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**REVIEW ARTICLES**

Levonorgestrel-releasing intrauterine device used for dysmenorrhea: five-year literature review
A. Imai, K. Matsunami, H. Takagi, S. Ichigo - Kasamatsu, JAPAN
LNG-IUD is equal or superior to treatment with systemic progestins or oral contraceptives in the treatment of dysmenorrhea.

Association of sympathetic nervous system activity with polycystic ovarian syndrome
W. Li, Y. Chen, L. Xu - Chengdu, CHINA
The possible etiology of polycystic ovarian syndrome may be related with the sympathetic neuroendocrine system.

**ORIGINAL ARTICLES**

Prolonged saltatory fetal heart rate pattern leading to newborn metabolic acidosis
I. Nunes, D. Ayres-de-Campos, A. Kwee, K. G Rosën - Porto, PORTUGAL
A saltatory fetal heart rate pattern exceeding 20 minutes can be associated with the recurrence of fetal metabolic acidosis.

Neonatal mortality rate and risk factors in northeast China: analysis of 5,277 neonates in 2005
J. Sun, S. Qu, C. Zhang, Z. Xiang, Z. Fu, L. Yao - Harbin, CHINA
The risk factors that influence neonatal mortality are examined in a population of northeast China.

Normal “high” thyroid stimulating hormone (TSH) levels and pregnancy rates in patients undergoing IVF with donor eggs
Mild abnormalities of thyroid function may adversely affect the pregnancy rates in patients undergoing in vitro fertilization with donor eggs.

Evaluation of uterine perfusion in postmenopausal women receiving hormone replacement therapy
A.S. Kara, A.I. Guzel, L. Önderoğlu - Ankara, TURKEY
Hormone replacement therapy during menopause has a protective effect on vessels and cardiovascular system.

A randomized-clinical trial examining a neoprene abdominal binder in gynecologic surgery patients
J.B. Szender, K.L. Hall, E.R. Kost - San Antonio, TX, USA
The abdominopelvic binder resulted in increased ambulations in the first postoperative day in patients at high risk for postoperative complications.

Craniofacial catch-up growth in intrauterine growth retarded rats following postnatal nutritional rehabilitation
M.E. Luna, F.A. Quintero, M.F. Cesani, M.C. Fucini, V. Priol, L.M. Guimarey, E.E. Oyhenart - La Plata, ARGENTINA
The effect of postnatal nutritional rehabilitation in craniofacial growth of rats with intrauterine growth retardation was analyzed.
Maternal serum pregnancy-associated plasma protein-A levels in hyperemesis gravidarum: a prospective case control study
B.S. Unlu, H. Energin, Y. Yildiz, E. Unlu, E.G. Yapor Eyi - Ankara, Turkey
Maternal serum pregnancy-associated plasma protein-A levels increase in hyperemesis gravidarum, even after excluding potential cofounders.

The influence of ritodrine alone or in combination with nifedipine on maternal cardiovascular side effects and pregnancy outcomes
M.J. Kim, I. Hwang, J.Y. Bae, W.J. Seong - Daegu, Korea
The combination regimen of ritodrine and nifedipine may be considered a safe and effective method to prolong gestation in patients with preterm labor.

The possible role of zinc in the etiopathogenesis of endometriosis
The relationship between zinc and endometriosis was evaluated.

Relation of peritoneal fluid and serum vascular endothelial growth factor levels to endometriosis stage
A. Kopuz, S. Kurt, Ö. Demirtaş, E. Töz, A. Taşyurt - Izmir, Turkey
Early-stage endometriosis is correlated with elevated serum vascular endothelial growth factor levels.

Study of individualization therapy for 61 patients with cesarean scar pregnancy
H. Shao, J. Ma, X. Su, L. Xu, C. Yang, X. Su, Y. Fu - Yuyao, China
Timing of curettage for cesarean scar pregnancy is determinant for the outcome of the treatment.

Fetal nasal bone length at 11+0-13+6 weeks of gestation: an evaluation of 554 consecutive cases
A. Cansu, H. Ozgur, S. Guven, G. Dinc, H. Dinc - Trabzon, Turkey
A nasal bone length monogram was found to be useful in prenatal screening and diagnosis of syndromes associated with nasal hypoplasia.

Expression of anti-inflammatory mediator lipoxin A4 and inflammation responsive transcriptive factors NF-kappa B in patients with preeclampsia
L.L. Huang, S. Su, R. Awale, Y.Y. Zhang, L.L. Zhong, H. Tang - Nanning, China
Lipoxin A4, lipoxin receptor, and NIK-kBp65 may be involved in the disease process of preeclampsia.

Sexual dysfunction in Turkish women with dyspareunia and its impact on the quality of life
B. Artunc Ulkumen, M.M. Erkan, H.G. Pala, Y. Bulbul Baytur - Manisa, Turkey
Dyspareunia has a major impact on women's sexual function and quality of life.

Serological prenatal screening and diagnosis for Down syndrome
Y. Duan, Y. Li, Q. Xue - Xinxiang, China
A review of recent prenatal screening for Down syndrome is reported.

CASE REPORTS

The triad of luteal phase ocular migraines, interstitial cystitis, and dyspareunia as a result of sympathetic nervous system hypofunction
J.H. Check, R. Cohen - Camden, NJ, USA
Treatment with sympathomimetic amines effectively treated a woman with a long history of the triad of premenstrual ocular migraines, interstitial cystitis, and dyspareunia.

Simultaneous heart valve replacement surgery and abdominal subtotal hysterectomy: case report
Lu Liu, Xue-rong Chen, Dong Huang, Hong-lin Zou, Ya-xiong Li, Xia Yu, Xu-mei Zhang - Kunming, China
An interdisciplinary approach for a case with heart valvulopathy and multiple uterine fibroids is described.
Matrix array transducer for the examination of fetal heart
R. La Torre, E. Bevilacqua, V. D’Ambrosio, G. Pasquali, C. Aliberti, F. Ventriglia, A. Giancotti - Rome, Italy
A new promising technology for X6-1 xmatrix array transducer compared with traditional technique.

Heart failure, metabolic acidosis, and postoperative multiple organ failure after anesthesia for cesarean section in a patient with Takayasu arteritis: a case report
Meiying Chi, Lifeng Qi, Ailan Cai, Yanwei Zhang, Fengguang Li, Xinquan Jia - Shandong, China
A case of a pregnant woman with Takayasu arteritis after anesthesia for cesarean section subsequently experienced heart failure, metabolic acidosis, and multiple organ failure.

Transvaginal repair of rectovaginal fistula by filling with bulbocavernosus fat pad and retaining scar tissue
A. Le, L. Shan, Z. Wang, X. Dai, T. Xiao, Y. Shen - Shen zhen, China
Repair of rectovaginal fistula by filling with bulbocavernosus fat pad and retaining scar tissue

Uterine preservation in placenta percreta complicated by unscarred uterine rupture at second trimester in a patient with repeated molar pregnancies: a case report and brief review of the literature
A. Ozdemir, I.E. Ertas, K. Gungorduk, C. Kaya, U. Solmaz, G. Yildirim - Izmir, Turkey
A case of successful uterine conservative management in placenta percreta complicated by unscarred uterine rupture at second trimester is reported.

Conjoined twins: three cases in one tertiary medical center and literature review
L. Kongling, X. Shi, Q. Yao - Chengdu, China
Early diagnosis was critical for obstetrics and perinatal management of three cases of conjoined twins.

Asymptomatic spontaneous complete uterine rupture in a term pregnancy after uterine packing during previous caesarean section: a case report
J. Zhang, S.F. Chen, Y.E. Luo - Shanghai, China
Dehiscence and rupture should be suspected in the presence of risk factors, as previous caesarean section.

A case of uterine rupture in mid-trimester spontaneous abortion: a complication of gemeprost vaginal administration
R. La Torre, E. Bevilacqua, V. D’Ambrosio, G. Pasquali, C. Aliberti, G. Perrone, A. Giancotti - Rome, Italy
Uterine rupture of a scarred uterus, for previous cesarean section, after induction with prostaglandins for spontaneous abortion.

Irreducible inguinal hernia containing rudimentary uterine horn, ovary, and fallopian tube
X. Yang, Q. Chen, J. Jiang, X. Ca - Hangzhou, China
An unusual case of indirect inguinal hernia with rudimental uterine horn, right ovary, and fallopian tube is reported.
Levonorgestrel-releasing intrauterine device used for dysmenorrhea: five-year literature review

A. Imai, K. Matsunami, H. Takagi, S. Ichigo
Department of Obstetrics and Gynecology, Matsunami General Hospital, Kasamatsu (Japan)

Summary
Intrauterine devices (IUDs) provide highly effective, long-term, safe, reversible contraception, and are the most widely used reversible contraceptive method worldwide. The levonorgestrel-releasing IUD (LNG-IUD), originally designed for long-term contraceptives, is now recognized to provide non-contraceptive health benefits. These include severe dysmenorrhea and/or heavy menstrual bleeding associated with uterine myoma, endometriosis, and adenomyosis. This report aims to review the last five-year literature on the efficacy and safety of the LNG-IUD in women with dysmenorrhea. Dysmenorrhea has been reported to decrease in all women. LNG-IUD seems to be superior over copper-releasing IUD for improving dysmenorrhea. The LNG-IUD is beneficial for symptom recurrence and endometriotic cyst recurrence after conservative surgery for patients with severe pain related to endometriosis. There is also evidence to support its role in menstrual problems of severely obese adolescent females. Expulsion, one of the important factors for IUD acceptability, is rare but more common in women with distorted uterine cavity. In the treatment of dysmenorrhea, the LNG-IUD is equal or superior to treat with systemic progestins or oral contraceptives even in adolescent or menopausal women.

Key words: Intrauterine device; Dysmenorrhea; Levonorgestrel-releasing intrauterine device (LNG-IUD); Adenomyosis; endometriosis.

Introduction
Intrauterine hormone delivery for contraception began with the invention of the progesterone-releasing intrauterine system in 1970 and this was soon followed by the much more effective and longer acting levonorgestrel-releasing intrauterine device (LNG-IUD) [1-5]. Non-contraceptive health benefits are now recognized as an important aspect of the overall impact of all hormonal contraceptives [6-9]. The LNG-IUD is particularly effective at producing a number of health benefits for women using the LNG-IUD as a contraceptive (reduced menstrual bleeding, reduced dysmenorrhea, and the potential for prevention of a number of gynecological conditions in the longer term, such as iron-deficient anemia, endometrial hyperplasia, adenomyosis, endometriosis, and perhaps others) [7, 10-14]. The device has received approval for indications other than contraception, such as the treatment of menorrhagia and protection of the endometrium during estrogen therapy in postmenopause in many countries [7, 10-12].

The LNG-IUD expulsion, which results in failure of contraception and/or failed relief from symptoms, may be experienced more often among patients with uterine cavity distortion [15-17]. The LNG-IUD is commonly positioned incorrectly in these patients and can be easily flushed out by heavy menstrual flow. This report attempted to review the literature, published within the last five years, regarding LNG-IUD indications for dysmenorrhea and its expulsion as a prognostic factor for safe and effective acceptability.
At 36 months, the overall satisfaction rate was 72.5% [19].

Retrospective analysis of the efficacy of LNG-IUD in Twenty-six of 192 (13.5%) women failed with LNG-IUS treatment laparoscopic conservative surgery, with 12-month follow-up. pelvic pain VAS, but a comparable reduction in dyspareunia VAS.

A double-blind RCT for pelvic endometriosis-related pain after LNG-IUD group had greater reduction in dysmenorrhea VAS and moderate to severe pain related to endometriosis. term therapy after conservative surgery for patients with LNG-IUD may be effective and well accepted for long-
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Prospective study for the efficacy of LNG-IUD in women with adenomyosis-associated symptoms, with 36-month follow-up. Of 94, 17 premature removals and 15 expulsions occurred within a three-year period. At 36 months, the overall satisfaction rate was 72.5% [19].

Cohort study of adolescent females with menstrual problems who underwent bariatric surgery over a two-year period. Ninety-two percent of patients underwent LNG-IUD placement. One of 25 experienced unanticipated expulsion [22].

Retrospective study of the efficacy and safety of LNG-IUD for adenomyosis-related menorrhagia and/or dysmenorrhea, with seven-year follow-up. Expulsion occurred in 25.3% with the conventional method, during seven-year follow-up. Dysmenorrhea greatly improved [15].

Prospective RCT for LNG-IUD vs. intrauterine copper device, in women with adenomyosis-associated symptoms, with 12-month follow-up. Similar and significant improvement with both treatments. Side-effects lower in the LNG-IUD group. No expulsion occurred. [18]

A double-blind RCT for pelvic endometriosis-related pain after laparoscopic conservative surgery, with 12-month follow-up. LNG-IUD group had greater reduction in dysmenorrhea VAS and pelvic pain VAS, but a comparable reduction in dyspareunia VAS. No expulsion occurred [20].

Retrospective analysis of the efficacy of LNG-IUD in perimenopausal women with dysmenorrhea for 12 months. Twenty-six of 192 (13.5%) women failed with LNG-IUS treatment receiving hysterectomy. No expulsion occurred [21].

Table 1. — Last five-years studies on the LNG-IUD use in dysmenorrhea.

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ture removals and 15 expulsions occurred within the three-year period.

Endometriosis is a disease that is less likely to be cure by conservative surgery. Postoperative measures are needed to prevent the recurrence of disease. Tanmahasamut et al. [20] followed up 55 women operated for deep infiltrating endometriosis using LNG-IUD. Compared with the control group, the LNG-IUD group had greater reduction in VAS and pelvic pain VAS but a comparable reduction in dyspareunia VAS. Two patients in LNG-IUD group (7.4%) and nine in the expectant management group (39.1%) had recurrent dysmenorrhea within one year postoperatively. Number-needed-to-treat to prevent one case with recurrent dysmenorrhea within the first year was three cases. The LNG-IUD may be effective and well accepted for long-term therapy after conservative surgery for patients with moderate to severe pain related to endometriosis.

Yoo et al. [21] retrospectively analyzed 192 women over 40-years-old for a two-year follow-up period on the changes in the amount and duration of bleeding and the pain scores for 24 months. Twenty-six (13.5%) women failed with LNG-IUD treatment and they received hysterectomy. When hysterectomy was performed, the average duration from LNG-IUD insertion to hysterectomy was 8.9 months. The participants who persisted with the LNG-IUD treatment for 24 months showed a success rate of 80.7%. They proposed that insufficient reduction of pain score during the first three months and menstrual blood loss during the first six months after insertion of the LNG-IUD are important factors that affect undergoing hysterectomy.

With the increasing prevalence of severe obesity during adolescence comes an increase in relevant obesity-related comorbidities and obesity-related menstrual concerns. A recent cohort study evaluated the prevalence of menstrual problems including dysmenorrhea and related medical comorbidities, and the acceptance rate of the LNG-IUD placed at the time of bariatric surgery among a sample of severely obese adolescents [22]. There is a high prevalence of menstrual problems, and the majority accepted the LNG-IUD, indicating it is a viable option among this population.

Because adenomyosis is usually associated with an enlarged uterus, uterine distortion of great retroflexed/ante-flexed uterine curvature, LNG-IUD is commonly positioned incorrectly in these patients and can be easily flushed out by the menstrual flow [23]. In addition, low positioning or partial expulsion of IUD may be related to a longer period of spotting and bleeding. Peng et al. [15] compared a novel insertion technique and conventional technique to overcome this problem. Expulsion occurs in 25.3% of patients with the conventional method, compared with 10.2% of patients with their novel method [15]. Hemoglobin levels and dysmenorrhea improve greatly in both groups after LNG-IUD insertion.

LNG-IUD induces some bleeding disturbances including unexpected breakthrough bleeding, which is an important reason for discontinuation [7, 10-12]. Jiménez et al. [24] compared the subendometrial microvascularization and uterine artery blood flow in LNG-IUD and copper-releasing IUD. There is an increased subendometrial blood flow in patients with severe dysmenorrhea and/or bleeding, after controlling for both IUD types. The results provide new data on the bleeding patterns related to these IUD types that may be relevant during contraception use.
Discussion

The use of LNG-IUD is an alternative for the medical treatment of adolescent to perimenopausal women suffering from dysmenorrhea. For women who do not wish to become pregnant, this device offers the possibility of at least five years of treatment following one single intervention. Most users experience a dramatic reduction in menstrual bleeding, and about 15% to 20% of women become amenorrheic one year after insertion [1, 2, 7, 10-12]. The device’s strong local effects on the endometrium benefit women with various benign gynecological conditions such as menorrhagia, dysmenorrhea, leiomyomata, adenomyosis, and endometriosis [1, 2, 7, 10-12]. There is also evidence to support its role in endometrial protection during postmenopausal estrogen replacement therapy, and in the treatment of endometrial hyperplasia. When compared to gonadotropin-releasing hormone (GnRH) analogues or depot progesterins, treatment with the LNG-IUD has resulted in favorable and similar symptom control. As with a GnRH analogue [25], a rapid therapeutic effect of the LNG-IUD is seen among those responding to the therapies. The follow-up of the initial study by Petta et al. [26] was extended up to five to seven years [15, 19]. Of the women still using the LNG-IUD at that time, the majority (78%) displays VAS scores of between 0 and 3 [15, 18-22]. Thus, among women responding, the LNG-IUD offers a safe and long-term therapeutic option for women suffering from endometriosis-related pelvic pain.

Problems with LNG-IUD insertion are often encountered in routine clinical practice among patients with adenomyosis; the LNG-IUD insertion was reported to be more difficult and painful than insertion of the copper device [15, 27], possibly because of its more rigid and broader insertion tube [28]. Expulsion is more common in women with adenomyosis [2]. The uterine cavity of women with adenomyosis is sometimes large and distorted by ante-flexion or retroflexion. This abnormal anatomy may lead to IUD placement in the lower uterine cavity. A significant higher expulsion rate and prolonged spotting are noted with a LNG-IUD situated in the cervical canal, compared with an IUD in the uterine cavity [29]. These factors may further hinder the insertion of LNG-IUD and lead to incorrect positioning, which is a risk factor for expulsion [16]. This could partially explain why LNG-IUD has a higher expulsion rate than copper-releasing device (about 4.9%) in therapy for menorrhagia [17]. Frequent confirmation by ultrasound may be required in patients with severe adenomyosis and distorted uterus. As Peng et al. [15] proposed, consideration should also be given to the difference in size between LNG-IUD and that of some uterine cavities in patients with adenomyosis; a standard-sized IUD may not be optimal in patients with heavy menstrual bleeding. It is possible that a variety of sizes of IUD may be required in the future.

The local endometrial effect has been studied in several endometrial biopsies from LNG-IUD users, and there is a significant change in endometrial vascularization, and demonstrated by a decrease in the mean vascular density and an increase in mean vessel area, suggesting an endometrial effect [30-33]. This is an important reason for LNG-IUD discontinuation [24]. Jiménez et al. [24] demonstrated that there is a significant increase in subendometrial blood flow in patients who presented with IUD-related side-effects (severe dysmenorrhea and/or bleeding).

Although the LNG-IUD is an excellent method, the possibility of failure and hormonal side-effects exists, and in some women extensive bleeding cannot be controlled. Expulsions are rare but may be followed by therapeutic failure and are more common in women with a distorted uterine cavity. Counseling prior to insertion and during use is mandatory to avoid premature discontinuation and must make reference to the few hormonal side-effects and expected bleeding patterns.


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Association of sympathetic nervous system activity with polycystic ovarian syndrome

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Summary
Polycystic ovary syndrome (PCOS) is a disease with high prevalence which has various clinical manifestations and increased risk of long-term complications, such as dyslipidemia, diabetes, metabolic syndrome, and hormone related tumor. However, the etiology of PCOS is still unclear. Consequently, the effect of symptomatic treatment is not always satisfactory and the prognosis is also unpredictable. Currently, commonly psychological syndromes and imbalance of sympathetic neuroendocrine system have been found in PCOS population, and increasing evidence highlighted the hypothesis that characteristics of PCOS could be partially explained by the instability of the sympathetic nervous system (SNS). Furthermore, surgical intervention of animal trials in order to normalize SNS could improve symptoms of PCOS. This review attempted to clarify the relationship between SNS and PCOS development and then discuss the possible new therapies in PCOS treatment via regulating the SNS.

Key words: Sympathetic nervous system; Polycystic ovary syndrome; PCOS.

Introduction
Polycystic ovary syndrome (PCOS) patients are at high risk of many long-term complications, such as dyslipidemia, diabetes, metabolic syndrome, and hormone related tumor, as well as some adverse pregnancy outcomes [1-5]. However, the etiology of PCOS remains unresolved, which may partly due to the complex of manifestations that deeply conceal the natural pathogenesis of PCOS. Under the Rotterdam consensus criteria, PCOS influence amount of the general female population, and the prevalence is higher in women at reproductive age than female adolescents (10% vs 3%), which is in accordance with the great increasing tendency of age related sympathetic traffic in women [6-8]. Currently, various therapies for PCOS mainly include lifestyle change (exercise and dietary-specific interventions), medical (clomiphene citrate (CC), metformin, combined oral contraceptive (OCP), etc.) and surgical treatments (laparoscopic ovarian ‘drilling’ (LOD), ultrasound-guided transvaginal ovarian needle drilling, etc.) which aims at optimizing pregnancy outcomes, restoring regular menses, ameliorating hormonal and metabolic disturbances, while improving quality of life. Although positive effect of these interventions had been found in PCOS treatment compared with placebo, these improvements analyzed in systematic reviews are not optimistic, especially regarding the live birth rate, ovulation, and/or menstrual cyclicity [9-14]. As the prognosis of PCOS is limited by its unclear etiology, and in view of the high prevalence, it is rationale to explore the nature and following targeted therapy of PCOS.

The sympathetic nervous system (SNS) is responsible for regulating many homeostatic mechanisms in living organisms, and fibers from the SNS innervate tissues in almost every biological system. Previous researches including animal model and human showed that sympathetic nerve activity controls ovarian steroid biosynthesis, follicular development, and ovulation [15, 16], especially the superior ovarian nerve (suspensory ligament, SON), a kind of sympathetic fiber associated with the suspensory ligament, which predominately innervates the interstitial glands and follicles of the ovary [17]. Furthermore, increasing evidences highlight that all the vital signs of PCOS (i.e. oligo- and/or anovulation, clinical and/or biochemical signs of hyperadrenalism and polycystic ovaries found during early follicular phase, elevated serum luteinizing hormone/follicle-stimulating hormone (LH/FSH) ratio, levels of obesity, and insulin resistance (IR)) [18] could be plausibly explained by the instability of the SNS in PCOS patients. The objective of this review is to summarize related studies about the relationship between SNS and PCOS development, in order to give insight to possible new therapies for PCOS treatment.

Influence of SNS on follicular development and apoptosis
As other organs, ovary is innervated by sympathetic fibers through neurotransmitter of catecholamines. Two main routes of receiving extrinsic sympathetic fibers have been detected: SON and ovarian plexus (ovarian plexus nerve, PN). SON has an obvious effect in regulating of interstitial glands function and follicular development, whereas the PN fibers has less norepinephrine (NE) synthesis and are mostly perivascular innervating [17, 19]. Over last years, evidences obtained underline the role of SON and its neurotransmitter in the ovarian phenomena.

Unilateral or bilateral section of SON were introduced to investigate the effect of sympathetic fibers on ovarian func-
It has been observed that the percentage of follicular atresia significantly increased in both unilateral and bilateral SON sectioned rats. In addition, the raised number of atretic follicles was accompanied by decrease of serum estradiol in unilateral SON section and of uterus weight in bilateral section group [20]. NE, the main neurotransmitter released by SON fibers, has been found to have lower content in large antral follicles than in small ones [17], suggesting that SON may have a stimulatory effect on follicular development and over-activated SON may produce more small ovarian follicles. Furthermore, in unilateral SON section model, compensatory ovarian hypertrophy has been detected in innervated ovary [20, 21], and section in phase around ovulation would lead to increased ovulation rate [22]. From those studies, it could be deduced that SON might innervate ovarian function through catecholamines and then suppress ovulation, while overstimulation of SON might lead to oligo- and/or anovulation (Figure 1).

The NE release activity from ovarian sympathetic nerve changes throughout the estrous cycle. It increases during proestrus and estrus, and has lowest activity in diestrus phase in the rat (Figure 1). Moreover, these cycle-related alterations negatively correlated well with a ligand-induced expression of β-adrenergic receptors [23]. Therefore, activity of SON has provided vital feature in regulating follicular growth and secretory function of ovarian physiological process.

**SNS related psychological change in PCOS patients**

Psychological syndromes are commonly detected in PCOS patients. Compared with healthy women, they have higher depression and anxiety scores, and symptoms are particularly heavier in PCOS patients with obese or infertility [24-27]. On the other hand, the odds of having PCOS are positively associated with scores of depressive symptoms and the main symptoms of PCOS will in turn increase psychological syndromes [28, 29]. Furthermore, ovaries can receive neural signals and engender corresponding biological effects from sympathetic fibers, mostly carried by SON, which predominantly innervate secretory ovarian cells [17, 19], and interestingly, increase density of catecholaminergic fibers or have been detected by histofluorescence in human polycystic ovaries [30]. Moreover, their psychological distress or anxiety scores are obviously related to signs of androgen excess, such as hirsutism or acne [31, 32].

Further study showed that impaired psychological function not only influenced the quality of life but was also linked with some typical metabolism disorders in PCOS women, such as IR, obesity, and dyslipidemia [27]. A case-control study included PCOS and BMI-matched healthy women test relationship between metabolic disturbances and psychological symptoms containing depression, anxiety, and both (assessed by Beck Depression Inventory, State-Trait Anxiety Inventory, Hospital Anxiety and Depression Scale, and General Health Questionnaire, respec-
It had been found that depression scores (test by depression, anxiety and reduced health-related quality of life, HRQOL) were significantly correlated with IR and lipid parameters. As it is clearly documented that PCOS has primary metabolic sequelae associated with IR and compensatory hyperinsulinemia, impaired psychological function may also be the central link in pathogenesis of the reproductive disturbances of PCOS [33].

Together these evidences, as anxiety and depression are intimately relate with dysregulated reactivity of the SNS [34-36], it is reasonable to deduce that the possibility of neuroendocrine disorders may also be involved in PCOS, and interaction between pathophysiological alternation and poor psychological function could participate in the control of PCOS development which will further aggravate clinical phenotypes.

Change of sympathetic system in ovary of PCOS

The over-activation of ovarian sympathetic nerve in ovary of PCOS is mainly supported by histofluorescence. It had been detected that polycystic ovaries from human patient with PCOS have an increased density of catecholaminergic nerve fibers compared with normal ovaries [37]. Many evidences based on animal model of PCOS induced by estradiol valerate (EV) also suggested the sympathetic hyperfunction in ovarian nerve: The release of NE from ovarian nerve terminals demonstrated significant time-dependent increase after EV injection accompanied by augmented NE content and incorporation of [3H]NE into ovarian tissue, and this phenomenon could be reversed by SON section [30, 38]. Contemporary, β-adrenergic receptors in thecal cell-interstitial tissue, which are directly innervated by sympathetic fibers, was distinctly down-regulated in the PCOS ovaries, and even lower during the estrous phase, phase with lowest β-adrenergic receptors concentration during normal estrous cycle [30] (Figure 2). These studies indicate that hyperfunction of SNS may play a role in the genesis of PCOS.

Catechol-O-methyltransferase (COMT) is the key enzyme which leads to inactivation of catecholamine neurotransmitters, such as dopamine, epinephrine, and NE. Inhibit this enzyme will lead increased granulosa cell (GC) proliferation and steroidogenesis [39]. Through immunohistochemistry, COMT expression had been clearly detected in cytoplasm of GC, theca cells (TC), and stromal cell layer in human ovary. In PCOS patients, COMT expression was dramatically increased in ovarian tissue (both in the follicular structures and ovarian stroma) in contrast with women who had proven fertility and normal ovulatory cycles [40]. Although whether the raised COMT expression in PCOS ovary is due to the over-release of catecholaminergic neurotransmitters from SON is still
unknown, these studies give us some clues: as GC is the main area for transforming testosterone into estrogen in ovary, the over expression of COMT in ovary tissue of PCOS may lead to decreased proliferation and steroidogenesis of GC, thus result in high testosterone in serum and follicular fluid and probably increase of serum metabolites of NE as well. In accordance, PCOS rat also manifest over-activated sympathetic function demonstrated by elevated mean systolic blood pressure (MSAP) and expression of tyrosine hydroxylase (TH), a marker for the biosynthesis of NE, in celiac ganglion projecting to the ovary [41, 42] (Figure 2).

**Alternation of sympathetic neurotransmitter in PCOS**

Recently, abnormal metabolism of several neuroendocrine factors related to SNS had been reported in PCOS patients, including dopamine (DA) and its metabolites homovanillic acid (HVA), and dihydroxy-phenylacetic acid (DOPAC), norepinephrine (NE), and its metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG), NE’s primary presynaptic metabolite named dehydroxy-phenylglyco (DHPG), vanillylmandelic acid (end-stage metabolite of epinephrine and NE, VMA), COMT, and its substrate 2-hydroxyestrogen.

Examination of catecholaminergic transmitters in peripheral organ systems also verified the abnormal activity of sympathetic system in PCOS patients. In the study with women with PCOS or hypothalamic-pituitary dysfunction, levels of NE’s metabolite MHPG in urine were much higher in PCOS group compared with hypothalamic-pituitary dysfunction women and control group [25]. Considered the impact of menstrual cycle on catecholamine metabolism, another similar study tested the catecholaminergic nerve systems activity according to the different phases of menstrual cycles. It had reported that although urinary DA, NA, and adrenaline had no significant difference between PCOS and control, total concentrations of NE’s metabolite MHPG remained higher in both early follicular and preovulatory phase and MHPG/VMA ratio were significantly higher in early follicular phase alone. In addition, the variation of those metabolites could not be modified by cabidopa administration, which inhibits DA synthesis mainly in peripheral of organic systems [26]. In another study compared infertility women with PCOS to those without PCOS, DA’s metabolites HVA in serum was also detected significantly lower in PCOS group [24] (Figure 2).

With regards to adolescents aged 14 to 20, alternation in sympathetic neurotransmitters detected in early follicular phase were similar to PCOS women in reproductive age [43]. The concentrations of HVA and DOPAC in urine, metabolites of DA, had also been found to be significantly lower in early follicular phase in PCOS patients compared with control subjects, despite no such significance had been found in preovulation. Although NE’s metabolite DHPG in plasma and urine was lower in PCOS patients than regular cycling control throughout the study, free dihydroxyphenylalanine (Dopa), A, NA, and total DA were similar in two groups. On the other hand, PCOS patients had higher urinary excretion of normetanephrine (NMN), NE’s ultimate metabolite generated by catalysis of COMT (Figure 2).

Another way to evaluate global sympathetic nerve activity is to directly record sympathetic nerve activity of muscle vascular bed (MSNA) in quiescent condition which correlates well with global examination. MSNA measured in early follicular phase (during 1~7 days in menstrual cycles) in subjects of reproductive age, was dramatically increased in PCOS group and positively correlated with the level of serum testosterone and cholesterol [44]. As early follicular phase well reflects basal situation of hormones, results above suggested that altered peripheral catecholaminergic metabolism including NA excess and DA deficiency was one of the features in PCOS patients. This provided insight that PCOS might be associated with neuroendocrine disturbance.

**Relationship between SNS and reproductive endocrinology in PCOS**

Although high LH/FSH ratio and elevated LH levels are inconstant symptoms and has little use in PCOS diagnosis, they still influence approximately 45% of PCOS women [45]. Further analysis revealed that higher level of LH might be related to amenorrhea and increased adrenal androgenic activity [45, 46]. Abnormal catecholaminergic neurotransmitters founded in previous were related to aberrant reproductive endocrine in PCOS patient, especial elevated levels of NE’s metabolite MHPG which maybe associated with some of the hormonal derangements. It was reported that there were positive correlations between MHPG and LH, LH and T, and levels of MHPG and DHEA-S, the precursor molecule of testosterone which positively correlates with acne in PCOS [25, 47]. Generally, the preovulatory LH surge appeared soon after the time when hypothalamic NE secretion was elevated, concomitant with increased expression of TH mRNA in noradrenergic neurons, LH releasing hormone (LHRH) level, and also LH secretion, whereas complete removal of adrenergic input to ovary through ovarian neurectomy could dramatically decrease concentrations of LHRH, expression of beta-adrenergic receptors and LHRH-binding activity [48-51]. For the amplitude of pulsatile LH is regulated by LHRH, it is possible that imbalance of sympathetic neuroregulation of hypothalamo-hypophyseal system will indirectly aggravate the disorders of PCOS resulting from high LH level. Moreover, increased the level of NE’s metabolites and decreased level of DA’s metabolites suggested high NE and low DA tone may contribute to inappropriate hypothalamic secretion of LH in PCOS. In accordance, administration of DA and its agonist caused a decrease of LH levels in PCOS patients [52, 53], and PCOS patients of central genesis had been detected with excess of serum LH that was conditioned by the falling influence of dopaminergic system [54]. As NE acts as an vital activator in
LH release indirectly through stimulating GnRH secretion [55], while the dopamine system acts as inhibitor in GnRH production [52], these give further credence that inappropriate tone of catecholaminergic neurotransmitter may influence PCOS development through central mechanisms and further arouse aberrant secretion of LH.

Hyperandrogenism is another well-known feature of PCOS generated by multiple antral follicles. Physiologically, the secretion of androgen is under the regulation of hypothalamic-pituitary-adrenal/gonadal (HPA) axis which is dominated by sympathetic nervous system. In PCOS patients, the mean ratio of catecholamine metabolites DOPAC, a marker of central dopaminergic activity, against norepinephrine metabolites DOPEG (dihydroxyphenyl ethylene glycol), one of the indicator of adrenergic activity, was significantly higher than control group, and DOPEG or the DOPEG/DOPAC ratio was also significantly correlated to free testosterone. It is indicated that altered catecholamine activity in PCOS women is not only related to psychological disorder but also correlated with hyperandrogenic status [56]. In animal mode of PCOS induced by isoproterenol (ISO), a beta-adrenergic receptor agonist, the ovaries obtained characterized PCO change (increased number of pre-cystic and cystic ovarian follicles) and increased androgen secretory activity of ovary accompanied by increased plasma LH levels (Figure 3). Moreover, most of these phenomena could be reversed by propranolol (PROP), a beta-adrenergic receptor antagonist. In summary, epinephrine-like effect stimulated by ISO could produce PCOS related symptoms containing increased LH plasma levels, PCO change of ovaries, and enhanced androgen ovarian secretory on animal model, which strongly suggested that beta-adrenergic agitation maybe definitive part of PCOS development [15].

**Relationship among sympathetic system, IR, and obesity in PCOS**

IR influences about 50% to 70% of PCOS women and appears to underlie many endocrine features of this disease through its secondary hyperinsulinemia [57]. Currently, IR and central obesity are considered to be the core of pathophysiological changes of PCOS [33].

Compared with obese control, the obese women with PCOS exhibited blunted response of noradrenaline to insulin induced hypoglycaemia. In addition, the response of noradrenaline to hypoglycaemia negatively correlated with fasting insulin levels in PCOS women (pooled obese and non-obese) but not in control group [58]. The lower responding activity to insulin indicated that there could be potential IR in SNS of PCOS women. Further study on rat examined the relationship among sympathetic system, IR and PCOS. It has been reported that cold stress induction, which could trigger increased sympathetic nerve activity to rat, promotes typical polycystic ovary morphology, low ovu-
lation, thickened theca cell (hyperthecosis) of antral follicles, elevated testosterone, and estrogen in estrus, and also ovarian hyperstimulation through hCG treatment in vitro experiment [59] (Figure 3). Besides, these PCOS like changes were accompanied by local sympathetic and selective ovarian resistance to insulin [16, 59] (Figure 3). All pathophysiological signs mentioned above are the typical changes in PCOS women. It was manifested by low response of NE release to insulin in ovary, especially in theca-interstitial cells (TC) compared with granulosa cells (GC) [16] (Figure 2).

Until now, the relationship between sympathetic system and IR is still a chicken-and-egg riddle. Insulin demonstrates positive effect on enhancing sympathetic activity in central nervous system by suppress inhibitory pathway of sympathetic outflow between the hypothalamus and brainstem sympathetic centers [7]. Persistent IR in peripheral organic systems is associated with increased sympathetic activity in women with history of pre-eclampsia [7]. On the other hand, many evidences have indicated that epinephrine overflow from sympathetic system can reduce the insulin-mediated glucose uptake and further produce IR [60, 61], and β-adrenergic receptor may play more important role than α-receptor in this process [62-64]. Thus, these two factors form an vicious circle and further pay impact on PCOS development, and it is rational to be speculated that the symptoms will be improved if any of them is inhibited.

Except IR, the aberrant relationship between SNS and adipocyte also occurs in PCOS. Current evidences demonstrated that pronounced truncal-abdominal body fat distribution (waist hip ratio, WHR) inversely correlated with basal levels of noradrenaline in obese women with or without PCOS [58]. To understand the role of SNS in PCOS obesity, a study focusing on subcutaneous fat cells has been explored that adipocytes in non-obese PCOS patients are about 25% larger and had 40% reduced noradrenaline-induced lipolysis compared with matched, healthy control. These can be probably explained by significantly decreased protein content and sensitivity of β2-adrenergic receptors in adipocyte [65]. According to the evidence list above, the detected morphological change (enlarged fat cell size) and functional alternations (catecholamine resistance of lipolysis) in adipocyte of PCOS may further promote later development of obesity in PCOS.

**Effect of SNS-related surgery on PCOS**

At present, the therapies for PCOS is symptomatic treatment, such as medicine for descending androgen, inducing ovulation, promoting follicular maturation regulating menstrual cycle or ameliorating IR. However none of them can resolve all the symptoms and metabolic abnormalities alone. As the sympathetic systems may be the pivotal point in the development of PCOS pathophysiological process (Figure 2), the authors assumed that to change the abnormal status of sympathetic systems in PCOS may be a suspected effective therapy. Based on published evidences, two obese PCOS patients with high blood pressure had undergone renal denervation with the credence that renal nerve ablation can reduce sympathetic spillover and further improve IR and hypertension [66]. After three-month follow-up, over-activated of SNS demonstrated by elevated NE outflow and muscle sympathetic nerve activity in those women was reduced. Contemporarily, down-regulated sympathetic activity is associated with substantial improvement in insulin sensitivity assessed by euglycemic hyperinsulinenic clamp in the absence of weight changes. Also in PCOS patients undergoing bilateral ovarian wedge resection, when compromising the hilum (the point of sympathetic nerves entry into the ovary), the prognosis has been shown efficacious especially in women with standard hormonal therapy resistance [30].

In animal model, intervention focus on regulating SNS also had demonstrated a positive effect on PCOS symptoms. After unilateral or bilateral sectioning of SON, PCOS rats induced by EV presented regular estrous cycles and recovered serum levels of testosterone and estradiol. The unilateral sectioning of the SON in these EV-induced PCOS rats resulted in higher spontaneous ovulation rates and less number of ova shed in the denervated ovary, while did not affect ovulation in wild type, which suggested that the denervated ovary recovered from PCO status since transection of SON [38, 67]. In addition, elevated estrogen, androgens, and testosterone were all significantly relieved after SON bilateral section [38, 67], and the SON transection also reversed elevated NE concentration and caused up-regulation of beta-adrenoreceptors of innervated ovary in EV induced PCOS rats. In accordance, to agitate beta-adrenergic receptor by ISO or to stimulate sympathetic system by chronic cold stress will lead PCOS-like changes in rats [15, 16, 38, 59] (Figure 3). Furthermore, over-secretion of androgen and estradiol from ovary stimulated by both ISO and HCG could be reversed by selective SON transection in EV-treated PCOS rat [38]. As PCOS is the risk factor of ovarian hyperstimulation syndrome (OHSS), it could be speculated that the over-function of β-adrenergic tone might play an important role in pathophysiological process in PCOS. In PCOS rats induced by cold stress, to down-regulate their sympathetic activity through bilateral electrolytic lesions in locus coeruleus (LC), the noradrenergic nucleus which regulate the hypothalamus-pituitary-adrenal axis and connect to the ovarian sympathetic pathway, can also improve CO status, including reduced numbers of cystic follicles and small follicles, improvement of ovulation, and also decrease of serum estradiol and testosterone [59].

To summarize, these evidences suggest that (1) overactive function of SNS and related imbalance of catecholamine homeostasis have an crucial role in the PCOS development, (2) SNS may directly regulate ovarian functions and thus involve in PCOS genesis, (3) alternations in ovarian cycles, estrogen, androgens, and testosterone in PCOS rat may be controlled by neural information arriving...
to the ovary through SON. Thus, it seems possible that the imbalance of SNS plays an important part in PCOS development through influencing ovarian function through both central and peripheral pathways. To resolve the overacted sympathetic activity either the central or peripheral nervous system will normalize ovarian cyclicity, ovulatory capacity, and hormone level in PCOS. Evidence supported by SON section modules of PCO rat reveal an optimistic future in developing new treatment. Otherwise, further studies are still needed for the efficacy and safety before widely used.

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References


Prolonged saltatory fetal heart rate pattern leading to newborn metabolic acidosis

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Summary
Purpose: The saltatory pattern, characterized by wide and rapid oscillations of the fetal heart rate (FHR), remains a controversial entity. The authors sought to evaluate whether it could be associated with an adverse fetal outcome. Material and Methods: The authors report a case series of four saltatory patterns occurring in the last 30 minutes before birth in association with cord artery metabolic acidosis, obtained from three large databases of internally acquired FHR tracings. The distinctive characteristics of this pattern were evaluated with the aid of a computer system. Results: All cases were recorded in uneventful pregnancies, with normal birthweight singletons, born vaginally at term. The saltatory pattern lasted between 23 and 44 minutes, exhibited a mean oscillatory amplitude of 45.9 to 80.0 beats per minute (bpm) and a frequency between four and eight cycles per minute. Conclusions: A saltatory pattern exceeding 20 minutes can be associated with the occurrence of fetal metabolic acidosis.

Key words: Heart rate, fetal; Cardiotocography; Signal processing; Computer-assisted; Fetal hypoxia; Saltatory pattern.

Introduction
Most fetal heart rate (FHR) patterns are comprehensively described in the scientific literature, and their physiology is well known [1-5]. The saltatory pattern remains a controversial entity, and little is known about its pathophysiology or clinical significance. There is currently no agreement between major FHR interpretation guidelines on the description, significance, and management of this pattern. The International Federation of Obstetrics and Gynecology (FIGO) guidelines of 1987 describe the pattern of “increased variability”, corresponding to a long term-variability in excess of 25 beats per minute (bpm), and classify it in the suspicious category [1]. The Royal College of Obstetricians and Gynecologists (RCOG) guidelines of 2001 [4], and the joint effort with the National Institute of Clinical Excellence (NICE) in 2007 [5], make no mention of this pattern or any other form of increased variability. The latest version of the American College of Obstetrics and Gynecologists (ACOG) guidelines, elaborated in association with the National Institute of Child Health and Human Development (NICHD), and the Society for Maternal-Fetal Medicine (SMFM) [3], describe a pattern of “marked baseline variability” defined as a long term-variability greater than 25 bpm, and classify it in Category II FHR tracings.

The saltatory pattern appears to have been first described by Hammacher et al. in 1968 [6], as a “baseline variation” observed in intra-partum tracings, in association with cord complications. It was considered “a sign of fetal distress” and related to low Apgar scores. Edward Hon described a pattern of “marked irregularity” but did not attribute any specific pathological significance to this finding [7-9]. More recently, the saltatory pattern has been described as a pattern of unusual appearance, where rapid FHR variations occur with a frequency of three to six cycles per minute and an amplitude range greater than 25 bpm [10, 11].

In this case series the authors report four cases of FHR saltatory pattern occurring in the last minutes of labor that were associated with umbilical cord metabolic acidosis.

Materials and Methods
The authors searched two research databases [12,13] (n = 12,270) and the clinical database of a tertiary care university hospital (n = 1589), all containing internally monitored intra-partum FHR records acquired in near-term singleton fetuses, in order to select cases with a saltatory FHR pattern occurring in the last 30 minutes before birth and the documentation of cord artery metabolic acidosis. The saltatory pattern was defined as the occurrence of wide and rapid oscillations of the FHR with and amplitude exceeding 25 bpm. Metabolic acidosis was defined as adequately sampled umbilical blood gas values [14], with an umbilical artery (UA) pH < 7.05 and a base deficit in the extracellular fluid (BD(c)) ≥ 12.0 mmol/l [15, 16]. Patient authorization for the use of their clinical data for research purposes was obtained during the construction of each database.

Four such cases were identified. The clinical records of these cases were reviewed in order to extract the main characteristics of pregnancy and labor. The corresponding tracings were analyzed with the aid of a system for computer analysis of the FHR [17], in order to quantify the main characteristics of the saltatory segments.
Results

The main clinical characteristics of the selected cases are summarized below.

Case 1

Primigravida, uneventful pregnancy, spontaneous labor at 41 weeks, no epidural analgesia, ST Segment Analysis (STAN) for fetal intrapartum monitoring was started at 12:20 hours (Figure 1). Oxytocin was started at 12:42 hours at six mU/min and raised to ten mU/min at 13:17 hours. At 13:31, seven cm of dilatation with vertex presentation at stage 0 was recorded. At 13:52 oxytocin was increased to 14 mU/min. Active pushing started at 15:40 hours. Birth occurred at 16:31 hours, of a newborn girl weighing 3,000 g, Apgar scores 4/7/9, UA pH = 6.89, BDecf = 12.8 mmol/l, umbilical vein (UV) pH = 7.18, admitted to the neonatal intensive care unit (NICU) because of meconium aspiration and pneumothorax requiring assisted ventilation. No neurological abnormalities were registered.

Case 2

Primigravida, uneventful pregnancy, induction of labor at 39 weeks due to premature rupture of membranes, no
Prolonged saltatory fetal heart rate pattern leading to newborn metabolic acidosis

Epidural analgesia, STAN recording commenced at 01:54 hours (Figure 2). Active pushing started at 03:00 hours. Birth occurred at 03:37 hours, of a newborn girl weighing 2,990 g, with one nuchal cord, Apgar scores 8/8/9, UA pH = 7.04, BDecf = 13.8 mmol/l, UV pH = 7.28. No NICU admission, with an uneventful neonatal period.

Case 3
Primigravida, type 1 diabetes with adequate blood glucose control (third-trimester estimated fetal weight in the 70th percentile), spontaneous labor at 39 weeks, no epidural analgesia, STAN monitoring commenced at 13:20 hours (Figure 3). Full dilatation and cephalic presentation at stage 0 registered at 14:40 hours, active pushing started 20 minutes later. Oxytocin infusion at four mU/min was begun at 15:00 and increased 15 minutes later to eight mU/min. Fetal blood sampling at 15:25 hours - pH 7.02, vacuum extraction began at 15:40 and oxytocin was increased to 16 mU/ml. Birth occurred at 15:44 hours, after three tractions, of a newborn boy weighing 3,700 g, Apgar scores 9/9/10, UA pH = 6.97, BDecf = 15 mmol/l, UV pH = 7.00. Admitted to a medium care unit for surveillance, with an uneventful neonatal period.
Case 4

Primigravida, uneventful pregnancy, labor induction at 41 weeks because of fetal tachycardia detected on intermittent auscultation. Continuous FHR monitoring began at 23:50, with ST information from 00:10 onwards (Figure 4). Failed epidural analgesia recorded at 00:14, pethidine 100 mg IV given at 2:30 and pethidine 150 mg IV given at 6:20. Oxytocin infusion began at 3:00 at two mU/min, increased in steps of two mU/min every 30 minutes. Full dilatation registered at 7:10, with oxytocin infusion at 16 mU/min. Active pushing began at 9:24, oxytocin infusion increased to 20 mU/min at that time. Birth occurred at 10:33 hours, of a newborn girl weighing 3,615 g. Apgar scores 5/6/6, UA pH = 7.00, BDcfr = 13.0 mmol/l, UV pH = 7.11. Admitted to NICU, with an uneventful neonatal period.

In all these cases, the saltatory pattern started between 24 and 52 minutes before delivery, lasted 23 to 44 minutes, and exhibited a mean oscillatory amplitude (difference between maximum and minimum FHR values measured in one-minute windows) between 45.9 and 80.0 bpm. The frequency of oscillations varied between four and eight cycles per minute.

Discussion

The present report describes four cases of intra-partum saltatory pattern lasting more than 20 minutes shortly followed by the vaginal birth of a newborn with cord artery metabolic acidosis. In all cases, hypoxia appeared to be moderate, and there were no cases of hypoxic-ischemic encephalopathy.

To the authors’ knowledge, this is the first report of salta-

tory patterns monitored internally in the final minutes before delivery, leading to newborn metabolic acidosis. The small interval between the occurrence of the FHR pattern and the documentation of metabolic acidosis at birth is necessary to establish a possible cause-effect relationship between the two, assuring that no other monitored or unmonitored FHR patterns occurred during the interval. Internal FHR monitoring assures the presence of good quality signals during the second stage of labor and does not use the processing algorithms that are applied to external signals (autocorrelation), and that provide only an approximation of real FHR values.

In a cohort of 1,304 term fetuses published in 1976 [18], Cibils reported a saltatory pattern in 7.8% of cases, and suggested that it occurs in a high number of cases of “fetal distress”. It was observed in association with fetal tachycardia or alternating with periods of reduced long-term variability, or “disguising” a deceleration, possibly representing a subtle sign of “fetal distress” [18, 19]. In 1992, a retrospective observational study of 433 consecutive intra-partum tracings reported the saltatory pattern in 2.3% of cases, all at term and during the active phase or the second stage of labor [10]. All infants were born with Apgar scores of 8/9 or 9/9 but no cord blood gas values were reported. One year before, a case report was published describing a saltatory pattern at term associated with variable decelerations progressing to sustained tachycardia and ending in a prolonged deceleration, with low Apgar scores and cord blood gases consistent with mild respiratory acidosis [11].

Despite many proposed hypothesis, the physiopathology of the saltatory pattern remains uncertain. Some have suggested that it is associated with augmented alpha-adrener-
gic activity, causing selective vasoconstriction [20]. Experimental studies conducted in fetal sheep subjected to episodes of brief and acute hypoxia [21], identified a pattern of increased variability, followed by a decrease in this parameter as hypoxia was maintained [22, 23]. This biphasic pattern has also been documented clinically, using power spectral analysis, when comparing acidotic fetuses with controls [24]. The occurrence of fetal seizures is another proposed hypothesis. In 1999, an example of seizures and increased variability during “terminal” fetal hypoxia was reported by Westgate et al. [25]. Fetal seizures together with both abnormal breathing movements and fluctuation in blood pressure and heart rate resulting in increased FHR variability were observed in brain-damaged fetal sheep shortly after an asphyxic insult.

Only four cases of prolonged saltatory pattern resulting in cord artery metabolic acidosis were found in the three large databases evaluated in this study, suggesting this association to be rare. However, the present study was not designed to allow an estimation of incidence. Several saltatory segments of lesser duration were identified in the final minutes before delivery in association with normal cord blood gas values. Saltatory segments of different length also occurred in earlier stages of labor, but the absence of an objective marker of hypoxia close to their occurrence, precluded any inference of their significance. Finally, there was uncertainty regarding the classification of the saltatory nature of many segments. There is no consensus in the scientific literature as to the definition of this pattern, and the well-demonstrated inter-observer disagreement in visual interpretation of FHR tracings is another limitation of this study. It was felt that, for a true evaluation of the incidence of saltatory segments, it is necessary to develop a computer algorithm that is able to identify them and to run this algorithm in the entire database. Such a project is currently being undertaken.

The saltatory pattern has inherent characteristics that allow it to be identified by computer algorithms, and thus real-time alerts can be generated on its occurrence. This could prove to be a useful clinical adjunct, particularly for the less experienced healthcare professionals in the labor ward. For the development of such algorithms, it is essential to identify “index cases”, such as the ones described in this study, where good quality signals, a short interval to birth, and a well-documented newborn hypoxia are pres-
ent. A similar line of thought can be applied for the building of clinical experience.

It may be that the clinical significance of prolonged saltatory patterns, as described in the current paper, is different from the transient episodes that have been observed in labor in association with normal fetal outcome [10]. The fact that some of these reports do not include umbilical blood gas values raises additional uncertainties. It is well known that episodes of moderate and/or time-limited hypoxia may not reflect on Apgar scores.

Conclusion

The present case series suggests that clinicians need to be aware of saltatory patterns exceeding 20 minutes duration, as these can be associated with the occurrence of fetal hypoxia. There is a need to determine whether similar patterns may also result in normal neonatal outcomes.

Acknowledgments

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References


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Neonatal mortality rate and risk factors in northeast China: analysis of 5,277 neonates in 2005

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Summary

Background: Healthcare has dramatically improved for both mothers and neonates over the last three decades in China. However, the reported rates of morbidity and mortality vary among different regions of China, and the exact rates in Northeast China are unknown. This study aimed to determine neonatal morbidity and mortality rates and the associated risk factors in Northeast China.

Methods: Neonates born in 2005 at seven hospitals in five major cities of Heilongjiang province in Northeast China were recruited. Standardized questionnaires on both the mother and neonate were conducted by trained investigators. The questions included demographic data on the mother, the mother's weight, gestational age (GA), complications during pregnancy, method of delivery, neonate's gender, weight, general health situation, and complications after delivery.

Results: A total of 5,277 neonates were included, with a male to female ratio of 1.07. The incidence of preterm delivery was 8.7%, which was associated with an increased age of the mother, a history of preeclampsia-eclampsia, premature rupture of membranes, and intrauterine distress. Morbidity occurred in 7.0% of neonates, including hypoxic ischemic encephalopathy (2.4%), asphyxia (1.6%), pneumonia (1.6%), hyperbilirubinemia (0.5%), intracranial hemorrhage (0.5%), meconium aspiration syndrome (0.2%), and ingestion syndrome (0.2%). The overall mortality was 9.5%. Preterm delivery, maternal history of preeclampsia-eclampsia, hypoxic ischemic encephalopathy, intracranial hemorrhage, pneumonia, asphyxia, and meconium aspiration syndrome were independent risk factors for mortality with odds ratios (95% confidence interval) of 17.42 (7.31-38.9), 12.52 (Table 3) (3.91-16.82), 10.13 (2.52-19.86), 9.77 (2.35-19.93), 4.15 (1.78-9.52), 2.18 (1.21-5.47), and 2.76 (2.11-6.32), respectively (all \( P < 0.01 \)).

Conclusions: In 2005, the overall morbidity and mortality was 7.0% and 9.5%, respectively in northeast China, and preterm delivery was the highest risk factor for neonatal mortality. The prevention on preterm delivery should be a top priority for the improvement of neonatal healthcare.

Key words: Neonates; Morbidity; Mortality; Preterm delivery.

Introduction

With the accelerated development of the social economy and culture, as well as the improvement of public health care coverage and prophylactic and therapeutic techniques in China, the morbidity and mortality of both mothers and neonates have dramatically decreased over the last couple of decades [1]. However, some data from various regions of China have demonstrated significant variation in neonatal morbidity and mortality, presumably due to the imbalanced development and progression of economy and culture among the regions [2]. For example, studies conducted in southern and southeastern China have demonstrated significant decreases in morbidity and mortality [1-3]. In contrast, no reports on morbidity and mortality are available for Northeast China.

Heilongjiang province is located in Northeast China with middle level economic and cultural development. As a consequence of economic development and increases in education and hygienic levels in Heilongjiang province, the healthcare system, including maternal and child health care, has improved significantly over the past three decades. The major objective of maternal and child health care is to lower the mortality of both the mothers and neonates. Thus, data on the mortality and morbidity of mothers and neonates are not only major indicators of the effectiveness and success of the healthcare system, but are also the basis for policies that further improve the healthcare system. However, there has been a relative lack of large-scale clinical data in China, especially in northeast China.

Therefore, the aim of the present study was to determine the mortality of neonates and the related risk factors, based on data prospectively collected from seven hospitals in five cities in Heilongjiang province.

Materials and Methods

Participating hospitals
The seven hospitals involved in the study included three teaching hospitals (Hongqi Hospital affiliated to Mudanjiang Medical College, The First Hospital affiliated to Jiamusi University Medical College, and The Second Hospital affiliated to Harbin Medical University) and four municipal and specialty hospitals (Daqing People’s Hospital, The First Municipal Hospital of Qiqihar City, Mudanjiang Maternity Hospital, and Jiamusi Maternal and Child Health Care Center). Each of the aforementioned hospitals had over 100 beds in the Department of Obstetrics and Gynecology.

Subjects and data collection procedures
Between January 1, 2005 and December 31, 2005, neonates who were born in the Department of Obstetrics and Gynecology, and those who were admitted to the Department of Neonates due to complications during pregnancy, method of delivery, neonate’s gender, weight, general health situation, and complications after delivery. Results: A total of 5,277 neonates were included, with a male to female ratio of 1.07. The incidence of preterm delivery was 8.7%, which was associated with an increased age of the mother, a history of preeclampsia-eclampsia, premature rupture of membranes, and intrauterine distress. Morbidity occurred in 7.0% of neonates, including hypoxic ischemic encephalopathy (2.4%), asphyxia (1.6%), pneumonia (1.6%), hyperbilirubinemia (0.5%), intracranial hemorrhage (0.5%), meconium aspiration syndrome (0.2%), and ingestion syndrome (0.2%). The overall mortality was 9.5%. Preterm delivery, maternal history of preeclampsia-eclampsia, hypoxic ischemic encephalopathy, intracranial hemorrhage, pneumonia, asphyxia, and meconium aspiration syndrome were independent risk factors for mortality with odds ratios (95% confidence interval) of 17.42 (7.31-38.9), 12.52 (Table 3) (3.91-16.82), 10.13 (2.52-19.86), 9.77 (2.35-19.93), 4.15 (1.78-9.52), 2.18 (1.21-5.47), and 2.76 (2.11-6.32), respectively (all \( P < 0.01 \)).

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to certain diseases or adverse conditions in the seven participating hospitals, were enrolled in the present study. After birth, a standardized questionnaire was completed by a trained investigator for each neonate. The questionnaire covered information on both the mother and the neonate, which included demographic data on the mother, gestational age (GA), complications during pregnancy, the mother’s weight, method of delivery, gender, weight, general health situation, and complications after delivery. Pregnant women were included if they stayed in the city for monitoring during their pregnancy. Neonates and mothers transferred from other hospitals were excluded. The Institutional Review Boards from each of hospital separately reviewed and approved the study protocol. All parents or guardians provided informed written consent.

Quality control and data input
At each hospital, one designated expert in data management was responsible for the quality assurance of the completeness and accuracy of the questionnaires. All investigators received training prior to the study. Unreliable or incomplete questionnaires (n = 500) were regarded as invalid, and were thus excluded. Upon the confirmation of data collection, data were entered into the database established with Epi data software (The EpiData Association, Odense, Denmark). Data verification was carried out by comparing input data to data on randomly selected questionnaires (1% of all questionnaires). If the errors exceeded 10%, all data had to be input again by another investigator.

Classification of GA and definitions of morbidity and mortality
GA was classified into three terms: preterm (<37 weeks), term (37-<42 weeks), and post-term (>=42 weeks). Preterm was also divided into two stages (<28 weeks and 28-<37 weeks). Neonatal morbidity was defined as the occurrence of preterm delivery, hypoxic ischemic encephalopathy (HIE), intracranial hemorrhage, hyperbilirubinemia, pneumonia, asphyxia, meconium aspiration syndrome (MAS), and/or ingestion syndrome (or swallowing syndrome of newborn) that occurred in all three terms. Fetal distress was judged entirely from the recorded evidence of instantaneous fetal heart rate and related parameters. Neonatal mortality was defined as deaths among live-born infants that occurred between the day of delivery and 28 days after delivery.

Statistical analysis
Continuous variables were presented as mean ± standard deviation (SD) when normally distributed, or as median (range) when abnormally distributed. Categorical variables were presented as counts or rates, with the odds ratios (ORs) and 95% confidence intervals (CIs) calculated. Comparisons between continuous variables were made using the student t-test, analysis of variance, or Mann-Whitney test, where appropriate. Univariate analyses on categorical data were performed by 2-tailed Pearson c² test or Fisher’s exact test. Multivariate logistic regression analysis on risk factors for neonatal morbidity and mortality were used. The maternal and neonatal variables such as GA, birth weight, age of mother, preeclampsia-eclampsia (PE-E), premature rupture of membrane (PROM) (which occurs in pregnancy when there is rupture of the membranes (rupture of the amniotic sac and chorion) more than an hour before the onset of labor), history of preterm delivery, and intrauterine distress were included in the logistic regression model for identification of the risk factors for morbidity. The maternal and neonatal variables and different morbidity variables were fitted into multivariate regression model to identify the risk factors for mortality. All statistical analyses were performed using SPSS 13.0 software (SPSS inc., Chicago, IL, USA).

Results
General information
A total of 5,277 neonates were born from 5,265 mothers during the period of the study, and were included in the data analysis. There were 12 pairs of twins. The neonatal male-female ratio was 1.07. GA was available for 4,944 (93.7%) of the neonates, with the shortest and longest GA being 25 and 44 weeks, respectively. Among the 5,277 neonates, 4,452 (84.2%) were classified as being term, with a median GA of 37 weeks and mean (±SD) birth weight 3789.3 ± 572.2 g (Table 1).

Neonatal morbidity and mortality
Morbidity occurred in 370 (7.0%) neonates, including hypoxic ischemic encephalopathy in 127 (2.4%), asphyxia

<table>
<thead>
<tr>
<th>Category</th>
<th>Proportion (%)</th>
<th>Median GA (weeks)</th>
<th>Weight (mean±SD, g)</th>
<th>Mortality (n (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 28 weeks (n=18)</td>
<td>0.3</td>
<td>27</td>
<td>1000.2 ± 38.7 (range: 960-1150)*</td>
<td>6 (333.4)*</td>
</tr>
<tr>
<td>28-&lt;37 weeks (n=439)</td>
<td>8.3</td>
<td>35</td>
<td>2769.2 ± 876.4*</td>
<td>27 (62.1) *</td>
</tr>
<tr>
<td>Term</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>37-&lt;42 weeks (n=4,452)</td>
<td>84.2</td>
<td>39</td>
<td>3789.3 ± 572.2</td>
<td>10 (2.2)</td>
</tr>
<tr>
<td>Post-term</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥42 weeks (n=46)</td>
<td>0.9</td>
<td>42</td>
<td>3897.4 ± 361.1</td>
<td>0</td>
</tr>
<tr>
<td>Missing data (n=333)</td>
<td>6.3</td>
<td>NA</td>
<td>NA</td>
<td>7 (21.0)</td>
</tr>
<tr>
<td>Total (n=5,277)</td>
<td>100</td>
<td>NA</td>
<td>NA</td>
<td>50 (9.5)</td>
</tr>
</tbody>
</table>

* = P< 0.001, compared with term and postterm neonates.
NA = not available.
in 85 (1.6%), pneumonia 85 (1.6%), hyperbilirubinemia in 27 (0.5%), intracranial hemorrhage in 27 (0.5%), meconium aspiration syndrome in 11 (0.2%), and ingestion syndrome in 8 (0.2%) (Table 2).

Overall, 50 neonates died in the Department of Obstetrics and Gynecology during or after birth (n=43), or within four weeks after being transferred to the Department of Neonates (n=7), resulting in an overall mortality of 9.5‰. The mortality rate was 72.0‰ in preterm neonates with a GA of <37 weeks (333.4 ‰ in neonates with a GA of <28 weeks, and 62.1‰ in those with a GA between 28 and <37 weeks), which was significantly higher than that (2.2‰) of term neonates with a GA between 37 and 42 weeks (OR=9.87, 95% CI: 2.72-37.91, P < 0.001).

**Risk factors for mortality and preterm delivery**

The incidence of preterm delivery was 8.7% (n=458). Maternal gestational hypertension-preeclampsia occurred in 199 (3.8%) mothers; the proportion of mild, moderate, and severe preeclampsia, and eclampsia was 24.1%, 21.1%, 21.8%, and 32.2%, respectively.

In univariate and multivariate analyses, preterm delivery, the maternal history of PE-E, HIE, intracranial hemorrhage, pneumonia and asphyxia, and MAS, were significantly related to the incidence of preterm neonatal death (Table 3). The multivariate adjusted ORS (95% CI) for preterm neonatal mortality were 17.42 (7.31-38.9), 12.52 (3.91-16.82), 10.13 (2.52-19.86), 9.77 (2.35-19.93), 4.15 (1.78-9.52), 2.18 (1.21-5.47), and 2.76 (2.11-6.32) for preterm delivery, maternal history of PE-E, HIE, intracranial hemorrhage, pneumonia, asphyxia, and MAS, respectively (Table 3, all P < 0.01).

Since preterm delivery was a major factor that was associated with a neonatal mortality rate that was 33-fold higher than normal delivery, the risk factors for preterm delivery were also determined. In both univariate and multivariate analyses, the age of the mother, PE-E, PROM, a history of premature delivery, and intrauterine distress were significantly associated with the incidence of preterm delivery (Table 4).

**Discussion**

Neonatal morbidity and mortality are closely related to the developmental levels of the domestic economy, medical science, and the maternal-infant health care system. With the development of the economy and medicine, and the increase in the standard of living in China, the morbidity and mortality rates of neonates have significantly decreased [4, 5]. The five cities (Harbin, Jiamusi, Daqing,

### Table 2. — The incidence of major morbidities in 5,277 neonates

<table>
<thead>
<tr>
<th>Morbidity</th>
<th>Number a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxic ischemic encephalopathy</td>
<td>127 (2.4)</td>
</tr>
<tr>
<td>Asphyxia</td>
<td>85 (1.6)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>85 (1.6)</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>27 (0.5)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>27 (0.5)</td>
</tr>
<tr>
<td>Meconium aspiration syndrome</td>
<td>11 (0.2)</td>
</tr>
<tr>
<td>Ingestion syndrome</td>
<td>8 (0.2)</td>
</tr>
<tr>
<td>Overall</td>
<td>370 (7.0)</td>
</tr>
</tbody>
</table>

a = Some neonates had two or more morbidities

### Table 3. — Related risk factors of neonatal mortality

<table>
<thead>
<tr>
<th>Factor</th>
<th>Incidence (%) of death</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm delivery (yes vs. no)</td>
<td>68.0:0.3</td>
<td>9.87 (2.72-37.91)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Maternal PE-E (yes vs. no)</td>
<td>57.5:3.2</td>
<td>4.73 (1.72-7.31)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HIE (yes vs. no)</td>
<td>32.7:1.8</td>
<td>3.12 (1.42-6.43)</td>
<td>0.005</td>
</tr>
<tr>
<td>Intracranial hemorrhage (yes vs. no)</td>
<td>19.4:0.7</td>
<td>1.23 (1.02-2.76)</td>
<td>0.009</td>
</tr>
<tr>
<td>Pneumonia (yes vs. no)</td>
<td>9.3:2.7</td>
<td>1.93 (1.21-3.63)</td>
<td>0.008</td>
</tr>
<tr>
<td>Asphyxia (yes vs. no)</td>
<td>8.6:3.3</td>
<td>1.49 (1.13-2.86)</td>
<td>0.005</td>
</tr>
<tr>
<td>MAS (yes vs. no)</td>
<td>9.2:3.1</td>
<td>1.97 (1.17-3.46)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

**PE-E** = preeclampsia-eclampsia; **HIE** = hypoxic ischemic encephalopathy; **MAS** = Meconium aspiration syndrome; **OR** = Odds ratio; **CI** = confidence interval.

### Table 4. — Risk factors for preterm delivery

<table>
<thead>
<tr>
<th>Factor</th>
<th>Incidence (%) of preterm delivery</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother age (&gt; 30 vs.&lt;30 years)</td>
<td>34.7:19.3</td>
<td>1.17 (1.01-1.43)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PE-E (yes vs. no)</td>
<td>17.9:3.6</td>
<td>3.53 (2.91-3.97)</td>
<td>0.005</td>
</tr>
<tr>
<td>PROM (yes vs. no)</td>
<td>10.7:3.1</td>
<td>3.67 (1.98-4.23)</td>
<td>0.008</td>
</tr>
<tr>
<td>History of preterm delivery (yes vs. no)</td>
<td>21.2:9.3</td>
<td>1.41 (1.23-1.65)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intrauterine distress (yes vs. no)</td>
<td>34.6:21.3</td>
<td>1.56 (1.31-1.76)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

**PE-E** = preeclampsia-eclampsia; **PROM** = premature rupture of membranes.
Mudanjiang, and Qiqihar) in Heilongjiang province of northeast China are representative of mid-level industrialized urban regions with an average level of domestic income.

This set of data exhibited that a male to female ratio of 1.07, which is lower than that of other regions nationwide [6]. The overall mortality rate was 9.5‰, which is lower than the nationwide average mortality rate (13.2‰) in 2005 [5]. The rate of preterm delivery was 8.7% in the present study, which is similar to that reported from developed countries, ranging from 9-12% in the last two decades [7]. Preterm delivery was closely related to neonatal death [8]. In the present study, the mortality was 333.4‰ for neonates with a GA of <28 weeks, and 62.0‰ for neonates with a GA of 28-37 weeks. In contrast, the mortality was 2.2‰ and 0‰ for term and postterm neonates, respectively. However, the overall mortality rate (9.5‰) observed in the present study was much lower than the rate reported in southern China in the 1980’s (24.5‰) [3] and nationwide data in 2005 (13.2‰) [5]. Moreover, the mortality rate in term neonates (2.2‰) was also much lower than the average rate of 33‰ (range 2 to 70 per 1000 live birth) in the developing world [9]. These findings imply that an improvement in maternal and neonatal healthcare has been achieved in northeast China.

The present study demonstrated that the age of the mother, history of PE-E, PROM, history of preterm delivery, and intrauterine distress were related to an increased risk of preterm delivery. Hsieh et al. reported that women aged 40 years and older in Taiwan were at an increased risk for preterm delivery (before 37 weeks of gestation) (adjusted OR 1.7, 95% CI 1.3-2.2) [10]. In women who had a completely uncomplicated pregnancy and a normal vaginal delivery, advanced maternal age was still significantly associated with early preterm delivery (before 34 weeks of gestation), a birth weight <1500 g, low Apgar scores, fetal demise, and neonatal death [10].

PE is one of the most common complications of pregnancy, with incidence rates of 2%-7% among healthy, primiparous women in the United States [11]. The only cure for PE is delivery, and it remains one of the most common complications resulting in a medically indicated preterm delivery [12]. In the present study, the incidence of maternal gestational hypertension-preeclampsia was 3.8%, which is lower than that previously reported in northeast Chinese women (4.5%) [13], but higher than American Chinese (1.8%) [14]. However, the characteristics of the patients in these three studies differed; thus these studies should be compared cautiously.

Maternal cervical anomaly and intrauterine infection and inflammation may be the major causes of some cases of PROM. The resulting premature neonates are more likely to have sepsis, respiratory distress syndrome, necrotizing enterocolitis, and intraventricular hemorrhage. Complications of infection include chorioamnionitis, maternal wound infection, and neonatal sepsis [15]. Prolonged oligohydramnios can result in pulmonary hypoplasia, pneumothorax, and skeletal deformities. In the present study, PROM increased the risk of preterm delivery (OR: 4.32, 95% CI: 1.69-7.31).

As reported, preterm neonates are at a higher risk of disease. Among these, respiratory diseases, such as pneumonia, asphyxia, HIE, and lung hemorrhage, are the most common complications due to immature lung development. Common nervous system diseases include intracranial hemorrhage. With the deep interaction of preterm cause and consequence, the mortality of preterm neonates further worsened. The present study demonstrated that the mortality of preterm neonates was correlated with GA; the shorter the GA, the worse the neonatal outcome. Thus, regular antenatal examination for pregnant females with advanced age and the aggressive prophylactic measures (such as use of antenatal steroid) of pregnancy complications are of the most importance for ultimately reducing the incidence of preterm delivery and the mortality of preterm delivered neonates.

Although late preterm delivery (before 37 completed weeks of gestation) has been reported to be related to a slightly increased risk of neonatal mortality with a small sample size [16], preterm delivery has been confirmed as the major determinant of infant mortality with the series reported here. Other factors, including PE-E, HIE, intracranial hemorrhage, pneumonia, asphyxia, and MAS were demonstrated to be related to an increased risk of neonatal death.

In summary, the overall mortality is approximately 10‰ in northeast China, with a mortality rate of approximately 2‰ in term neonates. Preterm delivery, maternal history of preeclampsia-eclampsia, hypoxic ischemic encephalopathy, intracranial hemorrhage, pneumonia, asphyxia, and MAS were identified as risk factors for mortality. Thus, the prevention of preterm delivery, strength of pregnancy monitoring, and improvement of preterm newborn support should be concentrated in the neonatal health care management in this region. However, the success of improving the preterm infant outcome is closely related to regional economic development.

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We thank Professor Kelun Wei from the Second Hospital Affiliated to Chinese Medical University for organizing this survey in the northeast region of China. We also thank Dr. Jinghua Zhang from Mudan Jiang Health Care Center for Women and Children and Dr. Dongyan Liu and Dr. Qingzhi Meng from The First Hospital Affiliated to Jiamusi Medical University for their assistance in collecting the clinical data.
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Normal “high” thyroid stimulating hormone (TSH) levels and pregnancy rates in patients undergoing IVF with donor eggs

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¹ University Center of Reproductive Medicine, Hospital Universitario of the Universidad Autonoma de Nuevo Leon in Monterrey, Monterrey (Mexico); ² Servicio de Ginecologia Hospital Vall d’Hebron, Universitat Autonoma de Barcelona in Barcelona (Spain)

Summary

Objective: To determine if a relationship exists between pregnancy rates obtained in patients undergoing in vitro fertilization (IVF) with donor eggs and levels of thyroid stimulating hormone greater than 2.5 mIU/L but still within a range considered normal. Study design: Retrospective comparative cohort study. With prior approval of the Ethics Committee, 233 patients undergoing IVF with donor eggs, in a two-year period, were included. Patients were grouped depending on the thyroid stimulating hormone (TSH) level. Pregnancy rates were compared. Statistical analysis was made with the Chi-square test. Results: Pregnancy rates, depending on the TSH level, were 56.6% in patients with TSH levels below 2.49 mU/L vs. 21.6%, in patients with levels above 2.5 mU/L. This difference was statistically significant (p < 0.001). Conclusions: Mild abnormalities of thyroid function may adversely affect the pregnancy rates in patients undergoing in vitro fertilization with donor eggs. A possible alteration in endometrial function may be associated.

Key words: Thyroid stimulating hormone; In vitro fertilization (IVF); Egg donation; Clinical pregnancy rates.

Introduction

Both clinical and subclinical hypothyroidism has been associated with an increase in menstrual disturbances [1,2] and fertility problems [3, 4]. Autoimmune thyroid disease has also been associated with increased rates of infertility [5, 6].

Subclinical hypothyroidism, also called mild thyroid failure, is a health problem with a reported prevalence between 3% and 8% in the general population. It is more common in women and with advancing age [7, 8].

Alterations in serum levels of thyroid hormones have also been described as factors that adversely affect the results of in vitro fertilization (IVF) programs and the course of pregnancies obtained through these techniques [9].

There is controversy regarding the upper limit of normal of thyroid stimulating hormone (TSH). Some authors suggest a TSH level of 2.5 mIU/L as the upper limit of normal; however, this suggestion is not fully accepted and there is still controversy about the clinical impact that this level may have. There are reports [10] that indicate an increased incidence of spontaneous abortions in the first trimester in patients with TSH levels above 2.5 mU/L, but still within normal range.

The aim of this study was to determine if a relationship exists between pregnancy rates obtained in patients undergoing IVF with donor eggs and levels of TSH greater than 2.5 mIU/L but still within a range considered normal (4.2 mU/L according to the normal parameters in the authors’ laboratory).

Results:

Pregnancy rates, depending on the TSH level, were 56.6% in patients with TSH levels below 2.49 mU/L vs. 21.6%, in patients with levels above 2.5 mU/L. This difference was statistically significant (p < 0.001).

Conclusions: Mild abnormalities of thyroid function may adversely affect the pregnancy rates in patients undergoing in vitro fertilization with donor eggs. A possible alteration in endometrial function may be associated.

Key words: Thyroid stimulating hormone; In vitro fertilization (IVF); Egg donation; Clinical pregnancy rates.

Materials and Methods

The authors carried out a retrospective comparative cohort at the Hospital Universitario of the Universidad Autonoma de Nuevo Leon in Monterrey, Mexico. With prior approval of the Ethics Committee, they reviewed the reports of patients who underwent IVF procedures at the present institution between January 2008 and December 2010. Patients were contacted by phone, e-mail or telegram to request their consent to participate in this study.

Patients aged 29 to 42 years, with primary or secondary infertility, undergoing IVF procedures with donor eggs, were included. In patients with two or more cycles, the authors included only the results of the first cycle for analysis. They reviewed the patient’s age and TSH levels before performing the procedure.

Depending on TSH levels, two groups were formed, the first (group one), included patients with TSH levels of 2.49 mU/L or less; the second (group two), included patients with TSH levels between 2.5 and 4.2 mU/L.

All donor eggs underwent a protocol of controlled ovarian stimulation with follitropin alfa. The initial dose was 225 IU per day. The dose was later adjusted according to the response; stimulation was initiated on cycle day 3. The authors monitored cycles by determining serum estradiol and also used transvaginal ultrasound to monitor follicular growth. They used a gonadotropin-releasing hormone (GnRH) antagonist, ganirelix 0.25 mg per day when at least one follicle equal to or greater than 14 mm in diameter was found or when serum estradiol levels were equal to or greater than 500 pg/ml. Human chorionic gonadotropin (hCG) 10,000 IU was administered intramuscularly when at least two follicles with a diameter equal to or greater than 17 mm were found. Recovery of oocytes was performed 34 to 36 hours after the administration of chorionic gonadotropin and embryo transfer was performed on day 2 post fertilization.

In patients receiving eggs, the endometrium was prepared for embryo transfer with leuprolide acetate, which was begun on day 21 of the cycle prior to transfer; 20 IU per day were given.

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until menstruation. The dose of leuprolide acetate was then reduced to 10 IU per day, a dose that was maintained until two days before embryo transfer. Likewise, the authors used estradiol valerate two mg orally for three days starting on the second day of the cycle, then four mg daily for three days followed by six mg daily for three days, finally eight mg per day until week twelve of gestation if a pregnancy was achieved, or until the day a negative pregnancy test was reported, usually at day 14 after embryo transfer. Two days before embryo transfer micronized progesterone was started at doses of 200 mg intravaginally every eight hours through week 12 of pregnancy if pregnancy was achieved or until day 14 post transfer if an immunological pregnancy test was negative.

A pregnancy immunoassay was performed at 14 days post transfer. Finally, transvaginal ultrasound was performed 21 days after the transfer date to document the presence of an intrauterine gestational sac. A new vaginal ultrasound using ultrasound was performed 28 days post-transfer to detect a fetal heartbeat.

Donor eggs were healthy university students in an age range between 21 and 25 years. All TSH levels in egg donors were below 1.92 mU/L. The authors reviewed the number of eggs retrieved, the fertilization rate, number of grade I embryos, as well as the number of embryos transferred. A maximum of three embryos were transferred at early pronuclear stage on day two after insemination.

A clinical pregnancy was defined as one with an intrauterine gestational sac with the presence of one or more fetuses with a heartbeat. The authors reviewed clinical pregnancy rates according to the levels of TSH and compared them depending on whether the hormone levels were below 2.49 mU/L or above 2.5 mU/L but still within normal limits (0.27 - 4.2 mU/L) according to the reference limits of the present laboratory. Results were analyzed using the Chi-square test and Fisher exact test, when appropriated. A p value < 0.05 was considered statistically significant.

**Results**

The authors included a total of 233 patients. Of these, a total of 173 patients show serum TSH levels of 2.49 mU/L or less and were included in Group 1; Group 2, were formed by 60 patients with TSH levels between 2.5 mU/L and 4.2 mU/L. The mean age of patients in Group 1 was 35.1 years (SD ± 4.3 range 30 to 42), whereas the mean age in Group 2 was 36.2 years (SD ± 4.7 range 29 to 42) with no statistically significant difference (p < 0.09).

Regarding type of infertility, in Group 1, the percentage of patients with primary infertility was 76.3% (132/173) while 23.7% (41/173) had a history of secondary infertility. The results in Group 2 were similar, 78.3% (47/60) had a history of primary infertility, and 21.7% (13/60) secondary infertility. The difference was not significant (p = 0.74).

The diagnoses that were the reason for IVF in Group 1 were: low ovarian reserve in 127 cases; poor response to conventional IVF using their own eggs, 29 cases; chromosomal abnormalities, 13 cases; and severe endometriosis, four cases. The diagnoses that were the reason for IVF in Group 2 were: low ovarian reserve in 43 cases; poor response to conventional IVF using their own eggs, ten cases; chromosomal abnormalities, four cases; and severe endometriosis, two cases.

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (SD ± 4.3, range 30 - 42)</td>
<td>35.1</td>
<td>36.2</td>
</tr>
<tr>
<td>Primary infertility (132/173)</td>
<td>76.3%</td>
<td>78.3%</td>
</tr>
<tr>
<td>Secondary infertility (41/173)</td>
<td>23.7%</td>
<td>21.7%</td>
</tr>
<tr>
<td>Oocytes recovered (SD ± 2.82, range 1 – 9)</td>
<td>6.21</td>
<td>6.89</td>
</tr>
<tr>
<td>Fertilization (%)</td>
<td>79.6</td>
<td>82.3</td>
</tr>
<tr>
<td>Grade I embryos (SD ± 2.21, range 1 – 10)</td>
<td>5.84</td>
<td>6.27</td>
</tr>
<tr>
<td>Transferred embryos</td>
<td>1.13</td>
<td>1.17</td>
</tr>
</tbody>
</table>

**Table 2. — Pregnancy rates and TSH levels.**

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH &lt; 2.49 mU/L</td>
<td>56.6% (98/173)</td>
<td>21.6% (13/60)</td>
</tr>
</tbody>
</table>

**Discussion**

Alterations in thyroid function have been widely associated with anovulation, menstrual irregularities, infertility, poor outcomes in assisted reproduction programs, as well as an increased frequency of abortions [1, 11, 4, 12]. These adverse outcomes have been demonstrated both in patients with overt hypothyroidism, as well as in patients with subclinical hypothyroidism [11].

The relationship between thyroid stimulating hormone levels and infertility has been previously reported. Two
studies report this association in patients with TSH levels within the normal range. Poppe et al. in 2002 [5] found higher mean TSH levels (1.30 mU/L vs. 1.10 mU/L) in infertile patients when compared with a control group of fertile women with a statistically significant difference [5]. Also, in 2004, Raber et al. [13] reported, when assessing the results of thyroid hormone treatment in patients with subclinical hypothyroidism, that the number of pregnancies was less if the levels of TSH were higher than 2.5 mU/L. Therefore it can be stated that even subtle alterations in TSH levels may be related to infertility.

With regards to TSH levels and pregnancy, the Endocrine Society [14] in its 2007 guidelines on the management of hypothyroidism during pregnancy and the postpartum period, recommends keeping TSH levels below 2.5 mU/L before the beginning and during pregnancy in patients diagnosed with hypothyroidism and who are undergoing treatment with thyroid hormone. It also recommends that in those patients who are diagnosed with hypothyroidism during pregnancy, treatment with thyroid hormone should be given until TSH levels below 2.5 mU/L are reached, mainly during the first trimester of pregnancy. One thing to consider is that the requirements of thyroid hormone during pregnancy increase from 30% to 50% during the first four to six weeks [14].

The results of this study showed a decrease in the number of clinical pregnancies obtained in patients undergoing IVF with donor eggs procedures with TSH levels within the normal range, but higher than 2.5 mU/L.

The effect of age on endometrial receptivity is a phenomenon previously reported [15]. In this study, the authors found that the number of pregnancies was lower in Group 2, which had an average age slightly higher than that of the patients in Group 1, but this difference in age was not statistically different. Therefore, and considering that in the present study the authors found no differences between the groups with regards to the number of oocytes recovered, the fertilization rate, and embryo quality, the authors can suggest that there may be an alteration of endometrial function associated with TSH levels above 2.5 mU/L, which could be independent of the impact of age in endometrial receptivity and very probably independent of the effect that thyroid function may have on the mechanisms of ovulation.

It is very important that the interaction of thyroid hormones and the endometrium be considered. On the one hand, endometrial receptors for both T4 and TSH among other hormones, have been described, likewise, the possibility that endometrial cells act as a producer site of thyroid hormones has recently been reported [16]. Thus, endometrium may play an important role in the genesis of abnormal reproductive function associated with thyroid function. Perhaps another explanation for the difference found in this study regarding the number of pregnancies may be related with a subtle alteration of the mechanisms of endometrial receptivity associated with thyroid hormone activity, which could be associated with mild elevations of TSH.

In this study the authors did not evaluate antithyroid antibodies. They evaluated anti-thyroid antibodies only when hypothyroidism, either clinical or subclinical, was diagnosed. The true role of antithyroid antibodies over clinical pregnancy rates in patients who underwent IVF with TSH levels in normal range should be clarified.

Conclusions

In conclusion, the authors found a decrease in the number of clinical pregnancies in patients undergoing IVF with donor eggs, with normal TSH levels, but higher than 2.5 mU/L. This may be related to a possible alteration in endometrial function; however, further studies involving a greater number of participants are needed to confirm these findings.

References


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Evaluation of uterine perfusion in postmenopausal women receiving hormone replacement therapy

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¹Dr. Zekai Tahir Burak Women’s Health Education and Research Hospital, Ankara, ²Hacettepe University, Department of Obstetrics and Gynecology, Ankara (Turkey)

Summary

Objectives: The authors evaluated uterine perfusion in postmenopausal women receiving hormone replacement therapy (HRT) by using transvaginal Doppler ultrasonography. Materials and methods: A total of 60 postmenopausal women receiving HRT were included in this prospective case control study. The patients were divided into two groups. The study group received HRT for at least one year. Uterine perfusion was evaluated by transvaginal Doppler ultrasonography and pulsatility index (PI) and resistance index (RI) of uterine arteries were also recorded with a 5-7.5 MHz transvaginal probe. All patients gave informed consent to the study. Statistical analyses were carried out by using the statistical packages for SPSS 15.0 for Windows. Results: Demographic characteristics of the cases showed no statistically significant difference between the groups. There was a statistically significant difference between PI and RI of uterine arteries. In the study group PI and RI were lower than in the control group. As the duration of HRT use was prolonged, a decline in PI and RI increased (p < 0.05). Conclusion: The current study showed that HRT has positive effects on uterine blood flow in postmenopausal women and may be evaluated by transvaginal Doppler ultrasonography.

Key words: Menopause; Hormone replacement therapy; Transvaginal; Doppler ultrasonography.

Introduction

Menopause is a time period in a woman’s life that is defined as the permanent cessation of menses due to termination of ovarian function, including increased secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) [1]. Climacterium indicates the period of time when a woman passes from reproductive stage of life through the perimenopausal transition and the menopause to the post menopausal years, menstrual cycle length increases, beginning at two to eight years before menopause [2]. The age at menopause varies among women and mean age reported is 54 years in Europe and 51.4 years in USA [3, 4]. Menopause is associated with some negative symptoms such as: hot flushes, vulvovaginal atrophy, vasomotor instability, osteoporosis, increased incidence of thrombo-embolic and ischemic heart disease, and psychological symptoms of anxiety, depression, and memory loss [5, 6].

Doppler ultrasound is a technique that is currently used to evaluate blood flow in artery vessels. In the recent years it has an increasing popularity in gynecological experience because it also enables an in-vivo assessment of uterine and endometrial vascularization [7]. Doppler ultrasound examination has a wide range of application in obstetrics and gynecology practice such as: high risk pregnancies [8], ovarian masses [9], precocious puberty [10], and hypoestrogenic amenorrhea [11]. Previous studies focused on vascular responses of postmenopausal women receiving hormone replacement therapy (HRT). Wender et al. [12] studied internal carotid artery, Guvenal et al. [13] cerebral blood flow, and Huang et al. [14] internal carotid and uterine arteries.

In current study, the authors evaluated uterine perfusion in postmenopausal women receiving HRT by using transvaginal Doppler ultrasonography.

Materials and Methods

This prospective case control study was conducted at Hacettepe University, School of Medicine, Department of Obstetrics and Gynecology. This is a tertiary referral and research hospital in the capital of Turkey. A total of 60 postmenopausal women were included in the study. The patients were divided into two groups as HRT receiving (study group) and not (control group). The duration of HRT use was one to five years. The patients received four different types of HRT: 0.625 mg conjugated estrogens + 2.5 mg medroxyprogesterone acetate, two mg estradiol valerate + one mg cyproterone acetate, two mg estradiol + one mg norethisterone and 2.5 mg tibolone. All women were amenorrheic for at least one year and all of the patients were naturally menopausal. Of the patients with surgical menopause, having menstrual irregularities in reproductive period, having systemic diseases, and with uterine and adnexal pathologies were excluded from the study. Transvaginal Doppler ultrasound and gynecological examination of the patients was managed by the same clinician. During ultrasound examination with empty bladder of patients, a vaginal probe 5.0–7.5 MHz was utilized.

Mean age, duration of menopause, endometrial thickness, serum FSH, LH, and estradiol (E2) levels and uterine artery (UA) pulsatility (PI) and resistance index (RI) of both UAs in three cardiac cycles were evaluated, and mean PI and RI values were also recorded.

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doi: 10.12891/ceog17272014
Table 1. — The demographic and clinical characteristics of the patients.

<table>
<thead>
<tr>
<th></th>
<th>Study group (n = 20)</th>
<th>Control group (n = 40)</th>
<th>Statistics and p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years], mean ± SD</td>
<td>49.3 ± 3.0</td>
<td>57.4 ± 7.2</td>
<td>p = 0.605</td>
</tr>
<tr>
<td>E2 (pg/ml)</td>
<td>61.6 ± 25.3</td>
<td>24.7 ± 20.9</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>ET (mm)</td>
<td>3.3 ± 1.0</td>
<td>2.18 ± 1.2</td>
<td>p &lt; 0.05</td>
</tr>
</tbody>
</table>

E2: estradiol; ET: endometrial thickness

Table 2. — The mean PI and RI values in study and control groups.

<table>
<thead>
<tr>
<th></th>
<th>Study group (n = 20)</th>
<th>Control group (n = 40)</th>
<th>Statistics and p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean UA PI</td>
<td>2.0 ± 0.7</td>
<td>3.4 ± 1.5</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Mean UA RI</td>
<td>0.7 ± 0.1</td>
<td>0.8 ± 0.1</td>
<td>p &lt; 0.05</td>
</tr>
</tbody>
</table>

Table 3. — Correlation between PI and RI values and age, menopause duration, HRT duration, blood E2 levels and endometrial thickness in study group.

<table>
<thead>
<tr>
<th></th>
<th>UA PI</th>
<th>UA RI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>-0.02</td>
<td>-0.23</td>
</tr>
<tr>
<td>Menopause duration</td>
<td>-0.25</td>
<td>-0.11</td>
</tr>
<tr>
<td>HRT duration</td>
<td>-7.74</td>
<td>-0.65</td>
</tr>
<tr>
<td>Blood E2 level</td>
<td>0.10</td>
<td>-0.01</td>
</tr>
<tr>
<td>Endometrial thickness</td>
<td>-0.37</td>
<td>-0.53</td>
</tr>
</tbody>
</table>

*: p < 0.05

Figure 1. — The effect of HRT duration on uterine artery pulsatility index.

Figure 2. — The effect of HRT duration on uterine artery resistance index.
Evaluation of uterine perfusion in postmenopausal women receiving hormone replacement therapy

Statistical analysis

Mean values and standard deviations (SD) were calculated for continuous variables. Independent sample t-test, Mann-Whitney U test (Wilcoxon rank sum test), correlation analysis, and correlation analysis were performed. Two-sided \( p \) values were considered statistically significant at \( p < 0.05 \). Statistical analyses were carried out using SPSS for Windows.

Results

The demographic and clinical characteristics of the patients are shown in Table 1. There were no statistically significant differences among the groups in terms of age, FSH, and LH levels. Endometrial thickness and E2 levels were significantly higher in the study groups compared with controls (\( p < 0.05 \)). UA PI and RI values were evaluated and their correlation between HRT duration, age, menopause duration, endometrial thickness, and type of HRT recorded. Table 2 shows the mean PI and RI values that were statistically significantly different between the groups and were higher in control group (\( p < 0.05 \)).

In study group correlation between PI and RI values and age, menopause duration, HRT duration, blood E2 levels and endometrial thickness are depicted in Table 3. There was a negative correlation between HRT duration and PI and RI values (\( p < 0.05 \)). As the HRT duration was longer, PI and RI values were decreasing. Age and menopause duration showed no correlation (\( p > 0.05 \)). Figures 1 and 2 show the correlation between menopause duration and UA PI and RI levels.

When the authors evaluated the correlation between endometrial thickness and other parameters, they noted that as HRT duration was longer, endometrial thickness was increasing. There was no correlation between HRT type and UA PI values between endometrial thickness. However, there was a negative correlation between UA RI and endometrial thickness (\( p < 0.05 \)).

Discussion

The authors conducted an analysis of uterine perfusion in postmenopausal women receiving different types of HRTs. Uterine artery PI and RI values were lower in HRT receiving postmenopausal group. As the duration of HRT use became longer, the reduction of UA PI and RI increased. No association between HRT type and Doppler values were found. Previous studies evaluated the effects of HRT on blood vessels and cardiovascular risk factors in HRT receiving postmenopausal women [15-17]. Some authors have also described that receiving HRT reduces morbidity and mortality from coronary artery disease [18, 19]. The present authors also found a decrease in PI and RI values of uterine artery and these results were similar to the literature and related to the cardio-protective effect of HRT.

Jurkovic et al. [20] reported their experience on Doppler studies in HRT receiving postmenopausal women and they also found vasodilatation in the UA after HRT treatment. In this study, the authors also found that HRT has a circadian rhythm on arterial blood flow. Achiron et al. [21] studied in their study the prolonged effect of HRT in postmenopausal women and reported that endometrial blood flow impedance was higher in non-HRT receiving group. Dörren et al. [22] also designed a study including two groups receiving HRT and not as controls. Their findings included increased blood flow in uterine vessels as in the present study. They also evaluated the endometrial thickness and found that duration of HRT has no effect on endometrial thickness. In contrast to this study, the present authors found an increase in ET in HRT group but not much than eight mm and pathology results were benign.

In conclusion, the authors believe that receiving HRT has a protective effect on vessels and cardiovascular system. These effects may be evaluated by non-invasive transvaginal Doppler ultrasonography. Clinicians may advise postmenopausal symptomatic women receiving HRT under regular visits.

References


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Introduction

One of the primary goals of postoperative pain management is to relieve pain so that normal physiologic functions including ventilation, gastrointestinal function, and mobility are minimally impaired [1]. It is standard practice is to provide postoperative pain relief with the use of parenteral, epidural, or oral analgesics. Patients undergoing laparotomy for gynecologic surgery are typically offered either patient controlled analgesia pumps (PCAs) or epidural catheters for initial postoperative pain management. However, narcotic use is associated with undesirable side effects including nausea, vomiting, ileus, headache, sedation, respiratory depression, and postoperative hyperalgesia [2]. Despite the frequent use of narcotics, pain after surgery continues to be a major management challenge. In a recent meta-analysis covering 800 publications and over 20,000 patients, it was found that 41% of all surgical patients experience moderate to severe acute postoperative pain and 24% report inadequate pain relief [3]. Portenoy et al. found that 42% of patients with ovarian cancer reported persistent and frequent postoperative pain [4]. Uncontrolled pain during the postoperative period interferes with recovery from surgery, contributes to fear and anxiety during continued treatment, and delays return to usual life activities [5, 6].

Novel pain control strategies have been developed in an attempt to provide better postoperative pain control and avoid the disadvantages of narcotic medications. These strategies generally incorporate traditional analgesic medications with non-pharmacologic or complementary strategies to provide both improved pain control and decrease the amount of required analgesic medication. Non-pharmacologic and complementary strategies which have been investigated include the use of support devices (binders), focused imagery, relaxation, distraction, therapeutic music, acupressure, acupuncture, electroacupuncture, massage, cold and hot compresses, transcutaneous electrical nerve stimulation (TENS), and osteopathic manipulation [7-12]. It is estimated that greater than 50% of patients use at least one non-analgesic pain control strategy in combination with traditional analgesics for the management of postoperative pain [7].

Wong et al. from the University of Texas Medical Branch at Galveston described the use of a novel light-weight neoprene abdominopelvic binding device in post-cesarean section patients [13, 14]. The binder consisted of a traditional abdominal elastic support device that was incorporated into an elastic pant component. The pant component was hypothesized to provide additional support to the lower abdominal musculature. The study compared the new abdominal binder to a traditional fishnet abdominal wound dressing in patients who underwent cesarean section. Their study showed that when compared to the traditional postoperative dressing the abdominopelvic binder decreased postoperative narcotic use as well as wound complications.

The purpose of this study was to determine if patients undergoing gynecologic surgeries through abdominal incisions would benefit from postoperative use of the abdominopelvic binder in a similar fashion to the study of Wong et al. The present authors’ hypothesis was that use...
of the neoprene abdominopelvic binder would provide mechanical splinting resulting in decreased abdominal pain and thus decreased pharmacologic analgesia.

Materials and Methods

This study was approved by the Wilford Hall Medical Center and Brooke Army Medical Center Institutional Review Board. Individual participants were enrolled in the study and written consent was obtained prior to the date of surgery. Patients were eligible for participation if they were scheduled for gynecologic surgery through an abdominal incision. Epidural analgesia, intravenous or intramuscular ketorolac, and oral analgesics were not used during the 24-hour study period. Patients with an allergy to morphine sulfate were excluded. Eligible participants were randomly assigned to either no binder or binder for the first 24 hours post surgery with the use of opaque, sealed envelopes containing assignments to either “binder” or “no binder.” All patients followed a standardized pain control protocol for the first 24 hours postoperatively consisting of a morphine sulfate patient controlled analgesia (PCA) pump with demand a dose of one mg intravenously every ten minutes, no lock-out, and no basal rate. All patients wore sequential compression devices on their lower extremities while in bed and participated in aggressive bed side pulmonary incentive spirometry. Patients received standard postoperative intravenous fluids until tolerating clear liquids. Patients’ diets were advanced as tolerated. A Foley catheter and the bandage remained in place for at least 24 hours postoperatively. After the 24-hour study period patients were managed at the discretion of their attending surgeon.

No placebo was used. Patients were allocated in a parallel fashion to receive the “binder” or standard treatment with a fishnet bandage support “no binder” in the pre-anesthesia holding area prior to moving the patient to the operating room by random drawing of an envelope assigned by the study nurse. There were no restrictions on the randomization. The surgical team was blinded to patient’s study group allocation until after the surgery was completed and the binder was fitted and placed on the patient before leaving the operating room.

Detailed patient and clinical information was collected including: age, weight, co-morbid medical conditions, past surgical history, indication for surgery, type of surgery, incision type, and incision length. Abstracted co-morbidities included hypertension, diabetes mellitus, coronary artery disease, chronic obstructive pulmonary disease, asthma, thromboembolic disease, cerebral vascular accident, epilepsy, chronic migraine headaches, depression requiring medication, moderate to severe fibromyalgia, and severe degenerative joint disease. For statistical analysis the co-morbidities were stratified to groups with no co-morbidities, one co-morbidity, or two or more co-morbidities, respectively. Prior surgeries were similarly stratified between no prior surgeries, minor surgery only, or one or more abdominal surgeries. The surgical indications were uterine leiomyomata, gynecologic cancer, and other indications, which included adnexal masses, pelvic pain, and menorrhagia. The type of surgical procedure was simple or complex. Simple surgeries included ovarian cystectomy, unilateral or bilateral salpingo-oophorectomy, myomectomy, and simple abdominal hysterectomy with or without salpingo-oophorectomy. Complex surgeries were gynecologic oncology procedures or extensive urogynecologic procedures. Type of surgical incision was horizontal and or vertical; the length of the incision was also recorded.

The amount of morphine sulfate used in the first 24 hours was determined by the PCA pump reading. All patients were asked to fill out a visual linear analog pain scale (VAS) preoperatively, as well as at 24 hours after surgery [15]. Patients were given a data collection sheet and asked to record the time of their first ambulation. Additionally they were asked to record each time they ambulated. The compliance with data collection was assured by the patient’s primary surgeon who saw all patients at least three times during the 24-hour study period. At the end of the 24 hours study period the patients were asked if they felt that binder helped relieve their discomfort and if they desired to keep the binder on beyond the 24 hours of the study.

The primary outcome studied was total morphine use (mg) in the first 24 hours postoperatively. Secondary outcomes include: postoperative VAS pain scores, time from surgery to the first ambulation, and the total number of ambulatory events in the first 24 hours postoperatively. Based on prior experience on the present post-surgical ward, the expected morphine use in the control group was 20 to 40 mg during the 24-hour study period. A 10% decrease in morphine use was considered to be clinically significant. A look up table based on employing the method of Kraemer and Thiemann [16] to obtain an initial estimate of the sample size was confirmed with 1,000 iterations of a Monte Carlo simulation until the power was between 80% and 85% with a level of confidence of 95%. According to this method, 37 subjects per group (74 total) would be needed to detect the expected difference with the desired level of confidence and power.

Continuous variables were presented as the mean +/- standard deviation and categorical variables as frequencies (percentage of patients) with 95% confidence intervals. Patient characteristics in each treatment group (no binder versus binder) were compared by using the Chi square test for categorical variables and the Kruskal-Wallis test or Student’s t-test for continuous variables, as appropriate based on the variance of the data. Spearman rank correlation was used to determine if significant relationships existed between the clinical variables of binder status, age, weight, co-morbidities, prior surgeries, indication for surgery, type of surgery, incision type, incision length, and the outcome variables. Significant relationships and trends identified by the Spearman rank correlation were subjected to hypothesis testing with the Student’s t-test. An unplanned subgroup analysis also took place following the initial analysis, again using the Student’s t-test. A p-value < 0.05 was considered statistically significant. All data were analyzed using the Sigma Plot version 11.

Results

Between January 2001 and November 2005, 75 patients were enrolled in the study and randomly assigned to one of the treatment groups (no binder versus binder) and enrollment was discontinued due to accrual of enough patients. Thirty-nine patients were randomized to the no binder group while 36 patients were randomized to the binder group. All patients received the allocated intervention. No patients were excluded from analysis. Comparison of patient characteristics in each of the treatment groups is shown in Table 1. The two treatment groups were similar with respect to all patient characteristics.

The major indication for abdominal gynecologic surgery was uterine leiomyomata (39.5%); gynecologic malignancy was the second most common surgical indication, (36.8%). Other indications included endometriosis, pelvic pain, adnexal mass, and menorrhagia (23.7%).
Preliminary data analysis using the Spearman rank correlation revealed statistically significant relationships between the number of postoperative ambulatory events and age ($p = 0.014$), complex surgery type ($p = 0.029$), and incision type ($p = 0.014$). Fewer ambulatory events were observed in older patients, those undergoing complex surgeries, and those with vertical incisions. This defined a high-risk population for poor postoperative ambulation.

Morphine use, postoperative pain score, and time to first ambulation were not significantly influenced by the binder or the other clinical variables.

Spearman rank correlation was also performed to evaluate for potential relationships between the four outcome variables: morphine sulfate used in the first 24 hours, postoperative VAS pain scores, time from surgery to the first ambulation, and the total number of ambulatory events in the first 24 hours postoperatively. Patients with increased postoperative pain scores were less likely to ambulate ($p = 0.024$), suggesting that the number of ambulatory events could be used as an adjunct for pain control. No correlation was observed between morphine use and the other outcome variables.

Table 2 shows the analysis of outcome variables based on binder allocation. There was not a significant difference between the amount of morphine used, postoperative pain scores, and time to first ambulation in the study and control groups. Abdominal binder use was correlated with increased ambulatory events ($p = 0.068$), however this relationship did not reach significance.

Subgroup analysis was performed by stratifying the highest risk patients identified by the initial analysis: incision type, age, and complex surgery. The abdominal binder increased the number of postoperative ambulatory events ($p = 0.068$) when all of the data was analyzed together. Patients with vertical incisions who used the binder averaged 2.52 ambulatory events in 24 hours versus 0.84 ambulatory events in the no binder group ($p = 0.002$). In patients with vertical incisions, further data analysis revealed that 87% (20/23) of patients in the binder group had at least one ambulation during the 24-hour study period compared to only 58% (11/19) in the no binder group, ($p = 0.038$).

Patients over age 50 years in the binder group had more postoperative ambulatory events than patients in the no binder group.
binder group, 0.75 to 2 ($p = 0.014$). Patients with complex surgeries in the binder group had more postoperative ambulatory events than patients in the no binder group, 0.73 to 1.78 ($p = 0.066$).

Compliance with wearing the binders for the 24-hour duration of the study was 100%. Seventy percent of patients elected to continue wearing the binder beyond the 24-hour study duration. All but one patient felt that the binder helped decrease their postoperative pain and helped with walking. That one patient was under age 50 and underwent a simple surgery through a vertical midline incision. Her indication for surgery was chronic pelvic pain. There were no adverse effects from the binder.

Discussion

The time period after a major abdominal surgery is associated with complex, potentially harmful physiologic changes. These physiologic changes place patients at risk for several well described complications including thromboembolic disease, pneumonia, and gastrointestinal tract dysfunction [3]. The control of postoperative pain frequently requires the use of significant amounts of narcotic medications leading to impaired mobility and respiratory function. Risk factors for thromboembolic disease include, but are not limited to: pelvic surgery, immobility, malignancy, and increasing age [17]. Risk factors for postoperative pneumonia include: increasing age, smoking, poor nutritional status, COPD, immobility, and respiratory splinting due to pain [18,19].

In the current study the authors have defined a subset of patients at high risk for postoperative immobility. This subset includes patients greater than age 50 years, those who are undergoing complex surgeries for gynecologic malignancies, and those who have vertical midline abdominal incisions. As defined above, this subset of patients is at high risk for thromboembolic disease and pneumonia after gynecologic surgery. Interventions that decrease the risks of venous thromboembolic disease and pneumonia should be aggressively pursued in this very high risk patient population. Early ambulation in the postoperative period has been shown to decrease the risks of both venous thromboembolic disease and pneumonia [20, 21]. In combination with venous thromboembolic prophylaxis, early and persistent mobilization is recommended in all patients undergoing abdominal gynecologic surgery [17]. While bed rest had been shown to promote venous stasis, ambulation has been demonstrated to promote venous flow through contractions of the lower extremity muscle groups. In addition, a recent study demonstrated that moderate-intensity exercise suppresses platelet activation and polymorphonuclear leukocyte adhesion to platelets deposited at sites of vascular injury under flow and thereby reduces the risk of vascular thrombosis and inflammation [22].

Early postoperative ambulation has further been shown to improve pulmonary function and reduce risk of postoperative pneumonia [21]. Decreased respiratory effort due to excessive opioid use or due to inadequate pain control reduces the depth of breathing and increase the chances a patient will develop pneumonia. Ambulation results in improved lung expansion compared with a supine position, in addition to the added respiratory effort due to the work of walking.

While there was no difference in the primary study variable, milligrams of morphine used in 24 hours, the neo-prene abdominopelvic binder used in the present study resulted in a marked improvement in postoperative ambulation in those patients at highest risk for thromboembolic disease and pneumonia: patients with age greater than 50 years, patients undergoing complex pelvic surgeries, and patients with vertical incisions. The present study was not powered to detect differences in morphine use between patients in the subgroup with all three risk factors and further studies of patients in this high risk group could be of use since the number of ambulatory events was correlated with the pain score in our multivariate analysis.

The mechanism of how the abdominal binder contributes to increased postoperative ambulation is likely multifactorial. The binder reduces shear forces at the incision interface resulting in less discomfort with sitting up, standing, and ambulating. Additionally, the pressure from the binder widely disperses the pain from the abdominal incision, resulting in the perception of pressure rather than pain. Finally, as the study was not placebo controlled, the binder group may have experienced a placebo effect, motivating patients to ambulate at a higher rate.

The time to first ambulation and the number of ambulatory events are also influenced by multiple factors. Specifically, some of the important factors include preoperative counseling and expectations for the postoperative course, postoperative counseling, postoperative pain control and the ability of the patient to ambulate without extra discomfort, the availability of nursing and ancillary staff to help the patient ambulate, postoperative encouragement by the operating team as well as the nursing and ancillary staff, and timing of Foley catheter removal.

A limitation of the current study was that it used morphine requirement through 24 hours instead of more clinically relevant variables such as pneumonia and venous thromboembolic events. The authors’ assumption was that morphine use would be inversely related to the postoperative pain and that decreased pain would increase ambulation. The reason for choosing this endpoint is that both pneumonia and venous thromboembolic events are relatively rare and would require a longer patient follow-up that outlasts most postoperative hospital stays as well as a significantly increased number of patients in the study. This assumption was valid, based on the post hoc analysis between all outcome variables.
Conclusion

The authors have defined a group of patients who averaged less than one ambulation in the first 24 hours postoperatively, those patients who are greater than age 50 years, have undergone complex surgeries, and who have vertical abdominal skin incisions. These patients are also at high risk for postoperative pneumonia and thromboembolic disease [17-19]. Early and frequent postoperative ambulation has been shown to decrease these complications and should be aggressively pursued [21]. They have shown that the use of a neoprene abdominopelvic binder results in increased ambulation in this high-risk population. Furthermore, the binder was well-tolerated, had no adverse side effects, and is relatively inexpensive. The authors recommend the use of a binder in patients with one or more of the following characteristics: over age 50 years, complex gynecologic surgery, or have vertical skin incisions.

References


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Craniofacial catch-up growth in intrauterine growth retarded rats following postnatal nutritional rehabilitation

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Summary

Purpose: The aim of the study was to analyze the effect of postnatal nutritional rehabilitation on the craniofacial growth in rats with intrauterine growth retardation (IUGR). Materials and Methods: Wistar rats were assigned to one of the following groups: control, Sham-operated, and IUGR. The IUGR was produced by uterine vessels bending (day 14 of pregnancy). At days 1, 21, 42, 63, and 84 of postnatal life, each animal was X-rayed, and neural and facial length, width and height were measured. Volumetric and morphometric indices were calculated. Results: The decreased maternal-fetal blood flow during the last-third of the gestation period modified cranial size and shape of both sexes at birth. Discussion: Postnatal nutritional rehabilitation is not fully sufficient to reverse the prenatal growth retardation. There are specific responses depending on the sex and the age of the IUGR pups. Regardless of the changes in size, the shape is not modified during all the postnatal period.

Key words: Intrauterine growth retardation; Postnatal nutritional rehabilitation.

Introduction

Fetal growth is a dynamic process that involves a balance between mechanisms that control the entry of substrates, fetal synthesis of proteins and lipids, and energy production to their metabolic requirements. In analogy with postnatal life, intrauterine growth is determined by the interaction of exogenous factors (nutritional, toxic, infectious), and endogenous (genetic) [1].

It is assumed that most prenatal growth restriction is due to interference in the placental contribution of nutrients, which can be at the entrance of maternal nutrients, placental blood flow or function of the placenta [2, 3]. In this sense, the authors have reported the impact of the reduction of maternal-fetal blood flow on fetal development, with direct consequences in determining intrauterine growth retardation (IUGR) in body weight and skeletal dimensions at birth [4, 5]. Epidemiological and experimental studies have reported that individual tissues and organ systems as a whole are programmed in the uterus during critical periods of development, and in stressful situations they have adverse functional consequences in postnatal life [6, 7]. Thus, children with IUGR have low nutritional reserves and feeding difficulties, and often 10% of them remain vulnerable during their growth [8, 9].

Morphological variation emerges from complex interactions between genetic and environmental factors that are modulated by sequential and interacting developmental processes [10]. In the postnatal period, different mechanisms may act to reverse the morphological modification leading to what is called “catch-up” [11, 12]. The degree of growth retardation may determine the ability to catch-up. In this regard, each organ or system has its own growth pattern which generates different responses to the prenatal stress. So, the skull of all vertebrates is not a single developing unit but a complex structure that comprises recognizable parts that are coherent according to their developmental origin, structure, and function. These parts can be thought of as modules in the sense that they are highly integrated by numerous and usually strong interactions, while the interactions among them are relatively weaker [13, 14, 15].

To date, however, it is still necessary to understand how the modifications of craniofacial growth as a consequence of a prenatal perturbation may affect the postnatal pattern of interaction between cranial traits. On this basis, the authors propose to analyze the effect of postnatal nutritional rehabilitation on the craniofacial growth in rats with intrauterine growth retardation.

Materials and Methods

The animals involved in this study were Rattus norvegicus albinus, var. Wistar, from the Instituto de Genética Veterinaria (IGEVET, UNLP- CONICET). The animals were kept free of pathogens and treated in compliance with standardized institutional guidelines. They were fed on a pelleted and sterilized commercial stock diet.

Fifty females (200–250 g body weight) were mated overnight with ten adult males. Pregnancy was assumed to commence after spermatozoa were found in the vaginal smear. Pregnant rats were housed in individual steel cages and fed on stock diet, with water ad libitum, and assigned to one of three experimental groups: (a) control (C) = control dams and pups did not receive any treatment; (b)
IUGR = a lower midline laparotomy was performed in the mothers of the IUGR group at day 14 of gestation. Animals were anesthetized intramuscularly with ketalar (0.005 ml 100 g body weight). Complementary light-ether anesthesia was administered during surgery. After opening the peritoneal cavity, the uterus was exposed. The uterine vessels near the lower end of each uterine horn were bent and fastened with a 3–0 silk suture. Pregnancy was allowed to go on until delivery [16]. (c) Sham-operated (SH) = The procedure applied to sham-operated animals was similar to that used for IUGR ones. However, the uterine vessels were not obstructed in order to separate the effects of surgery from that of vessel bending.

During lactation (1 to 21 days of age) IUGR and SH pups were cross-fostered to control dams. Litters were reduced to four males and four females each, to render lactation uniform across the groups. Pups suckled ad-libitum. During the postlactation period (from 21 days of age onwards) a standard diet was available ad-libitum to offsprings.

Each animal was X-rayed in dorsal and lateral position at 1, 21, 42, 63, and 84 days of age. In each X-ray, neurocranial length (NL), width (NW), and height (NH), and facial length (FL), width (FW), and height (FH) were measured (Figure 1).

To estimate the size variations of neural and facial components by age and sex, volumetric indices were calculated as follows: neural index = (VNI: 3ØNL x NW x NH); facial index = (VFI: 3ØFL x FW x FH). Finally, to evaluate changes in the skull shape, a morphometric neurofacial index (MNFI) was calculated as follows: (MNFI = VNI/VFI).

The normality of distributions was assessed by the one-sample Kolmogorov–Smirnov test. This test indicated no significant differences in all the indices, compelling the authors to use an ANOVA analysis to examine the factors significance, and the Least Square Difference test (LSD) for the comparison between groups. Percentage differences between means (PDM) were calculated in order to obtain standardized differences between treatments, according to the formula: PDM = 100 * (X1 – X2)/X1. For instance, X1= mean value of SH and X2= mean value of IUGR.

### Table 1. — Least Square Difference Test (LSD) for the comparison between SH and IUGR groups.

<table>
<thead>
<tr>
<th>Age (days)</th>
<th>Males</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Females</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VNI</td>
<td>VFI</td>
<td>MNFI</td>
<td>VNI</td>
<td>VFI</td>
<td>MNFI</td>
<td>VNI</td>
<td>VFI</td>
<td>MNFI</td>
<td>VNI</td>
<td>VFI</td>
</tr>
<tr>
<td>1</td>
<td>0.62**</td>
<td>0.57**</td>
<td>0.11**</td>
<td>0.31**</td>
<td>0.33**</td>
<td>-0.08**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>0.21*</td>
<td>0.19*</td>
<td>-0.02</td>
<td>0.11</td>
<td>-0.03</td>
<td>0.02</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>0.06</td>
<td>0.04</td>
<td>0.00</td>
<td>0.25**</td>
<td>-0.18</td>
<td>0.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>63</td>
<td>0.16</td>
<td>0.12</td>
<td>0.00</td>
<td>0.33**</td>
<td>0.29**</td>
<td>-0.01</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>84</td>
<td>0.24**</td>
<td>0.13</td>
<td>0.00</td>
<td>0.37**</td>
<td>0.20*</td>
<td>0.01</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*p < 0.05; **p < 0.01

### Results

The ANOVA test showed significant differences for age, sex and treatment factors in VNI, VFI and MNFI. The interaction between factors did not indicate any significant difference.

The post-hoc analysis between C and SH groups showed no significant differences in males, but significant differences in VNI, VFI, and MNFI at varying ages in females. Therefore, the last group was used as reference.

The comparison between SH-IUGR indicated, in both sexes, significant differences at birth in all the cranial indices. At weaning (21 days), there were significant differences in males for VNI and VFI. Nevertheless, in females there were no significant differences. At day 42 and 63, males showed no significant differences in any of the indices analyzed. However, significant differences were observed in females in VNI (42 days), and VNI and VFI (63 days). Finally, at day 84 there were significant differences in VNI (males), and VNI, and VFI (females). The MNFI showed no difference from day 21 onwards, in both females and males (Table 1).

### Discussion

**Birth**

The intrauterine environmental perturbation during the last third of pregnancy altered skull growth. Both neural and facial components showed growth retardation. In this...
sense, neural volume decreased about six percent and facial volume decreased 12% in males, while in females the reduction was of three and seven percent, respectively (Figure 2). Consequently, the different growth patterns of cranial structures led to shape changes. This non-proportional growth, in which the facial component was more affected than the neural one, was previously reported by Oyhenart et al. [17]. This can be explained because those cranial morphological features that are functionally related and development connected tend to co-vary with each other and to be independent of other characteristics, due to the modular organization of the craniofacial skeleton [18, 19].

**Lactational period**

Growth retardation observed in males pup at birth persisted even when they had a normal lactation. Thus, the catch-up growth in males was incomplete in both neural and facial components. Again, the facial volume was more affected than the neural one. Nevertheless, size variation was smaller than that found at birth (only 2%, approximately). In contrast, females had complete compensatory craniofacial growth. In this regard, Oyhenart et al. [17] reported an incomplete lactational catch-up growth in IUGR animals, since males reached control size only in neurocranial height, and females in neurocranial length, width and height, and facial height. Likewise, Jones et al. [20], in a model of gestational protein restriction, also reported compensatory growth in females after nutritional rehabilitation during lactation.

Furthermore, size changes were not accompanied by shape changes. This can probably be due to the fact that the variation in the skull shape decreases early postnatal growth [21, 10].

**Postlactational period**

It has been reported that compensatory growth can be associated not only with the intensity of stress but also with the time available for nutritional rehabilitation to produce an effect [17]. Both conditions were observed in the present study. At first, the male growth retardation seen in the neurocranial component from birth to the end of lactation continued during the postlactation period. In fact, the severity of the intrauterine stress acted in the formative period of neural structures and prevented its subsequent recovery.
Nevertheless, the facial component had a compensatory growth because the growth of the facial structures continued during the postnatal period [22]. However, the nutritional rehabilitation in the IUGR pups needed more time to achieve the control size.

Although IUGR females showed a catch-up growth in craniofacial size during lactation, a retarded growth was observed again during postlactation. These results may be explained mainly by the hypothesis of “fetal programming of life”, suggesting that fetal malnutrition triggers endocrine adaptations with a permanent change in the morphology, physiology, and metabolism [23-25]. The current theoretical perspective regarding the adaptive significance of fetal life programming emphasizes the benefit of reducing the nutritional requirements through a lower growth trajectory in the uterus [26]. Thus, adult phenotype depends largely on the operating stressors during intrauterine growth [27].

As seen in the previous ontogenetic period, morphometric phenotypic variation in shape appears to be stable.

Conclusion

The decreased maternal-fetal blood flow during the last third of the gestation period modifies cranial size and shape of both sexes at birth. Postnatal nutritional rehabilitation is not fully sufficient to reverse the prenatal growth retardation. There are specific responses depending on the sex and the age of the IUGR pups. Regardless of the changes in size, the shape is not modified during all the postnatal period.

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Maternal serum pregnancy-associated plasma protein-A levels in hyperemesis gravidarum: a prospective case control study

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Summary

Purpose: To investigate if maternal serum pregnancy-associated plasma protein-A levels are affected in hyperemesis gravidarum (HG). Materials and Methods: A prospective case control study was conducted in 169 HG cases who had one or more antepartum hospitalization for HG. The control pregnancies were 132 and were selected randomly among all women who had first trimester prenatal screening in antenatal outpatient clinic between 2011 and 2012. Results: Maternal serum pregnancy-associated plasma protein-A levels were significantly higher in hyperemesis gravidarum group compared with control group (p = 0.002 p < 0.05 95% CI). Power analysis of independent sample t-test, two-sided, for pregnancy-associated plasma protein-A was 0.88. Maternal serum free β-human chorionic gonadotropin values were not different between two groups (p > 0.05). Conclusion: Increased pregnancy-associated plasma protein-A levels associated with HG, even after excluding potential cofounders.

Key words: Pregnancy-associated plasma protein-A (PAPP-A); Hyperemesis gravidarum; Human chorionic gonadotropin (hCG).

Introduction

Hyperemesis gravidarum (HG) is a disease characterized with severe nausea, vomiting, and anorexia in early pregnancy and leading to dehydration, weight loss, electrolyte imbalance, and metabolic disturbance. As the etiology remains obscure, the treatment remains supportive and symptomatic. About 50% to 90% of pregnant women experience nausea and vomiting but HG occurs only in 0.3–2% of pregnancies [1, 2].

Although the exact pathogenesis of HG is unknown, it is widely accepted that gestational vomiting results from various metabolic and endocrine factors, many of placental origin. The most implicated factor is human chorionic gonadotropin (hCG). This link between hCG and HG is based largely on the temporal relationship between the peak of HG and the peak of hCG production, both of which occur between 12 and 14 weeks’ gestation. In addition, nausea and vomiting are often worse in pregnant women with conditions associated with elevated hCG levels, such as molar pregnancies, multiple gestations, and Down syndrome [3].

PAPP-A was one of four proteins identified in the plasma of pregnant women, and accordingly was given the name ‘pregnancy-associated plasma protein-’A’ [4]. During pregnancy, PAPP-A is produced by placental syncytiotrophoblasts and secreted into the maternal circulation where its concentration increases until term [5]. It has proteolytic activity against IGF binding protein-4 (IGFBP-4) in ovarian follicular fluid and in conditioned medium from fibroblasts, osteoblasts, granulosa cells, lung cells, and smooth-muscle cells [6]. PAPP-A was also found to be ubiquitously expressed with particularly high expression in kidney and bone, clearly indicating a role for PAPP-A outside pregnancy [7].

Pregnancy outcomes of HG is conflicting. Most of the studies have concluded that there are no adverse affects of HG on fetal outcome including gestational age, birth weight, incidence of prematurity, and Apgar scoring [8–10]. However some studies have reported lower birth weight associated with HG [11, 12].

There is only one study that had investigated the relation between maternal serum PAPP-A levels and HG therefore in this study the authors aim to evaluate the relation between PAPP-A, free β-HCG, and HG.

Materials and Methods

The study was conducted in Zekai Tahir Burak Women’s Health Hospital in Ankara, Turkey. Ethics approval was obtained from the institutional review board. Informed written consent was obtained from study participants. Study was designed as a prospective case-control study, in which the cases were singleton pregnancies, hospitalized with the diagnosis of HG, between 2011 and 2012 (n = 169). Controls were pregnancies who didn’t complain of emesis (n=132) and selected randomly, by using randomization table among all women who had first trimester prenatal screening in antenatal outpatient clinic and same gestational week as in each study case. Gestational age was calculated via combination of first trimester ultrasound findings and the last menstrual period.

Inclusion criteria confirmed singleton pregnancy, clinical HG (with dehydration and ketonuria), and one or more antepartum hospitalization for hyperemesis. Women with diagnostic cofounders such as hyperthyroidism (which diagnosed before), stomach diseases, gastroenteritis were excluded. Venous blood was collected to obtain the levels of hemoglobin, thyroid stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), aspartate aminotransaminase (AST), alanine aminotransaminase (ALT), and albumin as initial laboratory assessment on admission before any treatment. PAPP-A and β-HCG values of the subjects...
were obtained from routine first-trimester prenatal screening analysis performed at the authors’ hospitals. Upon collection, plasma samples were analyzed within three hours. Free β-HCG and PAPP-A kits were utilized. The plasma levels were expressed as gestational age-specific multiples of the median (MoM). In risk evaluation, the prenatal screening program was utilized.

Statistical analysis was performed using SPSS version 17.0 and power analysis was performed using NCSS 2007. The Kolmogorov-Smirnov test was used to evaluate the distribution of variables. Because the data of maternal age, PAPP-A, and TSH were normally distributed, parametric test (independent sample t-test) were used for analyses. For the other not normally distributed variables, non-parametric test were used for analyses. Logistic regression analysis was used for variables independently associated with HG.

Results

A total of 169 pregnant women with HG and 132 of healthy pregnancies as in control group were included in the study. Characteristics of this study are shown in Table 1. Maternal age was significantly higher in HG group compared with control group (p < 0.05 95% CI). Free β-HCG, T3, ALT, AST, and albumin values were not different between two groups (p > 0.05). Serum T4 levels were significantly higher in HG group compared with control group (p = 0.002 < 0.05 95% CI). Serum TSH levels significantly lower in HG group compared with control group (p = 0.002 < 0.05 95% CI). Serum AST levels were significantly higher in HG group compared with control group (p = 0.001 < 0.05 95% CI).

Power analysis in Table 2 reveals the power analysis of independent sample t-test, two-sided results of PAPP-A.

Logistic regression analysis in Table 3 revealed that: age, PAPP-A, T4, and ALT values were significantly correlated with risk of HG (p < 0.05 95% CI). There were no significant correlations found with HG risk and serum AST, and free βHCG values.

Discussion

HCG is often considered as the most likely cause of HG [3]. However in this study, there were no significant free βHCG level differences in HG group. The majority of literature, suggests a relationship between HG and high HCG levels. However few studies have not found any significant relation between HCG and HG as in the present study [13-15]. Possible explanation for the inconsistent finding of elevated HCG levels in HG patients is that HG is not simply caused by elevated HCG levels, but that specific isoforms of HCG are causing HG. In a study by Tsuruta et al., HG patients had significantly increased levels of the HCG fraction that contains HCG with asialo-carbohydrate chain [14]. Also, Jordan et al. had found HG group increased HCG concentrations in the more acidic half (pH < 4) of the chromatofocusing pH range than seen in control subjects [16].

This study showed that elevated PAPP-A levels are independently associated with HG, even after excluding potential cofounders. To the authors’ knowledge no other studies than Derbent et al. have investigated PAPP-A levels in combination with HG that have also been published to date [17]. In vivo, PAPP-A expression has been shown to be upregulated in response to acute injury in several systems. In healing human skin wounds, PAPP-A expression in dermal granulation tissue is induced over time in dermal granulation tissue [18]. Possible explanation for the inconsistent finding of elevated HCG levels in HG patients is that HG is not simply caused by elevated HCG levels, but that specific isoforms of HCG are causing HG. In a study by Tsuruta et al., HG patients had significantly increased levels of the HCG fraction that contains HCG with asialo-carbohydrate chain [14]. Also, Jordan et al. had found HG group increased HCG concentrations in the more acidic half (pH < 4) of the chromatofocusing pH range than seen in control subjects [16].

This study showed that elevated PAPP-A levels are independently associated with HG, even after excluding potential cofounders. To the authors’ knowledge no other studies than Derbent et al. have investigated PAPP-A levels in combination with HG that have also been published to date [17]. In vivo, PAPP-A expression has been shown to be upregulated in response to acute injury in several systems. In healing human skin wounds, PAPP-A expression is induced over time in dermal granulation tissue [18]. The proinflammatory cytokines tumor necrosis factor (TNF)-alpha and interleukin (IL)-1b are the most potent stimulators

Table 1. — The characteristics of the study groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>HG (n=169)</th>
<th>Control (n=132)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age</td>
<td>27.6 ± 5.14</td>
<td>25.5 ± 5.11</td>
<td>0.002*</td>
</tr>
<tr>
<td>PAPP-A (MoM)</td>
<td>1.19 ± 0.71</td>
<td>0.96 ± 0.54</td>
<td>0.002*</td>
</tr>
<tr>
<td>Free βHCG (MoM)</td>
<td>0.99 (0.71)</td>
<td>0.91 (0.55)</td>
<td>0.86*</td>
</tr>
<tr>
<td>TSH (mIU/ml)</td>
<td>0.96 ± 0.78</td>
<td>1.45 ± 0.87</td>
<td>0.000*</td>
</tr>
<tr>
<td>T4 (ng/dl)</td>
<td>1.31 (0.33)</td>
<td>1.18 (0.00)</td>
<td>0.001*</td>
</tr>
<tr>
<td>T3 (ng/dl)</td>
<td>3.09 (0.79)</td>
<td>3.21 (0.42)</td>
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</tr>
<tr>
<td>ALT (U/l)</td>
<td>17.00 (5.50)</td>
<td>17.50 (6.00)</td>
<td>0.071*</td>
</tr>
<tr>
<td>AST (ng/dl)</td>
<td>17.00 (5.50)</td>
<td>17.50 (6.00)</td>
<td>0.886</td>
</tr>
<tr>
<td>Albumin</td>
<td>4.41 (0.55)</td>
<td>4.19 (0.53)</td>
<td>0.202</td>
</tr>
</tbody>
</table>

* Independent sample t-test; ** Mann-Whitney U test. Values are given as median (IQR: interquartile range) or mean ± SD. 

‘p < 0.05 is significant.

Table 2. — Numeric results for two-sample t-test.

<table>
<thead>
<tr>
<th>Power</th>
<th>N1</th>
<th>N2</th>
<th>Ratio</th>
<th>Alpha</th>
<th>Beta</th>
<th>Mean 1</th>
<th>Mean 2</th>
<th>S1</th>
<th>S2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.88911</td>
<td>169</td>
<td>132</td>
<td>0.781</td>
<td>0.05000</td>
<td>0.11089</td>
<td>1.2</td>
<td>1.0</td>
<td>0.7</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Null hypothesis: mean1=mean2; alternative hypothesis: mean 1< > mean 2. The standard deviations were assumed to be unknown and unequal.
of PAPP-A expression in cultured human dermal fibroblasts and human coronary artery endothelial and smooth-muscle cells. Yet, starvation normally causes suppression of immune functions, Kaplan et al. prospectively compared the IL-1, IL-2, IL-6, IL-8 and tumour necrosis factor-alpha (TNF alpha) levels between women with HG, pregnant, and non-pregnant controls and found a significantly higher level of TNF alpha in HG patients [19]. These findings rather support an activated immune system which may stimulate PAPP-a expression in HG.

PAPP-A has primarily local biological effects [19]. There have been several studies, that demonstrated PAPP-A mediated enhancement of IGF bioactivity in vitro by its degradation of IGFBP-4 [20, 21]. IGFs are necessary for normal fetal growth. Low level of PAPP-A may cause impaired release of IGFs which may cause pregnancy complications. Therefore increased PAPP-A levels may reduce risk of pregnancy complications as Depue et al. who have demonstrated a reduction in fetal losses and Bashiri et al. showing a reduction in miscarriages in HG [22, 23].

Same TSH and T4 results has been observed in this study as the literature; however means of TSH and T4 were in normal ranges. Even though the mechanism of hyperthyroidism is unclear, it has been suggested that the high incidence of hyperthyroidism in HG patients is caused by elevated circulating HCG levels [24].

The findings in this study show significant increase levels of PAPP-A which may be the reason of possible activated immune system in HG. Also this increase in PAPP-A levels may lead to decrease in miscarriages and fetal losses due to PAPP-A’s effect on IGF, which is important in normal fetal growth. Further studies are crucial to understand, the role of PAPP-A in physiology and patho-physiology of pregnancy and in the pathogenesis of HG.

References


The influence of ritodrine alone or in combination with nifedipine on maternal cardiovascular side effects and pregnancy outcomes

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Summary
Objective: To compare the influence of ritodrine alone or in combination with nifedipine on maternal side effects and suppressing preterm labor. Materials and Methods: This retrospective study included 213 pregnancies with preterm labor (20–34 weeks) from May 2002 to April 2010 in Kyungpook National University Hospital in Daegu, Korea. Obstetric medical records were reviewed for both maternal characteristics and neonatal outcomes, including birth weight, Apgar score, admission to neonatal intensive care unit (NICU), ventilator support, and neonatal mortality. Maternal side effects such as tachycardia, pulmonary edema, and hyperglycemia were also reviewed. Results: Of 213 patients, 109 received ritodrine only and 104 were given ritodrine and nifedipine. There was no statistical difference between the two groups with regards to pregnancy outcomes and neonatal complications. Pregnancy prolongation over seven days was achieved more in the combination therapy group, with borderline statistical significance (59.6% vs. 72.1%, p = 0.055). Sixty-nine cases experienced maternal side effects; four cases were categorized as serious and 65 cases were mild. Conclusion: In the treatment of preterm labor, the combination regimen of ritodrine and nifedipine can be more effective than ritodrine alone for prolonging gestation over seven days. Moreover, as the combination did not cause severe maternal side effects, it may be considered as a safe and effective method to prolong gestation in patients with preterm labor.

Key words: Preterm labor; Pregnancy prolongation; Combination therapy; Ritodrine; Nifedipine.

Introduction
Acute tocolysis has the potential to delay preterm birth for 48 hours, the critical period for antenatal steroid administration and a transfer to tertiary center, or arrest an episode of preterm labor, thus delaying birth and improving neonatal outcome [1,2]. The β-sympathomimetic ritodrine has been studied as one of the most potent tocolytics in several randomized controlled trials since the 1970s [3, 4]. It acts by binding to β-2 adrenergic receptors on the myometrial cell membrane, which subsequently increases the levels of intracellular cyclic AMP and inactivates myosin light chain kinase [5]. To this day, ritodrine remains the first and only tocolytic FDA-approved for the treatment of preterm labor [6]. Because of this initial approval and acceptance by the medical community, ritodrine has been the most widely used as a first line tocolytic drug in Korea and Eastern Asia.

Calcium channel blockers, especially nifedipine, have gained popularity as tocolytic drug because of several reasons, such as the oral administration route, low incidence of maternal adverse effects, inexpensive cost, and variable options of formula and dosage.

There have been a few observational studies comparing the effect of ritodrine and nifedipine in spontaneous preterm labor, and nifedipine appears to be more effective than ritodrine in delaying birth at least 48 hours, and with fewer maternal and neonatal side effects [7,8]. However, very little is known about the combination of both tocolytics.

The authors performed this retrospective study to identify the safety and effectiveness of the ritodrine and nifedipine combination regimen for the purpose of gestation prolongation in patients with threatened preterm labor.

Materials and Methods
Women eligible for inclusion were those with a singleton pregnancy between 20 and 34 weeks of gestation, diagnosed with preterm labor defined as cervical changes and regular uterine contractions of four in 20 minutes or eight in 60 minutes. Exclusion criteria were rupture of membranes, cervical dilation over four cm at the time of admission, multifetal gestations, fetal growth restriction, preeclampsia, and incomplete medical records. In addition, women with diabetes mellitus, including gestational diabetes, thyroid diseases, and cardiovascular diseases, including hypertension, were also excluded.

Among 652 patients who were admitted with preterm labor pain from May 2002 to April 2010, 213 patients with singleton pregnancies who met the inclusion criteria, were selected and reviewed. Eligible subjects were managed with ritodrine only or ritodrine and nifedipine combination regimen. All medical records and laboratory tests were subsequently reviewed by two reviewers. Differences in interpretation were adjusted through an attempt to reach a consensus.

Of 213 patients, 109 received ritodrine only and 104 were given ritodrine and nifedipine in combination. Cervical cerclage was performed in patients with a history of repetitive preterm births or a second trimester pregnancy loss, or patients with a short cervix.
Table 1. — Maternal baseline characteristics and pregnancy outcomes.

<table>
<thead>
<tr>
<th></th>
<th>Ritodrine (N=109)</th>
<th>Ritodrine and nifedipine (N=104)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30.5±3.9</td>
<td>30.2±4.6</td>
<td>NS</td>
</tr>
<tr>
<td>Multiparity</td>
<td>55(31%)</td>
<td>58(56%)</td>
<td>NS</td>
</tr>
<tr>
<td>GA at admission (days)</td>
<td>209.8±26.8</td>
<td>209.6±27.8</td>
<td>NS</td>
</tr>
<tr>
<td>&lt; 28 weeks</td>
<td>32</td>
<td>31</td>
<td>NS</td>
</tr>
<tr>
<td>≥ 28 weeks</td>
<td>77</td>
<td>73</td>
<td>NS</td>
</tr>
<tr>
<td>Prior preterm birth</td>
<td>16(15%)</td>
<td>14(14%)</td>
<td>NS</td>
</tr>
<tr>
<td>Cervical cerclage</td>
<td>13(12%)</td>
<td>17(16%)</td>
<td>NS</td>
</tr>
<tr>
<td>Cervical length (mm)</td>
<td>14±9</td>
<td>16±7</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of ritodrine (days)</td>
<td>11.2±14.8</td>
<td>12.5±15.2</td>
<td>NS</td>
</tr>
<tr>
<td>Leukocytosis (&gt;15,000/mm3)</td>
<td>11(10%)</td>
<td>8(8%)</td>
<td>NS</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>1.1±2.8</td>
<td>0.9±1.5</td>
<td>NS</td>
</tr>
</tbody>
</table>

GA: gestational age. Values are given as number and mean ± SD. NS: not significant; p < 0.05: significant.

Results

Table 1 shows baseline demographic characteristics of this study. There were no differences between the two groups in maternal age, parity, gestational age, cervical length, cerclage or not, serum WBC count, and CRP. In the combination regimen group, the period of nifedipine treatment was 8.3 ± 12.3 days, and the dose was 41.7 ± 22.8 mg/day (mean ± standard deviation). Ritodrine and nifedipine were combined for 5.9 ± 10.7 days.

As shown in Table 2, there was no statistical difference between the two groups in either pregnancy outcomes or neonatal complications, such as birth weight, NICU admission rate, Apgar score, and neonatal mortality. Neonatal mortality was mainly caused by extreme preterm birth.

Table 3 represents adverse events, which were found in 69 patients. Four cases were categorized as serious events,
and 65 cases were mild. One patient experienced severe dyspnea without pulmonary edema and recovered after application of an oxygen mask. Three patients showed abnormal change of ECG after administration of tocolytics. In all patients, myocardial infarction was ruled out because serum cardiac enzyme levels were within the normal range. All patients who experienced adverse events recovered without persistent disability or incapacity. There was no intrauterine fetal death. No differences were found between the two groups with regard to mild side effects. The rate of pregnancy prolongation over 48 hours was not different between the two groups (Table 4). Pregnancy prolongation over seven days was achieved more frequently in the combination therapy group, though with borderline statistical significance (59.6% vs. 72.1%, \( p = 0.055 \)). When patients were subgrouped by gestational age at the time of enrollment (< 28 and ≥ 28 weeks of gestation), there was no difference in pregnancy prolongation between the two groups.

### Discussion

Meta-analyses have shown that \( \beta \)-sympathomimetics, especially ritodrine, are associated with a delay of delivery of 24 hours, 48 hours, and seven days. However, such delay has not been associated with a significant reduction in either perinatal mortality or morbidity [10,11]. Due to the high incidence of side effects of \( \beta \)-sympathomimetics, the search for better drugs has become an important issue in preterm labor research. The oxytocin receptor antagonist atosiban newly appeared as a tocolytic in 2000. However, despite the clear advantage in the lack of relevant side effects of this new agent, perinatal mortality and morbidity still have not been modified. It is also expensive and is not yet FDA-approved; therefore, its worldwide use has limitations [12].

On the other hand, nifedipine is a very familiar and widely used calcium channel blocker. It reduces the intracellular entrance of calcium through the slow channel, producing an inhibition of contractile activity of nonpregnant, pregnant, and postpartum myometrium. It also reduces the amplitude and frequency of contractions and the basal myometrial tone, and it acts more strongly in pregnant than in non-pregnant women. The mean half-life in pregnant women is short (81 min); therefore, its effect is reversible [13, 14]. It was introduced as an antihypertensive drug, but its hypotensive effect is mild in normotensive pregnant patients. Many reports have evaluated the efficacy of nifedipine as a tocolytic agent. A large-scale systematic review, which included 12 randomized controlled trials with a total of 1,029 participating women, compared the efficacy of nifedipine with that of ritodrine. Nifedipine was found to be more effective than ritodrine in prolongation of pregnancy beyond seven days and was also much less likely to cause maternal side effects. Furthermore, nifedipine can be administered orally and is also cost-effective [15].

However, little is known about combinations of tocolytics. There have been only a few reports about combination of tocolytics, such as \( \beta \)-sympathomimetics with magnesium sulfate, or \( \beta \)-sympathomimetics with atosiban [16,17]. To the best of the present authors' knowledge, there was no prior study on the combination of ritodrine and nifedipine in patients presenting with threatened preterm labor, although there were several animal and in vitro studies. There was a rat model study by Gallagher et al., which showed that the combination of two drugs was more effective in inhibition of labor than a single agent [18]. Hajagos-Toth et al. studied the uterus-relaxing effects of \( \beta \)-sympathomimetics with nifedipine on rats and the human myometrium, and showed that the effect of nifedipine was tripled by the addition of \( \beta \)-sympathomimetics [19]. Doret et al. reported on a rat model study that used ritodrine, atosiban, and nicardipine, and proved the ritodrine and nicardipine combination regimen had a good inhibitory effect on myometrial contractility (78.5%), although the effect of the ritodrine and atosiban combination regimen was slightly better (88.9%) [20].

The results obtained in this study showed that ritodrine and nifedipine combination regimen could be more effective than ritodrine alone for prolonging gestation over seven days in the treatment of preterm labor, although of borderline statistical significance. Moreover, the combination did not induce severe maternal side effects, such as myocardial infarction and pulmonary edema. Therefore, the present authors propose that combination tocolytic therapy, specifically ritodrine and nifedipine, can be considered as a safe and effective method to prolong gestation in patients with preterm labor, though no improvements were found in neonatal outcomes.

Many obstetricians have general concerns about pulmonary edema or severe cardiovascular side effects while using \( \beta \)-sympathomimetics or calcium channel blockers for preterm labor. However, as shown in the present study, maternal side effects of the combination regimen did not exceed the side effects of the ritodrine only regimen.

Despite the present results, careful observation of pregnant women who receive tocolytic therapy, especially those

### Table 4. — Pregnancy prolongation after the usage of tocolytics.

<table>
<thead>
<tr>
<th>Pregnancy prolongation</th>
<th>Ritodrine (N=109)</th>
<th>Ritodrine and nifedipine (N=104)</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>48 hours</td>
<td>90 (82.6%)</td>
<td>93 (89.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>&lt;28 weeks</td>
<td>24/32</td>
<td>27/31</td>
<td></td>
</tr>
<tr>
<td>≥28 weeks</td>
<td>66/77</td>
<td>66/73</td>
<td></td>
</tr>
<tr>
<td>7 days</td>
<td>65 (59.6%)</td>
<td>75 (72.1%)</td>
<td>0.055</td>
</tr>
<tr>
<td>&lt;28 weeks</td>
<td>20/32</td>
<td>22/31</td>
<td></td>
</tr>
<tr>
<td>≥28 weeks</td>
<td>45/77</td>
<td>53/73</td>
<td></td>
</tr>
</tbody>
</table>

Values are given as number of patients (%); \( p < 0.05 \): significant.
with multiple pregnancies or undergoing steroid therapy, must continue. Close hemodynamic control and patient selection is mandatory to avoid severe side effects. Moreover, despite many reports on the use of nifedipine, this drug has not been licensed for use in pregnancy. In the present worldwide context of litigation, this fact should also be considered [21].

In conclusion, the present authors found that ritodrine and nifedipine in combination did not lead to a higher incidence of serious adverse side effects than ritodrine alone, and the combined regimen could be considered for prolonging pregnancy.

References


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The possible role of zinc in the etiopathogenesis of endometriosis

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¹ Department of Woman, Child and of General and Specialized Surgery, Second University of Studies of Naples, Naples
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Summary

Purpose of investigation: Aim of the study was to evaluate the possible involvement of zinc in the complex pathogenic process behind the onset and perpetuation of endometriotic lesions. To study the level of zinc serum between a group of patients affected by endometriosis and a group of healthy patients. Materials and Methods: The study included 86 women: 42 patients whose histodiagnosis had revealed pelvic endometriosis and 44 healthy patients. The authors measured the serum zinc concentration for all patients. Results: The group of patients with endometriosis presented serum zinc concentration of 1,010 ± 59.24 µg/l. The observation group presented a serum zinc concentration of 1,294 ± 62.22 µg/l. Conclusion: The results showed that serum zinc levels in women with endometriosis are decreased and this seems to actually confirm that this micro-element can possibly affect the multifactorial pathogenesis of the disease. As a matter of fact, zinc interferes with many biological processes, among which inflammation and immunity, which seem to be the base of the development of the lesions. Therefore, the authors believe that this hypothesis requires more attention and further investigation to determine its reasonableness. If the results are confirmed, this study opens up future prospects as for the treatment of endometriosis, taking into account also the role of zinc in the onset of male sterility and the development of testicles. Zinc could in fact be used as marker to detect women at high risk of endometriosis and for the elaboration of a new treatment for sterility, from which these women often suffer.

Key words: Serum zinc levels; Endometriosis; Role of zinc.

Introduction

Due to its wide and underestimated spread, endometriosis is considered a very interesting subject in gynaecological practice and research. Nonetheless, the etiopathogenesis of this affliction is still to be fully defined. As a matter of fact, despite the many studies carried out, to this day the greatest difficulty is obtaining scientific evidence that may justify its pathogenesis with special reference to both genetic and environmental predisposing factors. In general, the most recognized etiopathogenic hypotheses are three: possible retrograde menstrual flow causing the dispersion of endometrial cells through the tubes and into the peritoneal cavity; possible metaplastic process of the coelomic epithelium [1]; or possible lymphatic or haematogenous spread of endometrial cells [2]. In spite of these hypotheses, it is widely known that the illness onset depends on a complex series of factors which constitute the ground needed for many molecular events to spark off and lead to the disease [3]. This study is part of this debate and aims at assessing the possible involvement of zinc in the complex pathogenic process behind the onset and perpetuation of endometriotic lesions. In fact, this micro-element seems to be involved in many pro-apoptotic and antioxidant processes, as well as in the remodelling of the extracellular matrix whose alteration could transmit to the endometrial cells a potential invasive endometriotic phenotype. Concerning this, the authors assessed the difference in quantity of zinc serum between a group of patients affected by endometriosis and a group of healthy patients to establish whether a change in the quantity of such metal in the two groups could be statistically associated to endometriosis in a significant way.

Materials and Methods

After obtaining their informed consent, the authors selected 42 patients whose histodiagnosis had revealed pelvic endometriosis and gathered them at the general practice for gynaecology and obstetrics and/or sterility of the Department of Gynaecologic Obstetric and Reproduction Sciences, Second University of Naples, Naples (Italy). They were compared to an observation group of 44 young women presenting negative anamnesis with regards to dysmenorrhoea, dyspareunia, pelvic pain, negative CA–125 levels, and negative pelvic ultrasound with regard to ovarian cysts. The latter group was therefore considered supposedly not affected by endometriosis and examined in the same place and period. The protocol for the research project was approved by the Ethics Committee of our University Department.

The average age was 34 years (range: 19–45) in the group with endometriosis and 29 years (range 22–45) in the observation group (Table 1). The authors excluded from the study all the patients with amenorrhoea, declared menopause, related pathologies, and possible cases of endometriosis without histological evidence.

To detect the serum zinc concentration the authors took a sample of blood from all the patients and kept it at -20°C until the dosage, which was performed at the department for health, preventive medicine and medical statistics of Second University of Naples.

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The zinc analysis on the serum was carried out with a Perkin Elmer 5,000 atomic absorption spectrophotometer using an air-acetylene flame at the following operative conditions: zinc (wavelength 213.9 nm, slit 0.7 nm, air-acetylene flame); calibration performed using solutions at concentrations of 0.00 - 0.05 - 0.10 - 0.20 - 0.50 - 0.80 - 1.00 - 1.50 - 2.00 mg/l).

**Results**

The authors achieved the following results: the group of patients with endometriosis (42 women, average age of 34.21 years, age range between 19 and 45 years, standard deviation -SD-value 5.8, median value 35) presented serum zinc concentration of 1,010 ± 59.24 µg/L; the observation group (44 women, average age of 29.38 years, age range between 22 and 45 years, SD value 7.21, median value 26) presented a serum zinc concentration of 1,294 ± 62.22 µg/L (Table 2).

The results were analysed comparing the average values (± standard deviation) in the two groups and a statistical analysis using the Student’s t-test for unpaired data was carried out. The data obtained were considered statistically significant for one *p* < 0.05.

In Table 3, a comparison between the levels of zinc in the general population, those of the group with endometriosis, and those of the observation group is shown.

**Discussion**

From the study the authors gather that the serum zinc levels in the group of patients with histodiagnosis of endometriosis are lower than those in the observation group where patients are healthy and do not present any sign or symptom of the disease. The difference between the two groups is statistically significant. This micro-element could be involved in the etiopathogenesis and/or evolution of endometriosis (Figure 1).

Zinc is a basically intracellular micro-element that can be found in the whole body: in organs, tissues, intracellular and extracellular fluids, with a serum concentration ranging from 1,000 to 2,500 µg/L. 70% of it can be found in the erythrocytes, where it is integrated in enzymes and transcription factors which allow the hematopoietic cells to have a regular and physiological genic activity. Zinc also influences the regulation of homeostasis between cell-mediated immunity and humoral immunity with effects the immune system’s functionality. As a matter of fact, it seems that zinc can stimulate the production of lymphocytes, while its deficiency can reduce the efficiency of cell-mediated immunity [4].

In general, the highest level of zinc is detected in the brain and pancreas, probably due to its antioxidant functions and to the fact that it serves as cofactor for a large quantity of enzymes. Zinc is included in about 300 enzymes where it has a catalytic, cocatalytic or structural function. By the 3-10% it is a cofactor of proteins and responsible for proteins assembly and possible changes in conformation.

Thanks to its massive presence in the enzymes, this trace element is employed at every stage of the cell cycle, from replication to repair, as it is cofactor of enzymes such as DNA and RNA polymerase, reverse transcriptase, and thymidine kinase.
The possible role of zinc in the etiopathogenesis of endometriosis

Additionally, zinc serves as cofactor for the superoxide dismutase (SOD) enzyme (involved in the control of oxidative stress in cells) and for this reason it plays a leading role in the apoptotic process of programmed cell death [5].

Finally, zinc is responsible for the appropriate neurodegenerative equilibrium of the extracellular matrix, matrix metalloproteinases (MMPs) functionality also depends on it.

Having analysed and summarized all the functions carried out by zinc in the human body and by virtue of the results obtained through the present study, which show a quantitative reduction of zinc in patients with endometriosis, the authors assume a possible involvement of zinc in the pathogenesis and perpetuation of the aforementioned pathology.

The present authors cannot be certain that the deficiency of this metal is actually one of the factors that spark off processes which subsequently lead to the formation of endometriotic lesions. Nonetheless, they can surely identify a reasonable cause and effect connection between zinc deficiency and the ability of endometriotic cells to develop invasive, phlogistic, and anti-apoptotic features.

In fact, it is known that the endometrial cells that colonise ectopic sites acquire a special phenotype which makes them develop the ability to take root on a different tissue, elude the immune response, provoke neo-angiogenesis processes, stimulate the production of cytokines responsible for chronic phlogosis, and prevent the apoptotic process [6]. In literature it is extensively documented that zinc is involved in all the aforementioned processes and therefore the deficiency the authors detected in patients with endometriosis could be the single or joint cause of all the alterations entailed in this pathology.

Firstly, the authors will analyse the modifications in the immune system. In addition to the numerous functions carried out in the body, it is also well known that zinc assures the correct functioning of the immune system as it seems to stimulates the production of lymphocytes. Zinc deficiency causes a decrease in the ability of natural-killer cells to lyse, as well as in the percentage of precursors of cytotoxic T cells. The final result is the alteration of cell-mediated immunity [7, 8]. This statement is confirmed by the fact that zinc is proved to be necessary for the biological activity of thymulin (TT), an hormone produced by the thymus and essential for the differentiation and growth of CD4+ cells. The hormone presents itself in two isoforms: one is active and zinc-bound (ZnFTS), while the other is inactive and zinc-unbound (FTS). The ratio between total TT and active thymulin (AT) represents a marker to detect deficiency in the micro-element (TT/AT>2 = deficiency; TT/AT<2 = mild deficiency). Therefore, zinc acts directly on the functional homeostasis of the specific immune system defence processes through TT, for which it serves as cofactor. Thanks to all this it can be presumed that the defect in the intrinsic immune system - widely proved in women with endometriosis - can be both the result of an idiopathic alteration of the body, and the consequence of a constitutional or dietary zinc deficiency. The deficiency has negative effects on macrophages’ functionality and alters their intracellular death and phagocytosis processes and stimulate the production of cytokines. Such modifications increase the possibility for endometrial cells not only to survive, but also to take root. All this leads to a state of immune under-functioning, which has been proved also by a study carried out by Prasad et al. that showed that the reduction of IL-2, IL-1β and TNF-α gene expression occurs in conjunction with the decrease in zinc concentration available [9]. This effect is probably due to the ion action on the zinc-dependant transcription factors involved in the genes expression of these cytokines [10, 11].

Figure 1. — Zinc and etiopathogenesis and/or evolution of endometriosis.
This ion is also responsible for the inactivation of other enzymes (MMPs) which play a role in immune and phlogistic mechanisms. In their catalytic site, or active site, MMPs contain a zinc ion that interacts with a cysteine residue and prevents the binding and cleavage of the substrate keeping the enzyme in an inactive form. The concentration of this ion is therefore essential for the production and activation of MMPs [12].

In endometriosis, endometrial fibroblastic cells were also proven to increment the production of MMPs as a consequence of the increase in pro-inflammatory cytokines [13, 14]. The latter, in turn, further influence zinc metabolism [15]. As a matter of fact, many studies documented higher ion consumption when cytokines such as IL-6 and TNF-α were present [16]. Consequently, the ion was proven to be less disposed to bind to and then inactivate MMPs. The result is a massive activation of these enzymes which ease the advance of endometriotic lesions as they metabolize the extracellular matrix and facilitate the penetration of endometrial cells [17]. Furthermore, it seems that chronic phlogosis affects the homoeostasis of metallothionein, a protein which binds zinc after dietary absorption [18]. Metallothionein increases with age and in case of chronic inflammation and leads to a continuous zinc sequestration at intracellular level and to the subsequent decrease of zinc available to fulfill the enzymatic functions in which it serves as cofactor [19, 20].

Finally, it must be remembered that zinc has an antioxidant function especially crucial to prevent the starting of endometriosis. As a matter of fact, many studies showed how an increase in oxidative stress (or rather reactive oxygen species) can provoke pro-inflammatory reactions which serve as perfect substratum for the activation and taking root of endometrial cells. The proof that peritoneal fluid in women suffering from endometriosis contains a higher quantity of reactive oxygen species was already provided by Ota et al. in 2000 and confirmed by Shigetomi et al. in 2012 [21, 22]. The latter in particular proved that the increase in copper-zinc superoxide dismutase and glutathione peroxidase in women with endometriosis is persistent and constant. Superoxide dismutases are a class of tightly correlated enzymes that catalyze the dismutation of superoxide anion into oxygen and hydrogen peroxide. As zinc is one of the constituents of these enzymes, its deficiency could play a role in endometriosis [23]. This theory is supported by a study carried out in France on 20 people (aged between 59 and 85) which showed that zinc supplementation reduces the production of oxidized proteins generated by oxidative stress due to chronic inflammation [24, 25].

Ultimately, the present authors can affirm that this microelement directly or indirectly falls within all the factors that, at the moment, are supposed to concur in the etiopathogenesis of endometriosis. For this reason it is reasonable to conjecture a connection between this pathology and zinc deficiency.

In general, the influence of nutrition on health has been regarded with attention since the dawn of medicine. Concerning this, it must be noted that many studies show a cause-effect connection between zinc supplementation and the resolution of pathologies affecting the reproductive system, while others directly or indirectly associate zinc deficiency with endometriosis and the symptomatology related to it. In 1961 and 1966, Prasad et al. noticed that a daily zinc supplementation of 75 mg in Iranian patients about 20 years old, suffering from dwarfism, scarce development of genital organs, and limited brain liveliness determined the normalization of sexual functions and the increase in height within a period of about two months [26-30].

Another study carried out by Darwish et al. and conducted in the gynaecology and obstetrics department of the University of Assiut and Al-Azhar (Egypt) showed that the 18.8% out of 2,493 patients examined was affected by endometriosis. This signifies that the disease is common in Egypt where zinc deficiency was actually noticed in Egyptian and Iranian peoples. The present authors can moreover suppose a pathogenetic connection between zinc deficiency in these populations and the increase in the incidence of endometriosis [31].

Finally, in 2009 Mier-Cabrera et al. proved that women affected by endometriosis present a lower quantity of zinc, copper, vitamin A, C, and E than healthy women. The study also revealed a greater increase in the activity of superoxide dismutase and glutathione peroxidase in patients with endometriosis than in healthy patients after the administration of a diet with a high percentage of antioxidants for about three months [32].

These data are confirmed by the study carried out by Parazzini et al. which highlights the cause-effect connection between the type of diet and the probability to suffer from endometriosis. In particular, patients with endometriosis declared their diet was rich in red meat and ham, while healthy patients had a diet mainly based on vegetables and food rich in antioxidant elements and vitamins [33].

Other studies proved that the administration of antioxidants in patients with endometriosis can reduce symptomatology related to it, especially dysmenorrhea. Such data are certainly important, above all in order to manage patients whose symptomatology can not be cured through surgery [34, 35].

Conclusion

In conclusion, the present data are consistent with the claims of prior studies but, as the sample examined was exiguous, the authors cannot describe with certainty the actual role of zinc in the endometriotic pathology, nor establish whether its deficiency is the cause or consequence of a series of molecular mechanisms which cross and intersect with one another. Nevertheless, all the reactions explained
above in which zinc takes part are surely the cause of the reduction of zinc concentration. For this reason, even if it was proved that this micro-element is not a joint cause of pathogenesis, but rather one of the progression factors of the pathology, it would all the same have significant implications for its therapeutic employment. In conclusion, nowadays, endometriosis must be certainly considered a social disease and we must aim at further broaden our knowledge to try and understand the pathogenetic mechanisms and hence develop new treatments that may contribute to the fight against this disease. In this scenario, zinc could play a leading role.

The present results showed that serum zinc levels in women with endometriosis are decreased and this seems to actually confirm that this micro-element can possibly affect the multifactorial pathogenesis of the disease. As a matter of fact, zinc interferes with many biological processes, among which inflammation and immunity, which seem to be the base of the development of the lesions. Therefore, the authors believe that this hypothesis requires more attention and further investigation to determine its reasonableness.

If the results are confirmed, this study opens up future prospects as for the treatment of endometriosis, taking into account also the role of zinc in the onset of male sterility and the development of testicles. Zinc could in fact be used as marker to detect women at high risk of endometriosis and the development of testicles. Zinc could in fact be used as marker to detect women at high risk of endometriosis and the development of testicles. Zinc could in fact be used as marker to detect women at high risk of endometriosis and the development of testicles. Zinc could in fact be used as marker to detect women at high risk of endometriosis and the development of testicles. Zinc could in fact be used as marker to detect women at high risk of endometriosis and the development of testicles.

References


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Relation of peritoneal fluid and serum vascular endothelial growth factor levels to endometriosis stage

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Summary
Objective: It is a well known fact that endometriosis is linked with apoptosis, extracellular matrix formation, and angiogenesis. In this study, the authors aim to investigate the relation between the extent of endometriosis and vascular endothelial growth factor (VEGF). Materials and Methods: Twenty-one patients who received laparoscopic intervention due to endometriosis constituted the patient group, whereas 19 patients who were operated due to extra-endometrial benign cyst were included in the control group. Following the laparoscopic pelvic assessment, peripheral blood samples and two cc of free peritoneal fluid from the Douglas pouch were obtained simultaneously. The samples were studied with regards to VEGF level via solid phase sandwich enzyme-linked immunosorbent assay (ELISA) method. Results: In the patient group, eight cases were diagnosed with Stages I and II endometriosis, while 13 cases were diagnosed with Stages III and IV endometriosis. Among the Stage I and II cases, serum VEGF levels were statistically significantly higher, as compared to the Stage III and IV cases, as well as the control group. Discussion: In conclusion, the authors found a relationship between elevated serum VEGF levels and early stage endometriosis.

Key words: Endometriosis; Vascular endothelial growth factor.

Introduction
Endometriosis is a polygenic multifactorial disease that is defined as the ectopic presence of functional endometrial tissues outside the uterine cavity, affecting 9-33% of women of reproductive age [1,2]. Although the etiology of the disease has not yet been clearly described, there are studies indicating the involvement of changes in the immune system [3]. Recent studies suggest that endometriosis is related to apoptosis, extracellular matrix formation, and angiogenesis [4-6]. Vascular endothelial growth factor (VEGF) is one of the factors that is studied in this regard which is a member of the platelet-derived growth factor family and plays a role in the angiogenesis. VEGF was first defined as a factor increasing the vascular permeability, however, it also triggers proliferation, migration, differentiation, and capillary formation in the endothelial cells, as well [7]. Endometriotic tissues demonstrate elevated levels of protein and VEGF mRNA expression, thus triggering vascular development in the peritoneal region and facilitating the implantation and viability of the endometrial cells [7-8]. In this study, based on these data, the authors aimed to investigate whether there is any relationship between VEGF levels and the extent of endometriosis.

Materials and Methods
The study was conducted in the Third Clinic of S. B. Izmir Ege Obstetrics and Gynecology Teaching and Research Hospital between September 2010 and September 2011. Twenty-one patients aged 19-51 years who presented to the present clinic because of adnexal mass, chronic pelvic pain or infertility, and who were scheduled for laparoscopic diagnosis and treatment subsequent to the final assessments, constituted the patient group, whereas 19 patients with extra-endometrial benign ovarian cyst were included in the control group. The staging of the endometriosis cases was performed based on the classification of the American Society for Reproductive Medicine (ASRM) including visual pelvic assessment, largeness and depth of lesions, and adhesive properties. The cases of ASRM Grades I and II were defined as early stage, whereas the ones with an ASRM Grades III and IV were deemed as advanced stage. Following the laparoscopic assessment and staging, peripheral blood and two cc of free peritoneal fluid, from the pouch of Douglas, samples were obtained simultaneously prior to the surgical procedure. The serum was separated. The serum and peritoneal samples were stored in Eppendorf tubes at 80°C until the date of analysis. The cases with blood in the peritoneal fluid (ruptured cyst), ectopic pregnancy, abscess in the fallopian tube, or pelvic infection, as well as those suspected of malignancy along with patients in whom a sample of two cc free peritoneal fluid could not be obtained, were excluded from the study. The patients were asked about their general and gynecologic medical history, clinical symptoms, menstruation period, and cause of hospital presentation, and the responses were noted in a pre-made information form. Blood and peritoneal VEGF levels were measured twice with solid phase sandwich enzyme-linked immunosorbent assay (ELISA) method. VEGF values were evaluated in pg/ml.

The study data were analyzed with SPSS (Statistical Package for the Social Sciences) program. The distribution of the quantitative data was analyzed with the Kolmogorov-Smimov test, and homogeneity was evaluated by the Levene’s test. The parameters with normal distribution and homogenous variance were analyzed via parametric methods, while the parameters with non-normal distribution and heterogeneity were analyzed with non-parametric methods. Regarding the parametric methods, the intergroup comparisons were carried out with the Independent t-test. Regarding the non-parametric methods, intergroup comparisons were performed with
A. Kopuz, S. Kurt, Ö. Demirtaş, E. Töz, A. Taşyurt

Mann-Whitney U test and Moses test. The relationships between non-categorical parameters were analyzed by the Kendall’s Tau-b and Spearman’s rho test. The categorical parameters were compared using Chi-square, continuity correction, and Fisher’s exact tests. The data were studied using 95% confidence interval and \( p \) values < 0.05 were recognized as statistically significant.

Results

The patient and control groups had an age range of 19-51 years and the mean age was 30.38 ±7.58 and 33.15±10.41 years, respectively. Both groups were compared with regard to age, pregnancy, and parity, revealing that pregnancy and parity were higher in the control group, though there was no statistically significant difference (Table 1). Infertility history, irregular menstruation, non-cyclic pelvic pain, dysmenorrhea, and dyspareunia were more common in the patient group than in the control group (Table 2).

Regarding the endometriosis staging, eight patients (38.1%) were early stage (Grades I-II), whereas 12 patients (61.9%) were advanced stage (Grades III-IV) (Table 3). There was no statistically significant difference between the patient and control groups with regards to blood and peritoneal VEGF levels (\( p > 0.05 \)) (Table 4).

The comparison of blood VEGF levels among the patient subgroups revealed that early stage patients had significantly higher VEGF levels (\( p = 0.047 \)). The comparison of early stage patient subgroup and the control group with regard to blood VEGF levels showed that the early stage patient subgroup had significantly higher blood VEGF levels as compared to the control group (\( p = 0.032 \)). However, there was no significant relationship between the advanced stage patient subgroup and the control group in terms of blood VEGF levels (\( p = 0.924 \)) (Table 5). There was no statistically significant difference between the early stage and advanced stage patient subgroups (\( p = 0.176 \)), between early stage patient subgroup and the control group (\( p = 0.213 \)), and between advanced stage patient subgroup and the control group (\( p = 0.825 \)) (Table 6).
Discussion

Endometriosis is a disease of unclear etiology with high morbidity that affects 9-33% of women of reproductive age which reduces quality of life by accompanying infertility and pelvic adhesion, as well as chronic pelvic pain symptoms [1, 9, 10]. The definitive diagnosis including the extent of the disease, is achieved by laparoscopic pelvic examination, lesion excision, and histopathologic examination [11, 12]. Since the diagnosis is established with an invasive method, investigators have been looking for new markers that can improve the non-invasive diagnostic methods [13, 14]. To date, many of the studies aiming to unveil the etiopathogenesis of endometriosis have focused on macrophages in the peritoneal cavity, cytokines secreted from those macrophages, and growth factors. VEGF is one of those cytokines and growth factors which is studied by in vivo and in vitro researches [7, 15].

Although VEGF is a platelet-derived growth factor, it is also an important mediator of local angiogenesis [16]. Angiogenesis is one of the factors playing a key role in the occurrence, development, and progression of endometriotic lesions [17]. Endometriotic lesions have been shown to have different vascular patterns depending on the localization and stage (early or advanced) [18]. In peritoneal endometriosis, vascularization is intense in early active (red) lesions and those lesions include many angiogenic vessels that are indicative of high mitotic index. However, dark endometriotic foci contain mature vessels. Ovarian and deep infiltrative endometriotic foci are highly vascularized and have vessels with no immature pericytes [19]. Therefore, angiogenetic factors are observed to increase in patients with endometriosis, peritoneal implants, as well as in the peritoneal fluid of patients with ovarian endometriosis. The presence of elevated VEGF levels has been shown in the peritoneal fluid of ovarian endometrioma cases [20].

Matalliotakis et al. and Goter et al. showed increased serum angiogenetic factor levels in endometriosis patients as compared to the non-endometriotic patients [21, 22]. In the present study, blood and peritoneal VEGF levels were higher in the patient group than in the control group, however, the difference was not statistically significant. Gagne et al. found no relationship between endometriosis and blood-peritoneal VEGF levels. In their study, the exact time of sample collection during menstruation was not noted [20]. However, it is reported that VEGF levels may differ at different times of menstruation. In a study supportive of this opinion, Pupo-Nogueira et al. compared peritoneal VEGF concentrations at proliferative phase and early secretion phase in women with definitive diagnosis of endometriosis. Late secretion phase demonstrated significantly higher VEGF levels in the peritoneal fluid [23]. The authors believe that using no specific time point for the collection of blood and peritoneal samples and the balance generated by the elevated blood VEGF levels in patients with early stage disease and the blood VEGF levels at advanced stages, may have influenced their results.

The most significant result of this study was the evidences indicating a relation of VEGF level with early and advanced stage endometriosis. The authors determined significantly higher blood VEGF levels in the early stage endometriosis subgroup than in the advanced stage endometriosis subgroup and the control group. Fujishita et al. found higher blood VEGF levels in early stage endometriosis than in advanced stage endometriosis [24]. It is known that early stage endometriotic foci have higher amount of highly vascularized red lesions as compared to scar lesions [25]. This result helps us to see why VEGF level is higher in early stage endometriosis cases with rich vascularization.

In conclusion, VEGF level was found to be elevated in the early stages of endometriosis with rich vascularization. This result should be further supported by large-scale studies including exact timing of sample collection during various endometriotic stages. Thus, the authors believe that high VEGF levels can be useful in predicting the disease stage preoperatively and in establishing a differential diagnosis of endometriosis in combination with the other radiologic and serologic markers.

References


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Study of individualization therapy for 61 patients with cesarean scar pregnancy

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Summary

Objective: To investigate the clinical value of the individualization therapy for cesarean scar pregnancy (CSP). Materials and Methods: According to the individual characteristics of the CSP in 61 patients admitted and treated by the People’s Hospital of Yuyao City, China between March 2010 and February 2013, methotrexate (MTX) with leucovorin (CF) or uterine artery chemotherapy embolization (UACE) were used to kill the embryos, stanch, and prevent bleeding. Guided by hysteroscopy or B ultrasound, uterine curettage was carried out under the surveillance of laparoscopy if necessary. Results: Fifty-four cases of patients were treated by UACE. MTX with CF was used in seven cases. Uterine curettage was performed in 44 cases under the guidance of hysteroscopy. Six cases were under the surveillance of the B ultrasound and both hysteroscopic guidance and B ultrasound surveillance were used in seven cases. The lesions disappeared in two cases after transabdominal excision and two cases after UACE. All of the 61 patients were cured without hysterectomy. Conclusion: Selection of individualization treatment programs according to the characteristics of the disease could improve the efficacy and prognosis of patients with CSP. The appropriate timing to perform curettage was five to seven days after embryo killing in order to reduce bleeding and shorten the course of the disease.

Key words: Pregnancy; Cesarean scar; Ultrasonic classification; Individualization therapy; Uterine curettage timing.

Introduction

Cesarean scar pregnancy (CSP) indicates the ectopic pregnancy with embryo implanting in the scar for the uterine incision of the previous cesarean [1], which is a potential long-term serious complications after cesarean. The cesarean rate in China is high [2], accordingly, the incidence of the CSP is increasing year by year. The CSP has become the new critical emergency in obstetrics and gynecology and could be a serious threat to the physiological and psychological health of the majority of young women. With the increased awareness of the CSP and the development of diagnostic imaging technology, misdiagnoses are significantly reduced. However, the appropriate treatment is still in the exploratory stage due to the variation of the disease features in patients with CSP, especially establishing the treatment plan of killing and eliminating pregnancy lesions, reducing trauma and bleeding, preserving individual fertility suitable for the individual characteristics of the disease is still the hot issue to be urgently solved. In this study, the retrospective analysis was used to study the clinical data of the 61 patients with CSP, the clinical value of the individualization therapy for the CSP in order to provide the basis for further improving the curative effect of patients with CSP.

Materials and Methods

Subjects
Sixty-one patients with CSP were admitted and treated by People’s Hospital of Yuyao City during March 2010 and February 2013, the ratio to the total number of hospital deliveries in the same period of last year was 1:222 (61/13552), accounting 3.14% (61/1943) of the ectopic pregnancies treated by the hospital in the same period of last year. The ages of the 61 patients were between 23 and 40 (32 ± 4) years, pregnant times including the current were two to seven (4.0 ± 1.2) months, times of having babies were one to two (1.2 ± 0.4). A clear history of menopause was found in all the 61 cases, and the time of the menopause was between 32 and 105 (55 ± 18) days. Forty cases (66%) were found to have vaginal bleeding, including seven cases of bleeding after medical abortion and four cases of bleeding after artificial abortion. Nine cases (14.8%) had abdominal pains. The time of the cesarean from the previous one was 0.33-14 (5.8 ± 3.7) years. Fifty-two cases experienced cesarean for one time and nine cases two times. One case developed CSP again. The hematic β-human chorionic gonadotropin (β-HCG) level was 85 to 310,473 (42,191 ± 55,272) IU/l when the patients were admitted. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Yuyao People’s Hospital. Written informed consent was obtained from all participants.

Diagnostic basis

1) Patients with the history of cesarean and clinical manifestations such as menopause, vaginal bleeding, and elevated hematic β-HCG level. 2) In line with the transvaginal ultrasound imaging changes of the CSP according to the literature [3, 4], the ultrasound of the CSP was typed as endogenous (type I) with lesion protruding into the uterine cavity and the exogenous (type II) with lesion protruding into the serosa [5]. 3) Magnetic resonance imaging (MRI) was used to examine the relationship of the lesion site and the cesarean scar when the ultrasound examination could not determine the relationship between the lesion and cesarean scar [6, 7]. 4) Histopathological examination was used to observe the specimens of the lesion clearance.

Treatment
Embryo killing: drug therapy included methotrexate (MTX) with leucovorin (CF) (MTX-CF program) was chosen to treat the
patients with hemat β-HCG < 5,000 IU/l. Interventional therapy by uterine artery embolization (uterine artery chemoembolization,) was selected to treat the patients with hemat β-HCG ≥ 5,000 IU/l [8]. The total dosage of the MTX perfusion by bilateral uterine arteries was 100 mg for the patients with hemat β-HCG levels between 5,000 and 10,000 IU/l. For the patients with hemat β-HCG levels > 10,000 IU/l, MTX was increased by 50 mg for each additional 10,000 IU/l of β-HCG levels. The maximum infusion dose was 300 mg. Gelatin sponge particles were used to perform bilateral uterine arteries embolization (UAE) after perfusion.

Lesion clearance: uterine curettage was performed under the guidance of hysteroscopy and the surveillance of the B ultrasound for the type I lesions with the thickness of the surface muscle layer ≥ two mm. Uterine curettage was performed under the guidance of the hysteroscopy and the surveillance of laparoscopy for the type II lesions with the thickness of the surface muscle layer < two mm or mass diameter < four cm with less blood supply [10]. Lesion excision through abdomen and uterine repair were used for the patients with mass diameter ≥ four cm with rich blood supply or concurrent bleeding in the uterine curettage. According to the differences of the time between the embryo killing after the UACE or MTX+CF programs ending, the uterine curettage within seven days (≤ 7d) group and uterine curettage after seven days (> 7d) group were divided to compare the indexes relevant to the treatment.

Hemostasis: emergent UACE or UAE hemostasis were used to patients with concurrent more bleeding (≥ 200ml) at the time of admission or before the uterine curettage [11], the Foley catheter sacculus uterine hemostasis was used for the patients with bleeding volume ≥ 50 ml with uterine curettage.

Follow-up
Hemat β-HCG level was detected one week after leaving hospital until the β-HCG turning negative (<5 IU/l). The time of β-HCG turning negative was observed after the treatment of embryo killing. The re-examination by B ultrasound was performed one for two to three weeks to observe the healing of the uterine scars after leaving hospital. The time of menstruating again were followed-up by telephone after lesion clearance.

Statistical analysis
Statistical analysis was performed using SPSS19.0 statistical package. The comparison of the measurement data among different groups with homologous variance was performed using t test, and data with heterogenous variance using approximate t test. The enumeration data among groups were compared using corrected fourfold table χ^2 test. A p < 0.05 was considered to have statistical significance.

### Table 1. — Comparison of the partial clinical characteristics of type I and type II patients (χ ± s)

<table>
<thead>
<tr>
<th>Type</th>
<th>n</th>
<th>Early abortion history (n [%])</th>
<th>Mean diameter of the mass (cm)</th>
<th>Thickness of surface muscle layer (mm)</th>
<th>Amount of bleeding (ml) in uterine curettage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>54</td>
<td>6(11)</td>
<td>2.4±1.3</td>
<td>2.7±1.0</td>
<td>63±493</td>
</tr>
<tr>
<td>Type II</td>
<td>7</td>
<td>5(71)</td>
<td>4.3±1.2</td>
<td>1.6±0.5</td>
<td>183±310</td>
</tr>
</tbody>
</table>

χ^2 or t value: 11.445 -3.612 2.916 -0.948
P value: 0.001 0.001 0.005 0.386

Note: Two cases of type I with lesions disappearance after embryo killing and one case of the type II after direct transabdominal excision were not included in the number of total cases in the comparison of the amount of bleeding in uterine curettage. Approximate t test was used for comparison between groups due to the heterogeneity of variance.

### Results

#### Results and differences of classification by ultrasound
According to the vaginal ultrasound imaging, combined with the MRI examination findings if necessary, 54 patients were diagnosed with type I and seven patients with type II. The results of comparing the drugs or artificial abortion rates in the earlier period, the mean diameter of the gestational sac or the mass, the muscle layer thickness of the lesion surface, and the amount of bleeding in uterine curettage were shown in Table 1.

As shown in Table 1, compared with type I, more patients had a history of early miscarriage, the mass mean diameter was larger and the surface muscle layer was thinner in type II, which indicated that the difference was statistical significance (p < 0.01). The amount of the blood loss was also larger, but the difference did not have statistical significance (p > 0.05).

#### Overall results of treatment
Fifty-four cases (88.5%) experienced embryo killing by UACE, including five cases that experienced embryo killing by emergent UACE had concurrent hemorrhage with β-HCG > 5,000 IU/l when admitted. Of the 54 cases, 40 cases were performed with uterine curettage guided by hysteroscopy, six cases were performed with uterine curettage under the surveillance of B ultrasound, and five cases were performed with uterine curettage both guided by hysteroscopy and under the surveillance of B ultrasound. One case (patient with type II) with mass diameter of 4.8 cm with rich blood supply had a directly performed lesion excision through the abdomen with uterine repair. The lesions disappeared without curettage in two cases. Ten cases were performed using a Foley catheter sacculus uterine hemostasis for the patients with large amount of bleeding (50 - 400 ml). Seven cases experienced embryo killing by MTX+CF program, including four cases that were performed uterine curettage under the guidance of hysteroscopy, two cases under the surveillance of laparoscopy, and one case (patients with type II) with concurrent hemorrhage (800 ml) when uterine curettage was performed with lesion excision through abdomen and uterine repair. After the 61 patients were cured and discharged, there were no postoperative infections, hystere-
Study of individualization therapy for 61 patients with cesarean scar pregnancy

Table 2. — Comparison of different therapy results in different uterine curettage timing (χ ± s)

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>β-HCG before uterine curettage (IU/l)</th>
<th>Surgery duration (min)</th>
<th>Amount of intra-operative bleeding (ml)</th>
<th>Hospital stay (d)</th>
<th>Medical costs (RMB)</th>
<th>Time for turning negative of β-HCG (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 7d</td>
<td>22</td>
<td>8,673 ± 24,227</td>
<td>14 ± 7</td>
<td>43 ± 53</td>
<td>13 ± 6</td>
<td>13405 ± 3405</td>
<td>18 ± 7</td>
</tr>
<tr>
<td>&gt; 7d</td>
<td>35</td>
<td>2,830 ± 3,115</td>
<td>17 ± 7</td>
<td>74 ± 108</td>
<td>27 ± 12</td>
<td>14898 ± 3281</td>
<td>31 ± 11</td>
</tr>
<tr>
<td>T value</td>
<td>1.125</td>
<td>-1.597</td>
<td>-1.468</td>
<td>-5.862</td>
<td>-1.649</td>
<td>-5.486</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>0.273</td>
<td>0.116</td>
<td>0.148</td>
<td>0.000</td>
<td>0.105</td>
<td>0.000</td>
<td></td>
</tr>
</tbody>
</table>

Note: 1) Four cases, including one case was performed by turning to transabdominal surgery during uterine curettage complicating with massive haemorrhage and one case was directly performed via transabdominal excision and two cases with lesions disappearance after UACE were not counted in the number of total cases. 2) The four indexes including hematic β-HCG before uterine curettage, blood loss during surgery, hospital stay, and turning negative time of the hematic β-HCG after embryo killing were analyzed by approximate t test due to the heterogeneity of variance.

Result comparisons of the different timing for uterine curettage

The result comparisons of the relevant treatment for the uterine curettage within seven days (≤ 7d) group and after seven days (> 7d) group are shown in Table 2. As shown in the differences of the hematic β-HCG levels, timing for uterine curettage, blood loss amount during the operation, and medical expenses between the two groups before the curettage had no statistical significance (p > 0.05), while the hospital time and turning negative time of the hematic β-HCG for the uterine curettage within seven days group were shorter than that of the uterine curettage after seven days group, the difference had statistical significance (p < 0.01).

Pathological examination

The lesion clearance specimens of the 59 cases were sent for pathological examination, and all were diagnosed as degenerated with necrotic villus or placental tissues.

Follow-up results

The time of hematic β-HCG turning negative was 12 to 59 (27 ± 12) days after the end of the UACE or MTX+CF treatment program of the 61 patients. The first time of menstruation of the 51 cases (51/59, 86%) followed-up by telephone was 15 to 60 (34 ± 6) days after the operation. The healing of the uterine scars was re-examined by B ultrasound for three to seven days after the complete end of the second menstruation after leaving hospital [13]. Forty-seven patients (77%) were detected with good healing (scar thickness ≥ five mm), and 14 patients (23%) were detected with poor healing (scar thickness < five mm).

Discussion

Clinical significance of the ultrasonic type for the CSP lesions

According to the imaging findings, the CSP lesions were divided to be type I (endogenous) and type II (exogenous), the manifestations of the patients treated by abortion and uterine curettage due to misdiagnosing as intrauterine pregnancy were also type II. According to the observation in this study, compared with type I, more patients had a history of early miscarriage and uterine curettage, the gestational sac or the mass were larger, and the surface muscle layer was thinner in type II, which indicated that the difference was statistically significant (p < 0.01). The amount of bleeding was also large. Uterine curettage was substituted to abdominal incision due to the hemorrhage during uterine curettage in patients with type II. These results indicated that uterine curettage under the guidance of the hysteroscopy or the surveillance of B ultrasound was feasible for patients with type I, while it was better to perform uterine curettage under the guidance of the hysteroscopy and the surveillance of the laparoscopy for patients with type II in order to avoid uterine perforation or rupture, and the Foley catheter sacculus uterine hemostasis was used after the surgery. For type II patients with too large masses, rich blood supply and very thin surface muscle layer, it was better to directly perform lesion excision through abdomen and uterine repair. Therefore, the ultrasonic type of the CSP lesions in patients provided to be significant in effectively selecting lesion clearance surgery. Following the aforementioned principle, there were no uterine perforation occurring with lesion clearance surgery in this study, and the majority (77%) of the patients had good scar healing.

Clinical value of individualized treatment

The aim of the CSP treatment was to select the appropriate methods to kill embryos, clear pregnancy lesions, reduce the amount of bleeding, and preserve fertility. Currently, the main treatment methods included drugs, uterine curettage after killing the embryos by UACE, lesion clearance under the surveillance of the hysteroscopy or laparoscopy, lesion excision through abdomen used with uterine repair, and hysterec- tomy [14]. However, there was no standardized solu-
tion for the treatment of CSP. In this study, MTX+CF program was chosen to kill embryos for the patients with hematic β-HCG < 5,000 IU/l when admission, and UACE was selected to kill embryos or stop bleeding for the patients with hematic β-HCG ≥ 5,000 IU/l when admitted. Uterine curettage was performed under the guidance of the hysteroscopy or under the surveillance of the B ultrasound for the type I patients with thickness of the surface muscle layer ≥ two mm. Uterine curettage was performed under the guidance of the hysteroscopy or under the surveillance of laparoscopy for type II patients with thickness of the surface muscle layer < two mm, mass diameter ≥ four cm, and less blood supply. Lesion excision through abdomen and uterine repair were performed for the patients with a mass diameter ≥ four cm and rich blood supply or with concurrent hemorrhage during uterine curettage. Emergent UAE or UAE hemostasis was used for the patients had hemorrhage when admitted or before uterine curettage, and the Foley catheter sacculus uterine hemostasis was used for patients with large amount of bleeding. Following the principle of individual treatment mentioned above, there were no serious complications and hysterectomy cases, achieving the desired therapeutic effect. Therefore, the method of selecting individual embryo killing, lesion clearance, and method to stop bleeding according to the comprehensive factors such as hematic β-HCG levels, location, size, blood supply, the surface muscle layer thickness of the lesions, and vaginal bleeding for the CSP patients when admitted, had practical value in the improvement of the CSP curative effect and prognosis, which was consistent with the findings reported by Zhang et al. [15].

Rational for the application of interventional therapy

The vascular interventional therapy for CSP included MTX infusion chemotherapy and embolization. The drug directly entered and gathered locally in the pregnancy lesions when infused MTX through uterine artery. After first extracting the drugs by the lesions, the local drug concentrations when infused MTX through uterine artery were higher than systemic administration and bioavailability were higher than systemic administration, the toxicity was mild, and the infused dose for could surpass 1 mg/kg or 50 mg/m² of the systemic administration for one time. The maximum infusion dose reached 300 mg and there were no serious toxicities. The use of UAE following MTX infusion could play a dual role in embryo killing with chemotherapy killing and anti-ischemic damage. UAE could also quickly control bleeding and reduce the risk of bleeding in lesion clearance. According to the literature [16], the interventional therapy had advantages in reducing the amount of bleeding, reduce the hysterectomy rates, and shorten the hospital stays. In this study, embryo killing and hemostasis by UAE were used in the majority (88.5%) of the patients, and the desired therapeutic effect was achieved. Therefore, the interventional therapy was suitable for the embryo killing of the CSP patients with hematic β-HCG ≥ 5,000 IU/l, acute hemostasis of the concurrent vaginal hemorrhage, and the bleeding prevention of the high-risk patients with uterine curettage. According to the individualized treatment principle, the rational use of interventional therapy was the key measure of the standard treatment for CSP. However, there are complications such as certain femoral artery puncture injuries and infection, syndrome after embolism, and non-targeted vessel embolism in the interventional therapy. The long-term effects of the UAE on ovarian function also could not be ignored.

Timing selection of uterine curettage

The timing for uterine curettage after killing embryos by intervention therapy or drug had not reached consensus, mainly related to factors such as embryonic necrosis after the embryo killing treatment, the decline rate of the hematic β-HCG, and blood supply of the lesions [17]. At present, it was believed that gelatin sponge particles were absorbed normally in seven to 21 days after embolization, so that the recanalization of the blood vessel could be realized. In addition, embryo killing by MTX could act more completely after three to four days, when the embryo is necrotized [18]. Uterine curettage could be performed 24-120 hours after UAE according to the literature [19]. In this study, the timing of the embryo killing was divided into within seven days group and after seven days group. The results showed that the differences of the hematic β-HCG levels, timing for uterine curettage, blood loss amount during the operation, and medical expenses between the two groups before the curettage had no statistical significance (p > 0.05), while the hospital time and turning negative time of the β-HCG for the curettage within seven days group were shorter than that of the curettage after seven days group, and the difference had statistical significance (p < 0.01). Therefore, considering the factors such as reducing the difficulty and bleeding in the uterine curettage, five to seven days after embryo killing treatment was the appropriate timing for uterine curettage, which enabled complete removal of the lesion, reducing bleeding, and shortening the course of the disease and duration of hospitalization. Premature uterine curettage timing might increase the amount of bleeding and the rate of residual lesions.

Acknowledgements

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References


Study of individualization therapy for 61 patients with cesarean scar pregnancy


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Fetal nasal bone length at 11+0-13+6 weeks of gestation: an evaluation of 554 consecutive cases

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Summary

Purpose of investigation: To develop a nomogram for estimating nasal bone length (NBL) at 11+0-13+6 weeks of gestation in 554 consecutive cases and to determine the value of NBL measurement in screening for chromosomal abnormalities. Materials and Methods: NBL and crown-rump length (CRL) were examined in 554 fetuses at 11+0-13+6 weeks’ gestation. A nomogram for NBL was developed with data from 479 healthy fetuses in which fetal profile examination was possible. Reference values, including percentiles, were calculated for each gestational age. Result: A linear correlation was noted between CRL and NBL in healthy fetuses at 11+0-11+6, 12+0-12+6 and 13+0-13+6 weeks of gestation. Mean NBL was 2.18 ± 0.53 mm, 2.46 ± 0.45 mm, and 2.91 ± 0.55 mm in healthy fetuses, for these time frames, respectively. NBL increased significantly with CRL from respective means of 2.26 ± 0.43, 2.60 ± 0.48, 2.77 ± 0.43, and 3.16 ± 0.52 mm at 45 - 54.9, 55 - 64.9, 65 - 74.9, and 75 - 84 mm. Conclusion: The authors developed a NBL nomogram with data from normal, healthy Turkish fetuses at 11+0-13+6 weeks of gestation. These reference ranges may prove useful in prenatal screening and diagnosis of syndromes known to be associated with nasal hypoplasia.

Key words: Fetal nasal bone; Ultrasonography; Chromosomal abnormalities.

Introduction

Screening for fetal chromosomal abnormalities has become a very important part of prenatal fetal evaluation [1-3]. Nuchal translucency (NT) is the most commonly used sonographic parameter in first-trimester screening for chromosomal abnormalities [2, 3]. However, fetal nasal bone (NB) assessment has recently been proposed as an additional screening tool for fetal chromosomal abnormalities [1]. Cicero et al. [1] were the first to investigate the role of NB examination in first-trimester screening for trisomy 21. Several studies have noted a high prevalence of hypoplastic nasal bone in trisomy 21 fetuses at 11-14 weeks’ gestation [4-6]. At screening for trisomy 21 by maternal age, examination of the fetal profile for the presence or absence of the NB can significantly increase sensitivity and reduce the false-positive rate [1, 7]. However, studies have revealed that NBL exhibits ethnic differences [8, 9]; the determination of NB hypoplasia may therefore depend on ethnicity.

The number of studies in Turkey on this issue is quite limited [10-12]. The aim of this study was to develop a nomogram for estimating nasal bone length (NBL) at 11+0-13+6 weeks of gestation in a well-selected local Turkish population.

Materials and Methods

Fetal NB examinations were prospectively performed on 554 singleton pregnancies at the time of routine first-trimester screening (11+0-13+6 weeks of gestation) in the Departments of Obstetrics and Gynecology and Radiology of the Karadeniz Technical University Faculty of Medicine during the four years of study period. Pregnant women were selected consecutively. The study was approved by the Karadeniz Technical University Faculty of Medicine Ethical Committee and informed consent was obtained from all patients. Gestational age was calculated using mothers’ reports of the first day of the last menstrual period and subsequently confirmed by fetal crown-rump length (CRL) measurement. Sonographic examination was performed using an ultrasound scanner with a 1-4 MHz convex transducer. Approximately 25% of cases, in which transabdominal imaging was suboptimal because of inadequate fetal position or maternal obesity, were examined via a four to nine MHz transvaginal transducer. Examination of the fetal NB was incorporated in routine first trimester screening by CRL. In addition to the CRL and NB measurements, a detailed structural evaluation was performed on each fetus.

Examinations were performed by one of two authors. For examination of the fetal NB, a midline sagittal view of the facial profile was obtained at an insonation angle of approximately 45° when the fetuses were in the supine position. The fetal head, neck, and upper thorax were magnified until they filled the image area, and the ultrasound transducer was gently tilted from side-to-side to show three distinct lines the NB, the overlying skin, and the tip of the nose (Figure 1). The measuring calipers were placed in an out-to-out position, and the average of two measurements was used for analysis.

Following ultrasonography, patients were referred on the same day to the Karadeniz Technical University Medical Faculty Department of Obstetrics and Gynecology. All pregnant women with appropriate weeks of gestation were enrolled. Risk scanning was performed by combining mother’s age and NT levels, beta-human chorionic gonadotropin studied from mothers’ serum specimens and pregnancy-associated plasma protein-A values. Karyotype analysis was performed with amniocentesis by the relevant de-
A. Cansu, H. Ozgur, S. Guven, G. Dinc, H. Dinc

Department in 59 cases identified as at risk of chromosomal anomaly and whose families permitted the procedure. Karyotype results were recorded for those cases in which amniocentesis was performed. Perinatal outcome in the low-risk group was obtained from hospital records.

Exclusion criteria were abnormal karyotype, referral for suspected ultrasound anomaly, or fetal anomaly diagnosed at ultrasound examination or afterward, women having systemic disease (diabetes mellitus, hypertension, heart disease, etc.), women having obstetric complications or women having high risk pregnancy. Detailed ultrasonographic examination was performed in the second trimester for pregnant women included in the study. Ultrasound assessment of the fetal nasal bones was attempted in 583 fetuses. Thirty cases were excluded due to chromosomal and/or structural abnormalities. Examination of the fetal NB was not possible in 44 fetuses because visualization was inadequate due to inappropriate fetal position. One healthy fetus had no nasal bone and excluded for final analysis.

Statistical analysis was performed using SPSS. Data were analyzed via Pearson’s correlation test, and R coefficients were calculated. Regression analysis was performed with NBL values and the biometric parameters; regression coefficients were calculated and regression equations produced. Mean and standard deviation NBL values were calculated according to the CRL and gestational age using data for healthy fetuses; a local nomogram was thus developed.

Results

CRL and NBL were measured in 479 healthy normal fetuses. Of these 479 fetuses, 36, 186, and 257 were evaluated at 11-11+, 12-12+, and 13-13+ weeks of gestation, respectively. Mean gestational age at time of sonographic evaluation was 12.32 ± 0.5 weeks. Mean age of the women was 31.34 ± 6.78 years, range, 17-45 years.

Nasal bone measurements to CRL are shown in Table 1. NBL of normal cases increased linearly with CRL increase; a linear correlation was noted between CRL and NBL in healthy fetuses at 11-11+, 12-12+, and 13-13+ weeks of gestation. Regression analysis between NBL and CRL revealed a regression equation of $y = 0.781 + 0.030 \times \text{CRL}$, $R = 0.533$, $p < 0.001$, and a significant correlation was determined between CRL and NBL. Nasal bone measurements according to gestational age are listed in Table 2, while percentiles of these measurements by gestational age are shown in Table 3. Amniocentesis was performed in 59 fetuses for various reasons (advanced age of mother, maternal anxiety, family history of child with abnormal chromosomal anomaly, abnormal serum screening test, etc.) and revealed chromosomal abnormalities in 19. The results for the cases with chromosomal anomaly are given in Table 4.

Linear regression tables regarding NBL and gestation week and NBL and CRL are made in Figures 2 and 3. Regression analysis between NBL and CRL revealed a regression equation of $y = 0.781 + 0.030 \times \text{CRL}$, $R = 0.533$, $p < 0.001$, and a significant correlation was determined between CRL and NBL. The 2.5 percentile from mean NBL was considered the cut-off point for hypoplasia. Fetuses were considered to have a hypoplastic NB when NBL fell below 2.5 standard deviations from mean NBL.

Figure 1. — Sonographic measurement of the nasal bone length using a midline sagittal view of the facial profile.
Fetal nasal bone length at 11+0-13+6 weeks of gestation: an evaluation of 554 consecutive cases

Discussion

Evaluation of the fetal NB is one of the most important components of first-trimester screening for chromosomal abnormalities. It has been suggested that absence or hypoplasia of the fetal NB is highly associated with trisomy 21 and other chromosomal abnormalities at 11+0-13+6 weeks of gestation [1, 4-7]. Recent studies have shown that ethnicity is a significant determinant of fetal NB evaluation [8, 9]. Prefumo et al. [9] reported the largest series in the assessment of fetal NB in the first trimester, and demonstrated a significant difference in the rate of visualization of fetal NBs in mothers of different ethnic origins. Therefore, the normal reference values of the fetal NBL are of great importance for the definition of NB hypoplasia [1].

Normative data for the fetal NBL in the first trimester have been established in the Caucasian [13], African-American [8], Latin American [14], Chinese [15], and Korean populations [16]. In the Turkish population, Kelekci et al. [10], Sivri et al. [12], and Ozer et al. [11] studied fetal NBLs in different regions of Turkey. In the present study, the authors developed a nomogram by evaluating 479 healthy fetuses in the Eastern Black Sea region of

Table 4. — Data for 19 cases with chromosomal anomaly.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>CRL</th>
<th>Weeks</th>
<th>NBL</th>
<th>Karyotype</th>
<th>US findings</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22</td>
<td>58</td>
<td>12</td>
<td>1.9</td>
<td>Trisomy 18</td>
<td>Anencephaly, spina bifida</td>
<td>Discharge</td>
</tr>
<tr>
<td>2</td>
<td>36</td>
<td>65</td>
<td>13</td>
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<td>Hydrops</td>
<td>Discharge</td>
</tr>
<tr>
<td>3</td>
<td>32</td>
<td>70</td>
<td>13</td>
<td>2.4</td>
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<td>Omphalocele, extremity anomalies</td>
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<td>4</td>
<td>35</td>
<td>77</td>
<td>12</td>
<td>0.0</td>
<td>Trisomy 18</td>
<td>Choroid plexus cyst, clubfeet</td>
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</tr>
<tr>
<td>5</td>
<td>25</td>
<td>65</td>
<td>12</td>
<td>2.8</td>
<td>Triploidy</td>
<td>Hydrops</td>
<td>IUEF, discharge</td>
</tr>
<tr>
<td>6</td>
<td>20</td>
<td>56</td>
<td>12</td>
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</tr>
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<td>7</td>
<td>36</td>
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<td>66</td>
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<td>47,XY Y</td>
<td>Omphalocele, lemon sign</td>
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<td>10</td>
<td>26</td>
<td>70</td>
<td>13</td>
<td>2.2</td>
<td>Turner S.</td>
<td>Cystic hygroma</td>
<td>IUEF, discharge</td>
</tr>
<tr>
<td>11</td>
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<td>63</td>
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<td>Trisomy 21</td>
<td>Cystic hygroma, Echogenic bowel</td>
<td>IUEF, discharge</td>
</tr>
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<td>38</td>
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<td>Cystic hygroma</td>
<td>Discharge</td>
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<tr>
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<td>29</td>
<td>60</td>
<td>12</td>
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<td>Cystic hygroma, Cardiac anomaly</td>
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<tr>
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<tr>
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<td>37</td>
<td>62</td>
<td>12</td>
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</tr>
<tr>
<td>16</td>
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<td>52</td>
<td>11</td>
<td>2.3</td>
<td>Turner S.</td>
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<td>Live birth</td>
</tr>
<tr>
<td>17</td>
<td>29</td>
<td>64</td>
<td>12</td>
<td>1.5</td>
<td>Trisomy 21</td>
<td>None</td>
<td>Live birth</td>
</tr>
<tr>
<td>18</td>
<td>40</td>
<td>56</td>
<td>12</td>
<td>2.2</td>
<td>Turner S.</td>
<td>None</td>
<td>Unknown</td>
</tr>
<tr>
<td>19</td>
<td>25</td>
<td>52</td>
<td>11</td>
<td>2.3</td>
<td>47,XXY</td>
<td>None</td>
<td>Live birth</td>
</tr>
</tbody>
</table>

* mother’s age, IUEF: intrauterine ex fetus, CRL: crown-rump length; NBL: nasal bone length.

Figure 2. — Linear regression table regarding NBL and gestation week.

Figure 3. — Linear regression table regarding NBL and CRL.
A. Cansu, H. Ozgur, S. Guven, G. Dinc, H. Dinc

Turkey. Mean NBL according to CRL was higher than those reported by Kelekci et al. [10] and Sivri et al. [12], but not that reported by Ozer et al. [11]; NBL according to CRL in the 50% percentile and NB length of 2.5 mm at the 11th week of gestation, 3.3 mm at the 12th week, and 3.4 mm at the 13th week. Our values for the same weeks were 2.2, 2.5 and 2.9 mm, respectively. Compared with those from other countries, the present results were similar to the mean NBL at 11+0 - 13+6 weeks gestation reported by Orlandi et al. [5] and Sonek et al. [13]. On the other hand, mean NBLs were significantly higher than those reported for the Korean and Latin American populations [14, 16] and slightly higher than that reported for the Chinese population [15].

NB hypoplasia or absence in the first trimester is an important clue in the early identification of chromosome abnormalities such as trisomy 21. Zoppi et al. [17], Cicero et al. [1], Otano et al. [7], Orlandi et al. [5], and Ozer et al. [11], reported NB absence in 70%, 69.9%, 66.7%, 60%, and 66.7%, respectively, of fetuses with Down syndrome, and 0.2%, 0.25%, 0.5%, 0.6%, and 1% of unaffected fetuses. However, Wong et al. [18] estimated the rate of absent NB slightly lower in both Chinese fetuses with aneuploidy (40.0%) and normal karyotype (0.88%). They also reported NB hypoplasia/absence in other chromosomal abnormalities as well as trisomy 21 [1, 5]. Cicero et al. [1] showed absence of NB in 57.1% of 18 cases with trisomy 21 in the first trimester and 8.8% of cases with Turner syndrome. In parallel with other studies, the present authors determined that NBL was not visible in one of 480 healthy fetuses (0.2%), six of nine fetuses (66.6%) with trisomy 21, and two of four fetuses (50%) with trisomy 18. Moreover, when the values below 2.5 standard deviation were taken into consideration, the NBs of two of nine fetuses (22.2%) with trisomy 21 were hypoplastic, while the NBL was at the lower limit of the normal range in one fetus with trisomy 21. However, in contrast to Cicero et al. [1] and Zoppi et al. [17], the present authors were unable to show NB hypoplasia or absence in Turner syndrome. This may be attributed to the low number of our Turner syndrome cases.

One limitation of this study was that it was hospital-based and the present is a tertiary hospital. Incidence of chromosomal anomaly and amniocentesis level was therefore very high as a result of all problematic gravidas being sent from surrounding hospitals.

The results of previous studies estimating reference values for fetal nasal bone length in various populations are summarized in Table 5 [1, 5, 11, 13-16, 19]. Examination of the fetal profile for the presence or absence of the NB during the first trimester of pregnancy provides substantial information on fetal chromosomal abnormalities. Absence or hypoplasia of the fetal NB is usually associated with fetal trisomies. Although measurement of the NB is not currently used as a routine screening tool in prenatal sonographic evaluation, it will take its place among the powerful sonographic markers of trisomy 21. However, NB measurement ethnic and technical differences should be evaluated according to population-specific nomograms so that NB measurements can be accurately interpreted. The fact that the results of the present study are different from those of three studies [10-12] may support the present authors’ idea. This data on NBL measurement may contribute national data for the development of a national nomogram for the Turkish population.

Table 5. — Results of previous studies estimating reference values for fetal nasal bone length in various populations.

<table>
<thead>
<tr>
<th>Author</th>
<th>Place of study</th>
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<th>12 +0-6</th>
<th>13 +0-6</th>
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</thead>
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<td>1.3</td>
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<tr>
<td>Orlandi et al., 2003</td>
<td>Italy, Holland</td>
<td>2.0</td>
<td>2.5</td>
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<td>USA</td>
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<td>2.6</td>
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<tr>
<td>Chen et al., 2006</td>
<td>Chinese</td>
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<td>2.2</td>
<td>2.8</td>
</tr>
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<td>Moon et al., 2006</td>
<td>Korean</td>
<td>1.2</td>
<td>1.5</td>
<td>1.9</td>
</tr>
<tr>
<td>Casasbuenas et al., 2009</td>
<td>Chile</td>
<td>1.0</td>
<td>1.5</td>
<td>1.8</td>
</tr>
<tr>
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<td>2.5</td>
<td>3.0</td>
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<tr>
<td>Current study</td>
<td>Turkish</td>
<td>1.3</td>
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</table>

* Marked values represent 3%; † Marked values represent 97th percentile
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References


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Expression of anti-inflammatory mediator lipoxin A4 and inflammation responsive transcriptive factors NF-kappa B in patients with preeclampsia


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Summary

Objective: To evaluate the role of lipoxin A4 (LXA4), NF-xB p65 in preeclampsia. Materials and Methods: LXA4 in blood serum and the lipoxin A4 receptor (ALX-R), NF-xB p65 mRNA, protein expressions in placenta-specific tissues were obtained from patients with preeclampsia and normal pregnancy. Results: Levels of lipoxin A4 in women with mild preeclampsia was significantly high (p < 0.05). There was no significant statistical difference between normal pregnancy and severe preeclampsia (p > 0.05). The mRNA expression of ALX-R was significantly low in women with preeclampsia than in control group (p < 0.01) and mRNA expression of NF-xB p65 was significantly high in preeclampsia (p < 0.01). The immunohistochemical staining of NF-xB p65 protein was stronger in severe preeclampsia group whereas staining of ALX-R in placental tissue was weaker than in control group (p < 0.01). ALX-R mRNA was negatively correlated with NF-xB (p < 0.0001), but there was no correlation between LXA4 and ALX-R mRNA. Conclusion: There was an excessive maternal inflammatory response in preeclampsia. LXA4, ALX-R, and NF-xB p65 may be involved in the disease process of preeclampsia.

Key words: Preeclampsia; Lipoxin A4; Lipoxin A4 receptor; NF-xB p65; Inflammatory reaction.

Introduction

Preeclampsia is one of the common complications seen in pregnancy, and its severity can contribute significantly to maternal and perinatal morbidity and mortality. It is a multisystem disorder of unknown etiology. Studies have shown that preeclampsia is due to an excessive inflammatory response to pregnancy and the basic pathology is vascular endothelial dysfunction [1]. Vascular endothelial injury in eclampsia is due to involvement of factors like leukocytes, coagulation system, the complement system leading to excessive intravascular inflammatory response [2, 3], resulting in multiple organ dysfunction and in a variety of other clinical manifestations of eclampsia [1].

LXs are derived from arachidonic acid, a member of eicosanoid family made of 20 carbon fatty acids [4]. In the process of inflammation or other diseases, lipoxins are synthesized after stimulation of inflammatory cytokines like lipopolysaccharide, through transcellular biosynthesis pathway which involves catalytic action of different lipoxygenase (lipoxygenases, LOX) [5, 6]. According to the molecule hydroxyl position and different conformation, other members includes lipoxin A4 (LXA4), lipoxin B4(LXB4), aspirin-triggered LXs (15-epi-LXA4 and 15-epi-LXB4), which promote the resolution of inflammatory reaction, and is thought to inhibit the signal of endogenous inflammation [5]. LXA4 binds with its specific receptor (lipoxin A4 receptor, belongs to G protein-coupled receptor super family ALX-R) to exert its biological effects [7]. This receptor is widely distributed in bone marrow-derived cells, such as neutrophil, monocytes / macrophages; they are also expressed in endothelial cells, lymphocytes, and also in different tissues, such as lung, kidney, and placenta [7, 8]. Nuclear transcription factor NF-xB/Rel family consists of five members: Rel-A (p65), RelB, C-Rel, p50 (NF-xB1) and p52 (NF-xB2). They are widely present in different types of cells to regulate immune response, apoptosis, and inflammation responsive transcriptive factors. In inflammatory diseases, such as systemic inflammation, infectious diseases, NF-xB activity is significantly increased [9]. LX when combined with its specific receptor, can pass through PI3K/Akt pathway, through inhibition of mitogen-activated protein kinase 3/6 (MAPK kinase 3/6), and p38-MAPK phosphorylation level, inhibiting the activation of NF-xB [10].

In this experiment, preeclamptic patient is the study subject; in preeclampsia group and normal control group, the authors detected blood LXA4 levels and level of ALX-R, NF-xB p65 mRNA, protein expressions in placenta-specific tissues to determine the relation of LXA4 and its receptor along with NF-xB in development and occurrence of preeclampsia and to investigate its role in pathogenesis of preeclampsia.

Materials and Methods

Patients and samples

Serum specimen and placenta tissue samples were obtained by 30 preeclampsia patients and 20 normal late pregnant women who consulted in the present center. All the patients with preeclampsia
fulfilled the criteria of the American College of Obstetricians and Gynecologists [11, 12]. Placental tissue samples were obtained by cesarean section. Serum specimens and placental tissue samples were matched-pairs. All patients gave informed consent for the use of their samples in research. In both groups, the clinical characteristics of the patients (age, maternal BMI, gestational age, mean arterial blood pressure, serum C-reactive protein) were collected.

Supernatants of serum were obtained from the centrifugate of venous blood samples (3,000 g for 20 minutes at -4°C) and stored at -80°C until use. Placental tissue samples were fixed in 4% paraformaldehyde within 30 minutes of placentation and were paraffin imbedding. Other fresh placental tissue were conserved in -80°C freezer.

Measurement of LXA4 in serum

The LXA4 level in the supernatants of serum specimens was determined with an enzyme-linked immunosorbsent assay (ELISA) kit, according to the manufacturer’s instructions, which was specific for LXA4.

Assessment of human LXA4 receptor (ALX) and NF-κB p65 mRNA expression in placental tissue was via reverse transcription-PCR (RT-PCR).

Total RNA was extracted from the placenta using trizol reagent method, and cDNA was synthesized from three μg of total RNA using M-Mvc2 reverse transcriptase and oligo (dt) primers. According to the sequence of Genebank, gene was designed and synthesized.

The RT-PCR primers for human ALX-R were 5'- GAG TCT GCT GGC TAC ACT GTT C -3' (sense: bp) and 5'- GAG GTT GAT GTC CAC CAC GAT -3' (antisense bp), and the PCR product obtained with these primers was 276 bp in size. The primers for human NF-κB p65 were 5'- TCA ATG GCT ACA CAG CA -3' and 5'- ACC ACA GTG CAT GCC ATC AC -3', and the PCR product had a size of 308 bp. Human glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as the internal control, with two primers (5'- ACC ACA GTG CAT GCC ATC AC -3' and 5'- TCA CCA CCC TGT TGC TGT A -3') yielding an expected PCR product of 450 bp. For amplification, an initial reverse transcription step was followed by denaturing step (94°C for five minutes) and then by 30 cycles of denaturing (94°C for 30 seconds), annealing (61°C for 30 seconds for ALX-R, 62°C for 45 seconds for NF-κB p65), and extending (72°C for 60 seconds), followed by ten minutes at 72°C for elongation. The PCR products produced were separated by electrophoresis on 2% agarose gel. Results were photographed, scanned. Analysis was carried out with a by a gel imaging analysis system scanning.

Immunohistochemistry for ALX-R, NF-κB p65

The 4-μm histologic sections from the placenta glands were routinely deparaffinized, rehydrated, and incubated with a solution of methanol and hydrogen peroxide (3%) for 10 minutes. Antigen retrieval was accomplished by boiling tissue slides in a citrate buffer solution. Endogenous peroxidase was quenched with 5% bovine serum albumin (BSA) in 0.1 M phosphate-buffered saline (PBS) for 30 minutes, followed by incubation overnight with primary antibodies against ALX-R(1:30), NF-κB p65(1:25), and then rinse by PBS, five minutes each time for three times. Anti-rabbit detection reagent was incubated with supervision for ten minutes at home temperature. Immunoreactivity was visualized with DAB kit according to the kit’s instructions. The sections were counterstained with Harris hematoxylin, rinsed with deionized water, dehydrated, transparency, and mounted using resinene. Negative controls omitted the primary antibody in a histologic section while performing all the other immunostaining steps.

Evaluation of immunostaining

Immunohistochemical results were evaluated for cytoplasm ALX-R, NF-κB p65-specific staining only. The immunohistochemical expression for ALX-R, NF-κB p65 was evaluated by using the scoring method Immunoreactivity Score (IRS) [13]. Fields were at x10, x 40 magnifications. Four high-power fields in each section, were randomly selected, with a x400 magnification. The sections were examined by two independent researchers. Fields were at x400 magnification and the staining intensity in the Trophoblast and vascular endothelial cell was scored as 0, 1, 2, or 3 corresponding to the presence of negative, weak, intermediate, and strong brown staining, respectively. The percentage of positively stained cells (PP) was assessed in each field as: 0 (< 10%; stained cells), 1 (≥ 10%), 2 (≥ 25%), 3 (≥ 50%), and 4 (≥ 75%). The score of the staining intensity (SI) for each field was multiplied by the score of the percentage of stained cells (PP) to provide a combined immunoreactivity score value (IRS) (IRS: PP×SI). The mean of the four fields was the final IRS score for the sample.

Statistical analysis

The experimental data were analyzed by statistical software SPSS13.0. Quantitative data are expressed as mean ± standard deviation (SD). Mean values were compared by using unpaired t test (for parametric data). Non-parametric test with Kruskal-Wallis H test; correlation with Pearson correlation test, p < 0.05 was considered statistically significant differences.

Results

Clinical data in the pregnancy women with preeclampsia and control group showed that there was significant difference in patient’s clinical characteristics, such as gestational age, mean arterial blood pressure, and serum C-reactive protein level, but no difference in age and maternal BMI was seen (Table 1). Gestational age of severe preeclampsia is significantly less than control group (250.5 ± 12.38 vs 260.7 ± 8.65, p = 0.045). Mean arterial blood pressure was higher in the mild (114.14 ± 2.79, p = 0.000) and severe (125.05 ± 9.75, p = 0.000) preeclampsia in comparison with the control group (88.00 ± 3.59). In patients with preeclampsia, a tendency of high C-reactive protein was detected in mild (12.04 ± 9.09) and severe (10.31 ± 9.96) preeclampsia, and difference was statistically significant (p = 0.000 and p = 0.019, respectively).

LXA4 in serum of pregnancy women with preeclampsia and control: serum LXA4 level of the pregnancy women was measured by ELISA method (Figure 1A). The mean concentration of LXA4 in mild preeclampsia was 180.84 ± 65.69 ng/ml, which was significantly higher than in control group (91.58 ± 23.94, p = 0.046). In the severe preeclampsia group LXA4 level was in lower concentration than control group but there was no significant difference (92.76 ± 16.11, p = 0.085).

ALX-R and NF-κB p65 mRNA expression in placenta tissues of preeclampsia and control group: the authors examined the expression of ALX mRNA in placenta tissues of ten patients with mild preeclampsia, 20 patients with severe preeclampsia, and 20 cases with control group. The
expression of ALX-R and NF-κB p65 mRNA in placenta tissue was detected by RT-PCR. Figure 2A shows weaker expression of ALX-R mRNA signals in mild and severe preeclampsia group compared to control. On the contrary, NF-κB p65 mRNA signals were more strongly expressed in the mild and severe preeclampsia compared to control group (Figure 2C).

RT-PCR revealed statistically significant difference in expression of ALX-R mRNA between the three groups, \( p = 0.008 \), highly expressed by control group 1.62 ± 0.45, followed by mild preeclampsia 0.86 ± 0.96 and severe preeclampsia 0.49 ± 0.17, Figure 2B). There was statistically significant difference in expression of NF-κB p65 mRNA between the three groups, \( p = 0.001 \), lowly expressed by control group 0.55 ± 0.14, followed by mild preeclampsia 0.73 ± 0.19 and severe pre-eclampsia (1.20 ± 0.40, Figure 2D).

To assess the presence of ALX-R and NF-κB p65 in patients with severe preeclampsia, concentrations of ALX-R mRNA were significantly negatively correlated with those of NF-κB (Figure 1B; Pearson \( r = 0.8464 \), \( p < 0.0001 \)). In control group, concentrations of ALX-R mRNA showed significant negative correlation with NF-κB (Figure 1C; Pearson \( r = 0.7931 \), \( p < 0.0001 \)). There were no correlations between LXA4 and ALX-R mRNA, however, these indices decrease together with severe preeclampsia.

The immunohistochemical staining of the ALX-R and NF-κB p65 was observed in the cytoplasm of villous trophoblastic cells and blood vessel endothelial. The present results indicate that the staining intensity of ALX-R in placental tissue of the mild and severe preeclamptic group was weaker than the control group. (Figure 2A-C). However, the NF-κB showed the opposite pattern, with greater staining in the severe preeclamptic group compared to the control group (Figures 2D-F). Table 2 and Table 3 summarize the results which were categorized by the intensity of immunostaining. The staining intensity of ALX-R in the placental tissue of the severe preeclamptic group was weaker than the mild and normal controls \( (x^2 = 17.107; \ p < 0.001) \), while the staining intensity of NF-κB p65 was greater in the severe preeclamptic group \( (x^2 = 10.093; \ p = 0.001) \), Figures 3A-C).
Figure 2. — A) ALX-R mRNA expression in placenta tissues of preeclampsia and control cases. ALX-R mRNA was detected by RT-PCR in all placenta tissue samples. B) Comparison of the expression of ALX-R mRNA among placenta tissues of patients with preeclampsia and control cases. ALX-R mRNA expression was significantly stronger in control group (1.62 ± 0.45) than in mild preeclampsia (0.86 ± 0.96, p < 0.05) and severe preeclampsia (0.49 ± 0.17, p < 0.0165). C) NF-κB p65 mRNA expression in placenta tissues of the preeclampsia and control cases. NF-κB p65 mRNA was detected by RT-PCR in all placenta tissue samples. D) Comparison of the expression of NF-κB p65 mRNA among placenta tissues of patients with preeclampsia and control cases. NF-κB p65 mRNA expression was significantly weaker in control group (0.55 ± 0.14) than in mild preeclampsia (0.73 ± 0.19) and severe preeclampsia (1.2 ± 0.40, p < 0.0165). Results represent the mean ± standard deviation (n = 20 for control, n = 10 for mild preeclampsia, and n = 20 for severe preeclampsia). mRNA levels are shown relative to the mean value for internal control.

Figure 3. — Immunohistochemical analysis of ALX-R and NF-κB protein in the placenta-specific tissue. A), B), and C) expression of ALX-R in normal, mild preeclampsia, and severe preeclampsia placenta tissue. The staining intensity of ALX-R in the placental tissue of the severe preeclamptic group (C) was weaker than the mild and control group (B and A). D), D), and E) expression of NF-κB p65 in normal, mild preeclampsia, and severe preeclampsia placenta tissue. The staining intensity of NF-κB p65 in the placental tissue of the severe PE group (C) was greater than the mild and control group (B and A). VTC = villous trophoblastic cell, BVEC = blood vessel endothelial cell. Original magnification: ×400.
In this experiment both preeclampsia and control group expressed NF-κB p65 mRNA and protein. Expression of NF-κB p65 mRNA and protein were significantly higher in placent al trophoblastic cell and vascular endothelial cells of preeclampsia patient, especially in severe patients. It confirms the role of NF-κB in pathophysiological mechanism of preeclampsia; its increased activity is related with the oxidation stress and imbalance of cytokines in preeclampsia patient. It has been reported that, in inflammatory disease like generalized inflammatory response, infective diseases etc., NF-κB activity is significantly increased [9]. NF-κB along with cytokine network, oxidase system participates in pathogenesis of preeclampsia. It includes activation of inflammatory cells through NF-κB signaling pathway to promote their adhesion and chemotaxis, and the release of inflammatory mediators leading to vascular system damage [22], placental ischemia–reperfusion results in oxidative stress, activate NF-κB signaling pathway leading to activation of inflammatory mediator, and endothelial dysfunction [23]. NF-κB activates expression of growth factor causing [24] revascularization, arteriolar wall thickening, atherosclerosis, and increase the mean arterial pressure. Above reaction, which begins from utero-placental lesion, eventually leads to symptoms of preeclampsia as in systemic hypertension and proteinuria.

LXA4 exert extensive regulatory role in a various type of inflammatory cell function and inflammatory related gene. Gewirtz et al. [25] using cDNA microarray method found that 50% of downregulation action of LXA4 to pro-inflammatory gene was through the NF-κB signaling pathway. In vitro cell culture and animal model research also shows that LXA4 inhibits lipopolysaccharide induced intestinal epithelial cell expression of TNF-α mRNA. LXA4 can also inhibit LPS induced production of IL-1β, IL-6 and IL-8 from pulmonary microvascular endothelial cells. The aforementioned mechanism is one of the antagonistic mechanisms belonging to inhibition of NF-κB nuclear translocation and other signaling pathways [10, 26]. Recently from animal model rat’s LXA4 receptor, amino acid sequences were cloned, which have 74% homology with human ALX-R [27]. Rat model research shows that LXA4 combines with receptor and exerts anti-inflammatory response through inhibiting the NF-κB activity,

Table 2. — Immunostaining of ALX-R in mild and severe preeclamptic group and control group.

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The average rank: 25.50 135.22 130.86 240.08

Discussion

More and more researches reveal [14, 15] that pathological changes of preeclampsia are similar to uncontrolled inflammatory response of acute lung injury and acute respiratory distress syndrome. Moderate inflammatory reaction is physiological changes of the maternal fetus body which is well-adapted [16], and excessive inflammatory responses are likely to lead to pathological changes during pregnancy. CRP is a nonspecific and sensitive inflammatory marker [17]. In this experiment, serum CRP level of preeclamptic patient was higher than control group, similar to other reports [18, 19], suggesting that excessive inflammation is the basic pathophysiological changes in preeclampsia.

In this experiment maternal LXA serum concentration of both groups were detected (Table 1). In mild preeclampsia, serum LXA4 was higher than control group whereas in severe preeclampsia group there was decreasing tendency of serum LXA4 expression. The aforementioned results show that mild pre-eclamptic patients were in LXA4 activated state, and mechanism may be due to inflammation, local hypoxia, and cell toxins [20, 21]. Increased level of LXA4 plays important role in balancing the inflammatory response, protecting body tissue and organs. In severe preeclampsia, decreased level of LXA4 may be due to the imbalanced biosynthesis and loss of braking signal of LXA4 which may lead to persistence and/or deterioration of patient condition. It theorizes the important role of LXA4 level in normal and preeclampsia patient.

LXA4 through combining with ALX-R, exert biological effect [6], ALX-R protein, ad ALX-R mRNA were expressed in placental tissue (Table 1). In this experiment the authors found that placental tissue of preeclampsia patient expressed lesser ALX-R protein and ALX-R mRNA than control group. ALX-R is a specific receptor of LXA4 and decreased expression of LXA4 leads to weaker response of cells to LXA4, leading to development and progression of disease. Although there is a increased expression of LXA4 level during stress condition of mild preeclampsia, however receptor is not sufficient, making the biological activity of LXA4 limited; this explains why the disease is in a state of progression.

In this experiment both preeclampsia and control group expressed NF-κB p65 mRNA and protein. Expression of NF-κB p65 mRNA and protein were significantly higher in placent al trophoblastic cell and vascular endothelial cells of preeclampsia patient, especially in severe patients. It confirms the role of NF-κB in pathophysiological mechanism of preeclampsia; its increased activity is related with the oxidation stress and imbalance of cytokines in preeclampsia patient. It has been reported that, in inflammatory disease like generalized inflammatory response, infective diseases etc., NF-κB activity is significantly increased [9]. NF-κB along with cytokine network, oxidase system participates in pathogenesis of preeclampsia. It includes activation of inflammatory cells through NF-κB signaling pathway to promote their adhesion and chemotaxis, and the release of inflammatory mediators leading to vascular system damage [22], placental ischemia–reperfusion results in oxidative stress, activate NF-κB signaling pathway leading to activation of inflammatory mediator, and endothelial dysfunction [23]. NF-κB activates expression of growth factor causing [24] revascularization, arteriolar wall thickening, atherosclerosis, and increase the mean arterial pressure. Above reaction, which begins from utero-placental lesion, eventually leads to symptoms of preeclampsia as in systemic hypertension and proteinuria.

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which is similar to humans. In this experiment, severe preeclampsia group shows decreasing expression of LXA4 and ALX-RmRNA, whereas NF-κB p65 mRNA and protein were significantly higher than control and mild preeclampsia group. There was a negative correlation in expression of ALX-R mRNA and NF-κB p65mRNA. Insufficient synthesis of LXA4 and ALX-R, attenuated activity of NF-κB p65 together accelerate the progression of disease in severe preeclampsia patient.

In summary, this research illustrates, LXA4 and ALX-R, NF-κB p65 all participate in disease process of preeclampsia. In severe preeclampsia, lack of LXA4 and ALX-R may have weakened downregulation activity of pro-inflammatory gene through decreased NF-κB signal pathway, causing deterioration of patient’s condition. Preeclampsia patients showed excessive inflammatory response and further study about the expression and regulation of LXA4, ALX-R protein, NF-κB is needed. Through activation of ALX-R, inhibition of activity of NF-κB, it is hoped to control the inflammatory disease and lead to new direction in treatment of preeclampsia.

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Sexual dysfunction in Turkish women with dyspareunia and its impact on the quality of life

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Summary

Purpose of Investigation: The authors aimed to determine the prevalence of female sexual dysfunction (FSD) among Turkish dyspareunia women and to establish the associated factors with FSD. Furthermore, they aimed to investigate if dyspareunia and possible associated sexual complaints were related to impaired quality of life (QoL). Materials and Methods: The study included 154 women admitted to the present gynecology department at a tertiary center in the west region of Turkey, 67 of which suffered from dyspareunia. The remaining 87 sexually healthy women were included in the control group. FSD was assessed with 19-item validated female sexual function index (FSFI). QoL was assessed using short form 36 (SF-36). The chi-squared test and t-test were used for analysing the group differences. Pearson's correlation test was used to determine the effect of the variables of FSFI on the SF-36. Multivariance analysis and logistic regression was used to determine independent risk factors for FSD and to estimate odds ratio (OR) with 95% confidence interval (CI). Results: The incidence of FSD in dyspareunia group and control group was 86.57% and 36.8%, respectively ($p < 0.001$). Dyspareunia women had lower scores with regards to sexual desire, arousal, lubrication, orgasm, satisfaction, and pain domains at significant level ($p < 0.001$). Education level, time period after the last delivery, duration of marriage, parity, and dyspareunia were significantly related to FSD. However, dyspareunia was an independent risk factor for FSD (OR 11.49; 95% CI 4.95-26.67). Regarding the impact on the QoL, dyspareunia women had lower scores with regards to the physical role, social function, bodily pain, and vitality domains. Conclusion: The present results show that dyspareunia has a major impact on women’s sexual function and QoL. Clinicians have an important role for encouraging women to report their sexual complaints. Identifying dyspareunia and treating FSD may positively affect women’s sexual function and overall QoL.

Key words: Dyspareunia; Female sexual dysfunction; FSD; FSFI; SF-36.

Introduction

Female sexual dysfunction (FSD) was classified according to the two main systems until 1998s: 1) Regarding the International Classification of Diseases-10 (ICD-10) of the World Health Organisation (WHO), FSD is the various ways in which a person is unable to participate in a sexual relationship as he or she would wish.” [1]. 2) Regarding the classification of the mental disorders (DSM-4) of the American Psychiatric Association, FSD is comprised of the disorders in sexual desire and in the psycho-physiological changes that characterize the sexual response cycle and lead to marked distress and interpersonal difficulty [2]”. In 1998, American Foundation of Urological Diseases (AFUD) proposed a classification including both DSM-4 and ICD-10 and also including psychogenic and organic causes [3]. Accordingly, FSD is classified into four main categories: 1) sexual desire disorders; 2) sexual arousal disorders; 3) orgasmic disorders; 4) sexual pain disorders [3].

The estimated prevalence of female sexual dysfunction is approximately 40-50% [4]. However, the point is that all sexual plaints do not cause personal distress or interpersonal difficulty.

The commonly used scales in order to evaluate female sexual function are brief index of sexual function (BISF), Index of female sexual function (IFSF), and female sexual function index (FSFI) questionnaires. The FSFI is useful for assessing specific domains of sexual function such as sexual arousal, desire, satisfaction, lubrication, orgasm, and pain [5]. Whether dyspareunia affects the other sexual functions like desire or arousal or whether lower sexual scores are associated with impaired quality of life (QoL) is assured very little.

The authors aimed to investigate the association of sexual complaints between women with dyspareunia and sexually healthy women. Furthermore, they aimed to investigate if dyspareunia and possible associated sexual complaints were related to impaired QoL. They hypothesize that women with dyspareunia have also other sexual complaints, including sexual desire or arousal decrease, which result in low QoL.

Materials and Methods

Study design, study setting, and participants

This is a cross-sectional case-control study comprising of sexually active, reproductive-aged women with a stable sexual partner, admitted to the present gynecology outpatient clinic between February 2013 and June 2013. The study was approved by the Institutional Ethics Committee. Two hundred women were asked to participate in the study. Sixty-seven women with dyspareunia and 87 sexually healthy women were included in the study and completed the questionnaires. Forty-six women rejected to complete the FSFI questionnaire.
Women with neurologic diseases such as history of stroke, spinal cord injury, parkinson disease, multiple sclerosis; women with genital atrophy, previous genital surgery; women with endocrinopathies such as thyroid disease, diabetes, hyperprolactinoma; women with peripheric vascular disease; women taking some medications like antihistamines, antiandrogens, sedatives, antidepressants, and hypnotics, were excluded from the study. Women who were not sexually active, or women having pregnancy or being in puerperium, were also excluded from the study. Women who could not complete questionnaires were also excluded. All the participants signed informed consent at the time of the visit at outpatient clinic. completed the study questionnaire during the same day, and returned it to the doctor at the outpatient clinic.

Outcome measures and instruments
The primary outcome in this study is sexual function assessment of the women with dyspareunia compared to the sexually healthy women. The assessment was made with the 19-item validated FSFI [5]. The Turkish version of the FSFI was validated by Oksuz and Malhan [6]. The FSFI determines sexual function status and complaints during the last four weeks. The questionnaire consists of six main domains of sexual function: sexual desire, arousal, lubrication, orgasm, satisfaction, and pain. For each domain, a score is computed. Total score is the sum of the all domains. The minimum total score is 2.0, and the maximum total score is 36.0. A total score of more than 25.0 is mentioned as ‘normal sexual function’; whereas a total score less than 25.0 is defined as FSD [6].

The secondary outcome in this study was the assessment of the quality of life in patients with dyspareunia. This assessment was made with the Turkish version of the short form-36 (SF-36) which was validated by Pinar [7]. SF-36 is a 36-item questionnaire comprising of eight main domains: physical functioning (PF), role limitations due to physical problems (RP), bodily pain (BP), general health perceptions (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems (RE), and mental health (MH). Each domain is scored between 0.0 and 100.0 and evaluated separately, namely there is no total score ranging. Lower scores are associated with the impairment of that function.

Statistical analysis
The FSFI and SF-36 questionnaire scores of the women suffering from dyspareunia were compared to that of the control group. SPSS software version 20 was used for statistical analysis. The group differences were analysed with Chi-squared test and t-test. Pearson’s correlation test was used to determine the effect of the variables of the FSFI on the SF-36. Multi variance analysis and logistic regression was used to determine independent risk factors for FSD. A two-tailed p value < 0.05 was considered to be statistically significant.

Results
The demographic features of the dyspareunia and control groups are shown in Table 1. Dyspareunia women had significantly higher parity and significantly lower level of income (p = 0.040 and p = 0.002 respectively). In multivariate analysis, parity and level of income were not found to be independent predictors for dyspareunia.
The incidence of FSD in dyspareunia group and control group was 86.57% (58 of 67 women) and 36.8% (32 of 87 women) respectively ($p < 0.001$). FSFI scores in both groups are shown in Table 2. The women with dyspareunia had lower total scores and lower scores in each of the six domains at the statistically significant level ($p < 0.001$).

Table 3 shows SF-36 scores in dyspareunia and control groups. Women with dyspareunia had lower RP and SF scores at the statistically significant level ($p < 0.001$); lower BP and VT scores at the $p < 0.01$ level.

The correlations between FSFI scores and SF-36 domains are shown in Table 4. Total FSFI scores showed positive correlations with PF, RP, BP, VT, SF, and RE at the statistically significant level. Furthermore, total FSFI scores were highly correlated to BP ($r = 0.505$).

Table 5 shows demographic features of the FSD and NSF groups are shown in Table 5. Parity, duration of the marriage, time period after the last delivery, education level, and dyspareunia were significantly related to FSD. Dyspareunia was independent risk factor for developing FSD (OR 11.49; CI 4.95-26.67).

Table 6 shows SF-36 scores in FSD and NSF groups. Women with FSD had lower PF, RP, BP, and VT scores at the statistically significant level ($p < 0.05$).

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**Discussion**

FSD is a common problem accounting for 40% to 50% of all women [4, 8, 9]. Recent Turkish studies estimated similar rates of FSD such as 48.3% [6], 46.9% [10], and 50%
Dyspareunia is a very common and probably under-estimated clinical condition which deteriorates women’s sexual life. FSD was as high as 86.57% in the present dyspareunia group. Whether dyspareunia itself is a sexual dysfunction or whether it should be handled as a part of generalized pain syndrome is still controversial. Due to interfering with sexual intercourse, it has been classically thought as a sexual dysfunction [13]. However, the typical pain of dyspareunia can be created also by non-sexual stimuli such as gynecologic examination or tampon insertion. In the recent classification of DSM, dyspareunia was classified as genital pain disorders [4,13]. The present authors hypothesized that dyspareunia affects a woman’s sexual life at multidimensional aspects. In a Turkish study by Dogan comprising of 54 women admitted to a psychiatry department with sexual complaints, the most common FSD was vaginismus which was highly correlated with dyspareunia. In vaginistic women, there was also a high frequency of hypoactive desire and orgasm disorders [14]. Similarly in the present study, beside the pain domain, dysparonic women had significantly lower scores in sexual desire, arousal, lubrication, orgasm, and satisfaction domains. Vaginismus and dyspareunia are classified together as pain disorders and they cannot truly be differentiated from each other [13]. Furukawa et al. evaluated dyspareunia and sexual function in infertile women. The rate of dyspareunia was 37.6% in controls and 30.7% in infertile group. The rate of FSD was not significantly different in both groups [15].

In this study, the authors also evaluated the associated factors affecting FSD. Low education level, time period after the last delivery, duration of marriage, and presence of dyspareunia were main predictors for FSD (p < 0.05). Furthermore, dyspareunia was independent risk factor for FSD. Women suffering from dyspareunia were 11 times more vulnerable for developing FSD. In contrast to the present study, age was the main risk factor for some other studies [12,16].

Healthy sexual life is one of the major components of well-being and quality of life. In the present study, dyspareunia women had significantly lower scores in RP, BP, VT, and SF domains. Total FSFI scores showed positive correlations with PF, RP, BP, VT, SF, and RE at significant level. Dyspareunia clearly has significant impact on women’s sexual life and quality of life. Similarly, Knoepp et al. showed that dyspareunia women had clinically significant levels of sexual stress [17]. In this aspect, it is very important to evaluate dyspareunia women to improve their overall QoL.

As dyspareunia women had lower scores for vitality and bodily pain, they are more vulnerable to depression. The main limitation of this present study was that the authors excluded only women self-reporting depressive symptoms or using medications affecting sexual function such as SSRI’s. However, women who may have concomitant depression without reporting symptoms were included in the study. The second limitation was that the possible concomitant factors, such as partner compatibility, was not assessed in this study. However, recent studies showed no significant relation between FSD and partner’s sexual performance difficulties [17]. The third limitation was the population sample. The present study population consisted of women living at the west region in Turkey, where the generality of the population was conservative. Therefore, the present results cannot be generalized to the whole population in Turkey.

On the other hand, the present study is unique as it assessed the associated factors to FSD in dyspareunia women and as it assessed the association of dyspareunia to both FSD and QoL. The results showed that dyspareunia had strong association to FSD (OR 11.49). The authors additionally found that the greater the time period after the last delivery and the greater the duration of the marriage, the greater was the FSD. Besides, the lower the women’s education level, the greater was the FSD. However, these features were not found to be independent predictors of FSD in the present multivariate statistical model. Dyspareunia was the only independent predictor for FSD in the present multivariate model. Furthermore, the authors found no association between the mode of contraception, the mode of delivery, woman’s occupational status, socio-economic status, and FSD. However, the present study population may have not been large enough to establish this association.

FSD with longer duration of marriage may be due to decreased interest of the partners to each other, financial problems, or it simply may be a physiologic result of normal sexual behavior. In a study from Germany comprising of 1,865 students aged 19–32 who reported to be heterosexual and to live in a steady partnership, the association of duration of relationship and sexual motivation was evaluated. Similarly to the present results, they proposed that sexual activity decreased as the duration of partnership increased. Besides, sexual desire declined only in women as the duration of partnership increased [18].

FSD in women with longer duration after the last delivery was not assessed before. The present authors suppose that FSD may be due to increased responsibilities of the partners to their growing children and parents may face with some different problems of their children as they grow up (childrens’s needs, financial need for school, problems during adolescence period etc.).

Regarding the contraceptive methods, Li et al. evaluated the impact of the commonly used contraceptive methods on the QoL and sexual function among 361 Hong Kong Chinese women. They suggested that the combined oral contraceptives (COC), intrauterine devices, and female sterilization do not have significantly adverse effect on women’s sexual life and QoL [19].

Regarding the mode of delivery, similarly to the present results, Baytur et al. suggested that there was no significant
relation between long-term sexual function and mode of delivery [20]. However, in early postpartum period, women with vaginal delivery had better sexual scores [21].

**Conclusion**

The present authors suggest that FSD is very common among dyspareunia women. Dyspareunia is the only independent predictor for FSD. Additionally, dyspareunia and FSD have negative impact on QoL at multidimensional aspects. Clinicians have an important role for encouraging women to report their sexual complaints. Identifying dyspareunia and treating FSD may positively affect on women’s sexual function and overall QoL.

**References**


Serological prenatal screening and diagnosis for Down syndrome

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Summary

Objective: This study aimed to review and summarize the recent first-trimester and second-trimester prenatal screening and sequential prenatal screening to analyze the role of the existing prenatal screening system in the secondary prevention of birth defects. Materials and Methods: This study included 3,665 cases of 14~20-week pregnant women that underwent prenatal screening using double serum alpha-fetoprotein (AFP) and beta-human choriocarcinoma gonadotropin (β-hCG) and ultrasound screening; 512 cases of 9~12-week pregnant women underwent triple serological detection of serum β-hCG, pregnancy-associated plasma protein A (PAPP-A), and nuchal translucency (NT) for early screening. Results: The overall screening was with a high-risk rate of 8.52%. Among 356 cases of high-risk pregnant women, a total of 308 cases underwent karyotype analysis of fetal amniotic fluid cells. Of these, five cases of trisomy 21, one case of trisomy 18 and one case of “47, XXY” were diagnosed; among 37 cases of neural tube defect (NTD)-affected high-risk pregnant women, one case of anencephalus, and one case of open spina bifida were diagnosed. Conclusion: The overall detection rate for chromosome abnormalities was about 3.25% in the existing screening system, which could effectively prevent these seriously teratogenic fetuses from being born.

Key words: Down syndrome; Prenatal screening; Prenatal diagnosis; Chromosome abnormality.

Introduction

Among about 20 million newborns in China every year, the increased congenital deformity and mentally disabled children reach up to 1.2 million. The birth defects account for about four to six percent of total born population every year. As one of the main means of the secondary prevention of birth defects, prenatal screening and diagnosis play an important role in the prevention of birth defects in the country at present. Down syndrome (DS) had become one of the main objects of prenatal intervention in various countries due to its high morbidity and incurable characteristics. The direct prenatal diagnosis for DS fetuses requires much human and material resources with higher risk, but cost-effective prenatal screening could be one of the schemes in solution of this problem. In the 1950s, Penrose et al. [1] found that DS was positively correlated to the ages of pregnant women [2, 3]. In 1977, Hook and Chambers firstly reported that pregnant women over 35 years old were considered high-risk pregnancies [4], so that age became the earliest indicator used in prenatal screening. In 1984, Cuckle et al. [5] firstly discovered that the maternal serum alpha-fetoprotein (AFP) levels were decreased in those with DS fetus, so that AFP was suggested to be a screening indicator for detection of fetal DS in pregnant women under 35 years of age. In 1987 and 1988, researchers successively found that the serum human chorionic gonadotropin (hCG) levels and unconjugated estriol (uE3) levels in pregnant women were correlated to DS. In 1988, Wald et al. from St Bartholomew's Hospital in London put forward a triple screening test using AFP, beta-hCG (β-hCG) and uE3 [6]. In 1994, the American College of Obstetricians and Gynecologists officially recommended this method to the nation's medical community, which was been applied ever since. With the in-depth study, it was gradually found that maternal age alone as a indicator was not comprehensive enough, which should be associated with the combined screening diagnosis of maternal serum marker or ultrasonic morphology. The combined free β-hCG and pregnancy-associated plasma protein A (PAPP-A) screening based on ages was the most certainly serological screening programme during early pregnancy but with a low DS detection rate, which was only 60% - 65% when the false positive rate was five percent [7, 8]. The development of genetics ultrasound technology and the determination of fetal nuchal translucency (NT), the first ultrasound screening indicator, were included in the most significant progresses in the prenatal screening in the 21st century, which directly promoted the development of prenatal screening during DS early pregnancy (maternal age + NT + free β-hCG + PAPP-A) and increased the detection rate to 85% (when the false positive rate was 5%) [9, 10]. However, the ultrasound indicator was with poor accuracy and repeatability compared to the maternal serum indicator for the influence of various factors on the accuracy of NT screening, including fetal position, body shapes of pregnant women, physicians' experience and technology, etc [11, 12]. Therefore, the high technical requirement and low detected flux of NT screening limited its large-scale screening applications, which was difficult to spread even in the developed countries. However, some studies had shown differences in marker levels between races [13-15]. In this study, the recent first-trimester and second-trimester prenatal screening and sequential prenatal screening in the present hospital were reviewed and summarized to analyze the role of the existing...
prenatal screening system in the secondary prevention of birth defects and establish standard screening criteria adapted to Central China.

Materials and Methods

Among a total of 4,177 pregnant women with single pregnancy for regular checks-ups from 2008 to 2011, there were 3,665 cases of second-trimester screening (14~20 weeks) and 512 cases of first-trimester screening (9~12 weeks), who were aged from 19 to 34 years old. This study was conducted in accordance with the Declaration of Helsinki and with approval from the Ethics Committee of the Third Affiliated Hospital of Xinxiang Medical University. Written informed consent was also obtained from all participants.

Second-trimester screening (14~20 weeks) was performed in 3,665 cases. The maternal serological screening in the second trimester used the AFP + β-hCG serum biochemical marker screening programme. Since chromosome aneuploidy was often associated with other malformations at the same time, such as the hygroma on the back of the neck, duodenal atresia, pylrectasia, cardiac abnormalities, choroidal cyst, polyhydramnios, etc., in this research multiple ultrasound markers were selected for screening based on double serum biochemical markers screening to improve the positive detection rate; 512 cases underwent the first-trimester screening (9~12 weeks) using triple screening test using β-hCG, PAPP-A, and NT.

The pregnant women undergoing screening had two ml venous blood drawn, fully under the principle of informed consent. After natural coagulation, the serum was separated and the specimen was stored at -20°C for specialist detection. The timed-resolved fluoroimmunoassay (TRFIA) detector and prenatal risk assessment system were used; The used kits included the PAPP-A quantitative determination kit, human alpha-fetoprotein (hAFP) quantitative determination kit, free β-human chorionic gonadotropin (free-β-hCG) quantitative determination kit, and free estril (FE3) quantitative determination kit. The quality control was strictly performed according to the operating procedure to measure the coefficient of variation, which was repeated twice if there were abnormal results. The cutting value to distinguish standard DS from high-risk trisomy variation, which was repeated twice if there were abnormal results.

Table 1. — The range of normal values of three kinds of first-trimester screening markers.

<table>
<thead>
<tr>
<th>Gestation weeks</th>
<th>NT (mm)</th>
<th>PAPP-A (±g/ml)</th>
<th>β-hCG (±g/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>10</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>9.17 ± 3.97</td>
<td>191 ± 14</td>
<td>12.24 ± 0.79</td>
<td>177 ± 27</td>
</tr>
<tr>
<td>2.28 ± 0.35</td>
<td>105 ± 19</td>
<td>16.78 ± 3.42</td>
<td>157 ± 19</td>
</tr>
<tr>
<td>3.09 ± 0.29</td>
<td>14.89 ± 3.77</td>
<td>119 ± 19</td>
<td></td>
</tr>
<tr>
<td>2.86 ± 0.39</td>
<td>22.03 ± 1.67</td>
<td>98 ± 21</td>
<td></td>
</tr>
</tbody>
</table>

Discussion

The prenatal screening of DS was a very special group of preventive engineering [16]. The present study synthesized the current situation in the region of study, 4,177 pregnant women that underwent screening using the first-trimester triple indicators β-hCG, PAPP-A and NT or the second-trimester double indicators AFP and β-hCG serological indicators. High-risk pregnant women were 356, with an overall high-risk rate of 8.52%. The high-risk rate for DS was 5.70%, and close to reports in literatures [5, 17]. Forty-eight pregnant women rejected the prenatal diagnosis and the other 308 high-risk pregnant women underwent amniocentesis for karyotype analysis of fetal amniotic fluid cells at 18~24 weeks, in which five cases of trisomy 21, one case of trisomy 18, one case of open neural tube defects (anecephalus), one case of sex-chromosome anomaly, and two cases of chromosome structural abnormalities were diagnosed, with an overall anomaly detection rate of 3.25%. In was indicated that the first-
first-trimester triple indicators β-hCG, PAPP-A, and NT or the second-trimester double indicators AFP and β-hCG serological indicators could effectively prevent the seriously teratogenic fetus from being born to achieve the desired purpose.

Recent researches indicated that the first-trimester and second-trimester combined sequential screening might have a higher efficiency compared to the traditional second-trimester screening [18], but the sequential screening had been attempted in the present study. Specifically, pregnant women underwent the first-trimester prenatal screening to give the first-trimester risk value. The high-risk ones were advised for prenatal diagnosis, while the low-risk and middle-risk ones were advised for second-trimester screening, which were followed according to prenatal diagnosis or not. However, patients were found with poor acceptability and mostly low-risk pregnant women in first-trimester prenatal screening did not accept or refused second-trimester screening. Therefore, there was a low second-trimester returning rate. Even some pregnant women refused the first-trimester screening for “not heard”, which was also the common problem encountered in the implementation of sequential screening at home and abroad [19]. Finally, the statistical summary for sequential screening was abandoned because of the poor returning rate of first-trimester screening (less than 70%). It was indicated that the implementation of sequential screening in Henan region still needed to enhance the propaganda and education, as well as strengthen the learning and propaganda consciousness of new technologies and methods to medical staff. Therefore, expanded sample size was more expected in the early sequential studies to find out the more accurate standards in early screening compared to this study.

It was of great significance to popularize the prenatal screening for improvement of the quality of Chinese population. The result in the existing screening system was likely to be affected with screening method, screening programme, different races, different quality control, etc [20]. In addition, the false positives and negatives were also the major problems to be overcome. In recent years, some studies had also successively found that the inhibin A, cancer antigen 125 (CA-125), etc., were related to women pregnant with DS fetus, which might also be gradually applied to the prenatal screening for DS. In recent two years, in addition, the new DS screening using of free fetal DNA in maternal plasma was a comprehensive innovation from principle to technology, which would be the important direction in the authors’ future researches. It was believed that as the continuous progresses of various technologies, the occurrence of DS would be better controlled.

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The triad of luteal phase ocular migraines, interstitial cystitis, and dyspareunia as a result of sympathetic nervous system hypofunction

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Summary

Purpose: To evaluate whether ocular migraines can be related to sympathetic nervous system hypofunction, especially when associated with interstitial cystitis and dyspareunia. Materials and Methods: Dextroamphetamine sulfate was administered to a 34-year-old woman with a history of long-term interstitial cystitis, dyspareunia, and ocular migraines that were resistant to all other therapies. Results: In a short length of time the sympathomimetic amine therapy almost completely abrogated all of her symptoms and they have remained controlled while she continues on the drug. Conclusions: This is the first report of effectively treating ocular migraines with dextroamphetamine sulfate. The gynecologist should not be afraid to initiate therapy without referral to other specialists, especially if other symptoms of the sympathetic neural hyperalgesia edema syndromes exist, e.g., bladder pain of pelvic origin and dyspareunia.

Key words: Luteal phase; Ocular migraines; Sympathomimetic amines; Interstitial cystitis; Dyspareunia.

Introduction

The gynecologist is generally the main treating physician for most women. When a woman has a complaint of migraine headaches, usually the gynecologist will refer her to a neurologist to perform a history and physical and based on findings, determine what other investigations are necessary to rule out serious neurologic disorders. If organic pathological entities, e.g., tumors and aneurysms are excluded, the gynecologist will usually expect the neurologist to initiate pharmacologic therapy, e.g., ergotamines, beta-blockers or other drugs, e.g., topiramate.

Similarly if a woman has symptoms of interstitial cystitis, the gynecologist will usually refer the woman to a urologist or to a urogynecologist for appropriate diagnostic procedures and therapy.

Unfortunately, despite the exclusion of organic pathology, pharmacologic therapy frequently fails to improve symptomatology from these two entities.

Several case reports and editorials have been published especially in Clinical and Experimental Obstetrics and Gynecology regarding migraine headaches refractory to standard therapy, but very responsive to sympathomimetic amine treatment [5-7]. Similarly, there have been reports showing very quick effective therapy with dextroamphetamine sulfate in women with interstitial cystitis who had failed to respond to conventional therapy [8].

The present case report describes a woman with a different type of migraine, an ocular migraine, who also suffered from interstitial cystitis and dyspareunia who responded very well to dextroamphetamine sulfate therapy.

Case Report

The patient is a 34-year-old woman complaining of long menstrual cycle intervals of 50-60 days. However from the time of
ovulation, she would have daily very painful ocular migraines, sometimes occurring several times per day which would cease with menstruation. These migraines began with a small blind spot in the center of the right eye which would gradually become wider and was described as widening prisms, then severe pain in the right eye would occur.

Taking various ergotamine preparations at the time of the aura had limited effectiveness on the eye pain. Beta-blockers and topiramate were also of limited value. Supplemental progesterone once ovulation occurred did not help either. The only therapy that she was presently receiving was fluoxetine Hcl, which she took from ovulation to her menses. She stated that it did not help the pain as much as her anxiety over the pain.

The bladder problems were described as both dysuria and urgency. The problem began when she was 22 years of age. The problem was associated with nocturia of at least one to two times per night and would occasionally occur six to seven times per night. The interstitial cystitis was diagnosed after cystoscopy. Pentosan polysulfate did not help. She did have mild relief from bacillus calmette-guerin (BCG) injection which had been given for six months. The only time in 12 years that she had a remission was during pregnancy. Also, since age 22, she had a deep type of dyspareunia. It was always present but worsened premenstrually.

When she returned after one month of taking 15 mg of dextroamphetamine sulfate extended release capsules, she stated that her migraines, bladder pain, and dyspareunia were completely gone. She had noted marked relief in all of her symptoms after the first week of therapy. She has remained in complete remission while on dextroamphetamine sulfate therapy for 18 months. She has stopped the fluoxetine Hcl.

Discussion

The gynecologist frequently has become the primary care physician for women. The role of the primary care physician is to treat those disease entities that are within the scope of his/her expertise and refer to other specialists when the gynecologist thinks a different type of specialist would be more suitable to diagnose or treat a particular condition.

Unfortunately the various specialists are usually unfamiliar with the relatively common disorder of sympathetic nervous system hypofunction referred to as the sympathetic neural hyperalgesia edema syndrome [9]. Frequently, the female is subjected to a potpourri of expensive, painful, and sometimes risky tests and yet fails to achieve a diagnosis of the true pathological state. Frequently the female is subjected to a potpourri of expensive, painful, and sometimes risky tests and yet fails to achieve a diagnosis of the true pathological state. Frequently the female is subjected to a potpourri of expensive, painful, and sometimes risky tests and yet fails to achieve a diagnosis of the true pathological state.

For example, for the woman described in this report, the use of dextroamphetamine sulfate and the role of the sympathetic neural hyperalgesia edema syndrome as key etiologic factor in causing migraine headaches, interstitial cystitis, and pelvic pain including dyspareunia, has been mainly published in gynecologic journals [1, 5-8, 10-12].

Thus in this case, after recognizing a triad of seemingly unrelated symptoms that have been described as secondary to this disorder of sympathetic nervous system hypofunction, it would be reasonable to try sympathomimetic amine therapy before referring the woman to various specialists. It would be highly-unlikely that a brain tumor or leaking aneurysm would improve with this type of therapy. Even if the gynecologist is not comfortable and wants to at least acquire an opinion from a neurologist or urologist, in this case the patient is at least aware that her problem has improved and can decide if she wants to undergo other tests, possibly suggested by the consultant just to be sure there is no other underlying entity depending on their expense, discomfort or risk after considering her degree of improvement of symptoms.

Though sympathetic nervous system hypofunction is the underlying defect allowing the absorption of toxins into various tissues, there are other factors, i.e., genetic, infectious, hormonal or environmental, that cause one woman to have symptoms in one organ system, e.g., the neurologic systems, with the musculoskeletal system, or the gastrointestinal system, or the skin in others [9, 13]. It is interesting that in this woman, the interstitial cystitis problem was not related to the changes in hormone secretion during the luteal phase, but the ocular migraines and the dyspareunia were associated with corpus luteum function. One explanation for this is that the defect in the bladder allowing the absorption of chemicals and toxins was significant enough that the sympathetic hypofunction allowed the bladder symptoms all cycle. However, both pelvic and the brain tissues were able to inhibit the absorption of chemicals and toxins until the secretion of progesterone or other factors from the corpus luteum. This suggests the possibility that there is a further suppression of the sympathetic nervous system function during the luteal phase, which was now sufficient to allow the absorption of toxins into these tissues.

Though, there have been other case reports of marked improvement of migraine headaches with dextroamphetamine sulfate therapy despite resistance to standard treatments, this is the first report of successful treatment of ocular migraines [5-7].

References

The triad of luteal phase ocular migraines, interstitial cystitis, and dyspareunia as a result of sympathetic nervous system hypofunction


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Simultaneous heart valve replacement surgery and abdominal subtotal hysterectomy: case report

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Summary
A middle-aged woman with rheumatic heart disease, mitral valve prolapse and incompletely closed mitral valve medium, patent foramen ovale, merge multiple uterine fibroids, and moderate blood loss anemia underwent mitral valve replacement surgery with total abdominal hysterectomy under general anesthesia and cardiopulmonary bypass condition. The surgery was successful, and postoperative bleeding, blood clots, heart failure, and other related complications did not occur. Heart valve replacement surgery with the surgical treatment of uterine fibroids effectively improves the safety of surgical treatment for patients as well as reduces the patient’s medical expenses and risk of secondary surgery and trauma.

Key words: Heart valve replacement surgery; Uterine fibroids; Joint surgery.

Introduction
Patients suffering from valvular heart disease generally require cardiac valve replacement surgery. In cases wherein the patients also have uterine fibroids, determining the gynecological indications for surgery, surgical procedures, and the timing of surgery is a very important issue. However, only a few reports at home and abroad have focused on this issue.

Case Report
The patient, a female 42-years-old and married, was admitted to the cardiovascular surgery department of the present hospital because of chest tightness after certain activities and shortness of breath for four years with secondary aggravating conditions for one year. Body examination showed moderate anemia, no lip cyanosis, no jugular vein engorgement, clear lung breath, regular heart rate of 84 beats/min, abnormal heart border that expanded to the left, 2/6 systolic heart murmur at the apex, no enlargement of liver and spleen, and lower extremity edema. Echocardiography findings showed mitral valve prolapse and moderate to severe regurgitation, visible atrial septal central defect with a diameter of approximately four mm, patent foramen ovale, and pulmonary artery systolic pressure of 40 mmHg. The blood count showed 3.3 × 1,012 /l red blood cells, 81 g/l hemoglobin, and 0.3 erythrocyte hematocrit.

Supplementary information included the following: menstrual flow in the past five years increased significantly and was accompanied by a blood clot; each menstrual cycle was regular without extensions. Pregnancy history is as follows: 2-0-0-2, eutocia 2. Gynecological check revealed normal vulva, no abnormality in vaginal patency, smooth cervix, uterine enlargement similar to pregnancy, surface irregularities, normal activity, no tenderness, and hard texture. Gynecological ultrasound showed a full uterine shape with a diameter of 5.6 cm and a hypoechoic substance in the anterior wall of the uterus, protruding into the uterine cavity. Real hypoechoic with multiple diameters of 1.7, 2.0, 4.6, and 2.0 cm could be observed at the bottom, front, and rear walls of the uterus. Based on the ultrasound, the patient was diagnosed with multiple uterine fibroids. The medical history and laboratory examinations yielded the following admission diagnosis: 1) rheumatic heart disease, mitral valve prolapse, mitral valve with moderate regurgitation, and patent foramen ovale; 2) multiple uterine fibroids and moderate hemorrhagic anemia.

The patient resides in the poor mountainous area of Yunnan. Given the poor state of the economy in this area, special medical cases are referred to the present cardiovascular surgery, obstetrics and gynecology, anesthesiology, and related departments for consultation. For the patient under study, cardiopulmonary bypass, mitral valve replacement, patent foramen ovale repair, and abdominal subtotal hysterectomy were all carried out under general anesthesia. The surgery was performed under systemic compound anesthesia seven days after admission.

First, systemic heparin + auxiliary lower thoracic midline incision open-heart surgery for the cardiopulmonary bypass was completed. During this part of the surgery, doctors observed mitral valve prolapse, moderate mitral regurgitation, and patent foramen ovale. The doctors performed 27 mm ATS metal replacement for mitral a + foramen ovale sutured surgery. After surgery, doctors used an antagonist to balance the heparin. The chest cavity was closed immediately while the hysterectomy surgery was being performed under the abdominal incision.

During this part of the surgery, doctors observed that the anterior uterus was enlarged similar to pregnancy and irregularly shaped with a smooth surface, projecting approximately four cm to the right front wall and the bottom of the uterus. The specimens’ cutaway showed intramural uterine fibroids protruding into the uterine cavity and surface. The total number of myomas was five, each with a maximum diameter of approximately five cm.

Postoperative pathology report showed rheumatoid-like lesions in the mitral valve and (hysterectomy) submuosal and intramural multiple leiomyoma. The patient was given routine antibiotics

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after surgery to prevent infection as well as symptomatic and supportive treatment. Thirteen days after the patient’s condition stabilized with good wound healing, echocardiography was rechecked. The results showed normal artificial mitral mechanical valve function and the absence of atrial level shunt. Gynecological ultrasound showed no pelvic abnormality. The patient was thus sent home. A three-year follow-up showed secondary level heart function, no menstrual cramps, smooth cervix, and no abnormalities in the cervix and both ovaries.

Discussion

Young women suffering from rheumatic heart valvular disease and uterine fibroids are not uncommon in China. According to literature at home and abroad, heart valve replacement surgery is performed first, followed by uterine fibroid elective surgery. However, no study has reported on a case wherein two surgeries are performed simultaneously. With the development of medical science, heart valve replacement surgery has become an effective method for the treatment of severe valvular heart disease. Approximately 200,000 patients all over the world undergo this surgery every year [1]. Heart valve replacement surgery is prevalent in China, with the most popular one being that for mechanical valve. Postoperative patients need warfarin for life-long anticoagulant therapy to prevent embolisms caused by thrombosis, which will result in mechanical valve failure [2]. The ideal intensity of anticoagulant therapy is one in which the level of anticoagulation can keep the rates of thromboembolism and bleeding at the lowest [3]. Anticoagulant therapy after heart valve replacement would likely harm patients when they undergo subsequent surgery because of the hemorrhage and embolism attributed to improper anticoagulant therapy, which accounts for 75% of complications after mechanical heart valve replacement [4, 5].

Hysteromyoma (uterine leiomyoma) is the most common benign tumor in female genital mutilation. Hysteromyoma is composed of smooth muscles and connective tissue, and it occurs in 30% to 50% of women of childbearing age [6]. Uterine fibroids are benign tumors, with a malignant transformation rate of only 0.4% to 0.8% [7]. Therapy is divided into surgical and non-surgical. To date, a safe and effective non-surgical treatment with low recurrence rate is still lacking. Surgical treatment is still the best treatment for patients with symptomatic fibroids [8]. The chance of recurrence after a pure resection of hysteromyoma is 50%, and dysfunctional uterine bleeding and endometrial lesions are still possible [9]. Anticoagulant therapy definitely aggravates the condition of patients who suffer from both uterine fibroids and blood loss anemia and increases the risk of hemorrhage for the elective surgical procedures. However, stopping anticoagulants will easily cause cardiac thrombosis and increase associated complications. Moreover, heart damage and decline in cardiac function because of the heart valve replacement will bring greater risk for hysteromyoma resectioning. In this case, excessive menstrual blood volume leads to moderate hemorrhagic anemia, increased uterine size similar to pregnancy, and sub-mucous myoma for patients over 40 years old regardless of fertility. These conditions constitute the surgical indications of abdominal total hysterectomy or subtotal hysterectomy.

The risk of heart disease is higher than that of gynecological disease for the patient under study. However, as mentioned earlier, patients who undergo gynecologic surgery after heart valve replacement will face special risks, such as intraoperative and postoperative hemorrhage, infection, and complications such as thrombosis and heart function failure. This patient in this study, for example, had already suffered from moderate hemorrhagic anemia. Heart valve replacement requires long-term anticoagulation drug therapy. Anticoagulation can influence patients’ menstrual quantity and increase the severity of anemia. The patient in this study is from an impoverished mountainous area characterized by poor economic conditions. Therefore, the department of cardiovascular surgery, anesthesia, obstetrics and gynecology, through multidisciplinary joint consultation under general compound anesthesia and extracorporeal circulation auxiliary, recommended that warfarin be discontinued for two days before line mitral valve replacement and abdominal total hysterectomy, with the interim alternative use of low molecular heparin anticoagulation. PT is switched to 2.5 times normal before surgery [10]. The operative method of the joint line (simultaneous for different organs for heart and uterine surgery) effectively prevents the risks associated with complications during and after surgery, thereby maximizing the safety of surgical treatment for patients. This method also reduces the medical expense and the patients’ pain in secondary surgery. It is regarded as an emergency option for patients from poor mountainous areas who do not have immediate access to hospital services. Thus, this method requires further research to facilitate further popularization and application.

Conclusions

Through interdisciplinary multidisciplinary joint consultation, patients with both rheumatic heart disease, multiple uterine fibroids, and hemorrhagic anemia can undergo heart valve replacement and surgical treatment of uterine fibroids simultaneously under extracorporeal circulation during anesthesia to effectively prevent the risks associated with complications during and after surgery as well as to maximize the safety of the surgical treatment. This method also reduces medical expenses and patients’ pain in secondary surgery. It is regarded as an emergency option for patients from poor mountainous areas who do not have immediate access to hospital services. Thus, this method requires further research to facilitate further popularization and application.
Simultaneous heart valve replacement surgery and abdominal subtotal hysterectomy: case report

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Matrix array transducer for the examination of fetal heart

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Summary

The X6-1 xmatrix array transducer allows a completely new approach to the diagnostic ultrasound: it permits visualization of fetal heart in real time, without the need for gating, and it is unaffected by motion artefacts. It is obtained in real time, without any spatial reconstruction. The authors compared this technology with the traditional one in two case reports: a diagnostic doubt of small muscular ventricular septal defect was solved using this new technique; a diagnosis of complete atrioventricular septal defect was confirmed. Three-dimensional real-time imaging would seem very precise in the study of fetal heart: the defects were fully visualized from any angulations. This new technology is promising but from the authors' limited experience, there is no evidence to use it in routine practice. It should be very useful to commence a prospective study on fetuses at risk while testing the superiority of this technique.

Key words: Congenital heart defect; Matrix array transducer.

Introduction

Congenital heart defects (CHDs) are the most common congenital anatomic malformations [1] and are among the most frequently missed abnormalities by prenatal ultrasoundography. Beginning from four-chamber view in B-mode real time, sensitivity of ultrasound to diagnose CHDs is 35-48%. It increases to 78-86% with the left and right outflow tract views [2]. Although, the use of three-dimensional and four-dimensional echocardiography improved the diagnosis of CHDs, these are limited by artifacts produced by fetal movements, in combination with cardiac gating methods during volume acquisition [3, 4]. The X6-1 xmatrix array transducer allows a completely new approach to the diagnostic ultrasound: it permits visualization of fetal heart in real time, without the need for gating, and it is unaffected by motion artifacts [5]. Through electronic steering, the X6-1 xmatrix imaging is totally different from traditional mechanical volumetric imaging, because it is obtained in real time, without any spatial reconstruction. The authors compared this technology with the traditional one in two diagnoses of CHD after the women’s consent was obtained.

Case Report

Case 1

A 37-year-old gravida 2, para 0, was hospitalized at Umberto I Hospital of Rome at 39 weeks. Her current pregnancy was complicated by gestational diabetes, and a small muscular ventricular septal defect was suspected during a scan at 21 weeks. Fetal echocardiography was performed by two-dimensional echocardiography at 34 weeks and it did not clarify the diagnostic doubt. During hospitalization, the fetal heart was studied using the X6-1 xmatrix array transducer. The diagnostic doubt was easily solved using this new technology (Figure 1). Diagnosis was confirmed by postnatal echocardiography.

Case 2

A 33-year-old gravida 4, para 1, was followed in the present unit from 21 weeks of gestation when a complete atrioventricular septal defect was diagnosed (Figure 2). The authors were able to analyse the defect with the X6-1 xmatrix array transducer. Real-time three-dimensional imaging proved superior to conventional two-dimensional imaging in depicting the anomaly of valvular plane: the septal defect was fully visualized from any angulations. Such a comprehensive assessment was not possible with B-mode real time imaging.

Discussion

Three-dimensional and four-dimensional ultrasound technologies allow a more comprehensive investigation of fetal heart. The imaging modalities obtained with the X6-1 xmatrix array transducer give additional tools to the examiner, to better delineate normal, as well as complex, fetal cardiac anomalies. With the X6-1 xmatrix array transducer and x-plane imaging, it is possible to visualize the septum in transverse view, from the apex to the valve plane, in real time and with considerable accuracy; moreover, it does not require any post-processing capability because, in order to define the “desired” second plane, you have only to use the trackball [6]. So far, it seems that the best technologies allow a better diagnosis and a higher resolution of anatomical structure arrangement in major heart anomalies. Having better information about fetal heart anomalies prenatally could allow better postnatal management. Otherwise, detection of very small heart defects without clinical significance could cause anxiety in the couple.

This new technology is promising but from the authors’ limited experience, there is no evidence to support an ad-
vantage of using such technique. It should be very useful to commence a prospective study on fetuses at risk with CHD using matrix array probes, conventional two-dimensional ultrasound and/or four-dimensional ultrasound with spatio-temporal image correlation (STIC), and testing the superiority of any of these techniques.

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Heart failure, metabolic acidosis, and postoperative multiple organ failure after anesthesia for cesarean section in a patient with Takayasu arteritis: a case report

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Summary

The incidence of Takayasu arteritis (TA) is approximately one in 200,000. The prevalence of this disease is higher among Asian women under the age of 30. Most pregnant women with mild TA receive spinal anesthesia for cesarean sections. Despite difficulties in measuring blood pressure, the entire surgical process, including the administering of anesthesia, is generally stable. Studies in this area are rare. The authors report a case of a pregnant woman with TA who received anesthesia for a cesarean section and then suffered for heart failure, metabolic acidosis, and postoperative multiple organ failure. The authors hope to contribute to the clinical studies on the subject of anesthesia for pregnant women with TA.

Key words: Pregnant; Takayasu arteritis; Patients anesthesia; Cesarean section.

Case Report

The patient was a 20-year-old female weighing 62 kg and was 35 weeks pregnant at the time of the study. The patient was reported to have been suffering from cough and chest tightness for 13 days as well as from abdominal pain for 12 hours. This study was conducted in accordance with the declaration of Helsinki and with the approval of the Ethics Committee of Liaocheng People’s Hospital. A written informed consent was obtained from the participant who met the criterion set for the study: an individual suffering from pulmonary TA that has been left systematically untreated for the past three years. The following observations were made: stiff seated position, mild jaundice of the skin and sclera, shortness of breath, moist rales in the lower left lung, a heart rate of 135 beats/min without murmur, mild edema in the lower extremity, weak pulsatility index in the bilateral radial artery, and a blood pressure of 80/60 mmHg measured from the right upper limb. Results of the laboratory tests were as follows: HB: 79 g/l, ALT: 32 IU/l, AST: 42 IU/l, TBIL: 59 umol/l, DBIL: 40 umol/l, GLU: 2.2 mol/l, ECG: ST-T changes; echocardiography: LA: 37 mm, LV: 54 mm, RA: 53 mm, MPA: 29 mmHg, PASP: 53 mmHg, EF: 20%, diffuse left ventricular mobility: low, mitral valve: mild regurgitation, tricuspid valve: mild to moderate regurgitation, pericardial: a small amount of fluid.

The patient intended to undergo an emergency cesarean section. In the operating room, the patient underwent right radial artery pressure tests (blood pressure: 80/45 mmHg), right internal jugular catheterisation (CVP: 12 cm H2O), selection of general anesthesia and inhalation of pure oxygen for five minutes before the anesthesia. The anesthesia was made up of the following: 14 mg etomidate (0.05 ug/kg/min trace pumped remifentanil) and 80 mg succinylcholine chloride. The anesthesia was administered via intravenous injection 60 seconds after intubation. After three minutes, a baby girl was delivered with an Apgar score of 8, which was taken one minute after delivery. The patient was then administered with 0.1 mg fentanyl and five mg midazolam via intravenous injection. In addition, the patient was given a subcutaneous injection of ten mg morphine. After...
fetal expulsion, blood pressure dropped to 70/40 mmHg, CVP: seven cm H2O. Upon laying the patient on the operating table, blood pressure gradually rose to 85/50 mmHg. After five minutes, CVP also increased to 16 cm H2O upon adjustment of the operating table head to 30°. To control the infusion rate, the patient was slowly injected with 0.3 mg cedilanid.

Intraoperative blood gas analysis showed metabolic acidosis, pH: 7.09, Lac: 11.8 mmol/l and Glu: 0.8 mmol/l; HCO3+: 8.2 mmol/l and BEecf: -21.6 mmol/l (Table 1). After an intravenous injection of ten g glucose, blood sugar rose to 3.4 mmol/l. The blood gas analysis revealed the following after an intravenous infusion of 5% NaHCO3 (150 ml): pH: 7.13, Lac: 11.2 mmol/l, HCO3+: 13.0 mmol/l, and BEecf: -16.2 mmol/l and 300 ml bleeding was also observed. A compound solution of 200 ml sodium chloride and 200 ml erythrocyte suspension was also given during operation. The following were noted after the operation: blood pressure: 84/52 mmHg, CVP: 12 cm H2O and heart rate: 126 beats/min. A portable ventilator was used to control breathing. The patient was subsequently delivered to the ICU to continue treatment.

The following observations were made during the first day of treatment in the ICU: ventilator-assisted breathing, APACHE II score: 24 points, liver and kidney damage: further aggravated, jaundice: aggravated, ALT: 372 IU/l, AST: 1,603 IU/l, TBIL: 120.1 umol/l, DBIL: 63.7 umol/l, ALB: 22g/l, BUN: 10.2 mmol/l, CREA: 129 umol/l. Several blood gas analyses showed metabolic acidosis and ten mmol/l blood lactate. The patient then went into coma, with a heart rate measured at 130 beats/min and wet rales at the bottom lung. Ventilator support was given for four days, along with cardiac, diuretic, and hepatoprotective medications to correct metabolic acidosis and hypoglycemia as well as to prevent infection. When the patient gained consciousness, the following observations were recorded: heart rate: 100 beats/min, blood pressure: 96/60 mmHg and CVP: seven to ten cm H2O. Ventilator support was also necessary, In addition, wet rales in the lower end of the lungs were also observed in the endotracheal tube.

After four days of continued treatment, heart condition gradually improved from the ventilator. The endotracheal tube was also removed, but the patient still received continuous oxygen at four l/min, with spontaneous breathing of 20 times/min and an SpO2 level of 97%. Blood gas analysis revealed metabolic acidosis and nine mmol/l of blood lactate. During the second day off the ventilator, the patient experienced sudden difficulty in breathing and chest tightness. The following observations were recorded: breathing: 35 times/min, oxygen: seven l/min, SpO2: 80% and heart rate: 150 beats/min. Blood pressure could not be determined, and scattered moist rales were noted at the bottom of the lungs. Endotracheal intubation was immediately performed. The patient was placed on ventilator-assisted breathing as well as on cardiac and diuretic therapy. Further deterioration was observed, with the patient having a high fever of 41.3 °C, decreased urine output, severe respiratory and circulatory failure, as well as other internal disorders. Blood profusion within the endotracheal tube was also noted. After two hours, heart rate decreased rapidly to zero, resulting in the death of the patient.

### Discussion

In patients with TA, lesions are common in the aortic arch and its branches, followed by the descending aorta, abdominal aorta, and the renal artery. Lesions are also observed in the secondary branches of the aorta, such as the pulmonary and coronary arteries [1].

The lesions can be grouped into four types: brachiocephalic artery type (aortic arch syndrome), chest-abdominal aortic type, extensive type, and pulmonary type [1]. The brachiocephalic artery type and other types of mild lesions are generally less worrisome, as the arterial pulse pressure of the upper and lower limbs are greater despite the undetectable upper limb blood pressure [6]. Generally, lesions of the said type can be tolerated during pregnancy and childbirth, but blood vessels and cardiac function must be closely monitored, especially during pregnancy [3]. Patients with TA of the said type undergoing a cesarean section may choose to have either an epidural or spinal anesthesia [2-6]. For the extensive type and the pulmonary type of lesions, conditions are often serious, as characterised by ventricular dysfunction, as well as liver and kidney dysfunction. In particular, during late pregnancy, patients with cardiopulmonary diseases are prone to multiple organ failure, resulting in a high mortality rate. In severe cases, patients are generally recommended to take contraceptive measures to avoid pregnancy [7].
In the case described previously, the patient experienced heart failure, liver dysfunction, and echocardiography, suggesting a thickening of the pulmonary artery that resulted in a moderately high blood pressure. Therefore, the case can be classified as belonging to the extensive and pulmonary type. Epidural or spinal anesthesia is therefore inappropriate, as both forms result in an instability of the hemodynamic parameters, deterioration of cardiac functions, ischemia, and aggravation of metabolic acidosis, etc. General anaesthesia should be used because of the possibility of preoperative severe heart failure, hypoxia (SpO2: 70%) and metabolic acidosis (BEecf: -21.6 mmol/l). Radial artery and jugular vein cannulation manometry must be performed before administering anesthesia. To monitor treatment, pulmonary artery pressure should be closely measured with a pulmonary artery catheter, which is limited by differing conditions and time constraints. Obtaining the data from the pulmonary artery catheter monitoring can guide treatment and explain conditional changes. To shorten the time of the induction of anesthesia for fetal expulsion, anesthesia-inducing drugs may be used, as these have minimal effects on the cardiovascular drug etomidate. The micro pump Ru Ruifen (0.05 ug/kg/min) may be given to stabilise maternal cardiovascular functions, reduce stress response, and to hasten metabolism, all of which have minimal impact on fetal breathing.

Attention must be focused on monitoring intraoperative blood pressure and CVP changes, as well as on guiding transfusion to maintain hemodynamic stability. Abdominal pressure after the removal of the fetus is smaller because less blood flows back to the heart, which often manifests as a drop in blood pressure. A head-down tilt position may therefore be appropriate for the patient. Uterine contractions ease up after autologous blood transfusion. For patients with cardiac dysfunctions, fluid input must be controlled; otherwise, cardiac overload may occur because of the autologous blood transfusion after uterine contractions. In the case described above, the CVP decreased from 12 cm H2O (preoperative) to 7 cm H2O and then rose again to 16 cm H2O after five minutes from fetal expulsion. This finding reflects the dramatic changes in the circulating blood volume after the baby is delivered. Improper handling can thus cause further deterioration of the circulatory function.

After the cesarean section, the patient was observed to have an improved heart function, but the liver and renal dysfunction, the high levels of lactate and metabolic acidosis persisted. This finding indicates that pregnant women with TA are likely to suffer from severe multi-system, multi-organ atherosclerosis, which results in the hypoperfusion of the heart, lung, liver, kidney, and other tissues. As lactate production increases, the heart, lung, liver, and kidney dysfunctions become aggravated because of the restricted metabolism of lactate discharge. This restriction further damages the liver and kidney, thereby creating a vicious cycle that eventually leads to multiple organ failure.

Faced with economic issues, the patient under study failed to receive blood dialysis, which resulted in further health deterioration. With pulmonary haemorrhage, the patient experienced collateral circulation in pulmonary arteriosclerosis, pulmonary vascular ectasia, and bleeding. As the patient’s family refused an autopsy, a complete pathological report could not be obtained.

Pregnant women with severe TA, multi-organ atherosclerosis stenosis, and low perfusion are found to likely suffer from multi-organ dysfunction. Therefore, administering anesthesia and performing a cesarean section are difficult. Careful attention must be paid to the following points: 1) Comprehensive laboratory tests must be performed and effectively monitored, including invasive arterial measurement, central venous pressure measurement, pulmonary artery catheter monitoring, blood gas analysis, as well as heart, liver, and kidney function tests. In addition, respiratory and circulatory changes, as well as organ function status must be closely observed before, during, and after delivery, including follow-up treatments. 2) A reasonable interpretation of monitoring indicators, as well as the pathophysiological state of the patient must be ensured. Attention must also be placed on changes to the functions of the heart, lungs, liver, kidneys, and other vital organs. An active use of drug therapy, ventilator, haemodialysis, and artificial liver replacement therapy may result in a better therapeutic effect. This case study can serve as an important reference for the administering of anesthesia in and the postoperative treatment of pregnant women with severe TA.

As cited earlier, the patient could not undergo blood dialysis and accept an artificial liver because of economic difficulties. In pregnant women with TA lesions, damage to important organ functions are seriously common, adding burden to the patients who are already suffering from the pains of pregnancy and from the impending surgery. Even with the most comprehensive therapy, good treatment effects are difficult to achieve. The authors of this work deeply regret the death of the patient under study and hope to provide case materials that can aid in further research on the treatment and pathophysiological aspects of TA.

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Transvaginal repair of rectovaginal fistula by filling with bulbocavernosus fat pad and retaining scar tissue

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Summary
The authors performed transvaginal repair of rectovaginal fistula (RVF) with bulbocavernosus fat pad by incising left side of the labia majora and retained scar tissues which were formed after three months for one patient. Repair of the RVF was successful and the patient had normal diet and defecation at a week after surgery. Previous gynecological surgery performed on the patient resulted in RVF accompanied by weak rectal tissues. Retaining the tissues and scars surrounding to the fistula and filling the fistula with bulbocavernosus fat pad tissue increased rectal wall thickness and facilitated healing. The efficacy of this surgical technique will need further studies with larger patient cohorts to establish a clear success rate.

Key words: Rectovaginal fistula; Bulbocavernosus fat pad tissue; Reserving scar tissue.

Introduction
Rectovaginal fistula (RVF) is an abnormal connection between the vaginal epithelium and rectal mucosa. It is a pathological passage between rectum and vagina, also known as fecal fistula. The condition may manifest as fecal accumulation in the vagina and/or vaginal fecal discharge which is especially obvious with liquid stool. With a smaller fistula, vaginal discharge of feces may not happen, but vaginal gas may be released.

RVF can be congenital or acquired. Congenital RVF is defined as an abnormal opening of the rectum into the vagina due to anorectal agenesis; acquired RVF results mostly from obstetrical injury, surgical injury, trauma, tumors, or infection. It has been reported that 85% to 92% of acquired RVF are caused by obstetrical injuries [1]. In developed countries, the incidence of RVF resulting from childbirth is 0.06% to 0.1%, but it is higher in developing countries [2].

It has been proposed to classify RVF into high, middle, and low, and according to the location of the fistula opening in the vagina [3]. Common international classification of RVF is currently based on location, size, and etiology of the fistula in the vagina, and is described as simple and complex [4]. A simple fistula is defined as one that occurs in the lower vagina, and has a diameter of less than 2.5 cm. The fistula may have one opening, but two or more openings are possible, particularly when caused by trauma or infection. A fistula is considered complex when it is located in the higher vagina, and its diameter is greater than 2.5 cm. Causes of complex RVF include inflammatory bowel disease, radiotherapy complications, tumors, and recurrence of fistula after a failed repair.

Many surgical treatments provide solutions for RVF. Surgical methods vary due to diverse causes, location, and size of the fistula, and surrounding scarring tissues. When treating fistula at a high location in the vagina, difficult exposure, unclear anatomical localization, and a weakened rectovaginal septum often result in low success rates. Therefore, repairing the fistula directly through a transvaginal or transrectal approach is difficult. Conversely, middle and low fistulas are easily exposed, clearly localized, and the rectovaginal septum is relatively thick, thus the success rate is higher [5]. The authors treated a patient with RVF after she underwent surgical resection of a cervical squamous cell carcinoma. The patient’s fistula was repaired with a bulbocavernosus fat pad and scar tissues were retained.

Case Report
History
In 1998, the patient had an abdominal uterine fibroid myomectomy. In 2005, she underwent a laparoscopic myomectomy at the Shenzhen Sixth People’s Hospital affiliated to Guangdong Medical College. There was no history of hypertension, diabetes, heart disease, tuberculosis, hepatitis, trauma, and food or drug allergies. She had two pregnancies, one resulting in a live delivery, and the other was terminated by an abortion. On June 8, 2012, the patient underwent a colposcopy for excision of a cervical neoplasm. Pathological examination of the biopsy showed a cervical invasive non-keratinizing squamous cell carcinoma positioned at 10 o’clock, Stage IB1. On June 26, 2012, laparoscopic surgery was performed. The operation included wide hysterectomy, bilateral oophorectomy, pelvic lymph node dissection, and pelvic adhesiolysis. Intraoperative exploration found a slightly enlarged uterus, adhesions between the omentum and the abdominal wall, and dense adhesions between the intestine and posterior wall of uterine fundus. The postoperative diagnosis was CIN1 and cervical polyps, and the vaginal vault and lymph nodes showed no metastasis. Five days after surgery, vaginal discharge turned odorous, yellow-green liquid, increasing in...
through the tunnel. The suture ends from the previous step were knotted to fix the fat pad in place, and the distal vaginal wall around the fistula was stitched interruptedly with 2-0 Vicryl suture to close the top of the vagina.

The subcutaneous tissues and then the skin of the labia majora were stitched interruptedly using silk suture (No. 4). Afterward, the wound was covered with dressing. The intraoperative infusion volume measured 1,500 ml, and bleeding was about 50 ml. The patient’s urine was clear and measured about 100 ml. After the operation, the patient was safely moved into the general ward.

Postoperative conditions
After three days of fasting, the patient took liquid diet for an additional three days before resuming a normal diet. Appropriate antibiotics and haemostatic agents were used. She bathed with a 1:5,000 potassium permanganate solution after defecation. After wound stitches and urethral catheter were removed, the vagina was unobstructed and secretions were normal. She was discharged on October 30, 2012.

Discussion
Diagnosis of RVF is relatively straightforward. RVF requires surgery, and many physicians first consider conducting a diverting colostomy, expecting the RVF to heal on its own. In fact, simple diverting stoma surgery for RVF produces a lower spontaneous healing rate. Rex et al. reported that only 35.37% of patients who underwent a diverting colostomy spontaneously healed; while non-surgical treatments for some patients with RVF had a 71% healing rate [6]. In addition, Kosugi et al. conducted diverting stoma surgery for treating RVF caused by rectal cancer surgery. The spontaneous healing rate was only 42.9%; the average healing time was up to six months [7]. In patients with spontaneous healing, the only cause for surgery was anastomotic leakage with concurrent abscesses.

Patients with injured vaginal wall do not benefit from diverting stoma surgery. Patients with simple RVF who exhibit mild symptoms can receive non-surgical treatment and observation, instead of routine colostomy. Patients with severe symptoms should be treated surgically. In case of poor local condition and a long waiting time for surgery, diverting stoma surgery should be considered. Patients with complex fistulas (in particular after radiotherapy) should undergo diverting stoma and elective surgical repair. For patients with RVF caused by malignant invasion, diverting stoma surgery is necessary to improve quality of life. The patient in this study had cervical cancer and multiple postoperative fistulas, a shortened vagina, and increased vaginal secretions. Thus, surgery was the best course of treatment.

Timing of RVF repair surgery is under debate. Some physicians suggest that repair should be carried out six to 12 weeks after the RVF has occurred. A complexity of etiologies and clinical treatments of RVF suggest that treatment should be individualized in accordance with the specific circumstances of each patient. Surgical intervention should only be performed when the local infection or inflammation is under control. The patient with RVF described in the current study was repaired after three months.
Successful repair of RVF relies critically on the reconstruction of the rectal wall and restoration of the rectum and anal canal within the high pressure zone. However, local anatomical characteristics of RVF make surgery prone to failure. Subsequent surgery is often related with increased difficulty and failure rates. After three repairs, the success rate was reported at only 55% [8].

The present authors considered that their patient had weak rectal tissue. If the necrotic tissues around the fistula were scraped without resecting the fistula or surrounding tissues and scars, the blood supply would likely be inadequate and high local tension was likely to occur. Bulbocavernosus fat pad tissue has a rich blood supply, and using it as filling between the vagina and rectum created four layers consisting of the proximal vaginal wall, scar tissue, the fat pad, and the distal vaginal wall, ultimately resulting in a strengthened rectal wall. Postoperative recovery of the patient was satisfactory, eliminating the need for diverting colostomy or the occurrence of diaplastic surgical injury.

Effective prevention of low postoperative RVF should include: (1) a careful review of the patient’s history of pelvic surgery and/or radiotherapy prior to surgery, (2) an assessment of risk factors so that preventive measures are taken. Some patients who undergo resection or separation of the posterior wall in the perineum may have unsatisfactory outcomes. In these cases, preventive filling with bulbocavernous fat pad tissue in rectovaginal gap may be considered to ensure adequate blood supply and to build a barrier against inflammation or abscesses. (3) Placement of the postoperative drainage tube is also important in preventing anastomotic leakage and abscess formation. RVF is a rare occurrence, but it can seriously affect a patient’s quality of life. Ineffective treatment often gives rise to delayed postoperative rehabilitation and adjuvant therapy. Therefore, prevention strategies for RVF and risk assessment are of particular importance. Once a diagnosis of RVF is established, individualized treatment programs should be developed based on the type of disease and the patient’s condition. For the majority of patients, surgical repair is the best option to improve quality of life. The patient in this study underwent gynecological surgery and had weak tissues surrounding the fistula. Retaining the surrounding tissues and scars, as well as filling the opening with bulbocavernous fat pad tissue, increased rectal wall thickness and may have improved healing. The efficacy of this surgical technique will need large sampling studies to be confirmed.

Conclusions

Retaining the tissues and scars surrounding to the fistula and filling the fistula with bulbocavernous fat pad tissue increase rectal wall thickness for rectovaginal fistula. The efficacy of this surgical technique will need further studies with larger patient cohorts to establish a clear success rate.

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Uterine preservation in placenta percreta complicated by unscarred uterine rupture at second trimester in a patient with repeated molar pregnancies: a case report and brief review of the literature

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Summary

Placenta-percreta causing uterine rupture in unscarred uterus is a rare obstetric surgical emergency that can cause maternal and perinatal morbidity and mortality. A 25-year-old woman presented with abdominal pain for four days. Previously, she had undergone two suction curettages for complete hydatiform moles. Ultrasound revealed a non-viable fetus with an estimated gestational age of 21 weeks and free fluid and coagulum in the abdominal cavity. An emergency laparotomy was performed because of the acute abdomen. At exploration, the placenta had invaded the entire thickness of the myometrium and the non-viable fetus was in the abdominal cavity. The uterus was closed with a double-layer of interrupted sutures and uterine-sparing surgery was performed. The patient was discharged on postoperative day seven. The authors present a case of placenta-percreta in an unscarred uterus complicated with uterine rupture during the second-trimester that was managed successfully with uterine repair. They also review the literature briefly and discuss similar cases managed conservatively in the second-trimester.

Key words: Placenta percreta; Uterine rupture; Second trimester; Unscarred uterus; Uterine preservation.
male fetus, at nearly 21 weeks gestation; the uterine body had rup-
tured anteriorly. The placenta had invaded the entire myometrium
(Figure 1). The placenta was extracted from the ruptured part of
the uterus and curettage was performed to remove the rest of
the placenta. The uterine defect was closed with a double layer of in-
terrupted sutures. During the operation, she was infused with
2,000 ml colloid and crystalloid solutions, three units of red blood
cells, and two units of fresh frozen plasma. The patient was dis-
charged seven days postoperatively.

Discussion

The incidence of abnormal placentation ranges from one
in 540 to one in 93,000 and averages one in 700 [7]. Pla-
centa percreta, which is the rarest form of placenta accreta,
comprises five to seven percent of abnormal placentation
[3, 7, 8]. In most cases, placenta percreta is diagnosed in the
third trimester of pregnancy because of a massive post-
partum hemorrhage in an attempt to remove the placenta
or during subsequent curettage. Spontaneous uterine rup-
ture has been reported in all trimesters and most of the pa-
tients have a history of cesarean delivery or medical
induction of labor [7-10].

Beuker et al. [11] reported a relationship between suction
curettage and subsequent placenta accreta. They observed
myometrium in the products of conception in 44% of ter-
minal tissues and 35% of miscarriage tissues, and fre-
quent endomyometrial injury with vacuum termination or
dilatation and curettage after miscarriage, although the re-
lationship with subsequent placenta accreta was unclear.
The present patient had no history of cesarean delivery or other
major risk factors for placenta percreta, but she had
undergone two suction curettages for hydatiform moles.

The treatment of placenta percreta varies. The treatment
options include surgical removal of the uterus or conserva-
tive therapy. Generally, the main treatment is emergency
hysterectomy in most of the cases with scarred [4, 7-10] and
unscarred uterus [1, 2, 12-15] at all trimesters. Arulkumaran
et al. [16] first described the conservative method in 1986.
This involves leaving the placenta in situ with packing, uter-
ine curettage with packing, closing the uterine defect, lo-
ocalized excision and uterine repair, uterine packing with
uterine or hypogastric artery ligation, and leaving the pla-
enta in situ with adjuvant chemotherapy [3, 16, 17]. In an-
other study, [17] surgical methods for uterine conservation
were successful in 50 of 68 cases with anterior placenta
percreta; of the 42 successful cases that were followed over
a three-year period, ten subsequently became pregnant and
underwent uneventful cesarean sections. This paradigm
shift in treatment has been facilitated by the development
of methods for controlling blood loss during surgery, such as
embolization, ligation, and balloon occlusion of the arterial
supply, as well as the increased availability and safety of
blood transfusions, either from autologous or donor sources,
and modern intensive care [1, 3, 17].

The choice between hysterectomy and conservative ther-
apy also depends on the severity of the placenta percreta
and any additional complications. Reported complications
of placenta percreta include severe potentially life-threat-
ening bleeding, and the invasion of neighboring organs,
such as the urinary bladder, by the placental villi [18]. In
another study that used conservative methods, [6] when pla-
cental retention was allowed, the hysterectomy rate de-
creased from 84% to 15%. The placenta percreta cases in
unscarred uterus complicated with uterine rupture at sec-
ond trimester and managed conservatively by uterine re-
pair are summarized in Table 1 [3, 19-22]. The present case
shows that uterine conservation is feasible when hemosta-
sis is obtained by suturing and the patient wishes to remain
fertile. With the increasing number of cesarean deliveries,
the authors believe that the management of these life-threat-
ening cases will be more important in the future.

Conclusion

Spontaneous rupture is usually seen with vaginal birth
after cesarean or uterine anomalies in early pregnancy. The
authors believe that if a patient has risk factors for placenta accreta, a close investigation of the uterine wall and placentation should be performed in the first trimester to anticipate placenta percreta. The patient has to be informed about the treatment options and their possible consequences, such as the risks of sepsis and delayed hemorrhage that might occur when the uterus is conserved and the placenta is left in situ. Uterine conservation also requires a multidisciplinary team, including the obstetrician, intervention radiologist, anesthetist, urologist, and general surgeon in some cases. If a hysterectomy is performed during the operation, excess bleeding must be prevented by leaving the placenta in situ during the surgery. The classical incision can increase the exposure when abnormal bleeding occurs. Postpartum counseling about the risk of rerupture with subsequent pregnancies is important and it must be kept in mind that this condition is not always associated with prior uterine scar and disorders of placentation. The authors also suggest that all curettages be performed with prior uterine scar and disorders of placentation. The authors also suggest that all curettages be performed with prior uterine scar and disorders of placentation. The authors also suggest that all curettages be performed with prior uterine scar and disorders of placentation.

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Conjoined twins: three cases in one tertiary medical center and literature review

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Summary
Conjoined twins are so rare that most obstetricians will not be personally exposed to such cases during their professional lifetimes. The authors report three cases including one of dicephalic parapagus conjoined twins and two thoracopagus conjoined twins in the present tertiary medical center, and discuss the diagnosis and management details. They also review the incidence, embryological, diagnostic, obstetrical, and prognostic aspects of conjoined twins. Regular antenatal visits and serial ultrasound scanning are crucial for early diagnosis of conjoined twins, optimal obstetric management and perinatal preparation still remain challenging, and multidisciplinary cooperation is urgently needed.

Key words: Conjoined twins; Dicephalic parapagus; Thoracopagus; Prenatal diagnosis.

Introduction
Conjoined twins are very rare and associated with high perinatal mortality. It occurs once in every 50,000 to 100,000 births [1]. Accurate prenatal diagnosis of conjoined twins is possible in early pregnancy if the patients have regular antenatal visits and serial ultrasound scanning. However, a few of conjoined twins were detected during the third trimester or just before labor, and this makes obstetric management more complicated. The authors report a case of dicephalic parapagus conjoined twins and another two cases of thoracopagus conjoined twins.

Case Report
Case 1: Dicephalic parapagus
A 19-year-old unbooked primigravida, presented for prenatal care at 37 weeks’ gestation. Unlike other mothers, she had had no previous antenatal medical evaluation. Ultrasound examination during the first prenatal visit revealed conjoined twins. The abdominal ultrasonography showed a breech fetus with two heads, three arms, single thorax, two hearts (one of which with complete type endocardial cushion defect), single abdomen, single liver, double vertebra, and two legs. The amount of amniotic fluid was normal. According to these ultrasound findings, dicephalic parapagus conjoined twins was diagnosed. In view of the fact that the pregnancy was already full term, and given the poor prognosis, the decision was made to proceed with delivery of the babies via cesarean section. The authors performed cesarean section for the patient, because in this situation vaginal delivery is impossible for the full-term conjoined twins in breech presentation. An experienced obstetrician accomplished the operation and she chose the lower uterine segment incision. The whole process was completed without complication.

Case 2: Thoracopagus
A 24-year-old, G2P0 female presented to the department of obstetric care at 24 weeks’ gestation. She had two healthy children, and denied the intake of any medication during pregnancy. Routine antenatal laboratory investigations were all normal. However, the routine screening of ultrasound revealed conjoined twins. The twins, facing each other, were joined at the thoracic level. Each had a separate set of structures except for a shared heart and anterior chest wall. A thoracopagus conjoined twin pregnancy was diagnosed.

Since the fetuses were thought previable and having poor prognosis, the parents opted for immediate termination of pregnancy. Ethacridine lactate was administrated to the patient by amniocentesis. Two days later, the conjoined twins were delivered, which weighed 1,270 grams. The patient had no any severe genital tract laceration. It was seen that the twins were united from the upper thorax down to the umbilicus with the presence of cheiloplatanognathus. The upper and the lower limbs with normal morphology were in appropriate locations. They had male external genitalia. The placenta was monochorionic, weighing 1,100 grams. The umbilical cord was centrally located and included two vessels (one artery and one vein). The appearance was consistent with dicephalic parapagus (Figure 1).

The conjoined twins died 50 minutes following delivery. The parents declined an autopsy.

Case 3: Thoracopagus
A 30-year-old multigravid woman (G3P2) registered for antenatal care at 24 weeks’ gestation. She had two healthy children, and denied the intake of any medication during pregnancy. Routine antenatal laboratory investigations were all normal. However, the routine screening of ultrasound revealed conjoined twins. The twins, facing each other, were joined at the thoracic level. Each had a separate set of structures except for a shared heart and anterior chest wall. A thoracopagus conjoined twin pregnancy was diagnosed.

Since the fetuses were thought previable and having poor prognosis, the parents opted for immediate termination of pregnancy. Ethacridine lactate was administrated to the patient by amniocentesis. Two days later, the conjoined twins were delivered, which weighed 1,270 grams. The patient had no any severe genital tract laceration. It was seen that the twins were united from the upper thorax down to the umbilicus with the presence of cheiloplatanognathus. The upper and the lower limbs with normal morphology were in appropriate locations. They had male external genitalia. The placenta was monochorionic, weighing 260 grams. There was a single umbilical cord with three vessels (two arteries and one vein) (Figure 1). No autopsy was done due to the objection of the family.

* Revised contributed equally to this work.
screening ultrasound revealed conjoined twins. The two fetuses with a single heart were fused at chest and abdomen. Two separate spines were seen. Amniotic fluid was normal and there was a single placenta. All confirmed the diagnosis of thoracopagus conjoined twins. Since premature rupture of membrane occurred, cesarean section was carried out to deliver the twins. The doctor chose lower uterine segment incision. The operation went very well. The two female infants both had Apgar scores of 5, 7, and 9 at one, five, and ten minutes, and had a combined weight of 3,450 grams. The pediatrician intubated the twins and examined them carefully. They were fused from upper thorax down to the umbilicus with the presence of obvious gastrochisis. Each baby had respective arms and legs in the right positions, while only one heartbeat was palpable. There was a single placenta with two separate umbilical cords (one artery and one vein respectively), which coincided at a distance of ten centimeters from placenta (Figure 1).

The conjoined twins died six hours after delivery since the parents refused any advanced medical assistance. Autopsy was declined by the family.

Discussion

Incidence

Conjoined twins are monoamniotic, monochorionic, and monozygotic twins. They occur once in every 50,000-100,000 births [1], although it is speculated that many may result in a spontaneous abortion. Many authors reported a higher incidence of conjoined twinning in females, which is approaching 75-90% [2].

Etiopathogenesis

The exact etiology of conjoined twins is unknown. Zeng et al. reported that genetic or environmental factors other than abnormal X-inactivation must be involved in causing conjoined twins [3]. Steinman reported that a significant number of women with conjoined twins pregnancy were subjected to environmental triggers, such as preconceptional weight, use of oral contraceptives, and so forth [4].

There are two important theories proposed to account for the origin of conjoined twins. One involves the incomplete fission of a single embryonic disc, which occurs 13 to 15 days after the ovum is fertilized. The other is that two embryonic discs unusually unite. The latter theory is postulated on the fact that the ovum undergoes fission before the notochord develops, and there are separated notochords in most conjoined twins [5].

Classification

Conjoined twins are classified on the basis of site of union. Ventral unions account for 59% and are classified as: cephalopagus (11%), thoracopagus (19%), omphalopagus (18%), and ischiopagus (11%). Lateral unions, also described as parapagus, account for 28%. Dorsal unions occur in 13% of conjoined twins and are classified as: craniopagus (5%), rachiopagus (2%), and pygopagus (6%) (Table 1) [6].

Figure 1. — Conjoined twins (Case 1–Case 3).
Conjoined twins: three cases in one tertiary medical center and literature review

An amniotic membrane, constant relative positions, presence of fetal anomalies, and the identifications of more than three vessels in a single umbilical cord [8]. Polyhydramnios occurs in 50-76% of cases. Detailed scanning around 20 weeks’ gestation will demonstrate the extent of the conjoined area and provide an assessment of prognosis [9].

In the present cases, because all the families had chosen delivery proceeding or pregnancy termination, further diagnostic intervention like magnetic resonance imaging (MRI) has not been considered. MRI is an important adjunct to ultrasound, particularly in the evaluation of complex fetal anomalies. With its ability to differentiate soft tissues, MRI can provide excellent detail, increased tissue contrast, and reproducible fetal anatomy [10]. Prenatal MRI has also recently been found to be of value in planning for an extrauterine intrapartum procedure and immediate separation [11].

Delivery

Once the antenatal diagnosis of conjoined twins is made, the mode of delivery must be considered thoroughly to avoid obstructed labor and morbidity for mother and fetus. If the twins are considered to have poor survival chances, termination of pregnancy should be offered prior to viability. Beyond viability, pregnancy termination may or may not be possible, depending on the laws of each country. Vaginal delivery is recommended when the twins are dead or pre-term, but cesarean section may be required if the twins are large [12]. Although there are many reported successful vaginal deliveries of conjoined twins, selective cesarean section is the preferred method of delivery with near-term-sized twins, even if the fetuses are dead [13]. To avoid maternal trauma, craniotomy, decapitation, evisceration or amputation may be needed in some circumstances.

Prognosis

Approximately 40% of conjoined twins are stillborn and 60% liveborn, only about 25% of those that survived can live long enough to be considered for surgical separation [14]. Survival of conjoined twins depends largely on the site of fusion and the organs involved. Surgical separation is one of the options, which may be successful if organs critical for life are not shared. The surgery may also cause death of one twin to allow independence alive for the other. However, no surgical separation should be considered in the presence of complex cardiac fusion or where there would be a severe unacceptable deformity following separation (Table 1) [9].

Once the decision to proceed with the pregnancy is made, delivery should be planned to take place at or close to the surgical unit where separation will be performed. Surgical separation of conjoined twins involves communication, coordination, and multidisciplinary planning by a specialized team. On the other hand, the postpartum psychosocial counseling for the parents should be provided [15].

The parents in first and third cases declined any resuscitative efforts for the conjoined twins, as the prenatal assessments were insufficient. The babies were believed to be unlikely to survive.

Conclusion

The authors have reported three cases of conjoined twins with pictures in the present tertiary medical center, which are very rare and valuable. Early diagnosis is critical for optimal obstetric and perinatal management. The delivery option is determined by the complexity of union and the size of twins. The prognosis depends on the extent of organ sharing, and surgical separation may lead to an independent life for twins.
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Asymptomatic spontaneous complete uterine rupture in a term pregnancy after uterine packing during previous caesarean section: a case report

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Summary
Uterine rupture is a life-threatening obstetrical complication with significant neonatal and maternal morbidity. The authors report a 36-year-old woman with a history of previous caesarean section because of pre-eclampsia and antepartum haemorrhage at 31 gestational weeks during her first pregnancy. Postpartum haemorrhage occurred and the uterine cavity was packed with gauze for reducing blood loss. After two years, she underwent elective, repeat caesarean section at 38+1 gestational weeks because of mild pre-eclampsia and massive antepartum haemorrhage due to placental abruption. After the placenta was delivered, postpartum haemorrhage occurred. The uterine cavity was completely packed with gauze, without any dead space. The uterine incision was closed with continuous, unlocked double-layer sutures. A live baby was delivered. The postoperative course was uneventful. Uterine dehiscence and rupture should be suspected in the presence of risk factors such as previous caesarean section, especially uterine packing involved. Spontaneous silent rupture can occur in women without any alarming symptoms.

Key words: Uterine rupture; Pregnancy; Caesarean section.

Introduction
Uterine rupture is a life-threatening obstetrical complication with significant neonatal and maternal morbidity [1-3]. To the authors’ knowledge, full-term live birth after scar rupture due to uterine packing during a previous caesarean section has never been reported.

Case Report
A healthy, 36-year-old woman (gravida 2, para 1) underwent elective, repeat caesarean section at 38+1 gestational weeks. She had regular menstruation, no gynaecological history and no history of injuries predisposing to uterine scarring, such as perforation, uteroplasty, myomectomy, and cornual resection. In February 2011 during her first pregnancy, an emergency, low-transverse caesarean section was performed at 31 gestational weeks because of mild pre-eclampsia and massive antepartum haemorrhage due to placental abruption. After the placenta was delivered, postpartum haemorrhage occurred. The uterine cavity was completely and uniformly packed from fundus to cervix with a three-meter-long, four-cm-wide sterile gauze, without any dead space. The uterine incision was closed with continuous, unlocked double-layer sutures. The gauze was removed through the vagina 24 hours later. Late postpartum haemorrhage and puerperal infection did not occur. After delivery, her menstruation was regular.

She became pregnant for the second time after using contraception for one year. Regular prenatal examinations were begun at 17 gestational weeks in the present obstetric department. After 20 weeks, she was administered 50 mg aspirin and two grams of calcium daily to dredge the microcirculation and prevent vasospasm. The antenatal period was uneventful, with normal blood pressure and urine protein levels. She had no lower abdominal pain/tenderness or vaginal bleeding. Ultrasonography revealed adequate amniotic fluid volume and no fetal abnormalities. On December 5, 2012, she was hospitalized for an elective caesarean delivery. No fetal heart rate abnormalities or clinical symptoms such as abdominal pain, vaginal bleeding, hypertonia, and acute uterine contractions were present. The following parameters were noted on admission: blood pressure, 110/70 mm Hg; pulse, 76 beats/minute; symphysis-fundal height, 36 cm; haemoglobin, 120 g/l; and fetal heart rate, 144 beats/min. Caesarean section was performed on the day of admission. On incising the parietal peritoneum, a six- to seven-cm-long defect was found in the lower uterine segment, with complete separation of the uterine scar and disruption of the visceral peritoneum (Figure 1A). Unlike fresh rupture wound, the defect edges were older fibrous tissues without bleeding (Figure 1B). The intact amniotic sac containing the fetus, clear amniotic fluid and vernix, was exposed through the defect. A live baby girl was delivered with a one-min Apgar score of 10 and birth weight of 3.3 kg (Figures 1C–E). After the uterus was sutured in double layers, it firmly contracted, with no abnormal blood loss. The postoperative course was uneventful; she was discharged after three days.

Discussion
The median incidence of uterine rupture worldwide is 5.3/10,000 births [4]. Uterine rupture commonly manifests as fetal distress, abdominal pain, scar tenderness and vaginal bleeding, and rarely, as massive haemorrhage and hypovolaemic shock [5]. Asymptomatic, spontaneous, complete rupture at term is rare [6]. The present patient had a clinically silent uterine rupture, followed by a live birth, with no maternal complications. As the uterine scar from the previous caesarean section chronic ruptured, its defective edges formed fibrous tissues and the fetal membrane was suffi-
ciently tenacious to prevent rupture of membranes causing serious maternal or fetal complications.

Common predisposing factors for uterine rupture are previous caesarean section, uterine trauma, myomectomy or other uterine surgeries, uterine evacuation, manual removal of the placenta, and congenital uterine abnormalities. Uterine packing, a safe and effective technique for controlling intractable haemorrhage during caesarean section [7], is a previously unrecognized risk factor. Uterine packing can cause muscle stretching, especially, at the incision site, leading to poor healing. With uterine enlargement and increased intrauterine pressure during subsequent pregnancy, the lower segment gradually thins and lengthens, leading to scar dehiscence, which may progress to complete rupture.

Suture technique, quality of suture material, and physician’s operative experience are possible factors that determine the tensile strength of the resultant uterine scar during subsequent pregnancies. Locked, but not unlocked, single-layer closure has been associated with a higher uterine rupture risk than double-layer closure in women attempting a trial of labour in a future pregnancy [8]. In case of uterine packing, it is unclear whether continuous unlocked double-layer closure should be performed using a stronger suture material or whether a different suture technique should be used.

In conclusion, uterine dehiscence and rupture should be suspected in the presence of risk factors such as previous caesarean section, especially, when involving uterine packing. Spontaneous silent rupture can occur in women without any alarming symptoms.

References


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A case of uterine rupture in mid-trimester spontaneous abortion: a complication of gemeprost vaginal administration

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Summary
The only prostaglandin analogue licensed in Italy for induction of labour in spontaneous and therapeutic abortion is gemeprost. The authors report a case of spontaneous uterine rupture of a scarred uterus, for previous caesarean sections, in a woman at 20 weeks of gestation with a diagnosis of spontaneous abortion. She received a pessary of gemeprost every three hours. After the fifth pessary, she complained of severe pain. At the ultrasound examination, uterine cavity appeared empty and the dead fetus was dislocated in the abdomen. Emergency laparotomy was performed and uterine tear was repaired. To induce labour for fetal demise or therapeutic abortion in second trimester in women with scarred uterus, the authors decided to lengthen the time between administrations of pessary from four to five hours depending on patient’s symptoms. However the appropriate drug regimen has still to be found and more data are necessary.

Key words: Gemeprost; Spontaneous abortion; Uterine rupture.

Introduction
An increased rate of caesarean section has been registered worldwide in last decades [1, 2]. At the same time, a growing request for prenatal diagnosis and an improvement of prenatal diagnostic techniques allowed the detection of a higher number of fetal anomalies early in gestation [3]. Obstetricians have often to face labour induction in the trimester in women with a uterine scar. A potentially life-threatening complication in these patients is uterine rupture [4]. The rate of uterine rupture seems to vary in relation to many factors: medications used, week of gestation [4] and regimens [5]. The only prostaglandin analogue licensed in Italy for induction of labour in spontaneous and therapeutic abortion is gemeprost [6]. It is administered in the posterior fornix of vagina in a cycle of five doses usually at three- to six-hour intervals. It normally causes a softening and a dilatation of cervix, and growing uterine contractions that cause fetal expulsion. The authors describe a case of uterine rupture after administration of five pessaries of gemeprost in a case of spontaneous abortion in a woman at 20 weeks of gestation.

Case Report
A healthy 30 year-old woman, gravida 3, para 1, at 13 weeks of gestation, was referred to the present centre of Prenatal Diagnosis for a fetal urogenital anomaly detected during a routine scan in the first trimester. The pregnant woman had no past medical history of note, except an appendectomy in childhood. Her obstetrics history consisted in a voluntary termination of pregnancy in the first trimester and in two previous caesarean sections, ten years and eight years before, respectively. Ultrasound examination confirmed the presence of a severe urogenital malformation: mega bladder occupying all fetal abdomen was visualized. Biometry of fetal limbs was inferior to the mean for gestational age while cephalic biometry was normal. No further fetal anomalies were noted. An amniocentesis, performed at 16 weeks of gestation, showed a normal male karyotype, 46 XY. The patient underwent multidisciplinary counselling with obstetrics, geneticist, and paediatric surgeon that explained the grave prognosis of this malformation. The couple decided to continue the pregnancy. A sonographic examination at 19 weeks of gestation showed a worsening of fetal condition: mega bladder measuring 74 x 77 mm, bilateral dilated urethras, and hyperechogenic kidneys were visualized. Amniotic fluid was inferior to the mean. The next week during a routine scan no fetal heart activity was registered and a diagnosis of spontaneous abortion was confirmed. The woman was admitted to the present department for induction of labour. Preliminary obstetrics examination revealed a uterine size consistent with gestational age. Cervix was long, tubular, and closed. Blood test was normal. The patient was counselled for induction of labour with gemeprost. She signed consent form for the induction protocol. Five pessaries of gemeprost (one pessary every three hours) were administered in the posterior vaginal fornix. After the third pessary, the woman complained of pain and analgesia was prescribed. After a pause of five hours, the fourth and fifth pessaries were administered, three hours apart. Obstetric examination showed a contracted uterus with a cervix that was long and closed. It was decided to wait at least 12 hours before beginning a new cycle of gemeprost. After two hours from the last administration, the patient complained of important abdominal pain. Blood pressure was 80/40 mm Hg, pulse was 110 beats per minute and the uterus was tender, not contracted, with fundus two cm over the transumbilical plane. There was a minimal vaginal bleeding with clots. An obstetric ultrasound showed that the uterine cavity appeared empty and the dead fetus was dislocated in abdomen under left costal arch. Hemoperitoneum was present. Emergency laparotomy was performed. While opening the abdomen, a tear on the left lateral surface of the uterus was visualized extending into the homolateral broad ligament. From the breach extruded the umbilical cord while the gestational sac with the dead fetus was dislocated in the left hypochondriac region. The

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placenta, still fixed to the uterus, was manually removed from the fetus. The uterine tear was repaired. Two intraperitoneal drainage tubes were positioned. Emergency blood test showed severe anaemia. Volume replacement therapy was necessary (seven units of packed red blood cells, six vials of albumin, antithrombin III - 1,000 IU).

The patient had a rapid revival and an uneventful postoperative recovery. She was discharged ten days later in good clinical conditions. Her blood test was normal. The gynaecological examination showed a regular uterus with a thin endometrium and minimal fluid in the Douglas cavity.

Discussion

Uterine rupture is a catastrophic complication that often results in hysterectomy and can occur in a scarred or an unscarred uterus during induction of labour [4]. The reported incidence of uterine rupture in women without scarred uterus is 0.2% [7], compared to 3.8% - 4.3% risk of scar rupture of the uterus [7, 8]. Recently, a large retrospective analysis of gemeprost-induced termination of pregnancy, after previous caesarean delivery, was performed. The authors concluded that using gemeprost in late gestation for medically induced labour in women with a uterine scar seems to be effective and safe [9]. This is in compliance with the clinical guidelines from the Society of Family Planning for labour induction abortion: there is no clear evidence of an increased risk of uterine rupture with labour induction abortion in women with one prior cesarean delivery; for women, who had multiple cesarean deliveries, there are no data to make evidence-based recommendations [4]. Pregnancy with fetal demise may be treated similarly to abortion of a living fetus. However, the dosage usually necessary to cause fetal expulsion is lower, and the induction process is typically shorter [4].

The typical patients with uterine rupture are older and multiparous, have had an initiation-to-abortion interval > 24 hours, have received oxytocin for > 12 continuous hours, had a gestation age > 21 weeks [7]. Using one uterotonic agent at a time should help reducing the chance of uterine rupture, particularly in women with a history of uterine surgery [6]. The present patient was young and only one uterotonic was administered for induction of labour. She was closely monitored, above all for pain and long initiation-to-abortion interval. As soon as she developed the most common signs and symptoms of uterine rupture (cessation of contractions, abdominal pain, vaginal bleeding, maternal cardiovascular instability), quick decisions were made and her life and uterus were saved.

What was, therefore, missing? How can we predict which woman will experience a uterine rupture? To induce labour for fetal demise or therapeutic abortion in second trimester in women with scarred uterus, the authors decided to lengthen the time between administration of pessary from four to five hours depending on patient’s symptoms. However, many more data are required about induction in the second and third trimester in scarred uterus. The appropriate drug regimen has still to be found.

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**Irreducible inguinal hernia containing rudimentary uterine horn, ovary, and fallopian tube**

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**Summary**

The authors present a typical case of inguinal hernia containing rudimentary uterine horn, ovary, and fallopian tube. During the operation of herniorrhaphey the right ovary and fallopian tube with rudimentary uterine horn were found in the hernia sac. The woman underwent laparoscopic hysterectomy three months before herniorrhapsy and was diagnosed with unicorneate uterus. The authors reviewed the case and suggested that detailed examination such as gynecological examination and magnetic resonance imaging be performed routinely in those females with inguinal hernias.

**Key words:** Inguinal hernia; Uterus; Ovary; Fallopian tube.

**Introduction**

Iguinal hernia containing rudimentary uterine horn, ovary, and fallopian tube is rare. Most of the cases are female infants [1-5] and reported by gynaecologists. Usually general surgeons are not familiar with this condition. The authors present a typical case of an adult whose diagnosis was confirmed intraoperatively.

**Case Report**

A 40-year-old woman was admitted to the present hospital with an irreducible right inguinal mass for more than ten years. She denied pain in inguinal region. Her menstruation period was normal. Three months prior she underwent a laparoscopic hysterectomy due to uterus leiomyoma and the recovery was good. During this operation, no right uterine adnexa could be found and unicorneate uterus was diagnosed postoperatively.

On physical examination a hard irreducible mass without tenderness was palpated in the right groin. Ultrasonography revealed a long hypoechoic mass leading to the abdomen. The mass was movable and there was no visible peristalsis. A diagnosis of irreducible inguinal hernia was considered and exploration of the inguinal region was performed. During the operation, the right ovary and fallopian tube with rudimentary uterine horn were found in the inguinal canal (Figure 1). The hernia contents were reduced to abdomen under the consultation of the gynaecologists. High ligation of the hernia sac and tension-free herniorrhaphy were performed with a preperitoneal prosthesis. The patient recovered uneventfully after operation.

**Discussion**

The first case of inguinal hernia containing uterus and uterine adnexa was reported by Deutschman in 1923 [6]. Riggall et al. named such condition “hernia uterus inguinale” [7]. Although unicorneate uterus in abdomen is not rare, the presence of a rudimentary uterine horn and adnexa in inguinal sac is uncommon for most surgeons. The incidence of an ovary in the hernia sac is reported to occur in about 4% of asymptomatic girls [8]. Failure of the fusion of bilateral Müllerian ducts resulted in the formation of unicorneate uterus. Such condition was reported frequently associated with vaginal agenesis and renal abnormalities [9].

Herein, the authors report an adult case of an irreducible indirect inguinal hernia containing rudimentary uterine horn, right ovary, and fallopian tube. She has a daughter and her menstruation was regular. No vaginal and renal agenesis were found on examination. During the operation of herniorrhaphy the unicorneate uterus and right adnexa were approved by a gynecologist. It reminded us to review the history of the hysterectomy and found the unicorneate uterus was diagnosed at that time. It was difficult to make the definite diagnosis preoperatively just according to the physical and ultrasonographic examinations. Most reported cases were diagnosed during the herniorrhaphy. Although rare, it was important for general surgeons to be aware of genital tract abnormalities that may present in the inguinal canal. Some of those cases were accompanied by an ipsilateral renal anomaly. For this woman the renal abnormality and gynecological disease were excluded through detailed examinations.

The present authors selected the open procedure for this patient considering the inguinal mass was irreducible. Generally resection of the rudimentary uterine horn was suggested considering the risk of ectopic pregnancy [10]. For this patient, the authors reduced the hernia contents to peritoneal cavity because it was non-functioning and non-communicating.

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In summary, an accurate preoperative diagnosis of inguinal hernia contents is very important. The authors suggest that careful examination such as gynecological examination and magnetic resonance imaging be performed routinely in those females with an indirect inguinal hernia containing an asymptomatic palpable mass.

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