.

Key words: Polycystic ovary syndrome; Oral glucose tolerance test; Receiver operating characteristic curve.

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder in women of childbearing age. It causes amenorrhea, infertility, hirsutism, and acanthosis nigricans. It also increases the risks of metabolic and cardiovascular disorders. The authors previously found that patients with PCOS have abnormal glucose and lipid metabolism. Thus, a simple screening method for abnormal glucose metabolism is needed. In early 2010, the American Diabetes Association (ADA) formally considered hemoglobin A1C (HbA1C) as one of the criteria for diagnosing diabetes and identifying high-risk populations [1]. Many researchers believe that HbA1C detection is a simple and reliable method of diabetes diagnosis [2, 3]. Indeed, HbA1C detection has been extensively applied in diagnosing and screening diabetes [4]. However, pertinent studies on patients with PCOS are rare. In the present study, the oral glucose tolerance test (OGTT) was regarded as the gold standard for diagnosing and screening of diabetes. Moreover, the effects of HbA1C and fasting plasma glucose (FPG) on the screening of glucose metabolic disorders in patients with PCOS were analyzed and compared.

Materials and Methods

Subjects

A total of 161 patients with PCOS in the Fifth Affiliated Hospital of Zhengzhou University were selected from June 2009 to October 2012. PCOS diagnosis was based on the Rotterdam standards. Patients with thyroid, adrenal, ovarian, and sex-hormone disorders were excluded. All patients without essential hypertension, diabetes, and history of hormone application for three months were included. This study was conducted in accordance with the Declaration of Helsinki and with approval from the Ethics Committee of Zhengzhou University. Written informed consent was also obtained from all participants.

Research methods

All enrolled patients fasted overnight (10 hours) and received 75 g of oral glucose for OGTT. Their height, weight, and body mass index (BMI) were measured. Then, blood tests for FPG, two-hour plasma glucose (2hPG), fasting insulin, two-hour insulin, and blood lipids were performed. The measurements were made by a specially assigned person. Intravenous plasma glucose was detected by the glucose oxidase method and insulin and lipids were measured by chemiluminescence. HbA1C was measured by high-pressure liquid ion-exchange chromatography and insulin resistance was assessed by a homeostasis model assessment for insulin resistance.

Diagnostic criteria of the glucose metabolic state

The classification of the glucose metabolic state was based on the 2010 ADA diagnostic criteria [1]. The OGTT criteria were as follows: for normal glucose tolerance (NGT), FPG < 5.6 mmol/l and 2hPG < 7.8 mmol/l; for pre-diabetes and impaired fasting glucose (IFG), FPG = 5.6-6.9 mmol/l and 2hPG < 7.8 mmol/l; for impaired glucose tolerance (IGT), FPG < 5.6 mmol/l and 2hPG = 7.8-11.0 mmol/l; for impaired glucose regulation (IGR), FPG = 5.6-6.9 mmol/l and 2 h PG = 7.8-11.0 mmol/l; and for diabetes, FPG ≥ 7.0 mmol/l or 2hPG ≥ 11.1 mmol/l. The HbA1C detection criteria were as follows: normal, < 5.7%; pre-diabetes mellitus (PreDM), 5.7% - 6.4%; diabetes, ≥ 6.5%.
Statistical analysis

All data were statistically analyzed by SPSS 18.0 software. Measurement data were represented by $\bar{x}$ ± s. FPG and HbA1C were obtained from ROC curves, which represented the sensitivity and specificity related to the OGTT diagnosis of metabolic disorders. The ROC curves formula was as follows: positive likelihood ratio (LR+) = sensitivity / (1 – specificity); negative likelihood ratio (LR-) = (1 – sensitivity) / specificity. A $p < 0.05$ was considered statistically significant.

Results

General characteristics of subjects

The data of 161 patients with PCOS (average age = 23.68 years) were analyzed. The grouping depended on OGTT results. Table 1 lists the body measurement indicators and laboratory data of each group.

Diagnosis of glucose metabolic disorders

Table 2 lists the glucose metabolic states of all subjects. The diagnosis depended on OGTT results and HbA1C standards. Based on the OGTT standard, nine (5.6%) out of the 161 cases with PCOS were diagnosed with diabetes. Among them, three cases with only TPG or 2hPG met the diagnostic criteria, and six cases with both criteria met the standards; 12 patients (7.5%) met the diagnostic criteria for pre-diabetes.

HbA1C screening of abnormal glucose metabolism

OGTT was considered as the gold standard for diabetes screening and diagnosis. HbA1C ≥ 5.7% and FPG ≥ 5.6 mmol/l were also regarded as the screening standards. The glucose metabolic disorders, sensitivity, specificity, positive likelihood, and negative LRs are shown in Table 3. The sensitivity of HbA1C ≥ 5.7% was 76.7%, whereas that of FPG ≥ 5.6 mmol/l was 40.5%; the specificity of the latter was stronger than that of the former. In the ROC curves, the diagnostic capacity of HbA1C for IGT was superior to that of FPG. The areas under the curve were 0.968 (95% CI = 0.927 – 0.989) for HbA1C and 0.672 (95% CI = 0.593 – 0.744) for FPG ($p < 0.01$).

Discussion

Although FPG detection is considered as the primary method for screening glucose metabolic disorders, this approach has some limitations. First, it requires fasting for at least eight hours. Second, the diet, exercise, and storage time of subjects in the first few days before detection can affect the test results. Thus, a single FPG detection can result in a misdiagnosis in people with normal FPG and abnormal glucose tolerance, which delays timely interventions [3].
HbA1C reflects the average plasma glucose levels for the past eight to 12 weeks prior to testing [5], and has long been considered as an important indicator of blood glucose control. HbA1C is also regarded as an important clinical basis for determining whether treatment programs need to be adjusted [6]. Recent studies have used the HbA1C test as a diagnostic criterion for screening diabetes and high-diabetes-risk populations [7]. Compared with FPG, HbA1C detection does not require fasting. Its results are also not influenced by recent diet, exercise, and specimen storage methods, such as delayed detection or refrigeration. Moreover, HbA1C detection is more objective, accurately reflects long-term blood sugar changes, and is more closely correlated with chronic complications [8–13]. With the international standardization of HbA1C detection, several studies have shown that HbA1C detection can be used as an effective indicator for diabetes diagnosis and screening [14–20]. Recently, the International Diabetes Expert Group has systematically reviewed and discussed these pieces of evidence, and finally recommended HbA1C detection as one of the methods for diabetes diagnosis and screening [7]. In 2009, the ADA recommended two detection results for diagnosing diabetes, and HbA1C ≥ 6.5% was selected. In 2011, the WHO suggested that it become the diagnostic cut-off point of diabetes [21, 22].

In the current study, the new ADA standard was applied. Among the 161 cases with PCOS, seven cases had HbA1C ≥ 6.5%, among which three reached the 2hPG and FPG levels of diabetes, one showed elevated 2hPG and normal FPG, two reached the FPG diabetes standards and had normal 2hPG, and one showed increased HbA1C. These results suggested that HbA1C and FPG equally affected diabetes diagnosis.

Furthermore, the sensitivities of HbA1C ≥ 5.7% and FPG ≥ 5.6 mmol/l were compared by ROC analysis to analyze their effects. The result showed that HbA1C was better than FPG; the areas under the curve were 0.968 and 0.672, and the sensitivities were 76.7% and 40.5% for HbA1C and FPG, respectively. Therefore, about 60% of patients with abnormal glucose tolerance had missed diagnosis by FPG screening alone, and this rate of misdiagnosis can be reduced to about 23% by HbA1C screening. The combined application can reduce the rate of misdiagnosis of glucose metabolic disorders to a certain extent.

However, considering the long half-life of red blood cells in the blood, HbA1C cannot promptly reflect the short-term blood glucose levels and changes. A single HbA1C detection may miss patients with short-term abnormal glucose metabolism, and the update rate of hemoglobin can affect the HbA1C levels. Moreover, HbA1C measurements may be affected by various genetic, hematologic, and disease-related factors [23]. Therefore, these factors should be considered in the application of HbA1C screening or diagnosis of abnormal glucose metabolism. Overall, FPG or HbA1C was not the perfect indicator for screening abnormal glucose metabolism. However, their combination may reduce the misdiagnosis rate of glucose metabolic disorders to some extent. High-risk groups may still need to be subjected to OGTT to confirm the diagnosis.

References


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The effects of the informed consent given for cesarean section on anxiety and knowledge

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Summary

Purpose: To determine the effects of information given before cesarean section on women’s anxiety levels and their knowledge about informed consent regarding it. Materials and Methods: Sixty women who elected to undergo cesarean section were included in the study. The data were collected using the pregnancy-related clinical information form, informed consent form, cesarean information form, and State and Trait Anxiety Inventory. Kruskal-Wallis test, Mann-Whitney U test, chi-square test and Pearson correlation were used as statistical methods. Results: The women’s knowledge scores before and after they were informed about cesarean section were 14.8 ± 5.5 and 29.8 ± 2.6, respectively (p < 0.05). Their state anxiety scores before and after they were informed about cesarean section were 28.4 ± 6.6 and 28.0 ± 5.9, respectively (p > 0.05). Conclusion: It was determined that the participants’ pre-training knowledge scores about cesarean section increased significantly after they were informed, and that their state and trait anxiety scores decreased very little after they were informed.

Key words: Applied and professional ethics; Clinical ethics; Health personnel; Informed consent; Obstetrics and gynaecology.

Introduction

Cesarean section has become a common operation in developed and developing countries [1, 2]. The rate of cesarean delivery in the world in the last 15 years has steadily increased from five percent to over 20% [3, 4].

According to the Turkey Demographic and Health Survey (TDHS-2008) report [5], 36.7% of the babies born within five years preceding the survey were delivered by caesarean section. Cesarean section rates in this country are a lot higher than 15% recommended by the World Health Organization (WHO) in the scope of “Health for All in 2000” [1, 6].

It has been reported that maternal morbidity and mortality rates related to cesarean delivery are four to seven times more than those related to normal delivery [1]. In this context, it is extremely important for a woman to obtain sufficient information about the complications and risks mentioned above and to choose the most appropriate one for her in the process of receiving the informed consent [7]. Informed consent is the conscious, voluntary appreciation and understanding of the information under no external pressure by a patient with adequate decision-making capacity after he/she is informed about the diagnosis and treatment methods he/she is to undergo and alternatives of these methods and the possible risks and benefits of all these methods [8, 9].

In many countries, a patient’s right to be informed about his/her consent has been secured under special legal regulations of the countries [8, 9]. In Turkey, conditions regarding the limits of the information to be provided and the patient’s appreciation are not clear.

While patients’ consent is obtained, some difficulties are experienced due to cultural differences, the limits of the information to be provided for the patient, concern not to bother the patient, the patient’s education level, decision-making ability, and anxiety [10]. Therefore, since the birth event is a phenomenon causing anxiety for women, it is gaining importance that the woman should give her consent after having really understood what it is. The procedure through which informed consent is received from patients is quite a new practice for many patients in this country. The majority of patients do not have sufficient information regarding the importance and contents of an informed consent.

Although there are a limited number of studies conducted on to what extent informed consent is understood by patients, the present authors have not been able to access any local study investigating whether the information provided is likely to achieve its goal. In the international literature too, the number of the studies conducted on the retention of information by patients after they are informed and then their informed consent is obtained is very few. In a number of studies too, it has been stated that women are not provided with clear enough information nor can they understand the information provided for them [11, 12].

Revised manuscript accepted for publication March 26, 2013
The purpose of this study was to determine the effects of informed consent given before cesarean section on women’s anxiety levels and their knowledge about informed consent regarding cesarean.

The study is original since it determines the relationship between anxiety and informed consent which is obtained when a woman who is planned to have vaginal delivery throughout her pregnancy but decided to have cesarean section in 24 hours after being administered to the hospital. Obtaining the informed consent in a short time in the course of cesarean delivery can cause the patient to give the informed consent without being aware of the importance of it. On the other hand, the patient’s anxiety can affect her understanding as well. Therefore, clarification of the situation is of importance.

Materials and Methods

Patients

Written informed consent was obtained from each subject, and the study protocol was approved by the Human Ethical Committee of the university (Record No: 2010-03/16). The study was performed in accordance with the principles of the Helsinki Declaration. The patients were told that it was entirely their own decision whether or not to participate in the study, that the data obtained would only be used within the scope of the study, and that the confidentiality of all personal information would be strictly protected.

The research is an experimental one. A preliminary study was performed on 15 women to confirm the reliability of the questionnaire in the light of the literature. Those not wanting to participate in the study, diagnosed with emergency cesarean section, in the active phase of stage 1 of delivery, or having a mental or systemic disease preventing them from answering the questions, and having received information about cesarean section, were excluded.

Patients who presented to the Maternity Ward of Cumhuriyet University Hospital and were decided to have cesarean section comprised the population of the study. With the values of alpha = 0.01, beta = 0.10, 1-β = 0.90, the test power was assessed as \( p = 0.89694 \), and it was decided to enroll 60 individuals in the study.

Questionnaire

The following four forms were used to collect data:

- Socio-demographic characteristics and pregnancy-related clinical information form: this form includes questions about general socio-demographic characteristics and cesarean-pregnancy issues such as whether the patient has a chronic disease, whether she has developed any health problems during pregnancy, whether the pregnancy is voluntary, and how many cesarean sections she has undergone previously.

- Informed consent form: it is the form prepared by adding figures to the form previously prepared by the National Association of Obstetrics and Gynecology regarding cesarean section and used in clinics.

- Cesarean information form: this form was prepared within the framework of the informed consent after the literature was screened by the researchers [4, 13]. The form includes questions on how cesarean section is performed, its benefits, risks and complications, and alternative treatments.

- State and Trait Anxiety Inventory: it is designed to measure the patient’s state and trait anxiety and is based on a four-point likert-scale. It includes 40 items: 20 of them measure state anxiety and the other 20 measure trait anxiety. The scale is in a paper-and-pencil format [14]. Since each scale includes 20 statements, the total score obtained from each scale ranges between 20 and 80. Cronbach’s alpha of the inventory was determined to range between 83 and 92 for the state anxiety scale, and between 86 and 92 for the trait anxiety scale. The Anxiety Inventory was developed by Spielberg et al. in 1970. It was adapted into Turkish by Öner and Le Compte in 1977 [14]. In the present study, alpha coefficient was found to be 0.7091 for the State Anxiety Inventory and 0.6610 for the Trait Anxiety Inventory.

State anxiety refers to an acute situational-driven episode of anxiety. Trait anxiety refers to a personality trait that is stable over time. In the literature, it has been emphasized that the State Trait Anxiety inventory was found to reflect the relationship between anxiety and what pregnant women suffered [15].

The study did not include a control group. Women’s evaluations before they were informed were considered as the control. The data were collected between June and October 2010. In order to avoid bias, the questionnaires were filled in and collected not by the researchers but by specially trained pollsters through face-to-face interviews.

The pollsters first used the form questioning the woman’s socio-demographic characteristics and knowledge about cesarean section and then the state-trait anxiety scale form. Then the researcher verbally gave the patient information about cesarean section included in the informed consent using visual material. After the patient was informed, the same pollster who had filled in the state-trait anxiety scale form filled in the forms including the woman’s knowledge about cesarean section and anxiety status.

Statistical analysis

In statistical evaluation, the paired t-test was used to compare the knowledge scores with the anxiety scores both of which were achieved by the woman before and after she was given information. The relationship between knowledge scores and anxiety scores obtained before and after informing was evaluated with Pearson correlation.

For the evaluation of cesarean information scores, each correct answer was scored one point and each wrong answer was scored zero, and then the total knowledge score was obtained. Statistical analyzes were based on the total score.

In addition, Kruskal-Wallis test, Mann-Whitney U test, chi-square test and frequency were used as statistical methods. Significance was determined as \( p < 0.05 \).

Results

Table 1 presents the demographic and selected clinical data of the study population. Of the participants, 36 (60%) were in the 18-28 age group, 33 (55.0%) were primary school graduates, 55 (91.7%) were housewives, 33 (55.0%) had two or more cesarean sections.

The women’s knowledge scores before and after they were informed about cesarean section were 14.8 ± 5.5 and 29.8 ± 2.6, respectively. The knowledge score after they were informed was significantly higher than the
The effects of the informed consent given for cesarean section on anxiety and knowledge

The participants’ state anxiety scores before and after they were informed about cesarean section were 28.4 ± 6.6 and 28.0 ± 5.9, respectively. Their trait anxiety scores before and after they were informed about cesarean section were 65.2 ± 5.7 and 65.1 ± 5.7, respectively. When the pre- and post- state and trait anxiety scores were compared, it was determined that the difference was statistically insignificant (p > 0.05, Table 2).

According to the results of correlation analysis of the knowledge scores and state-trait anxiety scores before and after informed consent (Table 3), there were negative correlations between ESIACS and ESSAAIC (r = -0.09, p = 0.478) but they were not of statistical significance. There was a moderate, positive correlation between ESIBCS and ESIACS (r = 0.25, p = 0.050). There was a strong, positive correlation between ESSABIC and ESSAAIC (r = 0.69, p = 0.001), ESTABIC and ESTAAIC (r = 0.97, p = 0.001), the difference between them (ESIBCS and ESIACS) was statistically significant (p < 0.05).

There was no significant difference between the socio-demographic and selected clinical data of the study population, and their pre- and post-cesarean knowledge scores and state and trait anxiety scores. Only the difference between the increase in the mean state anxiety scores of the participants with no chronic disease (-0.8 ± 4.9) and that of the participants with a chronic disease (2.6 ± 3.6) was considered to be significantly low (p < 0.05).

The difference between the increase in the mean state anxiety scores achieved by the participants with elementary or higher education (-4.3 ± 3.0) and that achieved by the participants with lower than elementary education (0.3 ± 4.8) before and after they were provided information was considered significantly low (p < 0.05).

Discussion

It was determined that the participants’ pre-training knowledge scores about cesarean section increased significantly after they were informed, and that their state and trait anxiety scores decreased very little after they were informed.
The effect of anxiety

Of the studies investigating the association between informing and anxiety levels after informing, some found higher anxiety levels [16] whereas some found lower anxiety levels [17], but neither high levels nor low levels were statistically significant [18]. In the same study, it was indicated that there was no relationship between video-based informing and anxiety [18]. The very small decrease determined in anxiety scores of the participants before and after they were informed was considered statistically insignificant.

In several studies, it was stated that training programs reduced anxiety levels [17, 19], and that in patients who were informed preoperatively, both anxiety levels [19-21], but especially state-anxiety levels, were lower [20, 22]. On the other hand, in the literature, it has been reported that preoperative education provided about cesarean section reduces preoperative state anxiety levels to a very small extent [23]. In the present study too, anxiety levels decreased after informing, but it was not significant. This situation can be explained in such a way that the woman focuses informing process in order to get the information she needs, but that her anxiety is not significantly affected since uncertainty continues.

In a study of neurosurgical patients in which Amsterdam Preoperative Anxiety and Information Scale was used, a positive correlation was reported between the anxiety level and need for information [19]. In another study, it was reported that patients, especially female patients, were anxious during the preoperative period and that there was a weak correlation between their knowledge scores and anxiety levels [24], and these results were similar to the present findings.

In the literature, it is stated that informed consent can play an important role in women’s decision-making process and in experiencing less anxiety [25]. In the present study too, it was found that, although statistically not significant, women’s anxiety level after being informed was lower than that before being informed. The study on the use of decision aid by pregnant women, it was stated that their anxiety level decreased after informing, which supports the results of the present study [26].

In a study conducted on pregnant patients [27], no significant relationship was determined between anxiety and socio-demographic characteristics; however, in another study, a significant relationship was found between prenatal anxiety scores and socio-demographic and pregnancy history findings [28]. In an article entitled “comparative study of anxiety between informed and not-informed patients in preoperative period”, it was stated that there was no significant relationship between socio-demographic data and the level of anxiety [21]. In another study, it was reported that participants’ education level did not affect their state anxiety levels [22].

In the present study, no significant correlation was statistically determined between socio-demographic and selected clinical characteristics and their knowledge scores and anxiety scores. However, the increase in the mean state anxiety scores of those with primary and higher education was significantly lower. As the education level increases, the anxiety level decreases, which is due to the fact that education has a positive contribution to the ability to understand and interpret the information given. The reason why those with chronic diseases had higher anxiety scores might be due to their concerns that their chronic disease might put their health at risk and lead to an uncertainty about their health.

Information scores

In a study in which the participants were informed with audio-visual interventions, it was stated that there was no increase in their knowledge/understanding level. However, several other studies show that information provided through audio-visual interventions is long-lasting. Although, the intervention may also have small positive effects on the quality of information disclosed, and may increase willingness to participate in the short term, it is argued that this evidence is weak [29].

In a study aiming at developing and pre-testing a decision board to facilitate informed choice about delivery approach in uncomplicated pregnancy, it was stated that there was an increase in women’s knowledge scores, which is consistent with the present study results [30].

Conclusion

In decision-making, submitting sufficient information, ensuring reasonable involvement, and having the individual understand the information are important components of the informed consent. According to the results of the present study, informed consent increases pregnant women’s knowledge, and, although not significantly, decreases their anxiety level. As a result, it can be said that informed consent does not affect anxiety levels of women to undergo cesarean section, but increases their knowledge regarding it.

Limitations of the study and recommendations

The time between providing information for the patient and anxiety controls was short due to cesarean section and this may have influenced the results. The study can be repeated by including patients from different cultures and planning different periods between anxiety controls and providing information.

The study is expected to contribute to the literature since it draws attention to the fact that how appropriate criteria and strategies can be established when the informed consent is obtained from patients in case the time is limited. It may be a guide for the evaluation and revision of legal regulations regarding the informed consent at the national level.
References


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The criterion value of fetal cerebral lateral ventricular atrium width for diagnosis of ventriculomegaly

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Summary

Aim: To determine the distribution of cerebral lateral ventricular atrium width (LV AW) as established according to gestational weeks, and calculate the criterion value of LV AW that differentiates normal fetuses from abnormal fetuses. Materials and Methods: A total of 832 patients meeting the study’s criteria were included in the control group. An additional 43 fetuses with LVAW > ten mm formed the case group. Results: The criterion value of LVAW was 9.7 mm. It did not change significantly throughout gestation. In the case group, 23 fetuses were terminated for fetal abnormalities, two fetuses died in utero, and 18 infants were born alive. Most of the abnormal development coincided with LVAW values greater than 12 mm. Conclusion: The authors suggest 9.7 mm as the criterion value, based on receiver operating characteristic (ROC) curve analysis. When the LVAW is between 9.8 and 12 mm without other fetal abnormalities, it may be regarded as a variation of the normal.

Key words: Ventriculomegaly; Criterion value; Ultrasonography; Prenatal diagnosis.

Introduction

Ventriculomegaly is one of the most common sonographically detected fetal abnormalities. The diagnosis of ventriculomegaly leads to a more intensive management that includes ultrasound examinations, screening for infections, eventual magnetic resonance imaging (MRI), potentially dangerous procedures (amniocentesis), and patient anxiety. It is not surprising that many different approaches to the diagnosis of fetal ventriculomegaly have been suggested; however, the most sensitive value for cerebral lateral ventricular atrium width (LVAW) to detect ventriculomegaly remains undetermined. This difficulty in critical assessment of the LVAW introduces borderline ventriculomegaly, which is a poorly defined but frequent condition that poses a problem for patient counseling. This condition is defined by LVAW values that range between ten and 15 mm [1]. Recently, borderline ventriculomegaly has been divided into mild (10-12 mm) and moderate (12.1-14.9 mm) cases, and it is suggested to be a benign finding [2]. However, chromosomal abnormalities and neurological squeal have been reported in infants with borderline ventriculomegaly, raising the question of whether the ten-mm criterion value is appropriate or not [3]. There is also a question of whether or not this criterion, defined by old ultrasound equipment, is suitable for the measurements in tenths of millimeters that are possible with the new ultrasound equipment.

The aim of this study was to determine the distribution of LVAW values as established according to gestational weeks, and to calculate the criterion value of LVAW that differentiates normal fetuses from abnormal fetuses.

Materials and Methods

Measurements of fetal LVAWs of consecutive pregnant women at 16-24 weeks’ gestation over a period of four years were collected as part of a routine antenatal ultrasound examination. The informed consent of each patient was obtained and the prospective cross-sectional study was approved by the local ethics committee. Patients were divided into two groups. Fetuses with LVAW < ten mm and pregnancies with known normal outcomes were placed in the control group. The inclusion criteria were a singleton pregnancy and a fetus whose estimated fetal weight was between the 10th and 90th percentiles. In patients with regular menstrual periods lasting 28-32 days, the gestational age was determined by the last menstrual period (LMP). Otherwise, the earliest sonographic examination or measurements of crown-rump length (CRL) in the first trimester or biparietal diameter (BPD) in the second trimester were used to determine gestational age. Patients with fetal chromosomal or structural anomalies, multiple gestations, fetal death, preterm labor, premature membrane ruptures, and intrauterine growth restriction, oligohydramnios, and polyhydramnios, birth weights below the 10th percentile or above the 90th percentile, or maternal disease, and patients who missed their routine visits were excluded from the control group. Based on these exclusion criteria, 36 patients were excluded from the study. A total of 832 patients fulfilling the criteria were included in the control group. Aside from the control group, 43 fetuses with known karyotype analyses and with LVAW > ten mm formed the case group. These patients were ultrasonographically evaluated, as well, and a detailed inspection for other structural anomalies was also performed. Additional investigations such as karyotype and maternal serum toxoplasmosis, rubella, cytomegalovirus, and herpes simplex virus (TORCH) tests were performed in all cases with ventriculomegaly.

Each patient was examined during the study by an experienced ultrasonographer using an abdominal 2-5 MHz curvilinear transducer. Measurements of fetal biometry were taken in the standard planes and fetal anatomy was scanned routinely. According to the guidelines of the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG), LVAW was measured on a ventricular axial plane at the level of the glomus of the choroid plexus. The electronic calipers were positioned perpendicular to the long
axis of the ventricle along the inner aspect of the echogenic line of the medial and lateral walls of the atrium [4] (Figure 1). Because of the typical near-field artifacts, measurements obtained in the far field were recorded in the control group. If it was not possible to obtain a correct axial view of the fetal head, the ventricles were measured on the coronal plane for a detailed evaluation of the fetal brain. If any ventricle width was greater than ten mm, the patient was included in the case group. Four of the 43 patients in the case group were detected during the routine ultrasonography scan, and the remaining were referred to the present unit. All measurements were calibrated at 0.1 mm. Each measurement was repeated twice for each fetus, and the mean size was calculated. Patients found to have ventriculomegaly were followed further, with examinations every four weeks until delivery. These families received prenatal counseling. Three cases of agenesis of the corpus callosum were confirmed via MRI. At delivery, all neonates were examined by a pediatrician. In the case group, the findings of neonatal cranial ultrasound and neurodevelopment assessment at 12 months of age were recorded.

**Statistics**

Statistical analysis was performed with the SPSS 13.0 program and the MedCalc program, version 10.2.0. Descriptive statistical methods (mean, standard deviation) were used in the evaluation of the study data. The criterion value of LVAW was calculated with receiver operating characteristic (ROC) curve analysis and the authors performed linear regression analysis with matching LVAW values and weeks of gestation. The relations between dependent and independent variables were assessed with Pearson correlation analysis. Results were evaluated in a 95% confidence interval (CI 95%) and at a significance level of $p < 0.05$. To calculate the intraobserver variability, the intraclass correlation coefficient (intra-CC) was used with CI 95%.

**Results**

The study population consisted of Caucasian patients. The median age of the pregnant women in the control and the case group was 30.68 ± 4.41 (range: 19-45) and 28.73 ± 6.65 (range: 17-41) years, respectively. The mean gestational age in the control and the case group was 20.95 ± 2.23 and 20.26 ± 2.23 weeks, respectively. The mean LVAW in the control and the case group was 6.69 ± 1.10 and 13.52 ± 2.92 mm, respectively. Two measurements were performed for each patient. The intraobserver variability for the LVAW measurement (intra-CC: 0.93) was considered to be very good.

In the control group, LVAW values did not change significantly over the course of gestation (Figure 2). The criterion value of LVAW was found to be 9.7 mm with 100% sensitivity and 99% specificity using ROC curve analysis (Figure 3, Table 1).

In the case group, TORCH infections were not detected in any of the patients. In addition to ventricular dilatation, there were findings of associated central nervous system (CNS) abnormalities in 18 cases, while 14 fetuses had additional non-CNS abnormalities. The LVAW measurements and concomitant abnormalities in the case group are summarized in Figure 4 (Figure 4). In the fetuses with LVAWs between 9.8 and 12 mm, the authors observed the regression of LVAW values in three of the eight fetuses. Of the 32 fetuses with LVAWs greater than 12 mm, 14 fetuses had LVAWs greater than 15 mm. Ten of those 14 fetuses already had LVAWs greater than 15 mm upon presentation to this department. In the remaining four cases, there was an interval of up to 12 weeks between the initial detection of ventriculomegaly and the progression to severe ventriculomegaly.

Of the 43 pregnancies in the case group, 23 were terminated for fetal abnormalities, while two fetuses died in...
The criterion value of fetal cerebral lateral ventricular atrium width for diagnosis of ventriculomegaly

...and 18 infants were born alive. There were three neonatal deaths and two postneonatal deaths. Two infants underwent neurosurgical intervention for progressive postnatal ventriculomegaly and spina bifida. One of these had features of cerebral palsy; the other suffered from motor dysfunction in the lower extremities and autonomic dysfunction. One infant with a prenatal LVAW of 10.3 mm and MRI-confirmed agenesis of the corpus callosum developed normally by one year of age. The remaining ten fetuses were completely normal at birth and at the first year of life.

Discussion

The term “borderline ventriculomegaly” is commonly used to indicate cases of a LVAW of ten to 15 mm. It is possibly associated with other abnormalities, which may worsen the condition and the clinical follow-up later [5, 6]. Therefore, counseling parents following a diagnosis of isolated ventriculomegaly is difficult for obstetricians.

In a study by Alagappan et al., the mean value for LVAW was 6.6 ± 1.4 mm, and they used ten mm, 2.5 standard deviations (SDs) above the mean, as the upper limit of normal LVAW values [7]. Hilbert et al. proposed that 12 mm, a value approximately four SDs above the mean, would be a reasonable upper limit for normal values [8]. Senat et al. suggested that ten mm was approximately four SDs above the mean and would therefore be an acceptable upper limit, although this limit has not been universally applied to investigate ventricular abnormalities [9]. In light of the current and previous studies, there is agreement that the upper criterion value for LVAW should be ten mm [4, 10]. This criterion value represents a range of approximately three SDs above the pooled mean (CI 99.74%). If measured with old ultrasound equipment, it would correspond to a range of 9.6-10.5 mm as measured with newer equipment [11]. The present authors conducted this study to obtain data on the normal upper limit of LVAWs in fetuses without abnormalities and, thus, to reanalyze the upper limit of these measurements in the literature. The mean value of LVAW was 6.69 ± 1.10 mm, and a range of 3 SDs above this mean corresponds to ten mm. The LVAW did not show significant change over the course of gestation, as has been previously observed [12]. The mean LVAWs and SDs of this study and seven previous studies are presented in Table 2 (Table 2). The calculated average mean of these eight studies (6.5 mm) ± three SDs corresponds to 10.1 mm. The authors thus suggest 9.7 mm as the criterion value of LVAW with 100% sensitivity and 99% specificity using ROC

![Figure 3. — The receiver operating characteristic (ROC) curve of LVAW.](image)

![Figure 4. — Summary of prenatal findings and postnatal outcome in 43 fetuses with ventriculomegaly. NND: neonatal death; post-NND: post neonatal death; ACC: agenesis of corpus callosum; TOP: termination of pregnancy.](image)

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<td>1.2</td>
<td>10.1</td>
<td>11.3</td>
</tr>
</tbody>
</table>

* Standard deviation.
curve analysis, since it is approximately three SDs above the mean (CI 95%). This criterion value is in correlation with the current literature. However, it should also be validated by the clinical outcomes of borderline dilatation.

The lateral walls of the atrium are typically perpendicular to the ultrasound beam in the axial plane and these can be identified in virtually 100% of fetuses [17]. However, the identification of these walls may be troublesome in the second trimester due to large and echogenic choroid plexuses. In addition, they fill the entire lateral ventricle posterior to the foramen of Monro, tending to mask the isolated ventricle walls. This artifact appears when coronal, sagittal, and parasagittal images are obtained, as in this study, to visualize the area near the ventricle and to evaluate the fetal brain thoroughly. In this study, the LV AW was measured at the level of the glomus of the choroid plexus. Heiserman et al. showed that placement of the anterior and posterior calipers on the long axis of the ventricles is not significant for the accuracy of measurement, while the assistance of the internal parieto-occipital sulcus is useful in ventriculomegaly follow-up [13, 18].

Mercier et al. retrospectively examined 26 cases with borderline ventriculomegaly (10-15 mm) [19]. The LV AW regressed in ten fetuses and stayed constant in ten fetuses. Among the remaining cases, one had Down syndrome, one had porencephaly, and four had growth retardation. Senat et al. followed 14 fetuses that had unilateral ventriculomegaly [9]. They found that the LV AW was constant within the range of 11-13 mm in ten fetuses, and it reached 20-25 mm in four fetuses. They identified atresia of the foramen of Monro, Weaver syndrome, congenital toxoplasmosis, and cerebral atrophy in these fetuses. Three of the pregnancies were terminated, and postmortem examinations confirmed the diagnoses. In this study, during the antenatal period, the authors observed regression of the LVAW in three fetuses with LVAW values between 9.8 and 12 mm. However, LVAW increased in four cases with LVAW values greater than 12 mm. In these cases, the pregnancies were terminated.

Two studies reported abnormal neurological outcomes in 13% of fetuses with LVAW values greater than 12 mm, while this rate was only four percent in fetuses with LVAW values between ten and 12 mm [6, 20]. Similarly, the rates of abnormal neurological outcomes in this study were 12.5% in fetuses with LVAWs greater than 12 mm and nine percent in fetuses with LVAWs between ten and 12 mm. It has also been reported that the incidence of karyotype abnormalities observed in borderline ventriculomegaly is higher than in patients with severe ventriculomegaly [21]. Signorelli et al. examined 62 fetuses with LVAWs between ten and 12 mm [22]. They diagnosed one fetus with trisomy 21. Gaglioti et al. reported that aneuploidy is observed in 5% (3/57) of borderline ventriculomegaly cases [5]. In this present study, the authors diagnosed one case of trisomy 21 in the fetuses with LVAWs between 9.8 and 12 mm. The LVAW value of the other fetus diagnosed with trisomy 21 in this study was between 12.1 and 14.9 mm, while the LVAWs in the other two cases of karyotype abnormalities in this study were above 15 mm.

Breeze et al. examined the etiology and prognosis of 20 fetuses with severe ventriculomegaly (> 15 mm) [23]. Ten of the pregnancies were terminated and diagnoses were confirmed after delivery. Two infants died in the fourth month postpartum. Of the remaining eight infants, seven had abnormal neurodevelopment. In the present study, 14 fetuses with LVAWs greater than 15 mm were identified, and 12 of the pregnancies were terminated. One fetus died after cordocentesis. Only one of the 14 fetuses was born alive, but died within two months.

The present study had a few handicaps. First of all, there were few cases of ventriculomegaly. Following the patients in the postnatal period for a longer period of time would be more informative. Fetal MRI has been recently employed to diagnose subtle cerebral maldevelopment in fetuses with mild ventriculomegaly [24]. Since the authors’ experience in this field was limited, they did not use MRI in the evaluation of fetal mild ventriculomegaly cases, except to confirm diagnosis of agenesis of the corpus callosum. They could not obtain autopsy findings for the terminated pregnancies or postnatal deaths. Another difference between this study and others is that ROC curves were used here to analyze the criterion value of LVAW.

In conclusion, the authors suggest 9.7 mm as the criterion value with 100% sensitivity and 99% specificity using ROC curve analysis, because it is approximately three SDs above the mean. In order to avoid undue anxiety in parents, correct measurements should be obtained. When the LVAW is found to be between 9.8 and 12 mm and no other fetal abnormality is detected, this finding might be considered as a variation of the normal.

References

The criterion value of fetal cerebral lateral ventricular atrium width for diagnosis of ventriculomegaly


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Biomarkers of peritoneal fluid in endometriosis identified by surface-enhanced laser desorption/ionization time-of-flight

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Summary

Objectives: This work aims to detect the peritoneal fluid proteomic patterns in endometriosis patients, build diagnostic models, and evaluate its clinical significance. Study Design: The authors used SELDI-TOF-MS protein chip array technology to detect biomarkers of peritoneal fluid in endometriosis patients. Fourteen endometriosis patients and 16 persons without endometriosis as control group were tested. Results: Four potential biomarkers (4428m/z, 6891m/z, 13766m/z, and 6427m/z) were found. Conclusions: This method showed great potential in screening better biomarkers for endometriosis.

Key words: Endometriosis; Peritoneal fluid; Surface-enhanced laser desorption/ionization time-of-flight; Biomarkers; adenomyosis.

Introduction

Endometriosis, a gynecological disorder primarily of reproductive-aged women, is characterized by the presence of endometrial tissue (glandular and stromal epithelium) in sites outside of the uterus [1, 2]. Early diagnosis of endometriosis will greatly reduce its occurrence and reduce infertility [3]. Peritoneal fluid originates mainly from ovarian surface tissues exudation secondary to increased vascular permeability. Transudation from blood plasma as well as transudation/exudation from kidneys, liver, pancreas, intestine, and intra-abdominal fat may contribute to the overall peritoneal fluid volume, which is greatest at mid-cycle and in the early luteal phase (mean 8.7 ml; range, 1 - 21 ml) [4, 5]. Results of research into the flow of peritoneal fluid support the hypothesis that peritoneal fluid represents a specific microenvironment that could play a role in the pathogenesis of endometriosis [6-8]. CA125 is the most widely used biomarker of endometriosis and progressive elevation of CA125 has been observed in peritoneal fluid of endometriosis patients [9]. Recent studies showed that peritoneal fluid CA-125 levels were 100- to 1000-fold higher than serum levels in women with pelvic endometriosis [10]. However, many women with endometriosis have normal CA125 values whereas high CA125 values can be seen in women with other gynecologic diseases such as ovarian cancer [11, 12], and thus CA125 does not have an adequate predictive value. How to find another sensitive marker in peritoneal fluid is very important for early diagnosis of endometriosis.

The authors have used SELDI-TOF-MS protein chip array technology to detect the proteomic patterns of serum and eutopic endometrium in endometriosis patients [13, 14]. The purpose of our present study was to find the biomarkers of peritoneal fluid in endometriosis patients by using SELDI-TOF-MS protein chip array technology.

Materials and Methods

A total of 30 women who had normal menstrual cycles volunteered for this study. All of them had not received any hormonal treatment for at least six months before operation. At the time of surgery, pelvic organs were carefully examined for the presence and extent of endometriosis. Fourteen patients with ovarian endometriotic cyst or adenomyosis were identified as endometriosis group. Among them, nine had one side of ovarian endometriotic cyst, three had two sides of ovarian endometriotic cysts, and two had adenomyosis. The median age of the endometriosis patients was 35 years (range 23 – 44). Diagnosis was pathologically confirmed and specimens were obtained before treatment. The distribution of endometriosis according to the revised American Fertility Society classification [15] was as followed: Stage I (n = 2), Stage II (n = 3), Stage III (n = 5), and Stage IV (n = 4). The control group (16 cases), with a median age of 37 years (range 20 – 47), underwent surgery for tubal ligation (three cases) or hysterectomy for benign indications (13 cases). They had no visible evidence of endometriosis. All of the peritoneal fluid samples were obtained at the beginning of surgery and centrifuged at 1,000 rpm for two minutes and then the peritoneal fluid samples were stored at -80°C until use. This study was conducted in accordance with the Declaration of Helsinki and with approval from the Ethics Committee of Zhejiang University School of Medicine. Written informed consent was also obtained from all participants.

Peritoneal fluid samples in ice were thawed and centrifuged at 3,000 rmps for five minutes at 4°C, and supernatants were retained. Ninety µl of five g/l 1-(3-cholamidopropyl)dimethylammonio)l-propanesulfonic acid (CHAPS) (pH 7.4) was added into phosphate buffered saline (PBS) to make up ten µl of each peritoneal fluid sample, and vortex-mixed. The diluted samples were added to 100 µl Cibacron Blue 3GA (previously equilibrated thrice with five g/l CHAPS) in 96-well cell culture plate and agitated on a plat-
form shaker at 4°C for 60 minutes. After centrifugation at 1000 
rpm, 50 µL supernatants were sampled and further diluted by 150 
µL 20 mmol/l N-2-hydroxyethylpiperazine-N‘-2-ethanesulfonic 
acid (HEPES) (pH 7.4) and applied to each well of a bioprocessor 
containing hydrophobic surface (H4) chips previously activated 
with 20 mmol/l HEPES. The bioprocessor was then sealed and ag-
eated on a platform shaker for 60 minutes at 4°C. The excess peri-
toneal fluid mixtures were discarded, and the chips were washed 
three times by gently shaking on a platform shaker at a speed of 
700 rpm for five minutes with 200 µL of 20 mmol/l HEPES (pH 
7.4), were air-dried, and were crystallized by the addition of a-
cyano-4-hydroxycinnamic acid.

Chips were detected on the Protein Biological System II (PBS-
II) plus mass spectrometer reader. Data were collected by averag-
ing 65 laser shots with an intensity of 190, a detector sensitivity 
of 7, a highest mass of 30000 Da and an optimized range of 2000-
20000 Da. Mass accuracy was calibrated to less than 0.1% using 
the stepwise approach. The 
values were finally selected as potential biomarkers by 
considered. The 267 qualified peaks detected from the two 
groups, but the peaks of 13,766 m/z and 6,891 m/z seemed 
weakly expressed in control 
peaks of 4,428 m/z and 6,427 m/z were highly expressed 
in endometriosis patients but weakly expressed in control 
group, and the chips were washed 
three times by gently shaking on a platform shaker at a speed of 
700 rpm for five minutes with 200 µL of 20 mmol/l HEPES (pH 
7.4), were air-dried, and were crystallized by the addition of a-
cyano-4-hydroxycinnamic acid.

All these were performed using ProteinChip Software 3.1. 
SELDI-TOF-MS can produce thousands of peaks that mostly 
represent the peritoneal fluid proteins and peptides but also con-
tain the signals generated from the CHCA, the in-sample and 
sample-to-sample variations. To remove these signals, the au-
thors excluded all the signals with m/z values below 2000. The 
collected protein mass-dependent velocities (m/z) peaks were 
analyzed using an artificial neural networks (ANN) [16-18]. 
ANN are advanced computer algorithms, able to recognize com-
plex patterns in measured input variables which are not appar-
et to other forms of analyses. After processing of the incoming 
data by several transformation steps, the ANN produced an out-
put, indicating a specific category within a given classification 
[19]. ANN has been successfully applied to a broad range of bio-
medical problems. All of the calculations were made with the 
STATISTICA 6.0 software package.

Results

After filtrating noise by Ciphergen ProteinChip Soft-
ware 3.1, there were 267 peaks detected for discriminat-
ing endometriosis patients from healthy individuals. The 
peaks were 2 kDa to 30 kDa. Peaks with 
m/z < two kDa 
were mainly ion noise from the matrix and therefore ex-
cluded. The 267 qualified peaks detected from the two 
groups were ranked by receiver operating characteristic 
(ROC). The top four peaks with higher area under curve 
values were finally selected as potential biomarkers by using 
the stepwise approach. The m/z of the four can-
diate biomarkers were 4,428, 6,891, 13,766 and 6,427. The 
peaks of 4,428 m/z and 6,427 m/z were highly expressed 
in endometriosis patients but weakly expressed in control 
group, but the peaks of 13,766 m/z and 6,891 m/z seemed 
to be expressed in a contrary way, as shown in Figure 1. 
In the two groups, the p values of t-tests and the area 
under the ROC curve showed the statistical significance 
of all the four peaks, as shown in Table 1.

### Table 1. — The statistics of the candidate biomarkers; 
mean and standard deviation (SD).

<table>
<thead>
<tr>
<th>m/z</th>
<th>p value</th>
<th>Healthy (mean ± SD)</th>
<th>Endometriosis (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4428</td>
<td>0.0092446</td>
<td>2469.231 ± 1,772.43</td>
<td>4,752.407 ± 4,180.2754</td>
</tr>
<tr>
<td>6891</td>
<td>0.043213</td>
<td>1,360.464 ± 675.22</td>
<td>2,613.776 ± 4,002.54</td>
</tr>
<tr>
<td>13766</td>
<td>0.065073</td>
<td>3,794.985 ± 1,903.15</td>
<td>2,850.713 ± 1,462.49</td>
</tr>
<tr>
<td>6427</td>
<td>0.0092446</td>
<td>2469.231 ± 1,772.43</td>
<td>4,752.407 ± 4,180.2754</td>
</tr>
</tbody>
</table>

Discussion

This time the present study indicated that changes in the 
peritoneal fluid composition may contribute to the patho-
genesis of endometriosis. However, the analysis of peri-
toneal fluid protein fingerprinting by means of 
SELDI-TOF-MS can give only indirect insights into the 
process of endometriotic protein. Thus, this approach has 
to be considered as a form of screening assay, which al-

to the identification of important marker that might 
be relevant in the pathogenesis of endometriosis. Further 
research will be needed to determine the relationship be-
tween the peaks and protein in peritoneal fluid of en-
dometriosis. In summary, in the present study the authors 
used SELDI-TOF-MS protein chip array technology to 
find the biomarkers of peritoneal fluid in endometrio-
sis patients. Four potential biomarkers were found and 
the peritoneal fluid diagnostic system of endometriosis was 
built. Further studies should provide evidence that funda-
mental abnormal changes may occur within the peritoneal 
fluid of women with endometriosis compared to that of 
women without endometriosis.

Acknowledgments

This work was supported in part by the Project of Science 
and Technology Office of Zhejiang province (Grant 
No. 2011C24009).

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Case Reports

The sympathetic neural hyperalgesia/edema syndrome, a common cause of female pelvic pain, manifesting as a pseudopheochromocytoma with marked clinical improvement with sympathomimetic amines

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Summary

Purpose: To show that a common but not well-known disorder of the sympathetic nervous system can present with symptoms suggesting a pheochromocytoma. Materials and Methods: The standard treatment of this disorder (which is characterized by an abnormal water load test), i.e., sympathomimetic amine therapy, was given to a woman with paroxysmal tachycardia and hypertension. Results: Over a period of six months, the treatment eradicated the paroxysmal symptoms to which all other therapies had failed. Conclusions: This condition recently named as sympathetic neural hyperalgesia edema syndrome can present with symptoms of a pheochromocytoma and will respond to therapy with low dosages of dextroamphetamine sulfate. Key words: Pheochromocytoma; Sympathomimetic amines; Hypertension; Paroxysmal tachycardia.

Introduction

A condition predominantly involving women was described over 50 years ago in which women would experience unexplained edema and weight gain [1]. Typically the edema was worse in the feet and legs at the end of the day and involved the face and hands in the morning. Other symptoms included abdominal distention and nocturia [1]. The edema had remissions and exacerbations and the cause was unknown. Thus the condition was named idiopathic orthostatic cyclic edema [1].

A defect in the sympathetic nervous system was found to be etiologic in this condition [2]. The explanation for the edema, especially in the feet and legs which worsened with standing and improved by lying down, was that to compensate for the increase in hydrostatic pressure that occurred with standing, hence fluid would tend to leak from intracapillary to extracapillary sites. Thus to maintain intravascular volume, a signal is sent via the sympathetic nervous system to a pre-capillary sphincter causing the sphincter to contract and preventing leakage of fluid from intravascular to extravascular spaces [2].

Though treatment with standard diuretics, spironolactone, converting enzyme inhibitors, and bromocriptine have been proposed as therapies, their efficacy pales in comparison to the treatment with the sympathomimetic amine dextroamphetamine sulfate as far as control of the edema and weight gain are concerned [3].

Subsequently it has been determined that this disorder of the sympathetic nervous system may be the etiologic factor for various health problems, especially in women [4]. This disorder frequently presents with chronic pelvic pain, dysmenorrhea, dyspareunia, and/or mittelschmertz which is usually attributed to endometriosis. Whether endometriosis is present or not by laparoscopy, the pain responds better to treatment with sympathomimetic amine therapy than any other therapeutic measures including surgery [5-7]. Similarly, pain from interstitial cystitis, vulvodynia, and vulvovaginitis also responds quickly and effectively following treatment with dextroamphetamine sulfate [8].

Several gastrointestinal syndromes not only associated with pain but also with diarrhea and malabsorption, e.g., esophageal pain, gastroparesis, and pseudointestinal obstruction, have been demonstrated to respond very well to sympathomimetic amine therapy despite having failed to respond to previous standard therapies [9-11]. In fact recently a woman with a 12-year history of severe Crohn’s disease involving her entire colon, with complaints of about ten severely painful daily bowel movements, who had failed to respond to all conventional therapies, responded within one week to sympathomimetic amine therapy. Soon after therapy she had 90%
improvement and within one month was 100% relieved of all symptoms [12]. She has remained symptom-free for three years, including spontaneous closure of two perianal fistulas [12]. Other pain syndromes helped by sympathomimetic amines which had previously failed to respond to conventional therapy include: backaches [13], headaches [14], joint pain allegedly secondary to rheumatoid arthritis [15], carpal tunnel syndrome, and fibromyalgia [2, 4].

Other conditions that respond and improve considerably with sympathomimetic therapy that were resistant to other treatment include urticaria [16, 17] and chronic fatigue syndrome [18]. Vasomotor symptoms can be one of the presenting symptoms of a pheochromocytoma. Two cases were presented of women with severe vasomotor symptoms not responding to estrogen therapy whose symptoms were eradicated by treatment with dextroamphetamine sulfate. Biochemical testing failed to show evidence of a pheochromocytoma or carcinoid syndrome [19, 20].

The authors present a case of a woman who was incapacitated by episodes of severe tachycardia and hypertensive episodes resistant to other therapy but who responded to therapy with sympathomimetic amines.

Case Report

A 44-year-old woman presented with the main complaint of frequent paroxysmal episodes of severe tachycardia and severe rise in blood pressure associated with profound weakness, chest pain, shortness of breath, light headedness, and sweating that would leave her incapacitated. These symptoms had been present for several years. The frequency and severity of symptoms were so severe that she was house-ridden.

She had a history of hypertension dating back to her mid-twenties that was well-controlled on losartan. During pregnancy she was switched to alpfa methyl dopa. After her first pregnancy, her blood pressure normalized and no medication was taken.

At the age of 40 she re-developed hypertension but also sinus tachycardia. Her blood pressure and resting heart rate were both slightly high but there would also be paroxysmal episodes of sinus tachycardia with heart rates up to 200 beats per minute (BPM). Her blood pressure would markedly rise at this time with documented pressures of 165/120 mmHg. A referring cardiologist tried beta blockers but could not find one that she could tolerate (nausea, fatigue, and depression). Lisinopril 20 mg/day did not control the blood pressure adequately.

On physical examination, the patient had a blood pressure of 160/100 mmHg with a weight of 77 kg and pulse of 108 BPM. Otherwise, her physical examination was unremarkable. Neck evaluation revealed the absence of any thyroid enlargement or tenderness or carotid bruits. The lungs were clear, both anteriorly and posteriorly and with symmetric chest wall expansion. Cardiovascular examination revealed regular rate and rhythm, without any murmurs, rubs, or gallops. She had no peripheral edema.

Her laboratory tests were as follows: free thyroxin normal at 1.36 ng/dl (nl – 0.8-1.8 ng/dl), thyroid-stimulating hormone (TSH) normal at 1.36 mIU/ml (nl = 0.425 to 3.0), serum insulin 11.2 µU/ml (normal < 20 µU/ml). Her morning serum cortisol was normal at 9.7 mcg/dl and her 24-hour urine for fractionated metanephrines, was metanephrine 160 mcg/24 hours (nl = 58-203), normetanephrine 365 mcg/24 hours (nl = 88 - 649), and total metanephrine was 525 mcg/24 hours (nl = 182/739). The vanillylmandelic acid levels were very slightly increased at 6.2 mg/24 hours (nl = ≤ 6). One year later these tests were all normal.

Two years later, during an episode of paroxysmal tachycardia and hypertension, the total metanephrines were slightly elevated at 847 mcg/24 hours, with top normal fractionated metanephrine and normetanephrine (203 and 644 mcg/24 hours). During this time, urinary epinephrine was normal: eight mcg/24 hours (nl = 2 - 24), as were norepinephrine 94 mcg/24 hours (nl = 15 - 100), and dopamine with a level of 430 mcg/24 hour (nl = 52 - 480). A dexamethasone suppression test ruled out Cushing’s syndrome.

A computed tomography (CT) scan of her abdomen without contrast was performed to evaluate for pheochromocytoma, and this demonstrated a 0.8 x 0.8 cm left adrenal adenoma. Magnetic resonance imaging (MRI) of the abdomen with and without gadolinium found a small lesion on the left adrenal with normal abdominal vascular structure. A repeat CT of the abdomen without contrast one year later found no growth of the left adrenal lesion. A 24-hour heart monitoring found the minimum heart rate to be 67 BPM with a maximum of 156 with only two atrial premature contractions and 13 premature ventricular contractions. By examination the fastest heart rate ever documented was 200 BPM.

The woman performed a water load test where she excreted 50 of the 48 ounces of water ingested over a four hour time period, while supine but only 24 ounces erect. Based on this abnormal water load test, the woman was started on dextroamphetamine sulfate extended release capsules 25 mg/day.

When she was evaluated after eight months of taking the extended release capsule of dextroamphetamine sulfate, she was asked: what was the major benefit of taking the dextroamphetamine sulfate? She stated that she had almost complete elimination of any of the tachycardia paroxysms associated with the other aforementioned symptoms. She stated that she still suffers from general fatigue but on a scale of 0-10 she rated the improvement as a six. Nevertheless her blood pressure was still increased despite taking irbesartan and diltiazem.

Her fatigue improved with further treatment with dextroamphetamine sulfate. However one of her four children developed T-cell lymphoblastic leukemia and she was not able to return to the office for prescriptions. She continued the irbesartan but stopped the diltiazem because of side-effects. She reported a return of the paroxysmal tachycardia and the rest of the syndrome within one week of stopping the dextroamphetamine sulfate. The paroxysmal symptoms were much improved to almost non-existent within ten days of restarting the medication. It has been 18 months since restarting and she once again has been able to return to a functional life.

Discussion

It is unclear if the effectiveness of sympathomimetic amines in this patient was through diminishing vascular permeability; perhaps some toxic substance was thwarted from absorbing into the heart, thereby preventing irritation of the sinoatrial (SA) node, or by inhibiting edema of the heart and thus altering pressure on the SA node. The possibility of a toxic factor absorbing into heart tissue because of increased permeability related to a defect in
sympathetic nervous system is supported by the quick response to sympathomimetic amines in certain conditions before any improvement in edema is seen or in cases where there is no apparent edema [4, 8, 12, 14]. Possibly, the sympathomimetic amines work in some other way. Her seven-kg weight loss supports the possibility of the edema mechanism.

It is disappointing that the dextroamphetamine sulfate did not lower her generalized hypertension and only helped the paroxysmal symptoms. Perhaps the main abnormality was the paroxysmal tachycardia and the “fright” response triggered the other symptoms.

These data suggest that a pseudopheochromocytoma can be added to the list of various obscure treatment refractory conditions that seem to be related to a defect in the sympathetic nervous system and responds to sympathomimetic amine therapy. In this case, the defect in the sympathetic nervous system caused the paroxysmal symptoms, but the sustained blood pressure elevation was probably just essential hypertension.

References


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Ultrasonographic pattern of spontaneous resolving fetal ovarian cyst: a case report

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Summary
Fetal ovarian cyst is diagnosed at the rate of one per 2,500 live births and its behaviour in utero may range from spontaneous resolution with no further consequences to torsion, necrosis, and to the necessity of surgical treatment in the postnatal stage. Ovarian cyst torsion in a fetus results in the loss of its reproductive function in adult life. The authors present a case of spontaneous resolving fetal ovarian cyst. The lesion was diagnosed during an ultrasound scan in 30th week of pregnancy. An ultrasound scan performed two weeks later revealed symptoms of cyst torsion; the lesion was 5.7 cm in diameter, heterogeneous, and had a normoechogenic inside. A subsequent ultrasound exam showed a lesion with a diameter of 2.16 cm. An ultrasound exam of the newborn’s abdominal cavity performed on the second day showed that the cyst was six mm in diameter. However, the cyst did not show on an ultrasound scan made on the fourth day.

Key words: Ultrasonography; Fetus; Ovarian cyst.

Introduction
Fetal ovarian cyst is diagnosed at the rate of one per 2,500 live births and its behaviour in utero may range from spontaneous resolution with no further consequences to torsion, necrosis, and to the necessity of surgical treatment in the postnatal stage. The larger an ovarian cyst, the greater the risk of its torsion. Ovarian cyst torsion in a fetus results in the loss of its reproductive function in adult life.

Although there is no conclusion as to the developmental origin of fetal ovarian cysts, it is believed that one of the reasons they develop is the malfunction of the hypothalamic-pituitary-ovarian axis and such factors as maternal diabetes as well as fetal Rh-immunization or toxemia. All these cases may entail an increase of the gonadotropin level, which in turn increases the likelihood of an ovarian cyst developing in a fetus [1, 2].

There is no clear management approach to these cases in utero. The only described approaches include the monitoring of the lesion, as well as the puncture and decompression of a cyst in order to reduce the risk of its torsion [3].

Case Report
A 35-year-old woman (grav II partus I) turned up for an ultrasound scan in the 30th week of pregnancy. The patient’s history showed no current disorders and the course of pregnancy so far was regular. Ultrasound scans performed in the first and second trimester showed no abnormalities.

An ultrasound scan revealed an eutrophic female fetus with an anechoic lesion located in the left adnexal region. The mass showed no peripheral vascularisation, no internal echoes, and smooth internal outlines. The diameter was 2.1 cm.

An ultrasound scan performed two weeks later revealed symptoms of cyst torsion; the lesion was 5.7 cm in diameter, heterogeneous, and had a normoechogenic inside. A subsequent ultrasound exam showed a lesion with a diameter of 2.16 cm, a normoechogenic halo, and a trace of inner fluid.

Labour took place at the 40th week of pregnancy due to the threat of intrauterine asphyxia. The female neonate weighed 3,240 g, its first-minute Apgar score was 9, and its five-minute Apgar score was 10. The newborn was released from hospital on the fourth day. An ultrasound exam of the newborn’s abdominal cavity performed on the second day showed that the cyst was 0.6 cm in diameter. However, the cyst did not show on an ultrasound scan taken on the fourth day. The changing sonographic appearance of the ovarian cyst is shown in Figure 1.

Discussion
Cystic lesions in fetal abdominal cavity are usually diagnosed during an ultrasound exam in the second and third trimesters of pregnancy and it is of great importance for further diagnostics and treatment of a fetus and a newborn. The most frequently diagnosed lesions are simple cysts of different shapes and sizes [4]. Differential diagnosis should take into account ovarian, digestive tract, urinary system, liver, umbilical cord, as well as other abdominal masses. The incidence rate of ovarian cysts in female fetuses is one per 2,500 live births [5].

The presence of an ovarian cyst entails a risk of torsion, hemorrhagic changes within, and finally the loss of the reproductive function of the gonad in adult life. There are no clear guidelines as to the management of these cases. One of them is the expectant management during pregnancy, with possible surgical treatment after birth [6]. There are also reports on the efficacy of punctures and decompression of fetal cysts of more than four cm in diameter in order to reduce the probability of torsion [3, 7]. Galier et al. even proposed preterm delivery, following lung maturity stimulation in the case of bilateral ovarian
cysts in order to prevent the risk of torsion [8]. Although there is no definitive management approach, there is an agreement regarding the necessity of the prenatal monitoring of the lesions, as their image changes during pregnancy and may influence the management method [8, 9]. The monitoring of an abdominal cyst allows for a prenatal differential diagnosis and for the establishment of the postnatal management method.

References


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Dextroamphetamine sulfate, a very effective drug for pelvic pain relieved severe retroorbital stabbing pain in a woman with keratoconus who failed to respond to bilateral corneal implants

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Summary
Purpose: To determine if dextroamphetamine sulfate therapy could relieve severe headaches related to keratoconus of the eyes. Materials and Methods: Dextroamphetamine sulfate 20 mg daily was prescribed to a 45-year-old woman who complained of 20 plus years of severe stabbing retroorbital pain who was diagnosed with keratoconus but failed to gain relief from bilateral corneal implants. Results: Dextroamphetamine sulfate quickly and very effectively relieved the pain which has remained completely abrogated for over five years. Proof that the improvement was not fortuitous was demonstrated by quick return of symptoms when the drug was temporarily stopped after 2.5 years of relief but quickly dissipated upon resumption of therapy. Conclusions: Headaches are common in women. It is the gynecologist (who is more familiar with the condition of sympathetic neural hyperalgesia edema syndrome because it is the most common cause of pelvic pain) who may be the physician to introduce dextroamphetamine sulfate as a treatment since this condition is unknown by many specialists in other fields.

Key words: Retro-orbital pain; Keratoconus; Sympathetic hypofunction; Dextroamphetamine sulfate.

Introduction
The gynecologist is frequently consulted by women about chronic headaches not only because they are the primary care health physician for women but because there are gynecologic hormonal disorders, e.g., menopause, associated with headaches. Also some women complain about headaches associated with the menstrual cycle especially pre-menstrually. It is well known that the estrogen in oral contraceptives can cause migraine headaches.

There is another condition that is a relatively common cause of chronic standard treatment refractory migraine headaches caused by hypofunction of the sympathetic nervous system [1-3]. The sympathetic nervous system controls cellular permeability and hypofunction leads to the absorption of chemicals and toxins into tissues leading to inflammation and pain. Various physiological systems may be affected causing pain in various areas, muscle fatigue, and poor function involving skeletal muscle (causing fatigue) and smooth muscle (causing gastrointestinal motility disorders) and capillary vesicle permeability leading to urticaria and fluid retention [4, 5].

Unfortunately despite quick long lasting effective relief of symptoms following treatment with the sympathomimetic amine dextroamphetamine sulfate, most specialists, including neurologists, do not seem to be aware of this condition. The group of physicians most aware of this condition are gynecologists since this condition is the main cause of chronic pelvic pain which generally responds very well to dextroamphetamine sulfate [6, 7].

The gynecologist, playing the role of primary care physician for women, has to determine when to offer dextroamphetamine sulfate therapy and when to simply refer the patient to another specialist. Sometimes a specific diagnosis is made that seems to be outside of the gynecologists expertise. However, sometimes if the response to therapy by the particular specialists has not been especially good, the gynecologist should reconsider dextroamphetamine sulfate therapy.

A perfect example is a case of severe retroorbital pain from keratoconus, which would seem strictly an ophthalmologic entity, which failed to respond to corneal implants but responded very well to dextroamphetamine sulfate therapy.

Case Report
A 22-year-old woman was referred to an ophthalmologist for severe retro-orbital pain in both eyes with severe stabbing pain behind the eyes. She was diagnosed with keratoconus, i.e., curvature of the cornea.
After trying various oral and ophthalmologic preparations which all failed to improve her symptoms, the ophthalmologist recommended a corneal transplant for the worst eye, i.e., the right. The surgery did relieve some of the eye pressure but did not help at all the stabbing retro-orbital pain.

She suffered for the next 13 years. A different ophthalmologist suggested that she may experience significant improvement in the stabbing pain that persisted by having a corneal transplant in the left eye. Despite the corneal transplant there was no improvement in the retro-orbital stabbing pain.

She continued to suffer for another ten years. She consulted a top specialist at one of the world’s leading hospitals dedicated to ophthalmology and the consulting physician who told her that her eyes were useless and no further surgery could be done.

At the age of 45 she consulted our practice because she had heard from other acquaintances who had been treated successfully with dextroamphetamine sulfate despite failure to respond to various other treatments. Her pain was completely abrogated within two weeks of treatment with 20 mg dextroamphetamine sulfate.

She continued with no pain for 2.5 years. A shortage of dextroamphetamine sulfate developed so the woman thought that this was a good time to see if the treatment was still needed. The intense stabbing pain behind the eyes returned within one week and lasted for another month. The pain quickly ceased once again after she resumed the treatment with the sympathomimetic amine.

Discussion

If the woman had been seen in our office we would have thought it appropriate to seek the opinion of a neurologist and/or ophthalmologist for her complaints. Most likely we would not have challenged the impression that the stabbing pain was related to keratoconus and that corneal transplants would correct the problem.

However, in view of this case, if we saw a similar patient now we would still refer the woman to a neuro-ophthalmologist. However if a surgical procedure was recommended and the surgery was strictly for the pain, but was not a procedure of necessity otherwise, our suggestion would be to first try dextroamphetamine sulfate therapy.

Perhaps it would seem prudent to merely defer treatment to the neurologist or neuro-ophthalmologist but make them aware of this condition of hypofunction of the sympathetic nervous system and the great improvement seen in people with the sympathetic neural hyperalgesia edema syndrome following treatment with dextroamphetamine sulfate. However, we submitted another case report “Severe headaches from pseudo-tumor cerebri abrogated by dextroamphetamine sulfate”. The gynecologist would be relieved to know that if they had referred this patient to a neurologist the patient was found to have papilledema. This could have been a brain tumor but when tumor was excluded, the diagnosis was intracranial hypertension or pseudotumor cerebri. Clearly this would seem to be a case for the neurologist. However, standard treatment failed to show improvement in the headache or papilledema. We tried dextroamphetamine sulfate and in a short time the headaches completely disappeared. She had an appointment with the neuro-ophthalmologist and we were hoping to transfer the treatment responsibilities back to the neuro-ophthalmologist. A letter was sent explaining this defect in sympathetic nervous system hypofunction and the mechanism of action for dextroamphetamine sulfate. As the patient was having her fundoscopic examination, she explained her quick and completely effective headache relief from sympathomimetic amine therapy. The examining physician showed no interest in the patient’s improvement with the drug and merely stated “your papilledema is completely gone. I will see you in six months”. Thus, the primary gynecologist has to remain vigilant over diagnostic tests and treatment recommended by referring specialists and sometimes must intervene with therapy if the consultant is recalcitrant to new ideas.

Awareness of this condition and therapy can save patients pain, suffering, risk, and the expense. A 42-year-old woman seeking help for infertility stated that she may have to delay fertility testing for two months because she has had severe daily migraine headaches for 60% of each day which was attributed to temporomandibular joint (TMJ) syndrome which developed 22 years before from grinding her teeth from the pressures of law school and was scheduled in ten days for a new procedure where her jaw would be broken and then reset and it would cost her USD 8,000.00 out of pocket expense and her jaw would be wired and she would temporarily have to stop work for six weeks. We suggested that she try the dextroamphetamine sulfate before undergoing surgery and she had complete resolution of the headaches within one week. Thus surgery was cancelled.

Thus though most gynecologists would not know much about TMJ and would just not interfere with planned surgery. Thus the gynecologist, as the gatekeeper, has the responsibility to sometimes step in and treat other healthcare problems of women that seem to be out of the normal realm of obstetrics and gynecology. This case with more details has been submitted as a case report to Clinical and Experimental Obstetrics and Gynecology.

Thus if a woman would mention to the gynecologist that she has severe stabbing pain behind the eyes, and after referral to appropriate specialists a diagnosis of keratoconus is made, the gynecologist may suggest that rather than corneal implants one may consider dextroamphetamine sulfate therapy first. Of course the gynecologist should ascertain whether corneal surgery was needed other than to relieve headaches and with this information help advise the patient to make the right decision.
Dextroamphetamine sulfate, a very effective drug for pelvic pain relieved severe retroorbital stabbing pain in a woman etc.

References


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Recurrent peritoneal inclusion cysts successfully treated with oral contraceptives: a report of two cases

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Summary
Objective: To examine whether conservative treatment with oral contraceptives is effective in the shrinkage of a peritoneal inclusion cyst (PIC). This is a case report of two patients with a PIC that developed after gynecological surgery. Cases: Both cases were suspected of a PIC based on the medical history, laboratory data, and image findings. It was difficult in differentiating a PIC from an ovarian tumor. Surgery was chosen at first. However, PICs in both cases recurred after surgery and were treated with oral contraceptives as a conservative treatment. PICs shrank after the treatment of oral contraceptives in both cases. Conclusion: Due to the high rate of recurrence following surgery, conservative treatment is recommended to treat PICs. Hormone therapy using oral contraceptives seems to have some therapeutic benefit for the PICs.

Key words: Peritoneal inclusion cyst; Oral contraceptives; Conservative treatment; Sclerotherapy; Vibramycin.

Introduction
A peritoneal inclusion cyst (PIC) is a pseudocyst caused by the diminished ability of the peritoneum to absorb ascites and fluids from the ovaries due to the adhesions around the ovaries caused by pelvic surgery [1-3]. Conservative treatment is often chosen for the treatment of a PIC following surgery, including gonadotropin-releasing hormone antagonist (GnRHs), and hormone therapy using oral contraceptives [1,3-8]. The authors report two cases of recurrence of PIC after surgery, which were effectively treated with oral contraceptives.

Case Report
Case 1
A 46-year-old woman consulted a physician with a complaint of severe lower abdominal and back pains. She had undergone a total abdominal hysterectomy without removing the ovaries due to uterine leiomyoma two years prior. A computed tomography (CT) of the pelvis displayed a multilocular cyst. Magnetic resonance imaging (MRI) revealed a multilocular cystic mass measuring 95 x 60 mm in diameter. No sign of malignancy was noted. A preoperative diagnosis was a PIC or an ovarian benign tumor. She underwent an exploratory laparotomy (two years and 11 months after initial surgery). Based on intraoperative findings, the patient was diagnosed as having a PIC, and the adhesions were lysed. Her symptoms disappeared after surgery.

One year and four months after surgery (four years and three months after initial surgery), she complained of lower quadrant discomfort and lower back pain. An 83.9 x 73.3 mm-sized multilocular cyst was found with transvaginal ultrasound. MRI demonstrated a multicystic mass measuring 63 x 90 x 68 mm that showed hypointensity on T1-weighted images and hyperintensity on T2-weighted images (Figure 1). The tumor markers were within normal ranges (CEA: 2.6 ng/ml, CA-125: 11.1 U/ml, and CA19-9: 9.2 U/ml). Based on the history of the present illness, laboratory data, and image findings, the patient was diagnosed as having the recurrence of PIC. Due to the severity of lower quadrant discomfort and lower back pain, the content of a PIC was transvaginally aspirated with the drained amount of the fluid being 142 ml. The cytology of the fluid was of no malignancy. One month later, however, a PIC expanded up to 42.5 x 50.1 mm in size. Despite her severe symptoms of lower quadrant discomfort and lower back pain, the patient declined further treatment such as oral contraceptives. Thereafter, she was followed up at an outpatient basis, and her symptoms spontaneously disappeared.

Eight months after the aspiration (four years and 11 months after initial surgery), the symptoms developed again. The sclerotherapy using ethanol or GnRHs therapy was thought to be a candidate for the conservative treatment. The patient desired to avoid the side-effects of these therapies. The authors decided to use oral contraceptives since the patient had premenopausal symptoms such as malaise and fatigue, as confirmed by the endocrinological studies showing follicle-stimulating hormone (FSH) of 8.9 mIU/ml and estradiol of 51 pg/ml. The oral contraceptive therapy with Anjyu was begun. The 28-day treatment cycle pack consisted of four dosing phases; the first six days of levonorgestrel 0.05 mg/ethinyl estradiol 0.03 mg, five days with levonorgestrel 0.075 mg/ethinyl estradiol 0.04 mg, ten days with levonorgestrel 0.125 mg/ethinyl estradiol 0.03 mg, and seven days with placebo. After taking oral contraceptives, the PIC shrank to 12.8 x 8.4 mm in size four months later. The patient’s menopausal symptoms were abated immediately after the intake of the oral contraceptives. However, seven months after the beginning of oral contraceptives (five years and six months after initial surgery), the PIC grew to 73.9 x 37.5 mm during the continuous intake of oral contraceptives. The patient discontinued the oral contraceptives due to liver dysfunction. The patient did not desire other treatment, and was followed up at an outpatient basis. Nine months after cessation of oral contraceptives (six years and three months after initial surgery), she visited the present hospital with the worsening of the symptoms. Oral contraceptives were resumed again after confirming her recovery from liver dysfunction (Figure 2).

Case 2
A 38-year-old woman underwent a total abdominal hysterectomy and unilateral salpingo-oophorectomy for a tubo-ovarian ab-
Two years and ten months later, a transvaginal ultrasound revealed a 128 × 109 mm multilocular cyst. MRI showed an ovarian cystadenoma and fluid retention around the cyst, which was suspected of a PIC. An exploratory laparotomy was performed, which revealed an ovarian cyst and a PIC. The ovarian cyst was enucleated, and adhesions were lysed. Due to the severe adhesions, some of the PIC remained. The sites where adhesions were lysed were fixed with ethanol. Pathological diagnosis was a hemorrhagic corpus luteum cyst. A 74 × 53 mm-sized PIC remained after surgery (Figure 3).

Nine months later, she visited us for a follow-up of the surgery. She complained of lower quadrant discomfort with hot flashes. Transvaginal ultrasound revealed a multilocular cystic mass measuring 86.7 × 51.8 mm in size. With regards to the tumor markers, CA125 levels were slightly elevated up to 37.5 U/ml, but CEA (1.4 ng/ml) and CA19-9 (8.1 U/ml) levels were within normal ranges. The tumor was suspected to be a benign ovarian tumor. One month later, a transvaginal ultrasound revealed the enlargement of a multilocular cyst up to 100 × 66.3 mm (Figures 3 and 4). However, CA-125 levels returned to a normal level of 9.9 U/ml.

She was diagnosed as having the exacerbation of a remaining PIC. She was treated conservatively. The hot flashes were abated.

**Figure 3. — Chart of the course of case 2.**
with treatment with Chinese herbal medicines. However, menopausal symptom of chill remained, and the treatment with oral contraceptives (Anjyu) was begun. Serum levels of FSH were 9.2 mIU/ml and estradiol of 55 pg/ml. Immediately after the intake of contraceptives, lower quadrant discomfort and menopausal symptoms with chills disappeared and the remaining PIC shrank. One year and one month after the initiation of oral contraceptives (four years after the initial surgery), the PIC shrank to 46.6 × 33.3 mm (Figure 3). The patient has continued to take oral contraceptives, and the size of the PIC is of 57.8 × 63.4 mm (Figure 3).

Discussion

A PIC is a pseudocyst caused by the diminished ability of the peritoneum to absorb ascites and fluids from the ovaries due to the adhesions around the ovaries caused by pelvic surgery [1-3]. A PIC develops with an inflammation of the peritoneum as a result of pelvic surgery, infection, and endometriosis [1,2,4]. Capillaries and lymph ducts located throughout the peritoneum first become occluded and diminish the ability of peritoneum to absorb fluid [9,10]. Then, ascites are enclosed by the peritoneum, and the fluid is retained in those cavities instead of being absorbed [9,10]. The PIC often develops on the left-side of the pelvic cavity, since the broad mesentery of the sigmoid colon is extensively involved in the formation of closed cavities [4]. Retained ascites is mostly considered to be inflammatory exudate or fluid from the ovaries [1]. Especially when the ovary is enclosed with a closed cavity, secretions from the ovarian surface, blood from ovulation, or follicular fluid also flow into the closed cavity and helps the PIC to grow [6].

A PIC is one type of cystic mass within the pelvic cavity that needs to be differentiated from other masses. Establishing a diagnosis based on clinical manifestation and image findings is crucial to determine the treatment strategy. This is because PICs have a high rate (30-50%) of recurrence following surgery [2,4,9]. The ovary coming into contact with a closed cavity is a mechanism for the onset of a PIC [11]. Evidence of this contact is important for diagnosing a PIC [11]. Clinical manifestations and image findings of the PIC include: (1) a previous history of gynecologic surgery, endometriosis, and pelvic peritonitis, (2) the presence of an active ovary, (3) symptoms such as lower abdominal pains and lower abdominal discomfort, (4) image findings of a cystic mass with irregular margins and no solid component which fills the space inside the pelvic cavity, the ovaries located inside or outside of the margins of the mass, and (5) tumor markers within the normal range [11,12]. Once the diagnosis of the PIC is established, conservative treatment is recommended, given the high rate of the recurrence following surgery [9]. Surgical treatment should be adapted only to patients in whom PICs are hard to differentiate from ovarian tumors, those with large PIC lesions, and those with severe symptoms.

In the present cases, two patients had severe symptoms, and the differentiation between a PIC and an ovarian tumor was difficult. Surgery was chosen initially to treat PICs in both cases. In the first case the PIC disappeared with the lysis of adhesions but recurred afterwards, while in the second case a part of the PIC remained. The present cases also confirmed the high rate of recurrence following surgery and the difficulty in surgical procedure itself.

Aspiration is another choice to treat the PICs [13]. Sclerotherapy using vibramycin (doxycycline) or ethanol was shown to be effective when performed with aspiration [7,14,15]. The disappearance or shrinkage of PICs and a lower rate of recurrence in comparison with surgery have been reported with the combined therapy of sclerotherapy using vibramycin (doxycycline) or ethanol, whereas aspiration alone shows a similar recurrence rate to that of surgery [5,16]. In the first case, only aspiration was done to treat recurrence of the PIC, but a repeated recurrence occurred. In the second case, sclerotherapy with ethanol was combined with surgery, and recurrence did not occur in the lesion where sclerotherapy was performed. However, the remaining PIC became a problem later. When surgery is performed, combining sclerotherapy with surgery or aspiration could presumably curb the recurrence rate and increase the patient’s potential to recover.

Conservative treatment includes GnRHα therapy and hormone therapy using oral contraceptives. Currently, the response rate to hormone therapy using oral contraceptives is still remains unclear [1,6-8,17]. Oral contraceptives suppress ovulation, preventing fluid retention by a decreased fluid production [1,5] In both cases, the size of the PIC fluctuated during the treatment with oral contraceptives. Therefore, oral contraceptives cannot be categorically described as having sufficient effects on the shrinkage of PICs. Nonetheless, it was noticed that the PIC did not grow remarkably after the beginning of oral contraceptives. In the first case, the symptoms were not completely alleviated de-
spite the shrinkage of the PIC, but surgical treatment was not required (Figure 2). In this case, after cessation of oral contraceptives, severe subjective symptoms recurred. Thus, oral contraceptives have some therapeutic benefit as a conservative treatment for PICs in addition to an auxiliary benefit of treating menopausal symptoms.

An advantage of GnRHa therapy is its potential therapeutic benefit. Several reports have indicated that GnRHa therapy eliminates PICs and involves little recurrence rates [7,17]. GnRHa therapy should be the first choice when conservative treatment is chosen in patients with the PIC. The add-back therapy using contraceptives with GnRHa agonists is recommended to the case of patients with PICs and menopausal symptoms. After confirming the disappearance of PICs by GnRHa therapy, oral contraceptives may be used as a maintenance therapy. This treatment strategy may further prevent the recurrence of PICs.

Collectively, sclerotherapy using vibramycin (doxycycline) or ethanol is recommended for patients with a PIC as a surgical option, whereas conservative treatment with GnRHa therapy is a first choice. The present cases treated with oral contraceptives for the PICs suggest that oral contraceptives may also be another choice as the conservative treatment for the PICs.

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Asymptomatic large bladder diverticulum

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Summary

The authors report a case of a 61-year-old woman diagnosed with large bladder diverticulum. Diagnosis was performed only after a series of investigations carried out for the occasional finding of hypercreatininaemia. Although the significant volumes of post void residual (PVR) and the relevant urine stagnation in the diverticulum, subjective symptomatology was absent and urinalysis and urine culture were negative. The scheduled therapeutic plan consisted of fosfomycin three grams every ten days for six months, self-catheterization twice a day, voiding on a time schedule, and adequate fluid intake. The monthly scheduled follow-up at one year showed good general health, good compliance with the therapy, no urinary tract infections, a decrease in creatininemia to 1.2 mg/dl, and regression of nephrohydrosis to a mild stage. In conclusion, the absence of symptoms and negative urinalysis or urine culture allows expectant management despite the considerable size of the bladder diverticulum.

Key words: Bladder diverticulum; Hypercreatininaemia; Post void residual; Self-catheterizations.

Introduction

Bladder diverticula are projections of the mucous membrane through hernia openings in the bladder muscular coat (false diverticula) or, more rarely, projections of all the layers of the bladder wall (true diverticula) [1]. The causes are due to weakness of the bladder wall and/or to the increased pressure inside the organ, both due to urethral obstructions or to neurogenous alterations in bladder voiding. Bladder diverticula are generally classified into two groups as primary (congenital) and secondary (acquired). Primary diverticula develop as a result of congenital weakness of Waldeyer’s fascia sheath, without bladder outlet disorder, whereas secondary diverticula usually occur as a result of neurogenic bladder or infravesical obstructions, such as in the posterior urethral valve. Stage et al. [2] described iatrogenic diverticula occurring as a result of ureteral reimplantation, suprapubic cystostomy, or after closure of the rectovesical fistula as a third group. In general bladder diverticula develop from congenital detrusor muscle defect and frequently present with urinary tract infection, which occurs as a result of urinary stasis in the diverticula. Different clinical presentations, such as bladder outlet obstruction, cyanosis of the lower extremities, intestinal obstruction, ureteral obstruction (which may occur due to direct diverticular compression), and peritonitis due to spontaneous rupture of the diverticula, were previously reported. In contrast, “urethral stenosis” involves the narrowing of the urethral channel (diameter) usually due to fibrotic processes resulting from lesions with many different causes (inflammations, infections, neoplasias) and responsible for alterations in bladder voiding [3-7].

Case Report

A nulliparous 61-year-old woman, 24 BMI (height: 168 cm, weight: 67 kg), suffering from Hashimoto thyroiditis and gastroesophageal reflux, was in good health. At 38 years an abdominal subtotal hysterectomy with ovarian conservation was performed because of menorrhagia due to uterine fibromatosis, with regular postoperative period and no complication. Five months later, surgical removal of cervical stump was performed because of moderate vaginal haematojenous bleeding. The patient experienced urinary retention in the second postoperative day at the time of bladder catheter removal; therefore, the catheter was repositioned. At catheter removal 48 hours later, the patient still experienced difficult urination characterized by a slow flow, difficulties in voiding the bladder together with significant volumes of post void residual (PVR). Nonetheless, as urinalysis results were negative and no fever was reported, the patient was discharged and prescribed intermittent self-catheterization. About three months later, the patient on her own initiative gradually suspended intermittent catheterization and regular urination was re-established. Since then, the patient was in good health for about 23 years. At 61 years, she began to suffer from abdominal pain referred to a colitis; the general practitioner prescribed routine blood chemistry analyses and accidentally diagnosed hypercreatininaemia (2.2 mg/dl). Therefore, kidney and abdominal ultrasound were performed and showed: moderate bilateral nephrohydrosis with anterior-posterior diameter of the renal pelvis of 37 mm on the right and 32 mm on the left (such values remained unchanged in the post void examination); a distal ureteral ectasia on both sides in the juxta-vesicular area; bladder overdistension with significantly thickened walls and small projections of the false diverticula. The picture was compatible with stress bladder, therefore the patient was referred to the present urogynaecological department.

Revised manuscript accepted for publication September 23, 2013
The clinical assessment showed: soft vagina seven cm in length, no prolapse, no urethral hypermobility or pudendal neuropathy, good and preserved exteroceptive and proprioceptive sensitivity. The bladder diary over three days was within the physiological ranges (daytime urinary frequency: eight to nine times; night time frequency: once; voided volumes: 250 +/- 30 cc; daily fluid intake: 1,500 cc; no signs of urge or stress incontinence, nor urinary disorders reported). The uroflowmetry showed a continuous and slow flow with a maximum quantity of nine ml/sec (maximum flow), voiding time of 63 seconds, and voided volume (VV) of 300 ml. An ultrasound examination showed a large bladder diverticulum (Figure 1), compatible with a significant PVR: an extemporaneous catheterization with a Nelaton 8 catheter showed a residual volume of 1,200 cc. At cystoscopy, the insertion of the cystoscope was difficult due to a proximal urethral stenosis, requiring dilation of the urethra; the examination confirmed the presence of a large bladder diverticulum in the anterior wall with no endoluminal neoplasms and displaying a regular wall structure. Finally, an urodynamic assessment confirmed a continuous and slow flow as in case of urethral obstruction [10-13].

The prevalence of bladder/urethral outlet obstruction in women is unknown and has probably been underestimated. Moreover, no standard definitions are available for the diagnosis of bladder outlet obstruction in women. Usually, bladder outlet obstruction is defined as a persistent, low, maximum “free” flow rate of <12 ml/s in repeated non-invasive uroflow examinations, combined with high detrusor pressure at a maximum flow (pdet.Qmax > 20 cm H2O) during detrusor pressure–uroflow examinations. In conclusion, in the present case report the diagnosis was bladder diverticulum associated with obstructive urinary difficulties due to urethral stenosis.

As the etiopathogenesis of hypercreatininaemia was clear, self-catheterization twice a day was prescribed, as well as fosfomycin three grams every ten days for six months, voiding on a time schedule, and adequate fluid intake. Moreover, the patient was asked to fill in a precise bladder diary, to perform urine culture, and creatininemia every two weeks, to undergo ultrasonographic examination. The monthly scheduled follow-up at one year showed good general health, good compliance with the therapy, no urinary tract infections, a decrease in creatininemia to 1.2 mg/dl, negative urinalysis, and regression of nephrohydrosis to a mild stage. The scheduled pharmacological and life-style intervention plan will continue. Urethral dilatations will be performed if during follow-up urethral stenosis worsens or obstructive symptoms arise; diverticulectomy will be performed if PVR increases or becomes uncontrollable by self-catheterizations, and/or cause worsening bilateral nephrohydrosis.

Discussion

Bladder diverticula represent a herniation of the bladder urothelium through the muscularis propria of the bladder wall, resulting in the typical finding of a variably sized, thin-walled, urine-filled structure adjacent to and connecting with the bladder lumen through a narrow neck, or ostium. Bladder diverticula may be classified as either congenital or acquired, with different pathophysiology, presentation, and imaging. Congenital diverticula usually present during childhood, with a peak incidence in those less than ten years old, are usually solitary, occur most commonly in males, and are located lateral and posterior to the ureteral orifice, often in association with vesicoureteral reflux [14, 15]. The primary causation in those without coexisting lower urinary tract conditions appears to be a congenital weakness at the level of the ureterovesical junction and not bladder outlet obstruction. Congenital bladder diverticula have been noted in association with congenital connective tissue disorders (such as Menkes syndrome, Williams syndrome, Ehlers-Danlos syndrome); whether there is a genetic predisposition to the formation of bladder diverticula in individuals without congenital syndromes is unclear [16].

Acquired diverticula are often multiple, located most commonly at the ureterovesical hiatus but also occur elsewhere in the bladder, and associated with bladder outlet obstruction (anatomical or functional), infection, and
iatrogenic causes. Bladder diverticula in females are uncommon and quite rare in the absence of obstruction [16]. Bladder diverticula may also be iatrogenic: inadequate closure of the muscular layers of the bladder wall following a cystotomy for any indication may result in formation of a bladder diverticulum at a weak point of the suture line. In the present case report, the patient had undergone abdominal hysterectomy. A potential relationship between bladder diverticulum and hysterectomy has been suggested since bladder injury can occur during hysterectomy and diverticula may develop on sites of occult bladder wall injury; on the other hand, urethral stenoses can appear as a result of micro-traumas leading to phlogistic processes without obstructive symptoms. Unfortunately, in the present case it is not clear whether the obstructive urinary disorders were present before the first surgery but not well detected, or if they appeared later. Indeed, the patient never reported hyperthermia as- sociated with dysuria and positive urinalysis or urine culture.

The most common symptom is urinary tract infection, which occurs as a result of urinary stasis in the diverticulum due to inadequate quantity of muscle on the diverticular wall. A narrow pedicle of the diverticulum is another factor affecting urinary stasis. Additionally, hematuria and vesicoureteral reflux are common clinical presentations. Less commonly, urinary retention (bladder outlet obstruction), intestinal obstruction, and ureteral obstruction may occur due to direct diverticular compression; finally, ureteral obstruction may develop due to the inflammation secondary to diverticulitis. The relevant feature of the present case report is the complete absence of symptomatology despite the significant volumes of PV, and the negative results at urinalysis and urine-culture despite the relevant urine stagnation in the diverticulum. Such clinical data led to a conservative treatment including pharmacological and life-style intervention: self-catheterization twice a day, fosfomycin three grams every ten days for six months, voiding on a time schedule, adequate fluid intake, monitoring the kidney function as far as nephrohydrosis, creatininemia, and urinary tract infections. Incidentally found congenital or acquired bladder diverticula, even large, may require no further therapy unless associated with persistent symptoms, recurrent infections, obstruction, stones, malignancy, or other complicating factors such as ipsilateral vesicoureteral reflux. Indications for surgical interventions are worsening urethral stenosis or arising obstructive symptoms (urethral dilatations), increased /uncontrollable PVR or worsening bilateral nephrohydrosis (diverticulectomy). In conclusion the absence of symptoms and negative urinalysis or urine culture allows expectant management despite the considerable size of the bladder diverticulum.

References

Marked improvement of pain from long term fibromyalgia with dextroamphetamine sulfate in a woman who failed to improve with conventional pharmacologic treatment

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Summary

Purpose: To determine if treatment with the sympathomimetic amine dextroamphetamine sulfate, which has been so effective in treating a variety of pain syndromes, including severe pelvic pain and interstitial cystitis in women with the sympathetic neural hyperalgesia edema syndrome would also mitigate pain from fibromyalgia which was resistant to multiple therapies. Materials and Methods: Dextroamphetamine sulfate extended release capsules once daily was gradually increased to 25mg per day in a woman with treatment resistant fibromyalgia of 20 years duration. Results: Within a short time, the woman experienced dramatic relief of pain. Furthermore, her edema improved resulting in a 27 pound weight loss and her chronic fatigue improved. Conclusions: Fibromyalgia can be effectively treated with an innocuous dose of dextroamphetamine sulfate.

Key words: Sympathetic nervous system; Fibromyalgia; Sympathomimetic amines; Dextroamphetamine sulfate.

Introduction

There is a common defect of the sympathetic nervous system found more commonly in women that is associated with chronic pelvic pain, dyspareunia, dysmenorrhea, vulvovaginitis, backache, and interstitial cystitis [1-4]. One of the main functions of the sympathetic nervous system is to diminish cellular permeability. It has been hypothesized that various pain syndromes even outside of the pelvis may be attributed to the absorption of chemicals and toxic factors into the tissues (which leads to pain) [5-14]. In fact the elicitation of pain by installation of potassium in the urinary bladder is one of the ways to diagnose interstitial cystitis [15].

The purpose of the present study was to present another unique presentation for this disorder of sympathetic nervous system hypo-function – severe fibromyalgia responding extremely well to treatment with the sympathomimetic amine dextroamphetamine sulfate.

Case Report

A 36-year-old woman sought the authors’ medical opinion on why she has not been able to lose weight despite dieting. She was wondering if there could be an endocrinological disorder causing the problem.

She stated that following a traumatic brain injury following a fall 20 years ago, she began gaining considerable weight and over 20 years had gained 100 pounds. Not only was weight gain an issue but she had amnesia for much of her life before the injury and developed severe fibromyalgia which persisted for 20 years. All parts of her body developed hyperalgesia so that even the water from a shower hurt (allodynia).

She was surprised to hear that the authors’ opinion was that there was probably a connection between her unexplained weight gain and her fibromyalgia. They explained about the defect in the sympathetic nervous system that leads to increased cellular permeability and that it can lead to weight gain from the inability to compensate to the increase in hydrostatic pressure which would lead to translocation of fluid from intravascular to extravascular space were it not for a signal from the sympathetic nervous system causing a decrease in capillary permeability [16, 17]. She was advised that a controlled study proved the efficacy of treating this orthostatic edema with dextroamphetamine sulfate rather than conventional diuretics [18]. The reason why conventional diuretics fail to improve the edema is that they work predominantly on the ascending limb of Henle and to some degree the distal tubule, whereas the increased capillary permeability causes the fluid to extravasate from the proximal tubule. Dextroamphetamine sulfate, a sympathomimetic amine, replaces the defective neurotransmitter for the sympathetic nervous system and restores sympathetic activity, which allows these afflicted people to maintain body homeostasis by inhibiting capillary permeability when exposed to the increase in hydrostatic pressure [18].

Though the condition was originally termed idiopathic orthostatic cyclic edema [16-18], association with various pain syndromes has resulted in a change of name to the sympathetic neural hyperalgesia edema syndrome [1, 8]. The woman presently was taking five oxycodone-acetaminophen tablets per day. She had failed to respond to a multitude of treatments which in the early days included guaifenesin, non-steroidal anti-inflammatory drugs, and glucocorticoids none of which provided effective relief.

Subsequently she was treated with the tricyclic antidepressant amitriptyline and the dopamine receptor agonist ropinirole which also did not relieve the pain.
Finally she was treated with the newer balanced dual serotonin and norepinephrine receptor inhibitor duloxetine without relief of pain.

The final therapy that failed and in fact caused her more edema and weight gain was the anticonvulsant pregabalin which is in the family of alpha-2 delta-ligands known to have analgesic, anxiolytic, and anticonvulsant activity.

Within one month of treatment with 15 mg extended release capsules once daily of dextroamphetamine sulfate, she had improvement in her generalized pain which was reduced by 70%. Raising the dosage to 25 mg decreased the pain as she said tremendously to a degree that she could completely discontinue her opioid treatment. She also had lost 27 pounds in six months from 241 pounds to 214 pounds.

**Discussion**

Fibromyalgia syndrome is theorized to function as an abnormal central processing pain disorder which involvesafferent augmentation of peripheral stimuli, especially of the nociceptive types and a variety of neurogenic qualities with symptoms which include pain, fatigue disturbances, and alteration of cognitive/mood [19]. The pain is frequently described as a generalized tenderness without synovitis accompanied by edema, hyperpathia, and hyperalgesia [19]. Fibromyalgia has a prevalence of two to four percent of the general population and appears to be a genetic dysregulation with potential alteration in normal neuroendocrine, neuro-modulation, neurotransmitter, biochemical, and neuro-receptor function and physiology [19].

The pathophysiology of fibromyalgia involves abnormal levels of serotonin and norepinephrine (a sympathomimetic amine) which are key neurotransmitters in endogenous pain inhibiting pathways [20, 21].

The treatment of fibromyalgia employs a multidisciplinary team effort using combined treatment approaches, including patient education, aerobic exercise, cognitive behavior therapy and pharmacologic therapies (serotonin norepinephrine receptor inhibitors) (e.g., duloxetine, milnacipran) and alpha 2-delta receptor ligands (e.g., pregabalin) may improve symptoms as well as function of patients with fibromyalgia [19-22].

Though not her main complaint, the patient described having chronic fatigue. She said it was hard to separate pain and fatigue. As mentioned, fatigue is frequently part of the fibromyalgia syndrome. However, fatigue with or without pain may be part of the sympathetic neural hyperalgesia edema syndrome [23].

Dextroamphetamine sulfate is very well tolerated in general and in dosages up to 30 mg per day, is not addicting and can be stopped suddenly without dependence. Especially in women, e.g., the case described, it should be prescribed in women with a history of edema or weight gain over alpha-2 delta ligands, e.g., pregabalin which is notorious for causing edema and weight gain [22].

**References**


Marked improvement of pain from long term fibromyalgia with dextroamphetamine sulfate in a woman who failed to improve etc.


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Near death of a pregnant Somali woman due to neglected eclampsia

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Summary
Purpose: To report a case of cardiac arrest of a Somali woman in labor due to neglected eclampsia. Materials and Methods: A 16-year-old Somali primigravida was seen because of convulsions at 28 weeks gestation. She had two attacks of convulsions at home before coming to the hospital. She suffers from diabetes and is insulin-dependent. Her convulsions were controlled with diazepam. Vaginal examination showed a seven cm dilated cervix with high-breech. In the operating room, cardiac arrest occurred. Results: Cesarean section was performed during resuscitation. The patient’s maternal condition improved and was diagnosed with pulmonary edema and diabetic ketoacidosis. She was admitted to the intensive care unit (ICU) then transferred to the postnatal ward. She was discharged home and is in good general condition. Conclusion: Inadequate or lack of antenatal care of Somali pregnant women due to many factors, including ignorance, can result in medical catastrophic situations as illustrated in the current case.

Key words: Eclampsia;, Somali woman; Labor.

Introduction

Antenatal care is defined as the care that a woman receives from healthcare professionals during pregnancy [1]. It is considered an important and effective method for preventing, detecting, and treating high-risk pregnancy by implementing maternal education, screening for abnormalities and complications, ongoing assessment, and care. In recent years, with the current international immigration patterns, concerns have been raised regarding the care of migrant obstetric populations. The amount of antenatal care these women receive is variable. This is reflected by the higher mortality and morbidity rates among immigrant women compared to non-immigrant women [2]. There is growing evidence that the risks are further increased among Somali immigrants [3]. The aim of this case report is to document a case of cardiac arrest of a Somali woman in labor due to neglected eclampsia.

Materials and Methods

A 16-year-old Somali primigravida was seen in the emergency room because of convulsions at 28 weeks gestation. She was previously unregistered in the hospital. She had two convulsive attacks at home prior to coming to the hospital. She suffers from Type I diabetes mellitus and has been on insulin since childhood. On examination she was having convulsions and her vital signs were: pulse 120/minute, blood pressure 185/120 mm Hg, respiratory rate 30/min, and afebrile. Her convulsions were controlled intravenously with 5 mg of diazepam. Abdominal examination revealed a 28-week single viable breech presentation. Vaginal examination showed a seven cm dilated cervix. The decision was made to perform an emergency Cesarean section. In the operating room, before commencing the Cesarean section under general anesthesia, cardiac arrest occurred. Resuscitation was then performed.

Results

Cesarean section was performed during resuscitation. The outcome was 1,000 gram boy with Apgar score of 7, 8, and 10 at one, five, and ten minutes. The maternal condition improved and was transferred to the Intensive Care Unit (ICU) where she was diagnosed to have pulmonary edema and diabetic ketoacidosis which were treated accordingly. She remained in the ICU for four days and was then transferred to the postnatal ward. She was discharged home in good general condition on the 10th postoperative day. The baby was also well.

Discussion

Recent publications by Western health providers report peculiar experiences with Somali immigrants. The experience has been that Somali women are often hesitant to accept obstetric interventions, such as induction of labor or Cesarean delivery when indicated [3]. Somali women in the United States have expressed concerns that they fear Cesarean section and that healthcare providers prefer interventions, such as Cesarean delivery [4, 5]. There is substantial evidence that language barriers adversely affect access to healthcare, its quality, patient satisfaction, and health outcomes in all hospital services including obstetrics. Family members or friends are often used as informal interpreters in maternity care settings, although this arrangement can be unethical and potentially-implicated in clinical incidents because of the increased chances in misunderstanding medical words, hospital procedures, and facilities [6]. Therefore, proper translation by bilingual hospital workers is of paramount importance. Antenatal care services should be available for immigrant pregnant

Revised manuscript accepted for publication August 16, 2012
women. In the current center, medical care is free; however, some immigrant pregnant women do not register in the booking system and are not seen in the antenatal clinics during pregnancy. They present in the emergency room in labor. The hospital’s policy is to accept them and admit them to the hospital. Inadequate or lack of antenatal care of Somali pregnant women due to many factors, including ignorance, can result in medical catastrophic situations as illustrated in the current case. Extra care should be given to educate this group of Somali pregnant women.

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Introduction

Tuberous sclerosis (TS) or tuberous sclerosis complex (TSC) is a rare, multi-system genetic disease that causes non-malignant tumors to grow in the brain and in other vital organs such as the kidneys, heart, eyes, lungs, and skin [1]. TSC is caused by a mutation of either of two genes, TSC1 and TSC2, which encode for the proteins hamartin and tuberin, respectively. These proteins act as tumor growth suppressors, agents that regulate cell proliferation, and differentiation [2].

TSC1 encodes for the protein hamartin, is located on chromosome 9q34 and was discovered in 1997 [3]. TSC2 encodes for the protein tuberin, is located on chromosome 16q13.3 and was discovered in 1993 [4]. TS occurs in all races and ethnic groups. The live-birth prevalence is estimated to be between ten and 16 cases per 100,000 with more than half of these cases undetected [5].

The diagnosis of TS was established with Vogt’s triad, associated with learning disability, seizures, and facial angiofibroma. Despite all these, there are no pathognomonic clinical signs for tuberous sclerosis. Many signs are present in individuals who are healthy (although rarely), or who have another disease. A combination of signs, classified as major or minor, is required in order to establish a clinical diagnosis [6] (Tables 1 and 2).

In infants, the first clue is often the presence of seizures, delayed development or white patches on the skin. A full clinical diagnosis involves:

- Taking a personal and family history.
- Examining the skin under a Wood’s lamp (hypomelanotic macules), the fingers and toes (ungual fibroma), the face (angiofibromas) and the mouth (dental pits and gingival fibromas).
- Cranial imaging with non-enhanced computed tomography (CT) or, preferably, magnetic resonance imaging (MRI) (cortical tubers and subependymal nodules).
- Renal ultrasound (angiomyolipoma or cysts).
- An echocardiogram in infants (rhabdomyoma).
- Funduscopy (retinal nodular hamartomas or achromic patch) [7-8].

The incidence of disorders of certain organ system is variable, but neurological and renal complication are the leading causes of mortality and morbidity [9].

Case Report

The authors present a case of a 18-year-old female patient with a history of TS, epileptic episodes, mental retardation, and papillary formations in multiple organs located at the abdominal, axillary, cervical, facial, and genital region.

Key words: Multiple sclerosis; Angiofibroma; Fibroepithelial polyp.

Discussion

TSC is characterized by formation of hamartomas in multiple organ systems [10]. Although the majority of organs are susceptible, most patients exhibit dermatological, renal, and/or neurological manifestations [11]. More than 80% of people with TSC have central nervous system complications, such as severe and refractory seizures and autism [12]. Renal lesions are the most common lethal complication in patients with TSC [13]. Angiomyolipoma, hamartoma and renal cysts are major renal tu-
mors associated with TSC. Multiple and bilateral angiomyolipoma are found in around 80% of adult patients and the developed tumors with abnormal or immature blood vessels cause spontaneous bleeding [13-14]. Multiple and large renal cysts often lead to end-stage renal failure with bacterial infections and severe hypertension. A few percent of TSC patients show pulmonary lymphangiomyomatosis, particularly those in premenopausal women [15].

TSC is caused by the mutation of either TSC1 or TSC2 gene which both encode for the proteins hamartin and tuberin, respectively [16]. Loss of the TSC genes is directly related to enhanced cell size, altered cell proliferation, and abnormal organogenesis.

Neurologic manifestations of TSC were first described by D. M. Bourneville in 1880 and were later associated with clinical signs by Vogt in 1908. Vogt described what is commonly known as the classic triad of symptoms in TSC: seizures, mental retardation, and adenoma sebaceum (angiomyfibromas) [17]. However, studies have revealed that the triad occurs in only 29% with TSC and six percent lack of all symptoms [18].

Some clinical types of TSC such as neonatal infantile spasms revealing hypopigmented macules occasionally lead to diagnosis [19]. On the contrary, some features remain entirely asymptomatic [20].

Cardiac rhabdomyomas are commonly found in patients with TSC [21]. They usually occur on ventricular and septal walls. Most of them regress spontaneously or disappear before birth or during childhood. Cardiac rhabdomyomas typically do not cause symptoms at birth [22].

Pulmonary involvement assumes the form of lymphangiomyomatosis and multinodular pneumocyte hyperplasia [23]. The cutaneous lesions as first sign of the disease must be widely excised and be sent for histological examination. Other treatment options include CO2 laser, which provides efficient and bloodless excision of the lesion, or phenolization, which allows a better cosmetic result [24].

Recent therapies include the use of oral rapamycin to decrease the growth of the tumors associated with TSC. This may represent a major advance in therapy [25].

Table 1. — Major signs

<table>
<thead>
<tr>
<th>Head</th>
<th>Facial angiofibromas or forehead plaque</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fingers and toes</td>
<td>Non-traumatic ungual or periungual fibroma</td>
</tr>
<tr>
<td>Skin</td>
<td>Hypomelanotic macules</td>
</tr>
<tr>
<td>Skin</td>
<td>Shagreen patch (connective tissue nevus)</td>
</tr>
<tr>
<td>Brain</td>
<td>Cortical tuber</td>
</tr>
<tr>
<td>Brain</td>
<td>Subependymal nodule</td>
</tr>
<tr>
<td>Brain</td>
<td>Subependymal giant cell astrocytoma</td>
</tr>
<tr>
<td>Eyes</td>
<td>Multiple retinal nodular hamartomas</td>
</tr>
<tr>
<td>Heart</td>
<td>Cardiac rhabdomyoma</td>
</tr>
<tr>
<td>Lungs</td>
<td>Lymphangioleiomyomatosis</td>
</tr>
<tr>
<td>Kidneys</td>
<td>Renal angiomyolipoma</td>
</tr>
</tbody>
</table>

Table 2. — Minor signs

<table>
<thead>
<tr>
<th>Teeth</th>
<th>Multiple randomly distributed pits in dental enamel (minor)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectum</td>
<td>Hamartomatous rectal polyps</td>
</tr>
<tr>
<td>Bones</td>
<td>Bone cysts</td>
</tr>
<tr>
<td>Brain</td>
<td>Cerebral white-matter “migration tracts”</td>
</tr>
<tr>
<td>Gums</td>
<td>Gingival fibromas</td>
</tr>
<tr>
<td>Liver, spleen,</td>
<td>Non-renal hamartoma</td>
</tr>
<tr>
<td>and other organs</td>
<td></td>
</tr>
<tr>
<td>Eyes</td>
<td>Retinal achromatic patch</td>
</tr>
<tr>
<td>Skin</td>
<td>“Confetti” skin lesions</td>
</tr>
<tr>
<td>Kidneys</td>
<td>Multiple renal cysts</td>
</tr>
</tbody>
</table>

Figure 1. — Multiple angiofibromas localized in the left vulvar lip.

Conclusion

TSC is a multisystem disorder with clinical manifestations. The appropriate diagnosis requires a multidisciplinary approach to properly treat affected individuals. There is need of awareness especially of the cutaneous manifestations of the disease and of the coexistence of them with other body systems.

References


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A rare complication of vaginal delivery: labial adhesion

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Summary
Labial adhesions are mostly seen in teenagers and menopausal women, however they may be encountered rarely in the postpartum period. Surgical division under local anesthesia is more effective than topical estrogen. Case: In this article a young woman at the age of 23 years, who gave normal vaginal birth 12 months prior and who had difficulty in coitus because of labial sineaia is reported. During physical examination, an adhesion between right and left labia minora approximately three cm in length was observed. The adhesion was separated under local anesthesia and the patient was discharged from the hospital on the same day. On postoperative seventh day control, she had neither complaints nor complications. Conclusion: Labial adhesions are rarely encountered after normal vaginal childbirth. The most effective treatment of labial sineaia is surgical division under local anesthesia.

Key words: Postpartum; Labial adhesion; Treatment.

Introduction
Labial adhesions are mostly seen in teenagers and less frequently in older women. The predisposing factor of adhesions is attributed to relative hypoestrogenic condition at these ages. In reproductive period: female circumcision, lichen sclerosis, herpes simplex infections, diabetes mellitus, pemphigoid, recurrent urinary infections, lack of sexual activity, local trauma and caustic vaginitis play a secondary role in the etiology [1,2]. Labial adhesions after birth are rarely encountered.

Case Report
The primigravid woman at age of 23 years had given spontaneous vaginal birth at 38th week of pregnancy 12 months prior. She was discharged from the hospital the day after without any complications. She returned to the hospital because of difficulty in coitus after giving birth. During physical examination an adhesion between right and left labia minora approximately three cm in length was observed (Figure 1). Local anesthesia performed by one percent lidocaine containing epinephrine. The adhesion was divided with electro-catheter ablation in gynecologic position in the operating room (Figure 2). The patient was discharged from the hospital on the same day. On postoperative seventh day follow-up, she had neither complaints nor any difficulty with coitus.

Discussion
Labial adhesions are a simple occurrence, that are mostly encountered in teenagers and post-menopausal women; nevertheless they can be rarely encountered in reproductive period. The incidence of labial sineaia is unknown in the population, although the literature reports it to be in the range of 0.6% - 5% in total, but more frequent in the first two years of life [3-5]. Labial adhesions are benign diseases that are congenital or acquired [6]. Vulvovaginitis and mechanical irritation are presumed as the cause of labial adhesions but the real cause is not definite [3]. In reproductive period labial adhesions are rarely observed with the protective effect of normal sexual hormone levels; this impression supports that hypoestrogenic condition is a predisposing factor in labial and explains increased frequency of labial adhesions in post-menopausal women. Sometimes they can result from bad hygiene of the genital region [3,6].

Labial adhesions can be determined incidentally or as the result of various symptoms, such as vulvodynia, vaginal pruritus, voiding difficulty, change in urinary flow, urinary incontinence (stress and/or urge), recurrent urinary tract infections, urinary retention, enuresis, dysuria, dyspareunia, and pelvic pressure [2-4]. Similar as in this presented case, difficulty resuming sexual activity is the most commonly reported complaint in reproductive women with labial adhesion [1].

In treatment of hypoestrogenic women with atrophic mucosa, topical creams containing estrogen are preferred. Surgical division is a better alternative therapy in symptomatic thick adhesions than topical therapy and manual separation has failed, when recurrent adhesions occur with topical estrogens, and also when the patients did not accept the other treatment modalities. During surgical treatment, the adhesion is divided by blunt and sharp dissection under local anesthesia [3]. Although the role of the topical steroids and daily manual separation are certainly unknown, they are suggested to reduce recurrent labial adhesion. This presented case had a thick labial adhesion; for this reason, the authors opted for surgical division of the adhesion. Labium minors are separated with sharp dissection under local anesthesia. Topical estrogen is prescribed after the operation. At follow-up the authors did not observe recurrence and all complaints of the pa-
tient had improved. However, there are some reported cases in which recurrent adhesions have occurred and re-operation may be required in this group of patients [2,3,7,8].

Labial adhesion after normal vaginal birth is a rare situation and can be diagnosed earlier, simply with physical examination during the first visit after labour.

References


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Introduction

Hypoplastic left heart syndrome (HLHS), accounts for four percent of all cases of congenital heart disease (CHD). Infants will die soon after their birth unless they undergo surgical intervention. HLHS is the most severe form of the obstructive lesions of the left heart side.

Case Report

In the present case, a 36-year-old woman, gravida 5, para 3, of Muslim descent, rhesus positive, was referred to this outpatient clinic in the 18th week of gestation for monitoring of her pregnancy. A 22-week anomaly scan confirmed hypoplastic left heart syndrome (HLHS) but the parents declined any medical intervention. Here the authors present the management of a pregnancy and the expected quality of neonatal life.

Key words: Aortic atresia; Aortic hypoplasia; Congenital heart disease; Hypoplastic left heart syndrome; Mitral stenosis; Nuchal fold.

Discussion

HLHS, a collection of anomalies, accounts for four percent of all cases of CHD. Infants will die soon after their birth unless they undergo surgical intervention. HLHS is the most severe form of the obstructive lesions of the left heart side. The way HLHS is inherited is not clearly defined. Although there is male predominance, in this case report the affected fetus is of female gender. Tricuspid regurgitation is present in more than 50% of patients with HLHS preoperatively. In the present fetus, no regurgitation was detected.

A four-chamber view with a small left ventricle and a hypoplastic ascending aorta is the common view that guides the sonographer to the diagnosis of HLHS [1, 2]. Occasionally the left ventricle can be smaller than the right one but not enough to be clearly demonstrated in the four-chamber view until the late second- or early third-trimester of pregnancy. The right ventricle becomes more spherical [3]. The left ventricular wall may show decreased contractility and appear echogenic. The presence of atrial septal restriction should be taken into consideration as it increases mortality [4]. HLHS is associated with other heart anomalies such as ventricular septal defect, aortic arch interruption, transposition of the great vessels, and central nervous system abnormalities such as microcephaly, holoprosencephaly, and agenesis of corpus callosum. Magnetic resonance imaging (MRI) testing during intrauterine life has failed to detect fetuses with possible neurodevelopmental abnormalities after birth [5]. The fetus should go through a detailed sonography to exclude sonographic markers for trisomies and Turner Syndrome and amniocentesis should be offered if they are present [6]. In Doppler real time examination, there is retrograde blood flow to ascending aorta and aortic arch.
Embryos with HLHS have a normal intrauterine growth, but their prognosis after birth is extremely poor. If diagnosis is done before 24 weeks, termination of the pregnancy should be offered after informing the couple of the neonatal mortality and the complications of the surgical intervention. Parents need to be informed on available intrauterine surgical interventions [7]. If expectant management is desired from the parents, the embryo should undergo series of sonographic exams. Fetal growth should be assessed on a regular basis [1].

Delivery should be performed in a tertiary center with pediatric specialists and referral to cardiothoracic surgeons for initial palliation.

Prostaglandin therapy is given to affected infants after birth for keeping ductal patency with poor outcomes, as they begin to develop heart failure in the first day. Despite improved surgical outcomes, the majority of infants continue to receive no surgical care [8]. Surgical intervention can be heart transplantation or Norwood repair, a three stage surgery [9]. Stage 1 involves anastomosis of the pulmonary artery to the aortic arch for systemic outflow, placement of a systemic-to-pulmonary arterial shunt to provide pulmonary blood flow, and arterial septectomy to ensure unobstructed pulmonary venous return; the survival rate of fetuses diagnosed in utero is in the region of 40%. Stage 2 (in the sixth month of life) involves anastomosis of the superior vena cava to the pulmonary arteries [2]. The final stage is the Fontan operation, which can be performed between the ages of 18 months and four years. The operative mortality of the Norwood operation is ten percent, the postoperative long-term effects of surgical intervention survivors may include neurodevelopmental abnormalities [9, 10].

Conclusion

HLHS is the most common heart disease. It is detectable during pregnancy and the establishment of the diagnosis compels parents to face the dilemma of discontinuing the pregnancy or having conservative management of it.
Introduction

Angioleiomyoma or angiomyoma or vascular leiomyoma is an unusual benign mesenchymal neoplasm [1]. It is composed of smooth muscle cells and contains thick-walled vessels [1]. It most commonly occurs in the skin of lower extremities, head and trunk [2]. Uterine angioleiomyoma is extremely rare and only few cases have been reported in the English literature [1, 3-11].

The authors’ aim was to present a rare case of large uterine angioleiomyoma causing severe abnormal uterine bleeding and review current literature.

Case Report

The patient, a 53-year-old, gravida 2, para 2 premenopausal Greek woman presented to the 2nd Department of Gynaecology of St. Savvas Anticancer-Oncologic Hospital, with a complaint of severe abnormal uterine bleeding. On gynecologic examination there was a palpable pelvic mass. Preoperative computer tomography (CT) of the abdomen and pelvis revealed an intra-abdominal mass 25 x 15 cm with abnormally increased vascularization. She underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy, total omentectomy and elective pelvic lymph node dissection. Histopathology revealed uterine angioleiomyoma. Follow up 84 months after initial surgery showed no evidence of recurrence.

Conclusion

Despite the type of surgery, patients with uterine angioleiomyoma have very low risk of recurrence and excellent prognosis.

Key words: Angioleiomyoma; Angiomyoma; Vascular leiomyoma; Uterus.

Discussion

Angioleiomyoma is an unusual benign mesenchymal neoplasm. It most commonly occurs in the subcutis of the lower extremities [1,2]. It can also be located in the head and neck region, even in the submandibular gland [1,2,12,13].

Only few cases of angioleiomyoma of the female genital tract have been reported in the English literature [1,3-11,14-16]. Almost all of them located in uterus and only two cases located in ovary [1,3-11,14,15]. Perhaps they are underreported, because in many cases they are also recognized as benign leiomyomas with an unusual histological appearance [6].

It is a well-circumscribed or encapsulated tumor and contains minimal collagen [7]. It is composed of smooth muscle cells and contains thick-walled vessels [1]. The nature of vessels remains controversial [1]. An appreciable number
of angioleiomyomas are not true tumors but rather instances of vascular malformation [2, 17]. Angioleiomyoma most likely derives from tunica media of small blood vessels or from arteriovenous anastomoses [1,2,7,17,18]. Also some cases of angioleiomyomas are hamartomas, because they have variable proportions of mature adipose tissue, smooth muscle cells and anomalous thick-walled vessels [2].

They are classified into three histological subtypes: capillary or solid (66%), cavernous (11%) and venous (23%) [2,14,18]. Classification is based on the variable relationship among smooth muscles and vascular cavities of different shapes [4]. However, histological subtypes have no clinical significance [2].

It usually develops in women between the fourth and sixth decade of life [1,2,19]. Degenerative changes in angioleiomyomas are due to ischemia and they depend on the degree and rapidity of the onset of vascular insufficiency [2]. Myxoid and hyaline changes are the most common forms of degeneration [2,18].

The clinical presentation of uterine angioleiomyoma is usually nonspecific. The most common presenting symptoms and signs are: abdominal/pelvic pain, abdominal/pelvic mass and abnormal uterine bleeding [4,7,20]. The present patient presented with a large uterine angioleiomyoma causing severe abnormal uterine bleeding.

The exact mechanism of abdominal/pelvic pain in patients with uterine angioleiomyomas, remains inconclusive [1]. Perhaps it is pain-related with local ischemia from vessel contraction [1,2,18].

Also uterine angioleiomyomas that contain venous plexuses and dysregulation of growth factors and/or their receptors that regulate angiogenesis or have other effects on vascular structures, are responsible for abnormal uterine bleeding [1,4,21,22].

Usually uterine angioleiomyomas are small in size [7]. However in some cases they have an unusual large size, causing pain, and/or severe abnormal uterine bleeding [4,7,8]. The present patient presented with a large uterine angioleiomyoma causing severe abnormal uterine bleeding. Despite the large size of tumor, the authors did not find degenerative changes on histopathological examination.

The nonspecific nature of symptoms, signs, and imaging findings of uterine angioleiomyomas renders preoperative diagnosis exceptional [23]. All reported cases are diagnosed after surgery [7,23].

Treatment of choice in patients with uterine angioleiomyoma is complete surgical excision [1,4,7]. Either angioleiomyomectomy or hysterectomy, are effective treatment approaches with excellent results [1,4,7]. The present patient underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy, total omentectomy, and elective pelvic lynch node dissection because frozen section revealed mesenchymal tumor with suspicion of malignancy.

The present patient is well with no evidence of recurrence, 84 months after initial surgery. Her prolonged survival is in accordance with current literature [2,6,7]. Despite the type of surgery, patients with uterine angioleiomyoma have very low risk of recurrence and excellent prognosis [2,6,7].

References

Uterine angioleiomyoma causing severe abnormal uterine bleeding


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