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Premenstrual syndrome (PMS) is defined as recurrent moderate psychological and physical symptoms that occur during the luteal phase of menstrual flow and resolve with menstruation [1-5]. Symptoms must be linked to the luteal phase, beginning sometimes after ovulation, and ending by the conclusion of the menstrual flow, with a symptom-free interval before the next subsequent ovulation [1-5]. Physical symptoms of this disorder include headaches, breast tenderness, abdominal bloating, peripheral edema, and general fatigue, while psychological or behavioral disorders include irritability, mood swings, food cravings, social withdrawal, anxiety, and depression. While definitive diagnosis of these disorders remains debatable, a prospective record of cycle related symptoms is the gold standard for diagnosis by establishing a relationship between the symptoms and the late luteal phase of the menstrual cycle. Retrospective, self-reporting of symptoms is found to be reasonably sensitive [6, 7]. Up to 80 percent of women report one or more physical, psychological or behavioral symptoms during the luteal phase of their menstrual cycle without experiencing substantial disruption to their daily functioning [1, 8]. PMS, in which mild to moderate symptoms affect some facet of the woman’s life, occurs in 20 to 30 percent of premenopausal women; the more severe symptoms of premenstrual dysphoric disorder (PMDD) affect up to eight percent of premenopausal women [1, 8]. PMS and PMDD have been shown to negatively affect relationships, work attendance, productivity, and health care costs and utilization. [1, 9] This article aims to review the current understanding of the pathophysiological mechanisms underlying the premenstrual disorders. The role of serotonin is addressed in some detail because serotonergic antidepressants, selective serotonin reuptake inhibitors, are well-established, highly effective, and first-line pharmacologic therapy.

Etiology

The etiologies of PMS/PMDD are not definitive, but several candidate factors responsible for provoking symptoms of PMS are postulated (Table 1).

Progesterone

Women with PMS/PMDD appear to have more symptoms with normal cyclic levels of sex steroids [10]. In women whose normal cycles were blocked with administration of a gonadotropin-releasing hormone analog (GnRH), high doses of transdermal estrogen, and bilateral oophorectomy all have positive evidence as treatment options for prevention of PMS. However, because of these limitations and their substantial intensive care, these do not appear to be appropriate methods for conventional treatment of PMS. Serotonergic antidepressants, selective serotonin reuptake inhibitors, are well-established, highly effective, and first-line pharmacologic therapy.
Table 1. — Proposed pathophysiological mechanisms underlying premenstrual disorders.

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There is a number of studies suggesting oral contraceptive pills, regardless of the elimination of ovulation, can be associated with PMS-like negative affective and physical symptoms such as irritability, depression, anxiety, bloating, fatigue, and breast tenderness in a subset of women [11]. Taken together, the factor responsible for provoking PMS symptoms has been attributed to the exogenous progestogen and endogenous progesterone.

The role of progesterone in triggering adverse symptomatology is not straightforward. Compelling evidence points to the role of progestogen in the pathophysiology of PMDD. For example, PMS symptoms are absent during pregnancy, in spite of high sex steroid concentrations. In multiple studies, measurement of serum progestogen in women with PMS compared with controls failed to show any significant differences [1, 2, 12-14]. The most plausible explanation is that the classical progesterone receptor is not involved in this process. This proposal may be supported by lack of reduction in physical or behavioral manifestation of PMS with administration of the progesterone receptor antagonists, mifepristone [15].

γ Amino butyric acid (GABA)

Neurotransmitters, particularly serotonin and GABA, appear to be involved in PMS manifestations. The main inhibitory neurotransmitter in the brain, GABA, is a widely distributed neurotransmitter in the central nervous system and evidently is an important regulator of stress, anxiety, vigilance, alertness, and seizures [16, 17]. GABA is derived from glutamate by glutamic acid decarboxylase exclusively found in GABAergic neurons. Three subtypes of GABA postsynaptic receptors have been identified: GABA-A, GABA-B, and GABA-C. However, it is the GABA-A receptor that is the site of action of endogenous agents such as neuroactive steroids derived from progesterone or synthesized de novo in the central nervous system, as well as exogenous agents such as progestogens after metabolism to reduced steroids), benzodiazepines, barbiturates, alcohol, and anticonvulsants [18, 19].

In the ovary and the brain, progesterone is metabolized to form the potent neuroactive steroids, 3α-hydroxy-5α-pregnan-20-one (allopregnanolone) and 3α-hydroxy-5β-pregnan-20-one (pregnanolone) [16]. These metabolites act as positive allosteric modulators of GABA transmitter system in the brain [2, 16]. There is strong evidence that acute effects of the neurosteroids are not related to interactions with classical steroid hormone receptor that regulate gene transcription. However, chronic effects of neurosteroids are due to genomic (classical intracellular steroid receptors) and non-genomic rapid actions (ion channels and membrane receptors) in the brain. Furthermore, the genomic effects of neurosteroids are mainly due to their metabolic interconversion to traditional steroids. Overall, neurosteroids are not themselves active at intracellular steroid receptors. They modulate brain excitability primarily by interaction with neuronal membrane receptors and ion channels [16]. Finally, neurosteroids have been demonstrated to directly modulate the activity of ligand-gated ion channels, most notably GABA-A receptor [20].

Progesterone-derived neurosteroids may be important for the clinical manifestations of PMS [21, 22]. In normal women, allopregnanolone varies similar to progesterone throughout the menstrual cycle with greater levels in the luteal phase than in the follicle phase [23]. Thus, allopregnanolone could play an important role in the pathophysiology of PMS. Serum concentrations of progesterone metabolite allopregnanolone during the luteal phase are lower in women with PMS [24, 25] and withdrawal from progesterone (allopregnanolone) increases anxiety in animal models [26]. Both at baseline and after stress, an enhanced ration of allopregnanolone/cortisol has been reported [25]. There is a marked insensitivity to benzodiazepine therapy in patients with PMS [27], which might be due to the development of cross-tolerance between benzodiazepines and neurosteroids. Although neurosteroids represent promising approach for PMS, natural progesterone supplementation in women with PMS has no clear beneficial affect [28]. This could be due to several reasons, such as hormone side effects, disruption of ovarian rhythms or conversion of progesterone to other neurosteroids with negative properties [16].

The alterations in GABA-A subunit configuration and GABAergic activity likely contribute to the negative mood symptoms associated with PMS [29].

Serotonin

Amines (e.g. serotonin (5-hydroxytryptamine), histamine (1H-imidazole-4-ethanamine) and melatonin (N-acetyl-5-methoxytryptamine)) within the brain have been implicated in the modulation of mood, eating, arousal, and circadian rhythms. In particular, changes in serotonin level overlap symptoms associated with reduction in serotonin transmission. Biochemically derived from tryptophan, serotonin is primarily found in the gastrointestinal tract, platelets, and in the central nervous system of animals and humans. It is popularly thought to be a contributor to feelings of well-being and happiness. Serotonergic function has been shown to be altered during the luteal phase of menstrual cycle in women with PMS [2, 5, 12, 13, 30-35]. Serotonin depletion leads to anxiety and depressive-like symptoms. Serotonin turnover is also modulated in part by ovarian sex steroids. Ovarian sex steroids have also been implicated in serotonin uptake, turnover, binding, and transport [36, 37].

Serotonergic activity in the brain is affected by estrogen and progesterone; specifically sex steroids can modify serotonin availability at the neuronal synapses. For example, estrogen has been shown to increase degradation of monoamine oxidase (MAO), enzyme responsible for oxidation of monoamines [38]. Estrogen’s role in increasing degradation of MAO and COMT results in augmenting action of serotonin in regulating the availability of free tryptophan in the CNS and improving clinical effect of selective serotonin re-uptake inhibitors (SSRIs). In contrast, progesterone and its metabolites increases MAO activity, therefore decreases 5-HT availability, which may result in depressed mood (Figure 1) [39-42].
Treatment

As noted above, PMS does not occur during anovulatory cycles or in women who have undergone bilateral oophorectomy. Thus, ovulation suppression is an area of focus for diagnostic and treatment options. Many treatment studies have focused on suppression of ovulation with oral contraceptives, GnRHa, high doses of transdermal estrogen and bilateral oophorectomy all have positive evidence as treatment options for prevention of PMS and PMDD. Table 2 lists current evidence-based treatment for PMS.

1. Nonpharmacologic

Lifestyle modifications

Although some physicians recommend increasing exercise of decreasing intake of caffeine, salt, and refined sugar for PMS symptom relief, no current evidence substantiates these recommendations. Improved diet and exercise should be recommended for good health, but not as evidence-based treatment for PMS/PMDD [1].

Bilateral oophorectomy and/or hysterectomy

In order to eliminate ovarian function, women may desire to proceed with bilateral oophorectomy. This approach has been shown to be effective in women with severe PMS [43-45]. If bilateral salpingo-oophorectomy is being considered as treatment modality for severe and debilitating symptoms of PMS, it may be beneficial to consider a trial of GnRHa first to establish the relative contributions of endocrine-related pathology as the etiology of symptoms versus underlying other dysfunction. After bilateral oophorectomy, it is important to replace estrogen until the age of natural menopause in order to prevent the complications of premature menopause. It may be important to perform a hysterec-

tomy at the timing of bilateral oophorectomy in order to allow women to receive unopposed estrogen replacement and to avoid recurrent progestogen-induced premenstrual symptoms with the combined hormonal replacement.
**GnRHa**

Because they suppress ovarian function, the GnRHa has been tried off-label to reduce severe physical symptoms of PMS and PMDD [46-48]. However, adverse effects, especially hot flashes and decreased bone density, limit their use to only a few months. Estrogen can be added back, but this may cause PMS and PMDD symptoms to recur [46, 49]. Because of these limitations and their substantial cost, GnRHa does not appear to be appropriate agents for the conventional treatment of PMS and PMDD.

**Estradiol**

The therapeutic effect of ovulation suppression by increasing plasma estradiol levels has been demonstrated in improving symptoms of PMS. Unopposed estrogen may lead to endometrial hyperplasia and cancer but oral progesterone may worsen symptoms of PMS [50].

**SSRIs**

Medications affecting serotonin are first-line pharmacologic treatments for severe PMS or PMDD [12, 13, 31, 32]. SSRI, taken daily or only during the luteal phase of menstruation, significantly decrease physical and psychological symptoms of PMS compared with placebo [33]. In a study of PMDD treatment with the SSRI, symptom score were reduced by at least one-half in 60 percent of participants treated with an SSRI compared with 35 percent of participants in the placebo group: 80 percent of the PMS symptom reduction with an SSRI occurred within the first month of treatment [34, 35]. SSRIs may need to be administered for three to four weeks to affect symptoms of depression: PMS symptoms, however, appear to improve more rapidly [51]. Daily use of an SSRI with an increased dose during the luteal phase, especially if PMS symptoms are comorbid with major depression or generalized anxiety, is a reasonable alternative [51].

**Discussion**

Premenstrual syndrome is defined as recurrent moderate psychological and physical symptoms that occur during the luteal phase of menses and resolve with menstruation. It affects 20 to 32 percent of premenopausal women. Women with premenstrual dysphoric disorder experience affective or somatic symptoms that cause severe dysfunction in social or occupational realms. The Daily Record of Severity of Problems is one tool with which women may self-report the presence and severity of premenstrual symptoms. Symptom relief is the goal for treatment of premenstrual syndrome and premenstrual dysphoric disorder. There are a number of principles that should be adhered to, when managing women with PMS. Even without an evidence basis, there is little doubt that reduction of stress, for instance is a great help in ameliorating symptoms. Also awareness of the condition and training in it management is essential.

The two chief evidence-based medical treatments of moderate to severe PMS are categorized by ovulation suppression by GnRHa and SSRIs. When treating women with...
severe PMS, hysterectomy and bilateral oophorectomy has been shown to curative, but they are too invasive for most patients. A suggested treatment algorithm modified from the proposal by Panay [14] is shown in Figure 2.

Discontinuation of treatment should be considered when pregnancy is contemplated, and obviously this essential if the method is contraceptive. Treatment should be continued during the perimenopause as this is a time associated with potentially worsening of symptoms, but can be tentatively withdrawn when the patient is thought to be post-menopausal. There may be a need to resume treatment if ovarian activity persists.

References


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Relevance of parathyroid hormone (PTH), vitamin 25(OH)D3, calcitonin (CT), bone metabolic markers, and bone mass density (BMD) in 860 female cases

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Institute of Osteoporosis, the Fourth Affiliated Hospital of Jilin University, Changchun (China)

Summary
Objective: To study the relevance of PTH, 25(OH)D3, CT, bone resorption markers C-terminal telopeptide of type I (CTX-1), and tartrate-resistant acid phosphatase (TRACP), bone formation markers bone gla protein (BGP), bone alkaline phosphatase (BALP) with the femoral neck BMD in females. Materials and Methods: PTH, 25(OH)D3, CT, CTX-1, TRACP, BGP, and BALP were detected by an enzyme immunoassay analyzer and femoral neck BMD were measured by a BMD detector. The results of 860 females were divided into several groups according to standard of five-year age intervals. SPSS 13.0 software was used for statistical analysis. Results: The measured values of PTH, 25(OH) D3 and CT had no differences in 35-50 age group. The measured values of 25(OH) D3 began to decline after the age of 50, and 25(OH)D3 had positive relevance with BMD. The values of CT were decreased in the age groups from 65 to 79 years old, and were significant positive correlated with BMD. The CTX-1 and TRACP had negative relevance with BMD in 35-45 age group and BGP and BALP had positive relevance with BMD in 35-45 age group. The BGP, BALP increased significantly in 50-60 age group, and CTX-1, TRACP, BGP, and BALP had negative relevance with BMD in 50-60 age group. BGP and BALP began to decline and had positive relevance with BMD after the age of 65, and CTX-1 and TRACP had negative relevance with BMD after the age of 65. Conclusions: PTH, 25(OH)D3, CT, CTX-1, TRACP, BGP, and BALP were the important technical means for monitoring the level of bone metabolism and the diagnosis and differential diagnosis of osteoporosis.

Key words: calcium and phosphorus metabolism regulation indicators, bone metabolism markers, femoral neck BMD, relevance

Introduction
Osteoporosis is a multifactorial polygenic disease, associated with low systemic bone mass, bone structure damage, reduced bone strength, and increased fracture risk [1]. Basic life activities of bone tissue are the process of bone remodeling, including bone resorption and bone formation. Bone remodeling accompanying during a person’s life, with osteoclasts and osteoblasts together complete the update process of bone tissue, that is, bone degradation and an equal amount of new bone to replace [2, 3]. Bone remodeling is in a dynamic equilibrium under normal circumstances. When bone resorption is greater than bone formation, osteopenia or even osteoporosis will occur. Bone remodeling is affected by many hormones, cellular and humoral factors, and cell metabolites. These hormones and factors play a role in bone metabolic regulation through the promotion or suppression of the development of osteoblasts and osteoclasts, and enhance or inhibit the activity of osteoblasts and osteoclast [4].
At present, domestic and international studies have shown that osteoblasts and osteoclasts metabolic product, cytokines and humoral factors, and bone metabolism regulating hormones can be detected by biochemical detection technique. Previous domestic and international studies have reported the research result of different races, different ages, and different regions of bone metabolism markers [5-7], but are insufficient study indicators, due to the small sample size and the lack of a comparative study of the different age groups. In this study, the relevance of PTH, 25 (OH) D3, CT, CTX-1, TRACP, BGP, and BALP with the femoral neck BMD in females 35-79 years of age of Han nationality from Changchun were researched, and the correlation of bone metabolism markers in 860 cases of women of different age groups with bone mineral density were analysed. The authors’ purpose is to investigate the laws of bone metabolism markers and BMD changes and to prove its significance in the diagnosis of osteoporosis.

Materials and Methods
Subjects
The study included 860 cases of 35 to 79-year-old Han women in Jilin Province, including teachers, workers, cadres, service industry workers, and retired. Acute and chronic liver and kidney disease, diabetes, hyperparathyroidism, hypothyroidism, hyperthyroidism, hypothyroidism, and cancer and chemotherapy and
radiotherapy patients were excluded. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Jilin University. Written informed consent was obtained from all participants.

Detection method
Enzyme immunoassay analyzer was used to detect PTH, 25(OH)D3, CT, CTX-1, TRACP, BGP, and BALP, and femoral neck BMD was measured by a bone mineral density detector.

Statistical analysis
SPSS13.0 software was applied for statistical analysis of calcium and phosphorus metabolism regulation indicators, bone metabolism markers and BMD measurements of 860 cases, the relevance of calcium and phosphorus metabolism regulation indicators, and bone metabolism markers with BMD were analysed using linear correlation analysis. A $p < 0.05$ was considered statistically significant.

Results
The measured values of PTH, 25 (OH) D3, and CT showed no differences in 35-50 age group. The measured values of 25 (OH) D3 began to decline after the age of 50, and 25 (OH) D3 had positive relevance with BMD. The measured values of CT was decreased in the age groups from 65 to 79 years old, and was significant positively correlated with BMD. The CTX-1, TRACP had negative relevance with BMD in 35-45 age group and BGP and BALP had positive relevance with BMD in 35-45 age group. BGP and BALP increased significantly in 50-60 age group, and CTX-1, TRACP, BGP, and BALP had negative relevance with BMD in 50-60 age group. BGP and BALP began to decline and had positive relevance with BMD after the age of 65. The results of bone metabolism indicators and BMD of 860 female cases (g/cm²) are shown in Table 1. The results of calcium and phosphorus metabolism reg-
ulation indicators and BMD of 860 female cases (g/cm²) are shown in Table 2. The study on the relevance of bone metabolism indicators with BMD in 35-45 age group in female are shown in Table 3. The study on the relevance of bone metabolism indicators with BMD in 50-60 age group are shown in Table 3. The study on the relevance of bone metabolism indicators with BMD after the age of 65 are shown in Table 3. The study on the relevance of calcium and phosphorus metabolism regulation indicators with BMD are shown in Table 4.

Discussion

The body maintains calcium and phosphorus metabolism homeostasis under the fine-tuning of PTH, 25 (OH) D₃, and CT.

PTH is a kind of straight-chain polypeptide hormone consisting of 84 amino acids, synthesized and secreted by parathyroid cells. The main role is to increase bone calcium absorption and to reduce urinary calcium excretion. CT is a peptide hormone consisting of 32 amino acids and is secreted by thyroid C cells. Its main role is to inhibit bone resorption, reduce kidney reabsorption of calcium and phosphorus, and lower calcium in blood. 25 (OH) D₃ is necessary for absorption of intestinal calcium and phosphorus and bone mineralization. Under physiological conditions, 25 (OH) D₃ can stimulate the activity of osteoblasts and promote the formation of bone matrix. Large doses of 25 (OH) D₃ are an activating factor of osteoclasts [8]. Studies have shown that the levels of 25 (OH) D₃ decreased and the levels of PTH increased when age-related osteoporosis occurred, in order to regulate the metabolism of 25 (OH) D₃ [9]. This study showed that the measured values of 25 (OH) D₃ significantly decreased in the 65 -79 age group, and had positively correlated with BMD (p < 0.05). PTH increased slightly in the same age group, the difference was not significant. The levels of CT reduction appeared in the age of 65 -79 age group, and had positive correlation with BMD (p < 0.05). The changes of PTH, 25 (OH) D₃, and CT had no differences between the sexes.

CTX-1 and TRACP are important biochemical parameters reflecting bone resorption. The quality of bone is decided by bone microstructure, bone metabolism transformation, the degree of bone mineralization and bone collagen, and bone matrix nature [10]. CTX-1 are specific indicators to reflect the type I collagen decomposition. When the type I collagen structure, content, and stability is abnormal, it will result that bone turnover is accelerated and the peptide fragments of type I collagen are degradated into the blood, the CTX-1 levels in blood can be significantly increased [11]. TRACP is released by osteoclasts, increasing the activity of osteoclasts [12]. The authors’ previous studies have shown that BGP and BALP levels of 791 cases of Han population of 50 to 59-year-old females was significantly higher than in males, TRACP and CTX-1 was negatively related with BMD.

Brown bone is metabolism living tissue, osteoclasts continue to absorb old bone, and osteoblasts continue to form new bone, jointly completing bone remodeling. BALP and BGP are important biochemical parameters that reflect bone formation. BGP is the most abundant non-collagen protein in the bone tissue, composed of 49 amino acids, its physiological function is to maintain bone mineralization rate, inhibit the formation of the carboxyl apatite crystallization. The Owe Löfman et al. [14] found that BGP of 1-15 years postmenopausal women continues to rise and that of 65 to 80-year-olds decreased to a low level. Research has shown that osteocalcin is involved in bone remodeling via a negative feedback mechanism [15]. Serum BALP exists in multiple homodimeric forms, 50% from bone, which is secreted by osteoblast and is closely related with bone formation and bone mineralization [16]. This study shows that BGP and BALP levels of 50 to 64-year-olds was significantly higher than other age groups and negatively with BMD; Gomesz et al. [17] reported the same results. The study also showed that the BALP and BGP levels of women after the age of 65 began to decline and reached the same conclusion with Gomesz et al. Proven that bone metabolism of 1-15 years postmenopausal women was in a high conversion state, after the age of 65, bone resorption and bone formation were reduced gradually to enter the low conversion state [17, 18].

In summary, jointly using calcium and phosphorus metabolism regulation indicators, bone metabolic markers, and BMD in the diagnosis of osteoporosis is superior than BMD diagnosis independently. PTH, 25 (OH) D₃, CT, CTX-1, TRACP, BGP, and BALP have an effect on bone quality via interactive process of bone metabolism, and are important association with BMD, and the basis of molecular biology for the early and differential diagnoses of osteoporosis [9, 19-21]. They not only have an important clinical value on osteoporosis prevention and treatment, but can also be used as important technical means for the evaluation of drug treatment and screening for population at high risk of osteoporosis.

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References


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First trimester termination of pregnancy: methods in comparison between two European university hospitals

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² Department of Obstetrics and Gynecology of the University of Szeged, Albert Szent-Gyorgyi Medical Center, Szeged (Hungary)

Summary

Purpose of Investigation: To compare methods, epidemiological features, and legislations of first trimester termination of pregnancy in two European Union University Hospital: Szeged, Hungary, (UHS) and Rome, Italy (UHR). Materials and Methods: The study included 195 women in UHS and 197 women in UHR undergoing a termination of pregnancy. The method used in UHR was electric vacuum aspiration, while in UHS it is chosen according to the patients’ features. Results: Mean gestational week at the time of interruption was 8.21 ± 0.12 SD for UHS and 9.00 ± 0.08 SD for UHR (p = 0.0001). Previous artificial termination of pregnancy was 0.40 ± 0.05 SD for UHR, and 0.77 ± 0.07 SD for UHS (p = 0.0001). Foreign women were 32.5% in UHR and 0.5% in UHS. Incidence of side effects was 1% for UHS and 0.5% for UHR. Parity was 2.54 ± 0.12 SD for UHR and 3.00 ± 0.14 SD for UHS (p = 0.01). Conclusions: The methods for interruption resulted safe and effective. Antibiotic prophylaxis, routinely provided in UHR, turned out to be effective to prevent post-operative infections. Cervical priming with Laminaria is safe, but patient’s hospitalization is required. Different legislations may account for some epidemiological differences between the two hospitals.

Key words: First trimester termination of pregnancy; Cervical preparation; Karman method; Abortion legislation.

Introduction

An estimated 46 million pregnancies end in induced abortion each year. In almost all countries the law permits abortion to save the woman’s life and in most countries abortion is allowed to preserve the physical and mental health of the woman [1].

The legislative statement on abortion of every country shows several differences, such as in Hungary and Italy, which are ruled, respectively, by Act LXXIX of 17 December 1992 on ‘the Protection of the Life of the Fetus’. Latest modification: June 2000 (LXXXVII) and Law 194/78.

There are several different surgical techniques for first trimester termination of pregnancy, in particular dilatation and curettage (DC, to scrape out the contents of the uterus), vacuum aspiration (VA, sucking out the contents of the uterus with a manual or power-operated device). Literature data about DC are controversial. Preabortion medical or mechanical cervical preparation may reduce the incidence of cervical or uterine injuries [1–4].

The aim of this study was to compare first trimester termination of pregnancy between two European Union University Hospital: Albert Szent-Gyorgyi Medical Center, Hungary (UHS) and Policlinico Umberto I, University “Sapienza”, Rome, Italy (UHR). This comparison concerned methods used in the first trimester of pregnancy, in order to investigate their effectiveness and complications rates, epidemiological features, and legislations.

Materials and Methods

This retrospective study was carried out in the Department of Obstetrics and Gynecology of the University of Szeged, Albert Szent-Gyorgyi Medical Center, Hungary (UHS), and in the Operative Unit-Voluntary Interruption of Pregnancy (UO-IVG), Department of Obstetrical-Gynecological and Urological Science, Policlinico Umberto I, University “Sapienza”, Rome, Italy (UHR). Legislations, methods, and procedures of the two groups of study are described in the following paragraphs and summarized in Table 1.

UHS

In UHS, after a gynecological visit to attest the status of pregnancy, the woman is obliged to fill out a written application (except for medical indications) to ask the authorization to the “Service for the Protection of Families”. In fact the Health Insurance Fund covers abortion if it is carried out for medical reasons and the applicant is insured; in case of “serious crisis situation” (i.e. social indication), the woman has to pay a fee. Specially trained nurses for consultation and advice run this service. There is an obligatory waiting period of three days followed by a second visit to the Service. Compulsory counseling is to be attended twice (except for abortions performed on medical grounds). If the patient is still motivated to have the abortion after the second counseling session, the date of operation is scheduled. Artificial
termination of pregnancy in the first trimester is always performed surgically and in a regimen of deep sedation. A premedication is provided, on the day of operation, early morning, with any anxiolytic or sedative medication given orally.

The preoperative preparation consists of an accurate and detailed medical history, and blood tests: Hgb, and blood type.

The surgical procedures, for the interruption up to 12 weeks, performed in this department are the following: Laminaria (or Dilapan) and curettage; DC, Laminaria (or Dilapan), electric VA and curettage; Dilatation, electric VA, and curettage.

The cervical ripening with Laminaria tents (or Dilapan sticks) is always practiced in young women (under 18 years), nulliparous, multiparous with a history of caesarean section. Up to 12 weeks, one Laminaria tent is generally used. After the cervical insertion, it is left in place overnight, nearly for 12-16 hours and the woman is admitted to the hospital for that night. The following morning the Laminaria tent is removed and the interruption is performed.

In case of multiparous with previous vaginal delivery, the cervical dilatation is achieved with progressive Hegar dilators and it is followed by the curettage. This procedure is performed in a day-hospital regimen. According to the provider’s choice and orientation, curettage can be preceded by electric VA. Intraoperative ultrasound (US) examination is not routinely practiced. Passive Rh-immunization of all Rh-negative women with Rh-immunoglobulin is routinely provided at the time of the abortion procedure. The antibiotic prophylaxis is provided only in case of use of Laminaria [5], by administration of amoxicillin and clavulanic acid. In case of hypersensitivity of the woman to penicillin or related antibiotics, a macrolid was administered.

In all the procedures, the patients are usually discharged approximately six hours after the operation. Before leaving the unit the patients undergo a US examination, in order to avoid residual tissue or incomplete abortion. After the operation, no follow-up visit or tests are scheduled. In case of side effects the women can complain in a separate “outpatient unit”, where they will undergo a physical and US examination, and eventually be treated again. In any case the patients are suggested to visit her gynecologist, for a control examination and an eventual contraceptive counseling, four weeks after the surgery.

UHR

The UO-IVG is an operative unit providing women the following services: pre-abortion care, interruption of pregnancy, and post-abortion care. The whole procedure is completely covered by NHS for all women in Italy. According to the Law 194/78, to obtain an abortion, the woman must have a certificate attesting her requirement for interruption from her general practitioner, or a private physician or a public maternal-child health clinic, and must wait for seven days before the operation, in order to leave the woman time to reflect about her choice. Patient has a laboratory diagnosis of pregnancy (serum βHCG). Providers perform a transvaginal US examination in order to estimate the gestational age by the measurement of the CRL [6-8]. Pre-surgery preparation, consisting of detailed medical history, cardiological examination and electrocardiogram, blood count, hemoglobin, hematocrit, ABO and Rhesus group, prothrombine time, glycaemia, serum nitrogen, anti HCV, HBsAg, and urine test. After seven days the patient undergoes the interruption.

Termination of pregnancy is provided surgically with the procedure of the electric vacuum aspiration, applying the real “Karman’s Method” [9]. The procedure is preceded by a cervical dilatation with plastic dilators of progressive size, or with Porget’s olive-shaped point urethral catheters, and it is performed with the Karman’s cannula; this is a plastic, thin, flexible, disposable, inexpensive cannula, available in different diameters, related to the gestational week. It almost eliminates perforation, dilatation with rigid dilators, and anesthesia associated with conventional vacuum aspiration. In addition, because it could be used with any aspiration apparatus and then simply discarded, the Karman cannula also reduces sterilization costs and the risk of infection and cross-contamination between patients [10].

In particular cases, such as very young women, women in the 11th-12th gestational week, or women with uterine fibroids or stenosis, the mechanical dilatation is preceded by intravaginal administration of prostaglandins (gemeprost, one mg, at least three hours earlier) [11]. The intervention is always performed under the US guidance, in order to check for eventual retention of material (residual decidual tissue). In this case the procedure is completed by an angular cannula or, only sometimes by a gentle curettage [12]. During the procedure, under the patient’s request, an intrauterine device (IUD) can be inserted [13]. The termination is provided in a regimen of deep sedation [14], hypnosis, and pain control. At the end of the procedure, five I.U. of oxytocin are injected in order to increase the cervical dilatation and uterine contractions, and an intraoperative antibiotic prophylaxis is provided (cefuroxime two g e.v.). In case of hypersensitivity, a macrolid can be given.

### Table 1. — Legislations, methods, and procedures of the two groups of study (UHS and UHR).

<table>
<thead>
<tr>
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<th>Hungary</th>
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<td>Up to 12 weeks</td>
<td>- Up to 12 weeks, - Up to 12 weeks, if &lt; 18 years</td>
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<tr>
<td>Waiting period</td>
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<td>3 days</td>
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<tr>
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</tr>
<tr>
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<td>Frequent (Laminaria tents)</td>
</tr>
<tr>
<td>Cerv. mechanical dilators</td>
<td>Porgèt urethral Dilators</td>
<td>Hegar dilators</td>
</tr>
<tr>
<td>Antibiotic prophylaxis</td>
<td>Always</td>
<td>Only with Laminaria</td>
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<tr>
<td>Rh-immunization</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Anesthesia</td>
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<td>Deep sedation</td>
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<tr>
<td>Intraoperative ultrasound</td>
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<td>Not routinely</td>
</tr>
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<td>Postoperative ultrasound</td>
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<tr>
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<tr>
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<tr>
<td>- Transvaginal-ultrasound</td>
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<td></td>
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<tr>
<td>- Contraceptive counselling</td>
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<tr>
<td>Conscientious objection</td>
<td>Specific rule</td>
<td>Absence of specific rule</td>
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**Legislations**

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Passive Rh-immunization of all Rh-negative women with Rh-immunoglobulin is routinely provided at the time of the abortion procedure [15]. If the patient refuse deep sedation, or if any contraindication for it exist, local anesthesia with mepivacaine 2% is provided (paracervical block) [16]. This procedure is performed in a day-hospital regimen and women are usually discharged six hours after the termination of pregnancy. After the operation, patient takes 0.2 mg of methylergonovine maleate for five days or oxytocin, if it is contraindicated (i.e. uterine fibroids, hypertension). Ten days after the operation the patient is provided a follow-up visit, with βHCG test, and a transvaginal US examination, in order to verify that the abortion was complete. During the follow-up visit the woman is furthermore provided a detailed contraception counseling [17].

Data collection and analysis

The authors collected 195 women undergoing a termination of pregnancy during the first trimester at UHS, in the period between February 2010 and October 2011, and 197 women undergoing a termination of pregnancy at UHR, in the period between October 2010 and April 2011. Data were collected from the clinical records and concerned age of the patient, nationality, obstetrical history (vaginal births, preterm births, caesarean sections, spontaneous abortions, previous artificial terminations of pregnancy, total number of pregnancy, including the index pregnancy), gestational week of the current pregnancy, method of induced abortion, and side effects. Statistical analysis was performed using SPSS 16.0 for windows computer program. Level of statistical significance was set at $p < 0.05$.

Results

The comparison between the two groups of patients shows several significant differences in epidemiological and obstetrical features (Table 2). Mean age was similar in the two groups, in particular $29.62 \pm 0.49$ SD years for UHR, and $29.06 \pm 0.54$ SD years for UHS ($p > 0.05$).

Parity (including the index pregnancy) was $2.54 \pm 0.12$ SD for UHR and $3.00 \pm 0.14$ DS for UHS, with $p = 0.01$ (Figure 1). It is worth mentioning that the maximum number of pregnancies found was nine for UHR and 15 for UHS.

Patients treated at UHS had a mean gestational week at the time of interruption slightly lower than at UHR ($8.21 \pm 0.12$ SD vs $9.00 \pm 0.08$ SD, $p = 0.0001$). The different incidences of termination according to the gestational age of pregnancy are shown in Figure 2.

Table 2. — Epidemiological and obstetrical features of the two groups of study (UHS and UHR).

<table>
<thead>
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<th>Characteristic</th>
<th>U.H.R.</th>
<th>U.H.S.</th>
<th>$p$ value</th>
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<td>Age, years</td>
<td>$29.62 \pm 0.49$</td>
<td>$29.06 \pm 0.54$</td>
<td>ns</td>
</tr>
<tr>
<td>Parity</td>
<td>$2.54 \pm 0.12$</td>
<td>$3.00 \pm 0.14$</td>
<td>0.01</td>
</tr>
<tr>
<td>Gestational week at the time of interruption</td>
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<td>$8.21 \pm 0.12$</td>
<td>0.0001</td>
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<tr>
<td>Previous artificial termination of pregnancy</td>
<td>$0.40 \pm 0.05$</td>
<td>$0.77 \pm 0.07$</td>
<td>0.0001</td>
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</tbody>
</table>

Previous artificial terminations of pregnancy in UHS ($0.77 \pm 0.07$ SD) resulted to be more than in UHR ($0.40 \pm 0.05$ SD), with $p = 0.0001$. In particular, 73% of patients treated at UHR and 50% at UHS did not have previous interruptions, while 18% at UHR and 34% at UHS had one previous interruption. Finally, the maximum number of previous interruption was five for UHR and seven for UHS.

In UHS, 8.2% of women had a medical indication for the interruption, while 91.8% a social one. This data is not available for UHR, since in Italy patients should not provide any information about indication for termination.

Interestingly, in UHS almost all patients have local nationality (99.5%), while in UHR 67.5% of women were Italian, and the remaining 32.5% were foreigners.

The overall rate of side effects in the first trimester termination was 1% for UHS and 0.5% for UHR. One case of bleeding, that required a revision of the uterine cavity for residual decidual material, occurred in each group, in particular a nulliparous 25-year-old woman in UHS and a nulliparous 16-year-old woman in UHR. In UHS this was a
complication of Laminaria and curettage and in UHR of dilatation and electric VA. Finally, in UHS one case of moderate to severe pain, with signs of pelvic inflammation, that required an antibiotic treatment, occurred in a multiparous woman after DC.

The different methods used for the interruption were in UHS Laminaria + electric VA + curettage (27.69%), dilatation + electric VA + curettage (25.64%), Laminaria + curettage: (24.62%), and dilatation + curettage (22.05%). In UHR all cases were performed by dilatation + electric VA and in a limited proportion of women a curettage was also performed (3.55%).

Discussion
This study revealed significant differences concerning women obstetrical history. Indeed, parity resulted higher in UHS, the mean number of previous termination of pregnancy resulted higher in UHS, and the mean gestational week at the time of the abortion was higher in UHR.

Some of these differences may be partly related to the legislative statements on abortion of the two countries. According to the laws, the shorter waiting period in Hungary can shorten the time from application to intervention.

Another important issue regards the conscientious objection. In fact, the Italian law states that healthcare provider and operator of the ancillary activities are not required to take part in the procedures and in actions for termination of pregnancy if they have previously declared their conscientious objection, which must be communicated to the provincial doctor. In Hungary a healthcare provider may refuse to perform an abortion on ethical/moral grounds, but no official declaration or time limits are required.

The Hungarian law states that women have to pay for getting the pregnancy interruption, except for medical indications. Consequently, the indication for the interruption has to be reported in the patient charge. In Italy, the interruption is free of charge and the information about indications is not required.

The UHR data about patient nationality reflects the high number of immigrant women who access the healthcare system in Italy.

There is lack of conformity about DC in the literature, as this method seems to be less safe than VA [18], and it is considerably more painful for women because it requires greater dilation [19]. Moreover, the rate of major complications of DC is two to three times higher than VA [20]. Finally, a randomized controlled trial comparing DC with VA found that, up to ten weeks since last menstrual period, VA is quicker and associated with less blood loss than DC [21].

According to these data, WHO [1] and International Planned Parenthood Federation (IPPF) [3] recommended that where DC is currently practiced, all possible efforts should be made to replace it with VA, in order to improve the safety and quality of care. Where no abortion-related services are currently offered, VA should be introduced rather than DC.

A Cochrane review comparing VA and DC found that there were no statistically significant differences for excessive blood loss, blood transfusion, febrile morbidity, incomplete or repeat uterine evacuation procedure, re-hospitalization, postoperative abdominal pain or therapeutic antibiotic use [4]. Duration of operation was statistically significantly shorter with VA compared to DC. The review concluded that both DC and VA are safe and effective methods for first trimester termination of pregnancy and complications are rare.

The choice of the method depends on the setting and the availability of the equipment. Although the duration of procedure is shorter with VA compared to DC, DC may play a role when using local anesthetics or for busy clinics [4]. The present study confirms that both DC and VA are effective and safe methods of abortion.

All the procedures performed in the two University Hospitals showed a very low rate of complications (1% in UHS and 0.5% in UHR). The use of US (intraoperatively in UHR and six hours after operation in UHS) may help to reduce complications. Additionally, intraoperative US may confirm the success of the intervention, thus reducing the duration of hospitalization.

The routine use of perioperative antibiotics is debated in the literature. Indeed, WHO [1] and IPPF guidelines [22] state that antibiotic prophylaxis reduces the post-procedural risk of infection, while, according to a Cochrane review [23], there seems to be not enough evidence on routine antibiotics to prevent infection for women seeking care after incomplete abortion.

In the present study, only a case of pelvic inflammation, that required an antibiotic treatment, occurred in UHS. Thus, the choice to administer an antibiotic prophylaxis remains recommendable, though not fairly supported by data [5, 24].

A previous Hungarian study reported that premature labour was a serious problem in Hungary where it often results from a cervix injury by a previous first or second trimester induced abortion. The dilatory effect of Laminaria was a fair aid in the termination of both first and second trimester pregnancies [25]. An international review supported that the ability to easily achieve the desired dilation with rigid dilators is comparable with all the other methods of cervical ripening [26].

A Cochrane review asserted that modern methods of cervical ripening are generally safe, though with variable efficacy and side effects [27]. Adverse events, such as cervical laceration or uterine perforation, are uncommonly reported and there is no study investigating the impact of the type of cervical preparation on complications. The present study did not report any case of cervical laceration or uterine perforation, in spite of the use of different methods for cervical ripening.
According to the literature and to the results of this retrospective study, it seems reliable to assert that cervical dilatation can be safely achieved by means of plastic or semirigid dilators. However, the UHS protocol with Lamina requires the hospitalization of the patient, and consequently increased costs for the procedure. The UHR procedure, however, with mechanical dilators [28-30], requires a shorter operative time, as the procedure is practiced in a day-hospital regimen. Nonetheless, a case-by-case assessment should guide the provider in choosing the most appropriate cervical preparation.

The post-abortion care is different in the two countries. In UHS a follow-up visit is not planned, but in case of side effects women may refer to a different outpatient unit. However, the patient is suggested to visit her gynecologist (outside the hospital setting), for contraceptive counseling and control examination, four weeks after surgery. In UHR a follow-up visit including a transvaginal US examination and, according to the law 194/78, a detailed and free of charge contraception counseling are provided to all women.

In conclusion, the UHR healthcare system provides a more complete service to the women, although both the University Hospitals, by means of different strategies, warrants the care of the patients.

Conclusions

According to the laws, the termination of pregnancy seems to be more easily and readily available in Hungary due to a shorter compulsory waiting period and the lack of stated rules for conscientious objection. However, this procedure is free of charge in Hungary only for medical indications. All methods used for first trimester termination of pregnancy in this study result safe and effective. The choice of the method depends on the setting and the availability of the equipment. The use of intraoperative US may play a role in the reduction of complications rate.

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In memory of Professor M. M. Anceschi.

References


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A different technique for the closure of trocar sites

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\textsuperscript{1}Baskent University, Seyhan Research Hospital, Department of Obstetric and Gynecology, Adana, \textsuperscript{2}Baskent University, Seyhan Research Hospital, Department of Plastic and Reconstructive Surgery, Adana (Turkey)

Summary
This study aims to present a different technique for the closure of trocar sites in laparoscopic surgeries. \textit{Materials and Methods}: Retrospective records of cases who received the new closure technique were collected. Multifilament synthetic absorbable suture was used in this technique, with no additional tools. \textit{Results}: This technique was applied in a total of ten cases, which included myomectomy, hysterectomy, sacrocolpopexy, and ectopic pregnancy. No intraoperative and postoperative complications were seen in any of the cases. \textit{Conclusion}: This new and relatively easy-to-use technique can be used as an alternative technique for the closure of trocar sites in laparoscopy.

Key words: Laparoscopy; Trocar site closure; Trocar site herniation.

Introduction
Main complications associated with trocar site in laparoscopic surgeries include the incisional hernia and intraoperative and/or postoperative bleeding. These complications can be prevented with a careful intraoperative approach and simply by suturing trocar sites- Trocar site incisional hernias (TSIH), which are typically seen during late postoperative stage have been reported to be 0-6\% in different series [1-4]. Various trocar closure and suturing methods were reported in current clinical trials, though not compared with each other. This study describes a new port closure technique.

Materials and Methods
The retrospective medical and sociodemographic records of patients who received the present port closure technique were collected and the technique was described in this study.

The procedure was conducted at the end of laparoscopic surgery, with the intact pneumoperitoneum and under direct visualization. Following surgery, a suture with its needle was sent to the abdominal cavity, from the targeted hole by using a grasper, but the end of the suture remained on the outside (Figure 1). Then the grasper and trocar were removed and a laparoscopic needle holder from another trocar grasped the needle and stitched the peritoneum and fascia intracorporeally (Figure 2). After this, a grasper was sent from the targeted hole and grasped the suture (or needle) and was extracted from the hole. The suture was then tied extracorporeally just above the fascia (Figure 3). Through this technique, only the peritoneal and fascial layers were closed.

Results
This technique was applied in ten cases and used for the closure of ten-mm trocar site in cases with myomectomy, hysterectomy, sacrocolpopexy, and ectopic pregnancy. The mean age of patients was 40 ± 4 years, with a body mass index (BMI) of 26.4 ± 4.5. The time needed to apply this technique was calculated to be 5.5 ± 2.5 minutes. No intraoperative complications were observed during the procedure. Multifilament synthetic absorbable suture was used in this technique. None of the cases presented with an early postoperative incisional hernia and bleeding during postoperative short period.

Discussion
There are many techniques for the closure of trocar sites [4-6]. What distinguishes the present technique from the others is that it allows the closure of the trocar site just by using the tools available in the surgery room, and without using special tools. There are also no additional learning curves associated with the technique, and the technique can be applied by any surgeon performing standard laparoscopic surgeries.

It is well known that hernias found on trocar sites are subclinical, so it is strongly possible that their prevalence is higher than the rates reported in the literature. The incidence of TSIH has been reported to be higher when the trocar site is not sutured [3]. There is no data available concerning how the present method will affect the incidence of TSIH as this study lacks long-term follow-up. However, the incidence of TSIH will actually decrease after suturing and closure of the incision site. Comparative studies are required to evaluate its impact on incidence.

Some clinicians have reported that closure of trocar site does not prevent TSIH, and that TSIH does not depend on
trocar defect width [7]. Some authors claim that, when non-bladed laparoscopic trocars are used, that there is no of fascia closure [8]. Nevertheless, the present authors believe that the defect width at the trocar site is important; a great majority of TSIHs occurs with ten-mm trocars. Thus, the authors suggest that all ten-mm trocar sites should first be sutured. If five-mm trocars are inserted several times, the resulting weak tissues should also be sutured. This technique was applied only on ten-mm trocar sites, but there are no limitations concerning its use on five-mm trocar sites.

Some clinicians report of a possible increase in the infection rates of wound sites after suturing trocar sites [7]. This study found no infections on wound sites, which can be attributed to the suturing of only peritoneal and fascial structures without traumatizing the muscular and subcutaneous tissues. Moreover, dimple formation (dimpling) on abdominal skin is prevented by suturing only the peritoneum and the fascia. This provides a cosmetic advantage.

The authors conclude that this new method is simple, safe, and cost-effective because it is performed under direct visualization and it requires no additional instruments.

References


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Hysterosalpingography versus hysteroscopy in intrauterine pathology research of infertile patients

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1 Medical Center, "Kosovska Mitrovica", Kosovska Mitrovica; 2 University of Belgrade, Medical Faculty, Belgrade; 3 University Clinic for Obstetrics and Gynecology "Narodni front", Belgrade (Serbia)

Summary

Background: The objective of the present paper is to confirm the validity and reliability of hysterosalpingography (HSG) in intrauterine pathology research of infertile female patients by comparing the hysteroscopy (HC) findings to a “gold standard” test. Aim: To analyze HSG and HC findings in infertility patients. Materials and Methods: The research was conducted as a prospective study at the Gynecological and Obstetrics Clinic "Narodni front" in Belgrade. Results: HSG indicated pathological findings in 72.5% of patients whereas HC revealed abnormalities of uterine cavity in 77.5%. In 12.5% of patients, HSG demonstrated a normal uterine cavity, and HC confirmed pathological findings, while in 7.5% of patients with filling defects and irregular shapes on HSG images, HC reported normal findings. In 22.5% of patients normal finding as well as endometrial polyps were reported; congenital malformations (anomalies) were found in 32.5%, submucosal myomas in 12.5% and Asherman’s syndrome in 10%. Conclusion: HC finding was crucial in final diagnosing.

Key words: Hysterosalpingography; Hysteroscopy; Infertility; Uterine cavity.

Introduction

Congenital abnormalities and inherited uterine diseases may have a negative effect on the complex process of embryo implantation [1]. The abnormalities of the uterine cavity are the cause of infertility in 10% of women, whereas pathological endometrial anomalies were revealed in 45% of patients with unsuccessful conception in in vitro fertilisation trials [2]. Such infertility distribution called for investigation of uterine cavity condition as a routine procedure in diagnosing female infertility [3].

As diagnosing methods, hysterosalpingography (HSG) and hysteroscopy (HC) have different approaches in uterine cavity research. The image contrast charging indicated that HSG indirectly provides an insight into the condition of the uterine cavity. According to many clinicians, HSG has been a routine technique so far and the first line intrauterine pathology research of infertile patients [4, 5]. This diagnostic method has been used as a screening procedure in all infertility cases suspected to have intrauterine abnormalities as well as in tubal patency testing.

Due to the direct view of uterine cavity and cervical canal, HC provides accurate and precise diagnosing of intratuterine conditions. The great advantage of this method is definitely its therapeutic application which is considered superior to HSG [6].

The aim of this study is to confirm the validity and reliability of HSG in intrauterine pathology investigation in infertile female patients by comparing the HC findings to a “gold standard” test.

Materials and Methods

The method was conducted as a prospective study at the Gynecological and Obstetrics Clinic “Narodni front” in Belgrade. It involved 40 women with an average age of 32.79 ± 4.60 years who, due to conjugal infertility, came to the clinic for examinations and treatments. All the patients had a certain examination protocol. In evaluating the HSG validity in comparison to HC findings obtained by viewing the uterine cavity of the examined patients, the time difference between these two diagnostic methods should not have exceeded two or three months. This was the basic criterion for selecting or involving patients in the investigation.

HSG was performed on women following the eighth or tenth day of their menstrual cycle with a short intravenous anaesthesia, radiographic equipment, and iodinated water-soluble contrast medium. HSG findings contained a contrast image of the cervical canal and uterine cavity. The image projection of the uterine cavity was an equilateral inverted triangle in relation to the cervical canal, with sharp edges and homogenous shadow. As a long and narrow homogenous thread, the contrast shadow further spread along oviducts to abdominal cavity. The investigation of the HSG findings, made it possible to observe normal finding as well as endometrial polyps were reported; congenital malformations (anomalies) were found in 32.5%, submucosal myomas in 12.5% and Asherman’s syndrome in 10%.

HC was carried out during the same menstrual period or in the following three to six months, in the early proliferative phase, immediately after the cessation of the menstrual flow.
when endometrium was thin, porous, and invulnerable. Diagnostic HC was conducted by introducing a hysteroscope with an external shield (sheath) diameter of 5.5mm. The intervention required a dilation of the patient’s cervical canal. When the hysteroscope was inserted and cervical canal and uterine cavity visualized, followed the systematic scrutinization of the anterior and posterior cavity wall, both cornual regions, the left and right ostia, as well as the detection of possible abnormalities. As this diagnostic hysteroscope possessed a working channel where hysteroscope instruments could be guided (5 Fr), some minor surgeries were also possible. This referred to the lysis of focal and small intrauterine adhesions, endometrial biopsy, and resection of small pendunculated polyps and myomas.

More extensive cavity surgeries required a resectoscope with an external shield diameter of nine-mm and a large dilation. The resectoscope consisted of a multichannel shield for fluid inflow and outflow. Hysteroscope scissors were mostly used to remove uterine septums, adhesion partitioning, because the septums were most frequently avascular with very little bleeding. They were also removed with resectoscope, a monopolar needle with cutting effect and coagulation, with no bleeding. Pedunculated myomas and polyps were removed with HC monopolar trap. The application of bipolar electrodes required particular attention during the septum resection due to the heat transfer and possible damage of the surrounding healthy endometrium. Ispirol was firstly applied as a distension medium followed by the physiological solution (0.9% NaCl). An automatic pump controlled pressure and fluid flow so that the intrauterine pressure was not higher than 100 mmHg. Both procedures did not cause any serious complications during surgery nor during the recovery period.

Results

HSG indicated normal uterine cavity in 27.5% of patients, whereas 72.5% revealed findings that indicated intrauterine factor as a probable cause of infertility (Table 1). HC finding was crucial in final diagnosing. The frequency of HC diagnosing of uterine cavity reported congenital abnormalities in majority of patients, 13 (32.5%), endometrial polyps was confirmed in nine patients (22.5%), submucosal myomas in five (12.5%) patients, and Asherman’s syndrome in four (10%) patients.

HC reported a higher percentage of pathological anomalies in comparison with HSG as well as a lower percentage of normal findings. χ²-test statistical analysis did not report any significant discrepancy between normal and pathological findings of the two diagnostic methods (p > 0.05).

Kappa’s quotient was used as a reliability index to measure agreement between two diagnostic methods. The quotient value higher than 0.4 was considered as the evidence of useful correlation between HC and HSG. McNemar’s (MCN) test analysed discrepancy between results obtained with these methods; it was considered statistically significant at a value p < 0.05.

The HSG and HC correlation in diagnosing endometrial polyps/submucosal myomas was quantified by the Kappa’s index value (κ = 0.66) which confirmed positive agreement, as well as uterus subseptus finding (κ = 0.63), uterus bicornis (κ = 0.5), uterus arcuatus (κ = 0.67). Kappa quotient (κ = 0.89), as a clinical entity, confirmed excellent agreement between HSG and HC in inherited uterus anomalies, and for χ² MCN there was no statistically significant difference in relation to findings obtained in various conditions of uterine cavity (p > 0.05).

In evaluating HSG criterion validity compared to HC as a gold standard in the investigation of uterine cavity, the values for some features of HSG as a diagnostic method are shown in Table 2, whereas the values for each clinical diagnosis are given separately in Table 3. HSG and HC find-

<table>
<thead>
<tr>
<th>Hysterosalpingography</th>
<th>Hysteroscopy</th>
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</thead>
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<tr>
<td>Pathological finding</td>
<td>Normal finding</td>
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</tr>
<tr>
<td>Pathological finding</td>
<td>26</td>
<td>65</td>
</tr>
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<td>Normal finding</td>
<td>5</td>
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</tr>
<tr>
<td>Total</td>
<td>31</td>
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κ = 0.47; p > 0.05

<table>
<thead>
<tr>
<th>Hysterosalpingography</th>
<th>Dg</th>
<th>Acc¹</th>
<th>Sn²</th>
<th>Sp³</th>
<th>PPV⁴</th>
<th>NPV⁵</th>
<th>LR⁺⁶</th>
<th>LR⁻⁷</th>
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</thead>
<tbody>
<tr>
<td>Polyps/myomas</td>
<td>75%</td>
<td>71.43%</td>
<td>92.31%</td>
<td>83.33%</td>
<td>85.71%</td>
<td>9.2</td>
<td>0.29</td>
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<tr>
<td>Congenital anomalies</td>
<td>89%</td>
<td>92.31%</td>
<td>96.3%</td>
<td>92.31%</td>
<td>96.3%</td>
<td>24.95</td>
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</tr>
<tr>
<td>Uterus subseptus</td>
<td>92.5%</td>
<td>50%</td>
<td>100%</td>
<td>100%</td>
<td>91.89%</td>
<td>0</td>
<td>0.5</td>
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</tr>
<tr>
<td>Uterus bicornis</td>
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<td>100%</td>
<td>94.87%</td>
<td>33.33%</td>
<td>100%</td>
<td>19.49</td>
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</tr>
<tr>
<td>Uterus arcuatus</td>
<td>97.5%</td>
<td>100%</td>
<td>97.43%</td>
<td>50%</td>
<td>100%</td>
<td>38.9</td>
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</table>

¹: diagnostic efficacy, equivalency; ²: sensitivity; ³: specificity; ⁴: positive predicative value; ⁵: negative predicative value; ⁶: positive rate veracity; ⁷: negative rate veracity.

Table 2. — Hysterosalpingography validity.

<table>
<thead>
<tr>
<th>Hysterosalpingography</th>
<th>Dg</th>
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<th>Sn²</th>
<th>Sp³</th>
<th>PPV⁴</th>
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<th>LR⁺⁶</th>
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<td>100%</td>
<td>100%</td>
<td>91.89%</td>
<td>0</td>
<td>0.5</td>
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</tr>
<tr>
<td>Uterus bicornis</td>
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<td>100%</td>
<td>94.87%</td>
<td>33.33%</td>
<td>100%</td>
<td>19.49</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Uterus arcuatus</td>
<td>97.5%</td>
<td>100%</td>
<td>97.43%</td>
<td>50%</td>
<td>100%</td>
<td>38.9</td>
<td>0</td>
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</tr>
</tbody>
</table>
ings did not agree in all patients in diagnosing intrauterine adhesion, uterus septus, and uterus unicornis unicollis.

HSG findings correlate with HC findings, i.e. the total correlation of normal and pathological findings was 80%. Discrepancies in HSG and HC findings are given in Table 4. In five patients, HSH showed a normal uterine cavity, and HC confirmed pathological findings, endometrial polyps in three patients, uterine myoma, and uterus subseptus in one patient, while in three patients with flaws in contrast charging (filling defects) and irregular shapes on HSG images; HC reported normal findings.

Discussion

In our clinical practice, HSG method has been applied for many years, is still mandatory, and is the first diagnostic method used in the assessment of female infertility. Starting from this assumption, the present study should prove diagnostic accuracy, validity and reliability of the method in 40 female patients compared to HC, the gold standard method in the evaluation of intrauterine pathology.

In this study, HSG was the initial method in investigating conditions of uterine cavity. Pathological anomalies of uterine cavity were visualised as flaws in contrast charging (filling defects) and irregular shapes on HSG images. HSG demonstrated a normal uterus in 11 patients (27.5%) while anomalies on HSG images were reported in 29 (72.5%) patients. In the first group, HC confirmed normal findings in six patients, and pathological cavity abnormalities in five patients, i.e. HSG showed a false negative rate in 12.5% cases. Out of 29 patients with pathological findings on HSG image, HC noted pathological cavity abnormalities in three patients. Hence, HSG in this study showed a false positive rate in 7.5% of patients. Similar rates, both for false positive and false negative findings (11.7% and 13.3%) were shown by Prevedourakis et al. in a much larger number of female patients [7].

The results obtained by assessing HSG validity indicated that the this method could ultimately show intrauterine pathology in the patients who, according to diagnostic gold standard method - HC, actually suffered from this disease; the sensitivity was 83.87%. In the present investigation HSG specificity was not so high, 66.67%, but there was a high correlation between HC and HSG findings; total agreement between pathological and normal finding was 80%. The positive rate veracity (LR+) was 2.52, i.e. abnormal finding on HSG image was three times more likely to be found in patients with pathological findings reported by HC than the patients with normal HC finding. The veracity of the negative rate (LR) was 0.24 and indicates that HSG finding was almost impossible to find in patients with pathological cavity anomalies.

Many authors have demonstrated that HSG has high sensitivity 60-98%, but low specificity 15-81.8%, with somewhat false positive and false negative rates compared to the present study [6, 8-10].

Diagnostic accuracy of HSG compared to HC showed high values in the studies of Roma et al. (73%) and Filhoe et al. (85.2%), which agreed with the present results (80%) [4, 11].

The agreement of the two diagnostic methods was quantified by Kappa index which in the current study was $\kappa = 0.47$. The $\kappa$ value indicates regular agreement between HSG and HC results in intrauterine pathology research in infertile patients. In the similar study, the values of $\kappa$ quotient were interpreted as follows: 0.81-1.0 (excellent); 0.61-0.80 (good); 0.41-0.60 (normal); 0.21-0.40 (poor), and < 0.20 (very poor) agreement.

The direct sign on hysterosalpingogram of the presence of endometrial polyps in the cavity was the defect in contrast charging (filling defect), normal contours but without sharp and regular edges. Due to its soft consistency, they showed tendency to disappear as the contrast instillation in the cavity grew. They could be best observed on the first image when the contrast filled the cavity. The lack of fluoroscopy on the authors’ Roentgen apparatus and the magnitude of polyps may have influenced their finding and false negative rate.

HC identified polyps as localized pinkish-grey to white coloured anomalies, covered with mostly smooth and shiny-surfaced endometrium. The localization and the magnitude of polyps varied in patients, most frequently in fundal and isthmic area, magnitude 0.5 to two cm.

All endometrial polyps were removed by hysteroscopic monopolar trap and resectoscope loop. Material was sent on histopathological examination.

Hysteroagram showed submucosal myomas as round and regular defects in contrast filling. They most frequently induced partial anomalies, compressions, and reduction of uterine cavity as well as its enlargement.

In direct hysteroscopic visualization, submucosal myomas reported peripheral vascularization through atrophic endometrium and whitish fibrous myoma tissue compared to the surrounding colour of the normal endometrium. Tactile sensation with an inactive electrode provided the sensation of toughness compared to the surrounding soft myometrial tissue. The magnitude of submucosal myomas in patients varied from one to 2.5 cm, all of them being removed with a resectoscope loop in one act.
The HSG image demonstrated similar findings of polye
dometrial polyps and submucosal myomas, it was diag-
nostically difficult to differentiate them without hyste-
coscopy inspection, so they were marked as one clin-
ic entity in the statistical data procession. HSG indicated the possibility of the polyp/myoma presence in the cavity of ten patients. HC visualized endometrial polyps in nine patients examined and submucosal myomas in five. In two patients, the contrast filling defects on HSG image with a suspected polyp/myoma presence were artifacts, most probably air bubbles and cervical mucus, as HC confirmed normal finding in uterine cavity.

In the evaluation of uterine cavity in women with a large number of miscarriages, Filho et al. demonstrated a good agreement between HSG and HC ($\kappa = 0.79$), both for polyps and myomas. Diagnostic accuracy in the investigation of these anomalies was 98% [11]. In the study, Valenzano et al. confirmed normal cavity finding in ten patients with HC diagnosis for endometrial polyps and submucosal myoma [12].

According to some studies, HSG is superior to HC for the evaluation of lesions penetrating through myometrium, congenital anomalies as well as the changes in the contour of the uterine wall [13]. Small intrauterine lesions, polyps, submucosal myoma, and intrauterine adhesions that may have a significant influence on the successful implantation, are diagnosed more accurately and precisely by HC than by HSG [14].

HSG image projects intrauterine adhesions as a filling defect with irregular shapes; the result of a constantly present apposition of the anterior and posterior uterine walls and their inability to be distended and separated by contrast. Due to such HSG image finding, the presence of Asherman’s syndrome was suspected in three patients. In one patient, while injecting cannula and contrast, only dilated cervical canal was noted, with no further contrast penetration into the cavity.

HC diagnosed uterine synechiae in four patients with positive HSG finding. In two patients, the hysteroscope insertion led to breaking thin filmy adhesions apart. Intrauterine contraceptive device was inserted in one patient and the other patient was recommended HC after three months.

In the current study, HSG and HC showed a perfect correlation in diagnosing intrauterine adhesions ($\kappa = 1$) and diagnostic HSG accuracy was 100%.

Other studies did not report such good diagnostic HSG results. In diagnosing synechiae, Filho et al. had two false positive rates (3.7%), sensitivity 69.2%, and high specificity 95%. In their study, diagnostic efficacy was relatively elevated 88.9%, as well as the HSG and HC correlation $\kappa = 0.68$ [11].

Alborzi et al. showed that, due to the intrauterine adhesions confirmed in 17 patients, HSG had sensitivity 70.6% for Asherman’s syndrome, specificity 99.4%, PPV 92.3%, and NPV 97.1% [15].

In this study, congenital uterine anomalies are most frequent abnormalities, present in 13 patients. Innate uterine anomalies were similarly present in patients after both diagnostic procedures: HSG 30% and HC 32.5%. Precisely diagnosing congenital disorders is essential because of different surgery treatments and reproductive potential. Various surgery approaches in anomaly therapy require precise diagnosis in order to obtain adequate and optimal therapeutic approach for a patient.

Uterus septus is most commonly found in infertile patients (33.6%) [16]. In the present study, HSG reported cavity septum in three patients. HC diagnosed septums that divided cavum into two cavities, in one act septums were cut with bipolar resectoscope electrode and scissors.

In six patients HC confirmed uterus subseptus, small septums < two cm long, hysteroscopically resected with monopolar needle. In three patients, HSG suspected subseptum. As for other three patients, HSG image was normal in one of them and uterus bicornis was suspected in other two.

Uterus bicornis, is the result of the incomplete infusion of the Müllerian ducts. On HSG image the anomaly varies depending on the defect magnitude, from completely mild fundal depression to a complete separation extending to the inner estuary. On hysterosgram, uterus bicornis was suspected in three cases, but HC noted uterus bicornis in only one case, which was confirmed by laparoscopy in one act.

Maleck et al. suggested in their study that, due to accurate and precise investigation of the intravaginal anatomy, magnetic resonance was the optional method in detecting uterine irregularities in infertility patients. Laparoscopy and HC were applied in patients expected to have therapeutic treatment [17].

Uterus arcuatus on HSG image demonstrates a fundal saddle shaped depression. Such a finding could be found in two patients. Final diagnosing uterus arcuatus was reported in one patient by HC and laparoscopy, whereas in another case the finding was normal.

Today HSG combined with laparoscopy and HC, due to relatively high prevalence of uterine abnormalities, is considered optimal in diagnosing female fertility [18].

Table 3 shows values of HSG validity as compared to all represented clinical entities whose HSG and HC did not match. Such high values of sensitivity, specificity, PPV and NPV, as well as diagnostic accuracy, prove the features of HSG as a diagnostic method in detecting congenital malformations. Similar results in this study were shown by Alborzi et al. [15].

In the present study, HSG showed its discrepancy limitations between subsepted and uterus bicornis because of the similar uterine cavity form of the anomalies on the image. Regarding the fact that this study included a small number of patients, with a small number of diagnoses, it is not possible to assess the real diagnostic accuracy of HSG for congenital anomalies.
Finding discrepancies between HSG and HC also referred to the identification of endometrial polyps and submucosal myoma, because HSG did not detect these anomalies, probably due to the fact that lesions were so small to be shown as filling defects on images. HSG is a relatively reliable method in diagnosing intrauterine abnormalities. Although HC presents a gold standard method in the evaluation of intrauterine pathology in infertility patients, HSG as a highly sensitive method still remains initial diagnostic method in indirect cavity investigation. In the present study, HSG is, due to the simple performance, low cost, and relatively high reliability, supplement to HC in the investigation of intrauterine pathology.

Nowadays HC is a simple and efficient diagnostic method that enables treatment of cavity pathology and is unique in disclosing small and subtle lesions that other diagnostic methods are not able to detect. If HSG image noted intrauterine abnormality, the final diagnosing should be done by HC inspection of the cavity.

References


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An analysis of the main reasons that perimenopausal and postmenopausal women in China have for seeking outpatient treatment and factors influencing their symptoms: a single-center survey

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Summary
Objective: To explore the main reasons that perimenopausal and postmenopausal women have for seeking treatment and factors influencing their symptoms in order to provide (peri-) menopausal women with better healthcare treatments. Materials and Methods: Interviews were conducted with 357 (peri-) menopausal women who sought outpatient treatment at The Sixth People’s Hospital, Shanghai Jiaotong University from July 1, 2010 to March 31, 2012. The survey includes general questions and an evaluation of (peri-) menopausal symptoms using the modified Kupperman index score. Results: The average age of the women who took part in the study was 51.47 years old (standard deviation = 5.18). Of the women, 47.6% were perimenopausal, 34.7% were early postmenopausal, and 17.7% were late perimenopausal. The age of natural menopause was between 39 and 56 years, and the average natural menopause age was 49.3 years (standard deviation = 4.0). The incidence of (peri-) menopausal symptoms was 91%. Age, education level, and chronic diseases were associated with menopausal symptoms. The main reasons for seeking treatment were hot flushes, insomnia, bone and joint pains, mood swings, and palpitations. Conclusions: The main reasons for Chinese (peri-) menopausal women seeking treatment were hot flushes, insomnia, bone and joint pains, mood swings, and palpitations; age, education level, and chronic diseases are the main factors that influencing the (peri-) menopausal symptoms.

Key words: Peri-menopause; Perimenopausal symptoms; Epidemiological factors; Cross-sectional study.

Introduction
Perimenopause is a special period in a middle-aged woman’s life indicating the end of the fertile stage in her reproductive life cycle as her ovaries decline. These women will experience a range of menopause-related symptoms, including menstrual irregularity, hot flushes, night sweats, and bone and joint pains. Additionally, these symptoms may increase incidences of insomnia, depression, hypertension, diabetes, and urinary incontinence, which may adversely affect the quality of life of perimenopausal and postmenopausal women [1, 2]. The occurrence of perimenopausal syndromes differ between regions; occurrence rates are at 70% for women in Iran [3] and 85.8% for women in Sydney [4]. Main symptoms also vary between women. According to an insomnia research targeted at women over 40 years of age in Brazil, the incidence rate of insomnia was found to be 38.5% [2]. Other researches showed that the incidence rate of insomnia in perimenopausal and postmenopausal women was 50.8% [5]. Researches in America and Australia revealed that some of the reasons that (peri-) menopausal women had for seeking treatment were hot flushes, bone and joint pains, menstrual disorder, weight gain, insomnia, and irritability [6, 7]; while researches conducted in Japan showed that the main reasons were hot flushes, fatigue, and bone and joint pains [8]. The study of factors that could influence symptoms in (peri-) menopausal women is fairly common outside of China. Some of these factors, which can increase the occurrence of (peri-) menopausal symptoms, include age, education level, income, marital status, chronic disease, body mass index (BMI), and alcohol consumption [1, 4, 9-11]. China has a large population, with an estimated 120 million postmenopausal women. Due to the traditional notion that menopausal symptoms are natural occurrences that need no special care or treatments, very few women have sought treatment. As a result, there is a lack of research in China regarding reasons that (peri-) menopausal women had for seeking treatment and factors influencing symptoms in China.

Therefore, the purpose of this study was to investigate symptoms related to perimenopause and postmenopause based on women who sought treatment for menopausal symptoms in Shanghai city. By discovering the main reasons for seeking treatment and the factors that influence menopausal symptoms, information on improving the quality of life for (peri-) menopausal women can be provided.
Materials and Methods

Subjects
(Peri-) menopausal women who visited the Sixth People’s Hospital of Shanghai, Jiaotong University between July 1st 2010 to March 31st 2012 were selected based on the following criteria: (i) aged between 40 to 65 years; (ii) first-time visitors for menopause-related symptoms; (iii) those without a (peri-) menopausal-related treatment history; (iv) those who had not undergone a uterus hysterectomy or a bilateral oophorectomy; (v) those who had received primary education or higher. Patients were categorized as being either perimenopausal or post-menopausal based on their menopausal status. Premenopause is a period of one to five years prior to menopause whereas menopause refers to the period after menstruation has ceased for a year. The perimenopause stage includes those who presented with menopause-related endocrinological, biological and clinical symptoms, and those who reached menopause less than a year ago, while the postmenopause stage includes those who have ceased menstruation naturally for more than five years. This study was approved by the ethics committee from the Sixth People’s Hospital of Shanghai and participants had also given their informed consent.

Methods
Interviews were conducted in this cross-sectional study. Newly diagnosed patients were asked the following questions: (i) general questions, including: age, occupation, education level, income level, height, weight, menstrual history, reproductive history, menopausal history, medical history, alcohol consumption level, smoking history, attitude towards menopause, and self-assessment; (ii) evaluation of (peri-) menopausal symptoms (this section, which comprised of 13 parts, was conducted using a modified version of the Kupperman index score [12]); hot flushes, paresthesia, insomnia, nervousness, melancholia, vertigo, weakness, bone and joint pains, headaches, palpitations, fornication, sexual problems, and urinary tract infections (UTI). Each symptom was assessed based on a basic score and an extent score that was rated on a scale of 0-3 points. The severity of each symptom was calculated by multiplying the basic score with the extent score. The total score was the sum of the score of each symptom. The modified version of the Kupperman index was used to evaluate and describe the severity of each symptom as follows: a total score of less than or equal to 6 was considered normal, a score of between 7-15 was mild, a score of between 16-30 was considered moderate, and a score of more than 30 was considered severe. The body mass index (BMI) was calculated by dividing body mass (kg) by the square of height (m). According to WHO guidelines, a BMI of less than 18.5 is considered underweight, a BMI of between 18.5 to 24.9 is considered normal, a BMI of between 25 to 29.9 is considered overweight, and a BMI of 30 and above is considered obese [13]. Those who had problems like hypertension, diabetes, and coronary heart disease were deemed to suffer from chronic diseases.

Statistical Analysis
The results were analysed using the SPSS 18.0 software. The enumeration data was expressed as actual frequency and percentage, while the measurement data was expressed as ±SD. The descriptive statistics were used for the demographic characteristics and independent variables of the samples, and were interpreted through an analysis of the variance (ANOVA), student’s t-test, Chi-square test, and the correlation and multiple stepwise regression analysis. P-values less than 0.05 were considered statistically significant.

<table>
<thead>
<tr>
<th>Content</th>
<th>Range</th>
<th>Number of cases (persons)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>40-44</td>
<td>30</td>
<td>8.4</td>
</tr>
<tr>
<td></td>
<td>45-49</td>
<td>92</td>
<td>25.8</td>
</tr>
<tr>
<td></td>
<td>50-54</td>
<td>140</td>
<td>39.2</td>
</tr>
<tr>
<td></td>
<td>55-65</td>
<td>95</td>
<td>26.6</td>
</tr>
<tr>
<td>Menopausal status</td>
<td>Perimenopause</td>
<td>170</td>
<td>47.6</td>
</tr>
<tr>
<td></td>
<td>Premenopause</td>
<td>124</td>
<td>34.7</td>
</tr>
<tr>
<td></td>
<td>Postmenopause</td>
<td>63</td>
<td>17.7</td>
</tr>
<tr>
<td>BMI</td>
<td>&lt; 18.5</td>
<td>15</td>
<td>4.2</td>
</tr>
<tr>
<td></td>
<td>(18.5 - 24.9)</td>
<td>281</td>
<td>78.7</td>
</tr>
<tr>
<td></td>
<td>(25 - 29.9)</td>
<td>50</td>
<td>14.0</td>
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<tr>
<td></td>
<td>≥ 30</td>
<td>11</td>
<td>3.1</td>
</tr>
<tr>
<td>Marital status</td>
<td>Married</td>
<td>352</td>
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<tr>
<td></td>
<td>Divorced and separated</td>
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<tr>
<td></td>
<td>Single</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>Education level</td>
<td>Elementary school</td>
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<td>3.6</td>
</tr>
<tr>
<td></td>
<td>Junior high school</td>
<td>68</td>
<td>19.0</td>
</tr>
<tr>
<td></td>
<td>High School (including technical secondary school)</td>
<td>154</td>
<td>43.2</td>
</tr>
<tr>
<td></td>
<td>College and above</td>
<td>122</td>
<td>34.2</td>
</tr>
<tr>
<td>Occupation</td>
<td>Worker</td>
<td>88</td>
<td>24.7</td>
</tr>
<tr>
<td></td>
<td>Farmer</td>
<td>5</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>Government officer and technician</td>
<td>212</td>
<td>59.4</td>
</tr>
<tr>
<td></td>
<td>Self-employed and freelancer</td>
<td>43</td>
<td>12.0</td>
</tr>
<tr>
<td></td>
<td>Unemployed</td>
<td>9</td>
<td>2.5</td>
</tr>
<tr>
<td>Reproductive history</td>
<td>0</td>
<td>36</td>
<td>10.1</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>287</td>
<td>80.4</td>
</tr>
<tr>
<td></td>
<td>≥2</td>
<td>34</td>
<td>9.5</td>
</tr>
<tr>
<td>Income level</td>
<td>≤ 1,000 CNY</td>
<td>16</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>1,001-3,000 CNY</td>
<td>191</td>
<td>53.5</td>
</tr>
<tr>
<td></td>
<td>3,001-5,000 CNY</td>
<td>95</td>
<td>26.6</td>
</tr>
<tr>
<td></td>
<td>5,001-10,000 CNY</td>
<td>38</td>
<td>10.6</td>
</tr>
<tr>
<td></td>
<td>&gt; 10,000 CNY</td>
<td>17</td>
<td>4.8</td>
</tr>
<tr>
<td>Chronic disease</td>
<td>Yes</td>
<td>55</td>
<td>15.4</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>302</td>
<td>84.6</td>
</tr>
</tbody>
</table>

Results

Major demographic characteristics of research subjects
A total number of 357 women fit the requirements and were entered into this study. The mean age was 51.47 ± 5.18 years, with a total of 170 perimenopausal women (47.6%), 124 premenopausal women (34.7%), and 63 postmenopausal women (17.7%). The age of natural menopause was between 39 to 56 years, with a mean age of 49.33 ± 4.0 years. The major demographic characteristics are shown in Table 1.

Incidence of (peri-) menopausal syndrome and score comparison between women with different menopausal statuses
Based on the modified Kupperman index score, there were a total of 32 cases that had a score of 6 or less and a
An analysis of the main reasons that perimenopausal and postmenopausal women in China have for seeking outpatient treatment etc.

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Table 2. — The incidence rate of (peri-)menopausal syndrome in women of different age groups.

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Number of cases</th>
<th>0-6 points</th>
<th>7-15 points</th>
<th>&gt;16 points</th>
<th>Incidence rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-44</td>
<td>30</td>
<td>6</td>
<td>12</td>
<td>6</td>
<td>80</td>
</tr>
<tr>
<td>45-49</td>
<td>92</td>
<td>11</td>
<td>24</td>
<td>49</td>
<td>88.1</td>
</tr>
<tr>
<td>50-54</td>
<td>140</td>
<td>7</td>
<td>18</td>
<td>81</td>
<td>95</td>
</tr>
<tr>
<td>55-69</td>
<td>95</td>
<td>8</td>
<td>13</td>
<td>48</td>
<td>26 91.6</td>
</tr>
<tr>
<td>Total</td>
<td>357</td>
<td>32</td>
<td>61</td>
<td>190</td>
<td>74 91</td>
</tr>
</tbody>
</table>

*p = 0.039, by Chi-square test.

Table 3. — Kupperman index score of women with different menopausal status.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Kupperman index score</th>
<th>Normal (≤ 6 points)</th>
<th>Mild</th>
<th>Irregular (&gt;6 points) n (%)</th>
<th>Subtotal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perimenopause</td>
<td>170</td>
<td>20.82±10.584</td>
<td>20 (11.8)</td>
<td>34 (20)</td>
<td>89 (52.4)</td>
<td>27 (15.9)</td>
</tr>
<tr>
<td>Premenopause</td>
<td>124</td>
<td>23.51±10.068*</td>
<td>7 (5.6)</td>
<td>20 (16.1)</td>
<td>65 (52.4)</td>
<td>32 (25.8)</td>
</tr>
<tr>
<td>Postmenopause</td>
<td>63</td>
<td>24.11±9.754*</td>
<td>5 (7.9)</td>
<td>7 (11.1)</td>
<td>36 (57.1)</td>
<td>15 (23.8)</td>
</tr>
<tr>
<td>Total</td>
<td>357</td>
<td>22.33±10.34</td>
<td>32 (9)</td>
<td>61 (17.1)</td>
<td>190 (53.2)</td>
<td>74 (20.7)</td>
</tr>
</tbody>
</table>

*p < 0.05 vs perimenopause group by one-way analysis of variance (ANOVA) and Student-Newman-Kuels (SNK) paired comparison test.

Table 4. — Main reasons for seeking treatment in (peri-)menopausal women.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Patients</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot flushes</td>
<td>135</td>
<td>37.8</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>14</td>
<td>3.9</td>
</tr>
<tr>
<td>Insomnia</td>
<td>127</td>
<td>35.6</td>
</tr>
<tr>
<td>Nervousness</td>
<td>78</td>
<td>21.8</td>
</tr>
<tr>
<td>Melancholia</td>
<td>31</td>
<td>8.7</td>
</tr>
<tr>
<td>Vertigo</td>
<td>36</td>
<td>10.1</td>
</tr>
<tr>
<td>Weakness</td>
<td>65</td>
<td>18.2</td>
</tr>
<tr>
<td>Bone and joint pains</td>
<td>96</td>
<td>26.9</td>
</tr>
<tr>
<td>Headache</td>
<td>35</td>
<td>9.8</td>
</tr>
<tr>
<td>Palpitations</td>
<td>73</td>
<td>20.4</td>
</tr>
<tr>
<td>Formication</td>
<td>9</td>
<td>2.5</td>
</tr>
<tr>
<td>Sexual problems</td>
<td>23</td>
<td>6.4</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>21</td>
<td>5.9</td>
</tr>
</tbody>
</table>

Main (peri-)menopausal reasons for seeking treatment

The main (peri-)menopausal reasons for seeking treatment are reflected in Table 4. The top five reasons were: hot flushes (37.8%), insomnia (35.6%), bone and joint pains (26.9%), mood swings (21.8%), and palpitations (20.4%).

Frequency of (peri-)menopausal symptoms

As illustrated in Tables 5 and 6, the five most common symptoms reported by the 357 (peri-)menopausal women...
were: fatigue (85.7%), palpitations (75.1%), mood swings (74.2%), hot flushes (73.9%), and sexual problems (73.1%). The Chi-square test showed that the incidence of sexual problems and UTIs varied with the different age groups and menopausal statuses. Sexual problems were most common in postmenopausal women between 55-65 years of age while UTIs occurred most frequently in premenopausal women between 55-65 years of age. The incidence of each symptom and the outpatient rate were analysed using the Chi-square test and the results were statistically significant. (The χ² values were: 94.535, 207.242, 99.803, 196.207, 144.607, 208.062, 325.885, 147.036, 179.631, 213.454, 94.884, 331.181, 85.332; all p values were less than 0.001).

Multiple regression and correlation analysis of influencing factors of (peri-) menopausal symptoms

A stepwise multiple regression analysis was conducted using the Kupperman index scores of the (peri-) menopausal symptoms as dependent variables while the age, menopausal status, BMI, marital status, education level, reproductive history, occupation, income level, smoking history, alcohol consumption level, and existing chronic medical conditions were independent variables. Results in Table 7 show that age, education level, and existing chronic medical conditions were related to (peri-) menopausal symptoms. Related analysis revealed that these variables had a positive correlation with menopausal symptoms and the differences were statistically significant (r = 0.173, r = 0.169, r = 0.106, p values were 0.001, 0.001, and 0.046, respectively).

Discussion

Incidence of (Peri-) menopausal syndromes

Results obtained from the 357 cases in this study showed that the incidence rate of (peri-) menopausal syndromes was 91%, while the highest occurrence was found in the 50-54 age group. Although there were no statistical differences in the Kupperman index scores between the premenopausal and postmenopausal women, the Kupperman index scores of the menopausal women were significantly higher than that of the perimenopausal women.

The present results showed that the rate of incidence in Shanghai city was slightly different from that of cities in other countries. For example, reports showed that the rate of incidence was 70% for Iranian women [3], 85.8% for Sydney women [4], and 90.9% for Latin American women [14]. This research was targeted at women who were seeking treatment for (peri-) menopausal symptoms, which explains the higher incidence rates of (peri-) menopausal syndromes compared to that of women who only sought treatment for healthcare reasons. Therefore, a general survey should be conducted with (peri-) menopausal women in order to provide better healthcare treatment for them. Some examples include the setting up of clinics specializing in the treatment of women suffering from (peri-) menopause, implementing health consultation programs, and allowing universal access to hormone replacement therapies, which is necessary for the prevention of disease, deferment of senescence, and enhancement of quality of life in (peri-) menopausal patients.

### Table 6. — The number of cases and incidence rate of (peri-) menopausal symptoms in different menopausal status [n (%)].

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Perimenopause (n=170)</th>
<th>Premenopause (n=124)</th>
<th>Postmenopause (n=63)</th>
<th>Total (n=357)</th>
<th>χ²-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot flushes</td>
<td>117 (68.8)</td>
<td>96 (77.4)</td>
<td>51 (81)</td>
<td>264 (73.9)</td>
<td>4.697</td>
<td>0.095</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>85 (50.0)</td>
<td>61 (49.2)</td>
<td>41 (65.1)</td>
<td>187 (52.4)</td>
<td>4.964</td>
<td>0.084</td>
</tr>
<tr>
<td>Insomnia</td>
<td>122 (71.8)</td>
<td>95 (76.6)</td>
<td>43 (68.3)</td>
<td>260 (72.8)</td>
<td>1.661</td>
<td>0.436</td>
</tr>
<tr>
<td>Nervousness</td>
<td>123 (72.4)</td>
<td>92 (74.2)</td>
<td>50 (79.4)</td>
<td>265 (74.2)</td>
<td>1.182</td>
<td>0.554</td>
</tr>
<tr>
<td>Melancholia</td>
<td>77 (45.3)</td>
<td>66 (53.2)</td>
<td>34 (54.0)</td>
<td>177 (49.6)</td>
<td>2.394</td>
<td>0.302</td>
</tr>
<tr>
<td>Vertigo</td>
<td>97 (57.1)</td>
<td>86 (69.4)</td>
<td>38 (60.3)</td>
<td>221 (61.9)</td>
<td>4.679</td>
<td>0.096</td>
</tr>
<tr>
<td>Weakness</td>
<td>141 (82.9)</td>
<td>108 (87.1)</td>
<td>57 (90.5)</td>
<td>306 (85.7)</td>
<td>2.428</td>
<td>0.297</td>
</tr>
<tr>
<td>Arthralgia or myalgia</td>
<td>114 (67.1)</td>
<td>94 (75.8)</td>
<td>50 (79.4)</td>
<td>258 (72.3)</td>
<td>4.660</td>
<td>0.097</td>
</tr>
<tr>
<td>Headache</td>
<td>95 (55.9)</td>
<td>69 (55.6)</td>
<td>40 (63.5)</td>
<td>204 (57.1)</td>
<td>1.261</td>
<td>0.532</td>
</tr>
<tr>
<td>Palpitations</td>
<td>125 (73.5)</td>
<td>90 (72.6)</td>
<td>53 (84.1)</td>
<td>268 (75.1)</td>
<td>3.388</td>
<td>0.184</td>
</tr>
<tr>
<td>Formication</td>
<td>43 (25.3)</td>
<td>39 (31.5)</td>
<td>22 (34.9)</td>
<td>104 (29.1)</td>
<td>2.559</td>
<td>0.278</td>
</tr>
<tr>
<td>Sex life</td>
<td>111 (65.3)</td>
<td>96 (77.4)</td>
<td>54 (85.7)</td>
<td>261 (73.1)</td>
<td>11.545</td>
<td>0.003</td>
</tr>
<tr>
<td>Urinary infections</td>
<td>43 (26.5)</td>
<td>50 (40.3)</td>
<td>24 (38.1)</td>
<td>119 (33.3)</td>
<td>6.972</td>
<td>0.031</td>
</tr>
</tbody>
</table>

*Incidence rates significantly different from menopausal status by Chi-square test.

### Table 7. — Multiple stepwise regression analysis of factors affecting symptoms of (peri-) menopausal women.

<table>
<thead>
<tr>
<th>Factors</th>
<th>B</th>
<th>S.D</th>
<th>t-value</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.295</td>
<td>0.109</td>
<td>2.701</td>
<td>(0.080, 0.511)</td>
</tr>
<tr>
<td>Menopausal status</td>
<td>-0.871</td>
<td>1.409</td>
<td>-0.618</td>
<td>(-3.643, 1.901)</td>
</tr>
<tr>
<td>BMI</td>
<td>0.005</td>
<td>0.005</td>
<td>1.050</td>
<td>(-0.004, 0.014)</td>
</tr>
<tr>
<td>Marital status</td>
<td>4.532</td>
<td>3.594</td>
<td>1.261</td>
<td>(-2.537, 11.602)</td>
</tr>
<tr>
<td>Education degree</td>
<td>1.979</td>
<td>0.653</td>
<td>3.032</td>
<td>(0.695, 3.262)</td>
</tr>
<tr>
<td>Reproductive history</td>
<td>1.866</td>
<td>1.247</td>
<td>1.491</td>
<td>(-0.594, 4.313)</td>
</tr>
<tr>
<td>Vocational status</td>
<td>-0.739</td>
<td>1.403</td>
<td>-0.526</td>
<td>(-3.498, 2.021)</td>
</tr>
<tr>
<td>Economic status</td>
<td>-0.875</td>
<td>0.754</td>
<td>-1.161</td>
<td>(-2.358, 0.607)</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.432</td>
<td>1.021</td>
<td>1.203</td>
<td>(-0.331, 2.112)</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>1.596</td>
<td>1.304</td>
<td>1.421</td>
<td>(-0.403, 3.316)</td>
</tr>
<tr>
<td>Chronic disease</td>
<td>3.373</td>
<td>1.636</td>
<td>2.061</td>
<td>(0.155, 6.592)</td>
</tr>
</tbody>
</table>

*p < 0.05, by multiple stepwise regression analysis.
Furthermore, health advice can be provided in order for patients to develop a good lifestyle and eating habits. These measures would allow (peri-) menopausal women to heighten their own health awareness, understand how physiological changes can trigger various symptoms, and ultimately lead a stable and healthy life.

**Characteristics of (peri-) menopausal symptoms**

Based on the present research, the five most common (peri-) menopausal symptoms are: fatigue, palpitations, mood swings, hot flushes, and sexual problems. The rate of incidence of fatigue was at a high of 85.7%, which is consistent with Lu et al.’s [4] reported rate of 86% in (peri-) menopausal women in Sydney.Palpitations came in second with 75.1%, followed by mood swings at 74.2%, hot flushes at 73.9%, and finally, sexual problems at 73.1%. Results also showed that sexual problems and UTIs had the highest incidence rates for women between 55-65 years of age and this is in agreement with a previous report by Li et al., which indicated a low frequency of sexual intercourse for postmenopausal women [15]. The high incidence rate of sexual problems and UTIs in these women is probably due to ageing, fall in hormone levels, atrophy of the vaginal mucosa, vaginal dryness, atrophy of the urethral mucosa, and a weak immune system. However, the five main reasons that women in this study had for seeking treatment were: hot flushes, insomnia, bone and joint pains, mood swings, and palpitation, which is in accord with research done by Waidyasekera et al. [9]. The present data indicated that the incidence rate of each symptom was not consistent with the reasons for seeking treatment. This could be attributed to the extent of influence that the symptoms had on their jobs and lives as well as their recognition of each symptom. Hot flush is known as one of the most common symptoms in (peri-) menopausal women. Gjelsvik et al. [16] reported that the incidence of hot flushes peaked at the age between 53-54 years and gradually declined thereafter. Vanessa et al. [2] found that depression can result in an increase in the occurrence of hot flushes by 1.48 times. Other research [14] showed that hot flushes had the highest incidence rates in postmenopausal women. It has also been reported that the CYP1B1 gene is able to increase the occurrence of hot flushes by lowering the serum estrogen concentration [17].

Insomnia, which is the second reason for seeking treatment, refers to the inability to fall asleep or remain asleep (easily woken, waking early, or inability to fall asleep after waking up). It results in a decrease in sleep time and quality, an inability to fulfill an individual’s physiological needs, and an inability to function properly throughout the day. The incidence rate of insomnia in (peri-) menopausal women in this study was 72.8%, while a recent study in Mexico revealed that the incidence rate in (peri-) menopausal women was 53.3% and that insomnia and quality of life are closely related [18]. The correlation between insomnia and decline in estrogen levels have been reported, and Arakane et al. [19] observed a positive correlation between insomnia and severity of hot flushes, although the exact reasons are, as yet, unclear.

Bone and joint pains are the third most common reason for seeking treatment in (peri-) menopausal women. Previous studies showed that 73.3% - 74.4% of patients sought treatment for bone and joint pains [9, 20]. Moreover, studies have shown that the development of bone and joint symptoms are a precursor to menopause [10, 20]. The occurrence of osteoporosis increases with an extension of the menopausal period and increase in bone loss. However, there have been no reports on the correlation between bone pains and osteoporosis.

The fourth and fifth most common reasons for (peri-) menopausal women to seek treatment are mood swings and palpitations, respectively. Earlier studies have shown that mood swings could be a result of a decline in endogenous opioids like β-endorphin, which may cause a loss of balance of the neural transmitter that is between the angiotensin and γ-aminobutyric acid. This imbalance can result in problems like fatigue, irritability, and emotional instability [6]. Palpitations are a symptom of autonomic nerve disorders and a research conducted on animals in Japan revealed a positive correlation between fat intake and frequency of palpitations [8].

**Factors relevant to (peri-) menopausal symptoms**

(Peri-) menopausal symptoms are affected by several factors. The present study indicated that (peri-) menopausal symptoms have a positive correlation with age, education level, and chronic diseases, which is supported by research done by Karaçam an Seker [1]. However, Li et al.’s report suggested that a low education level actually increased the severity of the symptoms [15]. Those who are highly educated regard menstruation as a symbol of youth, while menopause is seen as a sign of old age and a loss of ability to reproduce. In contrast, those with a low education level think that menopause allows them to break away from menstrual pains and the use of contraceptive methods, which would make life more convenient for them. The different notions affect how (peri-) menopausal women adapt psychologically to the physiological changes, as well as their autonomic activity, which would in turn influence the incidence and the severity of their (peri-) menopausal syndromes. Similar studies have shown that chronic diseases are an independent risk factor for the incidence of peri-menopausal symptoms in Sri Lankan women [9]; age can increase the incidence rate of somatic symptoms in peri-menopausal women in Oman [20]; and a high education level can increase the occurrence of perimenopausal symptoms in Libyan women [21]. The present study showed that BMI was unrelated to the occurrence of symptoms, which is consistent with Guthrie et al.’s report on Australian women [22]. However, Moilanen et al. [10] indicated that
women with a high BMI were more likely to experience psychological and cardiovascular symptoms and others [8, 23, 24] have shown that overweight women are more likely to suffer from hectic fever. Further investigation using a large sample size is needed for a better understanding of how these factors affect (peri-) menopausal symptoms.

Conclusion

The average age of natural menopause of the 357 women who were entered in this study was 51.47 and 49.3 years, respectively. The results of this study showed that the incidence of (peri-) menopausal syndrome was relatively high. The main reasons for Chinese (peri-) menopausal women seeking treatment were hot flushes, insomnia, bone and joint pains, mood swings, and palpitations, while main factors that influenced their symptoms were age, education level, and chronic diseases. The information provided in this study could be useful for clinicians on improving the quality of life of (peri-) menopausal women.

This study was conducted on (peri-) menopausal women who sought treatment in hospitals, which accounts for the higher occurrence of (peri-) menopausal syndromes than normal. In addition, the sample size was relatively small, and future research using large sample sizes in different areas and on different people has to be conducted in order to provide personalized treatment programs for (peri-) menopausal women, which would enable them to improve their quality of life.

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References


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Single uroflow study as a tool in predicting the possibility of abnormal voiding symptoms after the administration of antimuscarinic agents in treating overactive bladder syndrome

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Chang Gung University, Kwei-Shan, Tao-Yuan (Taiwan)

Summary
Purpose of study: The aim of this study was to evaluate the efficacy of uroflowmetry in predicting the possibility of abnormal voiding symptoms following antimuscarinic treatment for overactive bladder syndrome (OAB) in Taiwanese women. Materials and Methods: A retrospective study was conducted on women with OAB. Forty-five women with abnormal voiding patterns shown by urodynamic study comprised the main group and 38 women with normal voiding patterns comprised the control group. All patients were prescribed two mg tolterodine once daily for one week. Follow-up on complaints of abnormal voiding symptoms was done one week later. Results: One woman in control group and 12 women in main group complained of abnormal voiding symptoms. There was a significant difference in the occurrence of abnormal voiding symptoms after antimuscarinic administration between main study group and control group (26.7 % vs 2.6 %, p = 0.02). Conclusion: Uroflowmetry is a non-invasive and simple tool to predict the occurrence of abnormal voiding symptoms after antimuscarinic use.

Key words: Overactive bladder; Antimuscarinics; Urodynamics; Voiding pattern; Uroflowmetry.

Introduction
The International Continence Society (ICS) has announced a definition of overactive bladder syndrome (OAB), which was from then on to be regarded as a syndrome whose diagnosis was made purely on the basis of symptoms presented without the need to perform urodynam ic examination [1]. Thinking behind, the definition was that the doctor could give their patients medicines directly according to their clinical complaints without any examinations before administration. Antimuscarinics are the first-line and also a safe pharmacotherapy for OAB at present [2-4]. Regarding antimuscarinics, dry mouth is the most common side effect and it has long attracted much attention [5, 6]. On the contrary, few of articles have showed the side effects of abnormal voiding symptoms caused by antimuscarinics. In the present authors’ clinical experience, they did often find them to cause abnormal voiding symptoms such as small caliber, slow stream or strained voiding, all of which can cause patients hesitancy to continue with antimuscarinics treatment. Some articles reported the idea that OAB symptoms can be caused by problems during the voiding phase and have led to a wider attention [7-9]. Some articles have showed that symptoms from the voiding phase may display as urinary frequency and urgency, which may in turn lead to wrong diagnosis and inappropriate treatment being offered [10, 11].

Up to now, there has been no better way to predict the possibility of abnormal voiding symptoms before administration of antimuscarinics. Therefore, this paper sets out to examine the possibility of abnormal voiding symptoms occurring because of antimuscarinic agent use in women with OAB. These agents were prescribed according to clinical symptoms without the aid of an urodynamic examination, relying on the value of uroflowmetry in predicting the occurrence of abnormal voiding symptoms.

Materials and Methods
In this retrospective chart-review study, the authors review 173 women with OAB syndrome treated by a week regimen of antimuscarinic agents From January 2004 through July 2009 at Chang Gung Memorial Hospital at Keelung. All patients suffered from one or more typical OAB symptoms for more than one year. The symptoms of OAB are defined as urinary urgency with or without urge incontinence, usually with urinary frequency (voiding eight times or more in a 24-hour period), and nocturia (awakening two times or more at night to void) [1].

Patients with complaints of abnormal voiding symptoms, previous abnormal urinary routine examinations, histories of urinary tract
abnormalities or lithiasis, surgeries of the pelvic floor or bladder, chronic pelvic pain, painful bladder symptoms, and other medical or neurogenic diseases were excluded. Patients on medication that would affect bladder function were not included. Combined symptoms of any type of urinary incontinence and abnormal voiding symptoms also constituted exclusion criteria. Pelvic examination revealed no obvious cystocele, uterine prolapse, and urogenital anomalies. Sonographic examination revealed no significant increase in the sizes of either the uterus or the pelvic mass.

All patients underwent a urodynamic examination consisting in the measurement of post-micturition residuals, urethral pressure uroflowmetry, electromyography (EMG), and cystometry according to the criteria of the ICS [12]. Uroflowmetry was performed under natural conditions. In general, typical uroflowmetry results showed a smooth single curve with a maximum flow rate exceeding 15 ml/sec and a voided volume above 200 ml (Figure 1A). If the curve was not smooth, had multiple interrupted peaks or showed an abnormal low flow rate, these patients were considered to be suffering from abnormal voiding patterns regardless of whether they had clinical symptoms or not (Figure 1B-1D). All procedures and the interpretation of the results were performed by one of the authors (H.Y.C.).

Follow-ups were done immediately after completion of the regimen in clinics. Observations included the presence of the usual abnormal voiding symptoms associated with regular protocol of tolterodine administration. The complaints of abnormal voiding symptoms such as small caliber, decreased force of urinary stream, urinary hesitancy, or strained voiding were recorded.

A three-day urinary diary had to be completed to make sure that the subjects included voided more than eight times per day, awoke two times or more at night to void, and had no fluid overload during the whole day. No questionnaires were used to quantify the impact of symptoms, but all subjects had these symptoms as their chief complaints, which significantly affected their quality of life. Of note is that the patients did not report any voiding difficulties or discomfort when having OAB symptoms.

All statistical analysis was conducted using a version of the 12.0 SPSS software program. Demographic characteristics of the patients are presented as the mean ± SD or percentage according to the variables. Furthermore, cross-tabulation was employed to describe the relationship between voiding patterns in urodynamics and voiding difficulties. Comparison of the relationship between voiding patterns in urodynamics and voiding difficulties after tolterodine treatment was made by the chi-square test ($\chi^2$) with $p < 0.05$ considered significant.

Results

Of the 173 women with overactive bladder syndrome at the present clinic arranged to undergo an urodynamic study
and that were enrolled onto the authors’ original database, only 83 women with OAB symptoms were subsequently offered and completed a week regimen of two mg once daily of tolterodine.

The demographic characteristics of these 83 subjects are listed in Table 1. All were Taiwanese. Their mean age was 48 years with no predominant age group found. There was no significant statistically discrepancy in the characteristic data between two groups. Among them, about 28% were postmenopause in two groups, indicating that menopause is not a very significant factor in the occurrence of OAB syndrome. In contrast, the rate of OAB cases for nulliparous women were only 7.89% and 13.33% in two groups, respectively. The majority of OAB patients (84.2% and 71.1%) in two groups were only implied a close relationship between NSD and OAB syndrome.

Table 2 shows the cross tabulation of voiding symptoms after administration of a week regimen of two mg once daily of tolterodine. Forty-five of 83 women (54.2%) with abnormal voiding patterns and 38 of 83 (45.8%) with normal voiding patterns were shown in an uroflow study. Twelve of 45 women (26.7%) with abnormal voiding pattern had complaints of abnormal voiding symptoms after taking tolterodine for one week. On the contrary, only one of 38 (2.6%) patients with normal voiding patterns had complaints of abnormal voiding symptoms after tolterodine use. The $p$ value was 0.002 which was statistically significant.

Twenty-four of 173 women (13.9%) did not return for follow-up or treatment after an original urodynamic examination during this study period. The authors conducted a telephone interview exploring the reasons why they refused to follow-up or receive treatment. Although they did not do any statistical analysis of their responses, they discovered two common reasons for their refusal to follow-up. These were the discomfort felt during the invasive examination procedure and a self-diagnostic misunderstanding thinking they had urinary tract infection due to irritative voiding symptoms, such as urine retention. These women with abnormal voiding symptoms after examination. Because of this misunderstanding, these patients lost confidence in the present authors’ care.

Table 1. — Characteristics of patients with overactive bladder symptoms.

<table>
<thead>
<tr>
<th></th>
<th>Normal voiding pattern ($n = 38$)</th>
<th>Abnormal voiding pattern ($n = 45$)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>$48.39 \pm 12.13$ (23-78)</td>
<td>$48.39 \pm 12.13$ (22-76)</td>
<td>0.164</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>$11 (28.95%)$</td>
<td>$13 (28.89%)$</td>
<td>0.995</td>
</tr>
<tr>
<td>NSD only</td>
<td>$32 (84.21%)$</td>
<td>$32 (71.11%)$</td>
<td>0.161</td>
</tr>
<tr>
<td>CS only</td>
<td>$2 (5.26%)$</td>
<td>$6 (13.33%)$</td>
<td>0.219</td>
</tr>
<tr>
<td>NSD and CS</td>
<td>$1 (2.63%)$</td>
<td>$1 (2.22%)$</td>
<td>0.905</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>$3 (7.89%)$</td>
<td>$6 (13.33%)$</td>
<td>0.433</td>
</tr>
</tbody>
</table>

Values are given as mean ± standard deviation (range) or n (%).
NSD: normal spontaneous delivery, CS: cesarean section.

Table 2. — Cross-tabulation of voiding symptoms after administration of tolterodine and voiding pattern. Incidences of voiding symptoms between the normal voiding pattern group and abnormal voiding pattern group.

<table>
<thead>
<tr>
<th></th>
<th>Abnormal voiding symptoms ($n = 13$)</th>
<th>No voiding symptoms ($n = 70$)</th>
<th>$p$</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal uroflow</td>
<td>1</td>
<td>37</td>
<td>0.002*</td>
<td>13.46</td>
</tr>
<tr>
<td>Abnormal uroflow</td>
<td>12</td>
<td>33</td>
<td></td>
<td>(1.66-109.14)</td>
</tr>
</tbody>
</table>

*Chi-square test

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Discussion

In this study, 105 of 173 (59.0%) OAB women demonstrated involuntary detrusor contractions on urodynamic examination. This result was similar to findings published earlier [13, 14]. It signified that around 40-50% OAB symptoms might be caused by problems originating from the Voiding phase. In the past, women’s abnormal voiding symptoms were often ignored or attributed to anti-incontinence surgery or pelvic organ prolapse. With a better study of physiology in pelvic floor, dysfunctions in voiding phase are now known to be the result of a spastic rhodospincher in the urethra or spastic levator ani muscle. It is common among women with problematic voiding habits, habitual refraining from voiding, or chronic pelvic pain [15, 16]. Often some of these women have complaints similar to typical OAB symptoms rather than abnormal voiding symptoms [5, 10].

Abnormal voiding symptoms, such as urine retention, are rare incidences caused by antimuscarinics (1.1 to 6%) [2]. Even lower dosage of antimuscarinics (two mg once daily of tolterodine) was used in this study; 13 of the 83 women (15.7%) were found to have abnormal voiding symptoms which caused them to cease taking medicine. The difference in the dosage used in most published reports and the present study may be due to the effect of medicines on differing body frames, i.e. between Western and Eastern bioavailability. This implies caution must be observed in the administration of antimuscarinic agents in treating OAB.

Diagnosis of overactive bladder can be purely based on history, physical examination, and clinical symptoms without urodynamics. In this study, OAB women with abnormal voiding patterns had a higher incidence of suffering from abnormal voiding symptoms after antimuscarinic treatment compared with those with normal voiding patterns (26.7% vs. 2.6%, $p = 0.002$). This implied that the importance of performing uroflow study before providing OAB women with prescriptions of antimuscarinic agents. Without the aid of uroflow study to find OAB women with abnormal voiding patterns, the abnormal voiding symptoms may occur subsequently. In fact, women with abnormal voiding pattern in uroflowmetry seem to have more severe voiding symptoms
than those without such abnormalities [9]. However, women with OAB symptoms may have voiding abnormalities that are missed by cystometrography only [9]. Therefore, uroflow study is useful for properly diagnosing such cases.

Urodynamic study is the useful examination to confirm abnormalities in both the storage and voiding phases, however the invasive nature and discomfort of urodynamics make its application limited in daily practice. Twenty-four of the 173 (13.87%) cases refused to return for follow-up appointments or treatment after undergoing urodynamic examination during this study period. Telephone interviews with these cases revealed that most of the patients complained of discomfort felt during the examination and/or voiding irritative sensations misunderstood by them to be a urinary tract infection due to the examination. To avoid possible infection during examination and the discomfort caused by placing the catheter, the authors suggested that a non-invasive single uroflowmetry examination can be done before antimuscarinic use to predict the possibility of abnormal voiding symptoms after it is used.

In the authors’ experience, they found Taiwanese women often could not tolerate a full dose of antimuscarinics over a long period. Side effects included not only dry mouth and abnormal voiding symptoms, but also dizziness, sleepiness, and constipation. They found patients were more concerned about the side effects rather than the effectiveness of the medication in the early treatment stage. This led the present authors to choose a half dosage in this study. Though there is no evidence confirming any difference due to ethnicity in antimuscarinic usage, the conjecture can be presumed from general pharmacology. The efficacy of medicine represents the observation of multiple processes that regulate drug disposition (pharmacokinetics) and response (pharmacodynamics). For orally administered antimuscarinic agents, their pharmacologic action relies on adequate intestinal absorption and distribution to sites of action, before their elimination by metabolic and excretory pathways. The entire process can be described as the LADMER system (i.e. liberation, absorption, distribution, metabolism, elimination and response). Furthermore, some metabolism reactions are primarily mediated by the cytochrome P450 (CYP) family of enzymes, which are highly related with gene and race.

The mechanisms of OAB might be caused by more complicated factors and merit further investigation. Attention that OAB women with abnormal voiding patterns had a higher incidence of abnormal voiding symptoms than in OAB women with normal voiding patterns should be paid before administration of antimuscarinics. Though urodynamic study is not a necessary for diagnosis and treatment of OAB, single non-invasive uroflowmetry may be a good tool for a prediction of abnormal voiding symptoms after antimuscarinic use. Some side effects due to ethnic differences after antimuscarinics should be applied with great caution. For example, prescription of a lower dose is recommended. There were only a small number of patients involved in this study. Larger case number are needed to investigate the feasibility and effectiveness regarding this issue.

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References

Decreed Bcl-6 and increased Blimp-1 in the peritoneal cavity of patients with endometriosis

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Summary

Purpose of investigation: The authors investigated the expression patterns of interleukin (IL)-1β and tumor necrosis factor (TNF)-α, cytokines associated with peritoneal inflammatory reactions, and of B cell leukemia lymphoma (Bcl)-6 and B lymphocyte inducer of maturation program (Blimp)-1, transcriptional factors associated with immunoglobulin (Ig) production; the concentrations of Igs, and their correlation, in patients with and without endometriosis. Materials and Methods: The authors analyzed the peritoneal fluid of 98 patients, 46 with endometriosis, and 52 with benign tumors. Results: IL-1β and TNF-α mRNAs and IgG and IgA concentrations were higher in the endometriosis group, but the differences were not statistically significant. However, Bcl-6 mRNA level was significantly lower and Blimp-1 mRNA level was significantly higher in the endometriosis group with significant correlations among transcriptional factors, Igs, and cytokines (p < 0.05). Conclusion: Peritoneal immune responses in patients with endometriosis may be due to increased IgG and IgA concentrations, as well as to changes in expression of proinflammatory cytokines and transcriptional factors.

Key words: Bcl-6; Blimp-1; Immunoglobulin; Endometriosis.

Introduction

Endometriosis is a chronic disease that causes dysmenorrhea and chronic pelvic pain, with severe endometriosis resulting in infertility. Depending on its severity, endometriosis results in the accumulation and activation of macrophages, B cells and T cells, and the secretion of various cytokines and chemokines, which induce various peritoneal immune responses [1, 2]. Macrophages and cytokines in peritoneal fluid are associated with inflammatory reactions, tissue repair, and neovascularization occurring in endometriosis. These macrophages and cytokines play an important role in the regulation of cell proliferation, activation, motility, adhesion, chemotaxis, and morphogenesis. Cytokines involved in the pathogenesis of endometriosis include interleukins (IL)-1, -2, -6, and -10; tumor necrosis factor (TNF)-α; interferon (IFN)-γ; and regulated upon activation, normal T-cell expressed and secreted (RANTES) [1, 3]. IL-1 and TNF-α, both produced by macrophages, are closely associated with inflammatory reactions to infection, and have an in vivo synergistic effect [4].

B cells present in the peritoneal cavity have been classified as CD5-positive B-1 cells and CD5-negative B-2 cells. B-1 cells are present mainly in the peritoneal and thoracic cavities, with fewer in the spleen, and none in lymph nodes and peripheral blood [5, 6]. In addition, unlike B-2 cells, B-1 cells not only secrete antibodies in the absence of external stimulation, thereby contributing to innate immunity, but also react with autoantigens, resulting in significant increases in B-1 cells in some autoimmune diseases and chronic lymphocytic leukemia [5-8]. Transcriptional factors involved in antibody production by B-cells include B cell leukemia lymphoma-6 (Bcl)-6 and B lymphocyte inducer of maturation program 1 (Blimp)-1. Bcl-6 is required for the generation of germinal center B cells, whereas Blimp-1 promotes differentiation by halting cell division cycle; thus, they are involved in the suppression and promotion of antibody production, respectively [9, 10].

Although previous studies investigated immune responses of various immune system cells in the peritoneal cavity, no study to date has investigated transcriptional factors involved in antibody production in patients with endometriosis. Thus, peritoneal changes associated with endometriosis have not yet been identified. The present authors therefore assayed the concentrations of IgG and IgA, immunoglobulins associated with chronic inflammation and the mucosal immune response, respectively, and the expression patterns of Blimp-1 and Bcl-6, transcriptional factors associated with the promotion and suppression of Ig production, respectively, in patients with and without peritoneal endometriosis. They also assayed the expression patterns of TNF-α and IL-

*Contributed equally to this work.
Table 1. — Primers for real-time RT-PCR.

<table>
<thead>
<tr>
<th>Name</th>
<th>Sequences</th>
<th>Annealing temperature</th>
<th>Product size (bp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bcl-6</td>
<td>F: 5’-TTATCTGTGCTCAAGCCTCAAGC-3’&lt;br&gt;R: 5’-ATCTGAGTACGACATCGCCG-3’</td>
<td>60</td>
<td>393</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blimp-1</td>
<td>F: 5’-ACGTCGAGGAGGTCACATTG-3’&lt;br&gt;R: 5’-AGTACGATCAGGATCAGTCCG-3’</td>
<td>55</td>
<td>210</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-1β</td>
<td>F: 5’-TATGACGGTCTACAGTTGCG-3’&lt;br&gt;R: 5’-GAGGTTTGCTACCAATGAGGC-3’</td>
<td>140</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNF-α</td>
<td>F: 5’-ATCTTTCGTCAACGCACAGTGC-3’&lt;br&gt;R: 5’-GGGTTTGCTACCAATGAGGC-3’</td>
<td>60</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-actin</td>
<td>F: 5’-GCGGAGAAGATGACCCCGATC-3’&lt;br&gt;R: 5’-GAGTACGACAGCTCGTGATAG-3’</td>
<td>60</td>
<td>77</td>
</tr>
</tbody>
</table>

RT-PCR: real-time-polymerase chain reaction; Bcl: B-cell leukemia lymphoma-6; Blimp: B-lymphocyte inducer of maturation program-1; IL: interleukin; TNF: Tumor necrosis factor-

1β, cytokines involved in various inflammatory and immune responses, and the correlations among these IgGs, transcription factors, and cytokines in these patients.

Materials and Methods

Materials

Peritoneal fluid samples were obtained from 98 patients who underwent laparoscopic surgery, including diagnostic laparoscopy, in the Department of Obstetrics and Gynecology at the present center between March 2010 and February 2013. Of these 98 patients, 46 had endometriosis and 52 had benign tumors. All patients provided written informed consent. Patients suspected of having inflammatory disease, lesions producing hormones, internal diseases, and immune diseases were excluded. The study protocol was approved by the institutional review boards (IRBs) of Vincent’s Hospital, The Catholic University of Korea and Kyung Hee University Hospital, and informed consent was obtained from each patient (VC13TISI0057, KMC IRB 1236-02).

RT-PCR

Peritoneal fluid was collected aseptically from the Douglas pouch during surgery, taking care to avoid bleeding. Total RNA was extracted from peritoneal fluid using RNA-Be solution kits according to the manufacturer’s protocol. First-strand cDNA was synthesized by reverse transcription in 20 ml reaction mixtures containing one mg of RNA, 1x reaction buffer, one mM of each dNTP, five mM random primers, 20 units RNase inhibitor, and 20 units AMV reverse transcriptase. The reaction mixtures were incubated at 42°C for one hour, and the reactions were terminated by heating at 95°C for five minutes. Primers specific for IL-1β, TNF-α, Bcl-6, and Blimp-1 are shown in Table 1. Real-time polymerase chain reactions (PCR) were performed using a real-time system and a supermix. Each 20-µl PCR reaction mixture included two µl of cDNA, ten µl supermix, two µl of each primer, and six µl PCR grade water. The amplification protocols consisted of an initial denaturation at 95°C for 30 seconds, followed by 45 cycles of denaturation at 95°C for five seconds and annealing and extension at 55°C to 64°C for 12 seconds. The point at which expression of each of the above cDNAs crossed with that of β-actin was applied to the formula, 2^(ΔΔCT) (β-actin), and the relative amounts were quantified.

Table 2. — Bcl-6, Blimp-1, and cytokine mRNA expression in the peritoneal fluid of patients with and without endometriosis.

<table>
<thead>
<tr>
<th></th>
<th>Control group (M ± SD)</th>
<th>Endometriosis group (M ± SD)</th>
<th>p value (Mann-Whitney U)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bcl6</td>
<td>0.095 ± 0.452</td>
<td>0.039 ± 0.036</td>
<td>0.036</td>
</tr>
<tr>
<td>Blimp-1</td>
<td>0.044 ± 0.159</td>
<td>0.539 ± 1.748</td>
<td>0.006</td>
</tr>
<tr>
<td>IL-1</td>
<td>0.030 ± 0.106</td>
<td>0.093 ± 0.292</td>
<td>0.626</td>
</tr>
<tr>
<td>TNF-α</td>
<td>0.078 ± 0.441</td>
<td>0.085 ± 0.408</td>
<td>0.108</td>
</tr>
</tbody>
</table>

Crossing point: 2^(ΔΔCt) as normalized. Bcl-6: B-cell leukemia lymphoma-6; Blimp-1: B-lymphocyte inducer of maturation program-1; IL: interleukin; TNF-α: Tumor necrosis factor-α; SD: Standard deviation

Enzyme-linked immunosorbent assay (ELISA)

Peritoneal fluid collected from patients was centrifuged, and the supernatants were stored at -80°C. IgG and Ig A concentrations were measured by ELISA. Briefly, 50 µl 1:100 goat anti-human lgG and/or Ig A in coating buffer (1.59 g Na2CO3+2.93 g NaHCO3+5% NaCl, pH 9.6) were placed in each well of a 96-well plate and incubated overnight at 4°C. The wells were washed six times, blocking antibody was added, 50 µl of sample was added to each well, and the plates were incubated at room temperature for three hours. The wells were washed six times, purified goat anti-human IgM conjugated to horseradish peroxidase in PBS/Tween/BSA solution was added, and the plates were incubated at room temperature. The plates were washed six times, substrate solution (2,2’-Azino-Bis) was added, and the optical absorbance was measured at 450 nm.

Comparison of effusion fluids

The level of each mRNA was compared in the endometriosis and non-endometriosis groups according to age, pregnancy history, and CA125 level. The authors also evaluated the correlation of these factors in the effusion fluid.

Statistical analysis

The Kolmogorov-Smirnov test was used to assess normality and Levene’s test was used to assess the equality of variances between groups. Between group differences in expression were determined using independent t-tests, with correlations assessed using the Pearson correlation test. All statistical analyses were performed using SPSS version 13, with a p-value less than 0.05 considered statistically significant.

Results

Characteristics of patients in the endometriosis and non-endometriosis groups

The mean ages of the patients in the endometriosis and non-endometriosis groups were 36.7±9.1 years and 40.8±10.2 years, respectively (p > 0.05), and their mean body mass indexes (BMIs) were 21.1 ± 3.3 kg/m² and 22.7 ± 3.2 kg/m², respectively (p > 0.05). Fertility and history of prior surgery were also similar in the two groups (p > 0.05), although CA125 was significantly higher in the endometriosis than in the non-endometriosis group (51.9 ± 5.4 IU/ml vs 29.8 ± 3.2 IU/ml, p < 0.05).

Expression of IL-1β, TNF-α, Bcl-6, and Blimp-1 mRNA in peritoneal fluid (Table 2)

IL-1β, TNF-α, Bcl-6, and Blimp-1 mRNAs were present in the peritoneal fluid of both groups. The levels of IL-1β...
and TNF-α were higher in the endometriosis group, but not significantly ($p > 0.05$ each). The Blimp-1 mRNA level was significantly higher ($p < 0.05$), while the Bcl-6 mRNA level was significantly lower ($p < 0.05$), in the endometriosis than in the non-endometriosis group.

Concentrations of Igs in effusion fluid (Table 3) Overall mean IgG and IgA concentrations were $1,695 \pm 30 \, \mu g/ml$ and $844 \pm 41 \, \mu g/ml$, respectively. The concentrations of IgG ($1,713 \pm 23 \, \mu g/ml$ vs $1,674 \pm 38 \, \mu g/ml$) and IgA ($864 \pm 33 \, \mu g/ml$ vs $821 \pm 25 \, \mu g/ml$) were higher in the endometriosis group, but these differences were not statistically significant ($p > 0.05$). The Blimp-1 mRNA level was significantly higher ($p < 0.05$), while the Bcl-6 mRNA level was significantly lower ($p < 0.05$), in the endometriosis than in the non-endometriosis group.

Correlations of clinical manifestations with transcription factor (Bcl-6 and Blimp-1), cytokine (IL-1β & TNF-α), and Ig (IgG and IgA) concentrations (Tables 4)

The authors observed significant correlations between clinical and demographic characteristics, including age, parity, and CA125 concentration, with IgA concentration in the two groups ($p < 0.05$ each).

Table 3. — Concentrations of immunoglobulins in the peritoneal fluid of patients with and without endometriosis.

<table>
<thead>
<tr>
<th></th>
<th>total control</th>
<th>Endometriosis</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG (µg/dl)</td>
<td>1,695 ± 30</td>
<td>1,674 ± 38</td>
<td>0.429</td>
</tr>
<tr>
<td>IgA (µg/dl)</td>
<td>844 ± 41</td>
<td>821 ± 25</td>
<td>0.525</td>
</tr>
</tbody>
</table>

*p < 0.05; Ig: Immunoglobulin

Table 4. — Correlation between clinical manifestations and the expression of Bcl-6, Blimp-1, cytokines mRNA, and immunoglobulins.

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>Endometriosis group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Bcl-6 -0.083</td>
<td>0.631</td>
<td>0.197</td>
</tr>
<tr>
<td></td>
<td>Blimp-1 -0.115</td>
<td>0.497</td>
<td>0.067</td>
</tr>
<tr>
<td></td>
<td>IL-1β -0.103</td>
<td>0.538</td>
<td>0.167</td>
</tr>
<tr>
<td></td>
<td>TNF-α -0.016</td>
<td>0.921</td>
<td>0.202</td>
</tr>
<tr>
<td></td>
<td>Ig G -0.018</td>
<td>0.911</td>
<td>0.209</td>
</tr>
<tr>
<td></td>
<td>Ig A -0.009</td>
<td>0.957</td>
<td>0.339</td>
</tr>
<tr>
<td>Parity</td>
<td>Bcl-6 -0.194</td>
<td>0.256</td>
<td>0.205</td>
</tr>
<tr>
<td></td>
<td>Blimp-1 -0.166</td>
<td>0.326</td>
<td>0.082</td>
</tr>
<tr>
<td></td>
<td>IL-1β -0.207</td>
<td>0.213</td>
<td>0.168</td>
</tr>
<tr>
<td></td>
<td>TNF-α -0.053</td>
<td>0.746</td>
<td>0.186</td>
</tr>
<tr>
<td></td>
<td>Ig G 0.160</td>
<td>0.323</td>
<td>0.290</td>
</tr>
<tr>
<td></td>
<td>Ig A 0.002</td>
<td>0.944</td>
<td>0.415</td>
</tr>
<tr>
<td>CA125</td>
<td>Bcl-6 0.211</td>
<td>0.347</td>
<td>0.452</td>
</tr>
<tr>
<td></td>
<td>Blimp-1 0.259</td>
<td>0.234</td>
<td>0.068</td>
</tr>
<tr>
<td></td>
<td>IL-1β 0.207</td>
<td>0.332</td>
<td>0.104</td>
</tr>
<tr>
<td></td>
<td>TNF-α -0.112</td>
<td>0.586</td>
<td>-0.011</td>
</tr>
<tr>
<td></td>
<td>Ig G 0.115</td>
<td>0.577</td>
<td>0.067</td>
</tr>
<tr>
<td></td>
<td>Ig A 0.446</td>
<td>0.029</td>
<td>0.432</td>
</tr>
</tbody>
</table>

* Table 5. — Correlation between immunoglobulin concentrations, and mRNA encoding transcription factors and cytokines in peritoneal fluid.

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>Endometriosis group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>Bcl-6 -0.041</td>
<td>0.810</td>
<td>0.034</td>
</tr>
<tr>
<td></td>
<td>Blimp-1 -0.069</td>
<td>0.683</td>
<td>0.012</td>
</tr>
<tr>
<td></td>
<td>IL-1β 0.146</td>
<td>0.382</td>
<td>-0.105</td>
</tr>
<tr>
<td></td>
<td>TNFα 0.110</td>
<td>0.498</td>
<td>-0.092</td>
</tr>
<tr>
<td>IgA</td>
<td>Bcl-6 0.049</td>
<td>0.776</td>
<td>0.131</td>
</tr>
<tr>
<td></td>
<td>Blimp-1 0.060</td>
<td>0.722</td>
<td>0.179</td>
</tr>
<tr>
<td></td>
<td>IL-1β -0.016</td>
<td>0.925</td>
<td>-0.072</td>
</tr>
<tr>
<td></td>
<td>TNFα -0.049</td>
<td>0.765</td>
<td>0.137</td>
</tr>
</tbody>
</table>

* Table 6. — Endometriosis group. Correlations between IgG, IgA, and IgM concentrations and mRNAs encoding Bcl-6, Blimp-1, IL-1β, -8, -12, and TNF-α.

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>Endometriosis group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA</td>
<td>IgG 0.473**</td>
<td>0.473**</td>
<td>0.269</td>
</tr>
<tr>
<td></td>
<td>TNFα 1.000</td>
<td>1.000</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>IL-1β -0.072</td>
<td>1.000</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Blimp-1 -0.072</td>
<td>1.000</td>
<td>0.000</td>
</tr>
</tbody>
</table>

* Table 6. — Correlation of transcription factor (Bcl-6 and Blimp-1), cytokine (IL-1β & TNF-α), and Ig (IgG and Ig A) concentrations (Tables 5 and 6).

In the two groups, none of these mRNAs was correlated with the IgG and IgA concentrations ($p > 0.05$ each) (Table 5). However, significant correlations were observed between the transcription factors and cytokines in the endometriosis group ($p < 0.05$ each) (Table 6).

Discussion

Endometriosis, which is characterized by disparate morphological, histological, and biochemical properties, is an inflammatory disease resulting from changes in the pelvic environment. Ectopic lesions secrete chemotactic molecules that recruit immune cells to the peritoneal fluid, with the latter cells secreting cytokines that promote lesional proliferation, which, in turn, triggers immune responses [11]. IL-1β and TNF-α are central to the extravasation of polymorphonuclear leukocytes (PMN) into the infected tissue. IL-1β activates B and T cells, epithelial and fibroblast proliferation, cytokine synthesis, and histamine release, inducing fever and bone resorption [12]. TNF functions sim-
ilarly to IL-1, with the two cytokines acting synergistically [13, 14]. The present found that the levels of expression of IL-16 and TNF-α mRNAs were higher in the endometriosis than in the non-endometriosis group, but neither of these differences was statistically significant. Differences, however, may depend on endometriosis severity, sample type (endometriosis tissue, peritoneal fluid, or serum), control group (normal subjects or those with benign tumors), disease type (diseases other than endometriosis), history of drug treatment in endometriosis patients, or genetic polymorphisms.

B cells, which play an important role in antigen recognition, antibody production, and immune system regulation, have receptors such as IgM and IgD, and surface markers such as CD19, CD20, and CD21. Stimulation of B cells by T-cell dependent and independent antigens results in B-cell proliferation or differentiation, with most of these cells undergoing apoptosis. B cells differentiate into plasma cells or memory cells that produce antibodies. Differentiated plasma cells initially produce IgM and IgD, and then produce IgG, IgA, or IgE after DNA remodeling. Thus, even in the absence of exogenous infection, various antibodies may be present in the peritoneal cavity. The present authors focused on two classes of antibodies: IgG, the class of antibody associated with chronic inflammation and auto-immune reactions; and IgA, the class of antibody associated with mucosal immunity. Previous studies showed that the concentration of specific IgG autoantibody was increased in the peritoneal fluid of patients with endometriosis and that endometrial glandular epithelial staining for both IgG and IgA was significantly increased, suggesting that endometriosis may be an autoimmune disease. Moreover, increases in IgG concentration may also suggest that patients have a precursor of endometriosis requiring treatment [11, 15, 16].

In the absence of bacterial infection, the peritoneal cavity is a sterile environment, in which B cells cannot produce antibodies due to the absence of external stimulation. IgM, however, is spontaneously produced in the peritoneal cavity in the absence of external infection by B-1 cells rather than by B-2 cells [5, 6]. Since few or no B-1 cells, however, are present in cervical lymph nodes and the spleen, immunoglobulin is not produced spontaneously. Although culture of peritoneal fluid from the patients in this study detected no bacteria, IgG and IgA were secreted into the peritoneal cavities of all 98 patients. The concentrations of IgG and IgA were both higher in the endometriosis than in the non-endometriosis group, but the differences were not statistically significant, a result likely due to the patients in both groups not having infectious disease and the absence of bacteria in peritoneal fluid. The present authors found, however, that IgA concentration in the endometriosis group increased according to age and parity. Although the exact mechanism remains to be identified, peritoneal adhesion and inflammatory reactions seem to be affected by the duration and severity of endometriosis, by age-related changes in immune responses, and/or by pregnancy-associated changes in hormone concentrations.

Bcl-6 and Blimp-1 are transcriptional factors involved in antibody production by plasma cells. The present authors found that the level of Bcl-6 mRNA was lower and the level of Blimp-1 mRNA level was higher in the endometriosis group compared with the non-endometriosis group. Bcl-6 has been reported to inhibit the differentiation of plasma cells and Blimp-1 has been found to regulate secretion by B lymphocytes [17, 18]. Although the level of Bcl-6 mRNA is higher in both resting and germinal center B cells, the level of Bcl-6 protein is 3–34-fold higher in the germinal center than in resting B cells. Bcl-6, which suppresses Blimp-1, inhibits the activity of STAT3, thereby blocking the differentiation of germinal center B cells into plasma cells during an early phase. In B lymphocytes, Blimp-1 protein regulates the expression of three genes, thereby playing roles in cell cycle arrest, induction of immunoglobulin secretion, and the inhibition of germinal center functions [19]. Blimp-1 is expressed in all plasma cells, both in response to primary stimulation by T-cell dependent and independent antigens, as well as in mature plasma cells present in the bone marrow and in memory cells responsible for secondary response [20]. The present authors found that Blimp-1 mRNA level was higher in the endometriosis than in the non-endometriosis group due to the decrease in Bcl-6 mRNA level, and that the increase in Blimp-1 level resulted in increased IgG and IgA concentrations, findings consistent with those of previous studies. Thus, the higher IgG and IgA concentrations in the endometriosis group were attributable to decreased Bcl-6 and increased Blimp-1 expression, with the latter due to the increased expression of the proinflammatory cytokines, IL-1β and TNF-α, showing that inflammation-related immune responses occurred more actively in the endometriosis group than in non-endometriosis group.

This study had several limitations. For ethical reasons, its control group consisted of patients with peritoneal masses rather than healthy subjects. Thus, despite the absence of peritoneal infection, immune responses related to the mass may have occurred. In addition, the authors assessed mRNA not protein expression. Thus, these mRNAs may not have been translated into proteins. Third, they measured transcriptional factors and cytokines at the mRNA level whereas immunoglobulins were measured at the protein level. Fourth, B-1 and B-2 cells are both present in the peritoneal cavity. As these two cell types were not sorted from the peritoneal fluid, it is not clear whether the measured concentrations of IgG and IgA were attributable to spontaneous secretion by B-1 cells or stimulated secretion by B-2 cells. Fifth, clinical manifestations and immune responses in patients with endometriosis may depend on its severity. However, the authors compared patients with or without endometriosis. Sixth, although they
analyzed mRNA and protein concentrations in peritoneal fluid, they did not compare these results with expression in serum or endometriosis tissues. Thus, there were no comparisons of immune responses between tissue samples from the endometriosis and non-endometriosis groups.

In conclusion, the expression of the proinflammatory cytokines, IL-1α and TNF-α, in the peritoneal fluid of patients with endometriosis was due to peritoneal inflammatory responses and immune responses. In addition, the levels of Bcl-6 and Blimp-1 mRNAs, which are associated with the peritoneal secretion of IgG and IgA, were lower and higher, respectively, in the endometriosis than in the non-endometriosis group, indicating a vigorous B-cell immune response in patients with endometriosis.

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References


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Prevalence of menopausal related symptoms and their impact on quality of life among Egyptian women

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Summary

Objective: To assess the prevalence of menopausal-related symptoms and to evaluate their impact on quality of life (QoL) among a sample of menopausal women from Egypt. Materials and Methods: A cross-sectional hospital-based study conducted at the Gynecology department, Suez Canal University, Ismailia – Egypt. A total 1,214 women aged 40 – 70 years were recruited and studied using an interview questionnaire. The questionnaire contains four main items: socio-demographic data, menstruation status assessment, modified Menopausal Rating Scale (MRS), and World Health Organization Quality of Life (WHOQOL-BREF) questionnaire. Results: Mean age was 48.1 ± 10.3 years, with 26.6% of the studied participants were illiterates. According to menstruation status, 40.9% of the studied women were postmenopausal, 41.4% were premenopausal, while 17.7% were perimenopausal. Most of the studied participants have mild/moderate somatic symptoms. Mild/moderate depressive mode, irritability, and anxiety have been reported in 63%, 58.4%, and 58.2% of women, respectively. Postmenopausal women have significantly higher scores on MRS except for urogenital score that was higher in perimenopausal women. They also had significantly lower QoL score in all subscales of WHOQOL-BREF except for psychological domain that was lowest among perimenopausal women. MRS total score has significant negative correlation to all domains of WHOQOL questionnaire. Conclusion: Postmenopausal women have higher prevalence of menopausal symptoms that significantly affect their quality of life more than pre- and perimenopausal women. Those in the transition period (perimenopausal) have higher prevalence of psychological symptoms with higher impact on their psychological welfare.

Key words: Menopause; Menopause Rating Scale; WHOQOL-BREF; Quality of life.

Introduction

Menopause is a normal physiological process that is directly caused by depletion of estrogen level and is defined as complete cessation of menstruation for more than twelve months [1 - 4]. It causes a host of symptoms that can be classified into vasomotor, physical, psychological, and sexual complaints. These symptoms can be severe enough to affect the normal daily life activities of menopausal women. It has been well documented that menopausal symptoms affect women’s quality of life [5 - 8]. The age of menopause is usually after the age of 45 years; however, menopause-related symptoms often start to occur several years earlier [9].

Menopause-related health issues and overall health and well-being of middle aged women have now become a major health matter [10]. There is increasing interest in menopausal women health as with the general increase in life expectancy, more women are expected to spend about one quarter to one third of their lives in a menopausal state [11-13].

Among Egyptian women, the mean age of menopause was estimated to be 46.7 years [14] which is relatively low compared to other countries. Due to many cultural and educational differences, the response and attitude of Egyptian women toward menopause is greatly different from that of women from western societies [15].

For research and epidemiological purposes, a lot of tools have been designed to estimate the menopausal symptoms. Among these tools, the Menopause Rating Scale (MRS) has been designed to measure the severity of age/menopause-related complaints by rating a profile of symptoms and is recommended for use in clinical practice [16]. It has been originally developed in German language [17] and translated into number of other languages [16].

Quality of life (QoL) has been defined by World Health Organization (WHO) QoL group as an individual’s perception of their position in life in the context of culture and values system in which they live and in relation to their goal expectations, standards, and concerns [18]. The study of QoL in post-menopause has become an essential component in clinical practice [19-21]. Unlike developed countries, little is available about menopausal symptoms and their effect on QoL of postmenopausal women in developing countries. The aim of the current study is to evaluate the menopausal symptoms and estimate their effect on QoL among Egyptian women in Ismailia city.
Materials and Methods

After approval of ethics committee of Faculty of Medicine, Suez Canal University, this cross-sectional descriptive study was conducted among a total of 1,214 women aged (40-70 years) living in Ismailia governorate. The study population was recruited among women attending gynecology outpatient clinic or their relatives visiting inpatients of Obstetrics and Gynecology department at Suez Canal University Hospital. The study was conducted through the period from January 2009 to January 2013. Women with induced menopause, premature menopause, receiving hormonal treatment, having medical problems like thyroid disorders, diabetes mellitus and hypertension, heart disease, or who were undergoing treatment for cancer, or were in remission, pregnant and breast feeding women, and those who refused to participate were excluded from the study. The required sample size was estimated based on power of study of 80% and α-error of 0.05 [22]. An informed written consent was obtained from all participants. Data were collected via structured interview questionnaire conducted by well-trained health personnel. The questionnaire included four main parts:

1) Socio-demographic data including age, marital status, educational level, current or previous job, and co-morbidities.

2) Menstruation status: The menopausal status was classified according to Stages of Reproductive Aging Workshop (STRAW) [23]. Women who reported the normal menstrual cycle for the last three months were classified as premenopausal. Women who reported change in the length of menstrual cycle for at least seven days from baseline or change in the menstrual flow i.e. lighter or heavier from their normal for the last three months were classified premenopausal. Finally, those last menstrual periods occurred 12 months or more ago were categorized as postmenopausal. Surgical menopause was defined as cessation of menstruation following removal of ovaries (with or without hysterectomy) [24]. According to this classification, the current study included 1,214 women grouped as premenopausal (503), perimenopausal (245), and postmenopausal (496) women.

3) Menopausal Rating Scale (MRS): Arabic translation was used. The translation was based on the original MRS questionnaire and was validated before the study population was recruited. Validation was tested to ensure that the questions were consistently delivered to women and that they carry the intended meaning they were designed for. In addition, our questionnaire matched the Arabic validated version that was described by Sweed et al. [25]. MRS is a self-administered instrument which has been widely used and validated and has been used in many clinical and epidemiological studies, and in research to assess the severity of menopausal symptoms [17]. The MRS is composed of 11 items and is divided into three subscales: (a) somatic - hot flushes, heart discomfort/palpitation, sleeping problems, and muscle and joint problems; (b) psychological - depressive mood, irritability, anxiety, physical and mental exhaustion, and (c) urogenital - sexual problems, bladder problems, and dryness of the vagina. Each of the 11 symptoms contained a scoring scale from “0” (no complaints) to “4” (very severe symptoms). The composite scores for each of the three dimensions (sub-scales) are based on adding up the scores of the items of the respective dimensions. The total score is the sum of the sum-scores of the three subscales. Women were asked whether or not they had experienced the 11 menopausal symptoms shown in the MRS in the previous one month (30 days).

4) The World Health Organization – Quality of life (WHOQOL-BREF) questionnaire comprises four domains containing 24 aspects in addition to one facet on overall quality of life and general health [26] evaluated in the previous four weeks. It is an abbreviated version of the WHOQOL-100 quality of life assessment [26]. There are a total of seven items in the physical domain (pain and discomfort, energy and fatigue, sleep and rest, mobility, daily living activities, dependence on medication, and working capacity), six in the psychological domain (positive feelings, thinking and concentration, self-esteem, physical image and appearance, negative feelings, and spiritual/religious/personal beliefs), three in the social domain (personal relationships, social support, and sexual activity), and eight in the environmental domain (physical safety and security home environment, financial resources, availability of health and social care, opportunities for acquiring new information and skills participation in recreation and leisure, physical environment, and transport). Each item was scored on a Likert scale ranging from 1 to 5, with a higher score indicating a favorable condition after reversing the direction of several items that were originally posed in a negative way; negatively-worded items need to be reverse-scored (Q3, Q4, and Q26), as shown in the formulae below. Higher scores denoting higher quality of life. In order to standardize the domain scores for comparison, the average score of each domain was calculated and then multiplied by four, as recommended by the WHOQOL-100 [27].

Physical domain = \((6\cdot Q3 + 6\cdot Q4 + Q10 + Q15 + Q16 + Q17 + Q18)\) x 4
Psychological domain = \((Q5 + Q6 + Q7 + Q11 + Q19 + Q26)\) x 4
Social Relationships domain = \((Q20 + Q21 + Q22)\) x 4
Environment domain = \((Q8 + Q9 + Q12 + Q13 + Q14 + Q23 + Q24 + Q25)\) x 4

TRANSFORMATION OF SCORES TO A 0-100 SCALE

Domain and facet scores can be transformed to a 0-100 scale using the following formulae: TR = \(\frac{\text{SCORE} - 4}{\text{SCORE} - 4} \times 100\) [27].

Due to the lengthy nature of the study, a registry at the Gynecology outpatient clinic was established to gather the data collected. Several members of the medical and nursing staff were involved in data collection after ensuring their full understanding of the questionnaires to ensure consistent delivery and filling of the different questions. The authors were available to provide assistance if needed. Data entry was the responsibility of an assigned clinic nurse and frequent verification was carried out by the authors.

Statistical analysis

Microsoft Excel 2003 and SPSS (Statistical Package for the Social Science) version 15 were used to analyze data. Data were statistically described in terms of mean, standard deviation, frequencies (number of cases), and percentages. For quantitative variables Student t test and analysis of variance were used to test significance of difference and for categorical data Chi square test was performed. A probability value (p value) less than 0.05 was considered statistically significant.

Results

Table 1 presents the socio-demographic characteristics of the studied participants. More than one quarter of the studied women were aged 40 – 45 years (27.6%) while...
Prevalence of menopausal related symptoms and their impact on quality of life among Egyptian women

20.5% were in age group 60 – 70 years. Most of the participants were married (67.1%). As regard religion, 95.6% were Muslims and 4.4% were Christians. Most of the studied women were housewives (37.1%). More than half of the studied women had moderate socioeconomic status. According to menstruation status assessment, 40.9% of women were postmenopausal, 41.4% were premenopausal, while 17.7% were perimenopausal.

The results obtained by MRS are presented in Table 2. Among somatic subscale items, the most common was joint and muscular discomfort (84.8%). Depressive mode, irritability, and anxiety have been reported among 76.4%, 74.9%, and 71.8% respectively. The most common psychological problem was physical and mental exhaustion (85%). More than half of the participants report having sexual problems (64.4%), while bladder problems were reported among 37.6% and vaginal dryness among 34.1% of participants.

The most common reported symptom among all subscales was joint and muscular discomfort (84.8%) and it showed no significant difference among women classified according to their menopausal status. Perimenopausal women have significantly higher prevalence of all Urogenital subscale items, all psychological subscales except physical and mental exhaustion and all somatic subscale items except joint and muscular discomfort (Table 3).

When comparing the total score and subscale scores among different groups of patients classified according to their menopausal status, it was found that premenopausal women had significantly lower somatic and psychological scores, while perimenopausal women had higher urogenital scores (Table 4).

Regarding the assessment of QoL, it was estimated that among all studied participants, psychological and environmental domains showed the lowest scores (55.8 and 54.9), while social relationships domain showed the highest score (56.9). Comparing the three groups according to menopausal status, it was found that postmenopausal women had the lowest scores in overall mean scores and all domains with statistically significant difference (Table 5).

Total score of menopausal rating scale was found to be significantly correlated with age (r = 0.3, p = 0.001). There was significant negative correlation between MRS total

Table 1. — Socio-demographic characteristics of the studied participants.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 –</td>
<td>335</td>
<td>27.6%</td>
</tr>
<tr>
<td>45 –</td>
<td>259</td>
<td>21.3%</td>
</tr>
<tr>
<td>50 –</td>
<td>189</td>
<td>15.7%</td>
</tr>
<tr>
<td>55 –</td>
<td>182</td>
<td>14.9%</td>
</tr>
<tr>
<td>60 –</td>
<td>128</td>
<td>10.6%</td>
</tr>
<tr>
<td>65 – 70</td>
<td>121</td>
<td>9.9%</td>
</tr>
<tr>
<td>BMI:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 30 Kg/m²</td>
<td>517</td>
<td>42.6%</td>
</tr>
<tr>
<td>≥ 30 Kg/m²</td>
<td>697</td>
<td>57.4%</td>
</tr>
<tr>
<td>Residence:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>546</td>
<td>44.9%</td>
</tr>
<tr>
<td>Rural</td>
<td>668</td>
<td>55.1%</td>
</tr>
<tr>
<td>Marital status:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>815</td>
<td>67.1%</td>
</tr>
<tr>
<td>Widow/divorced</td>
<td>346</td>
<td>28.5%</td>
</tr>
<tr>
<td>Single</td>
<td>53</td>
<td>4.4%</td>
</tr>
<tr>
<td>Parity:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>110</td>
<td>9.1%</td>
</tr>
<tr>
<td>Para 1-2</td>
<td>651</td>
<td>53.6%</td>
</tr>
<tr>
<td>≥ Para 3</td>
<td>453</td>
<td>37.3%</td>
</tr>
<tr>
<td>Religion:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muslim</td>
<td>1161</td>
<td>95.6%</td>
</tr>
<tr>
<td>Christian</td>
<td>53</td>
<td>4.4%</td>
</tr>
<tr>
<td>Educational level:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illiterate</td>
<td>323</td>
<td>26.6%</td>
</tr>
<tr>
<td>&lt; 12 years</td>
<td>286</td>
<td>23.6%</td>
</tr>
<tr>
<td>≥ 12 years</td>
<td>605</td>
<td>49.8%</td>
</tr>
<tr>
<td>Job (current/previous)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Housewife</td>
<td>450</td>
<td>37.1%</td>
</tr>
<tr>
<td>General worker</td>
<td>123</td>
<td>10.1%</td>
</tr>
<tr>
<td>Semi-professional</td>
<td>398</td>
<td>32.7%</td>
</tr>
<tr>
<td>Professional</td>
<td>243</td>
<td>20.1%</td>
</tr>
<tr>
<td>Socio-economic status:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>379</td>
<td>31.2%</td>
</tr>
<tr>
<td>Moderate</td>
<td>706</td>
<td>58.2%</td>
</tr>
<tr>
<td>High</td>
<td>129</td>
<td>10.6%</td>
</tr>
<tr>
<td>Menopausal status:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td>503</td>
<td>41.4%</td>
</tr>
<tr>
<td>Perimenopausal</td>
<td>215</td>
<td>17.7%</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>496</td>
<td>40.9%</td>
</tr>
</tbody>
</table>

20.5% were in age group 60 – 70 years. Most of the participants were married (67.1%). As regard religion, 95.6% were Muslims and 4.4% were Christians. Most of the studied women were housewives (37.1%). More than half of the studied women had moderate socioeconomic status. According to menstruation status assessment, 40.9% of women were postmenopausal, 41.4% were premenopausal, while 17.7% were perimenopausal.

The results obtained by MRS are presented in Table 2. Among somatic subscale items, the most common was joint and muscular discomfort (84.8%). Depressive mode, irritability, and anxiety have been reported among 76.4%, 74.9%, and 71.8% respectively. The most common psychological problem was physical and mental exhaustion (85%). More than half of the participants report having sexual problems (64.4%), while bladder problems were reported among 37.6% and vaginal dryness among 34.1% of participants.

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Regarding the assessment of QoL, it was estimated that among all studied participants, psychological and environmental domains showed the lowest scores (55.8 and 54.9), while social relationships domain showed the highest score (56.9). Comparing the three groups according to menopausal status, it was found that postmenopausal women had the lowest scores in overall mean scores and all domains with statistically significant difference (Table 5).

Total score of menopausal rating scale was found to be significantly correlated with age (r = 0.3, p = 0.001). There was significant negative correlation between MRS total

Table 2. — Menopausal symptoms according to MRS among studied participants.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Very severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatic subscale</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot flushes</td>
<td>334</td>
<td>27.5%</td>
<td>266</td>
<td>21.9%</td>
<td>434</td>
</tr>
<tr>
<td>Heart discomfort</td>
<td>377</td>
<td>31.1%</td>
<td>300</td>
<td>24.7%</td>
<td>401</td>
</tr>
<tr>
<td>Sleep problems</td>
<td>229</td>
<td>18.9%</td>
<td>283</td>
<td>23.3%</td>
<td>477</td>
</tr>
<tr>
<td>Joint and muscular discomfort</td>
<td>184</td>
<td>15.2%</td>
<td>73</td>
<td>6.0%</td>
<td>475</td>
</tr>
<tr>
<td>Psychological subscale</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressive mode</td>
<td>287</td>
<td>23.6%</td>
<td>409</td>
<td>33.7%</td>
<td>355</td>
</tr>
<tr>
<td>Irritability</td>
<td>305</td>
<td>25.1%</td>
<td>385</td>
<td>31.7%</td>
<td>324</td>
</tr>
<tr>
<td>Anxiety</td>
<td>342</td>
<td>28.2%</td>
<td>369</td>
<td>30.4%</td>
<td>338</td>
</tr>
<tr>
<td>Physical and mental exhaustion</td>
<td>182</td>
<td>15%</td>
<td>321</td>
<td>26.4%</td>
<td>529</td>
</tr>
<tr>
<td>Urogenital subscale</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sexual problems</td>
<td>432</td>
<td>35.6%</td>
<td>282</td>
<td>23.2%</td>
<td>379</td>
</tr>
<tr>
<td>Bladder problems</td>
<td>758</td>
<td>62.4%</td>
<td>132</td>
<td>10.9%</td>
<td>213</td>
</tr>
<tr>
<td>Vaginal dryness</td>
<td>801</td>
<td>65.9%</td>
<td>101</td>
<td>8.3%</td>
<td>218</td>
</tr>
</tbody>
</table>
Table 3. — Incidence of menopausal symptoms according to MRS among studied participants classified by menopausal status.

<table>
<thead>
<tr>
<th>Somatic subscale</th>
<th>Premenopausal (n=503)</th>
<th>Perimenopausal (n=215)</th>
<th>Postmenopausal (n=496)</th>
<th>Total (n=1214)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot flushes</td>
<td>367 72.9%</td>
<td>166 77.2%#</td>
<td>347 69.9%</td>
<td>880 72.5%</td>
<td>0.001*</td>
</tr>
<tr>
<td>Heart discomfort</td>
<td>332 66%</td>
<td>168 78.1%#</td>
<td>337 67.7%</td>
<td>837 68.9%</td>
<td>0.001*</td>
</tr>
<tr>
<td>Sleep problems</td>
<td>402 79.9%</td>
<td>186 86.5%#</td>
<td>397 80.1%</td>
<td>985 81.1%</td>
<td>0.001*</td>
</tr>
<tr>
<td>Joint and muscular discomfort</td>
<td>423 84.1%</td>
<td>185 86.1%</td>
<td>422 85.1%</td>
<td>1030 84.8%</td>
<td>0.8 (NS)</td>
</tr>
</tbody>
</table>

Table 4. — Menopausal symptoms according to MRS classified by menopausal status.

<table>
<thead>
<tr>
<th>Somatic score</th>
<th>All</th>
<th>Premenopausal (n=503)</th>
<th>Perimenopausal (n=215)</th>
<th>Postmenopausal (n=496)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatic score</td>
<td>6.1 ± 2.9</td>
<td>5.3 ± 1.4‡</td>
<td>6.3 ± 3.1#</td>
<td>6.4 ± 2.3</td>
<td>0.001*</td>
</tr>
<tr>
<td>Psychological score</td>
<td>5.6 ± 3.1</td>
<td>4.8± 2.9‡</td>
<td>6.7 ± 2.3#</td>
<td>6.8 ± 3.3</td>
<td>0.001*</td>
</tr>
<tr>
<td>Urogenital score</td>
<td>2.1 ± 1.9</td>
<td>1.7 ± 1.8</td>
<td>2.9 ± 2.5‡#</td>
<td>1.8 ± 2.1</td>
<td>0.001*</td>
</tr>
<tr>
<td>Total score</td>
<td>14.6 ± 6.1</td>
<td>11.8 ± 5.9‡</td>
<td>15.8 ± 6.9‡</td>
<td>13.9 ± 7.5</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

Table 5. — QoL assessment among studied participants.

<table>
<thead>
<tr>
<th>Physical domain</th>
<th>All</th>
<th>Premenopausal (n=503)</th>
<th>Perimenopausal (n=215)</th>
<th>Postmenopausal (n=496)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychological domain</td>
<td>55.8 ± 16.5</td>
<td>56.8 ± 13.5‡</td>
<td>55.5 ± 15.3#</td>
<td>55.2 ± 17.2</td>
<td>0.001*</td>
</tr>
<tr>
<td>Social relationships</td>
<td>56.9 ± 13.7</td>
<td>56.7 ± 18.7‡</td>
<td>57.2 ± 19.2#</td>
<td>55.1 ± 15.1</td>
<td>0.2 (NS)</td>
</tr>
<tr>
<td>Environmental domain</td>
<td>54.9 ± 18.2</td>
<td>51.9 ± 13.6‡</td>
<td>56.4 ± 15.9‡</td>
<td>53.2 ± 16.9</td>
<td>0.002*</td>
</tr>
<tr>
<td>GH (Q1)</td>
<td>3.32 ± 0.92</td>
<td>3.5 ± 0.79‡</td>
<td>3.3 ± 0.89‡</td>
<td>3.28 ± 0.79</td>
<td>0.001*</td>
</tr>
<tr>
<td>GH (Q2)</td>
<td>3.28 ± 0.93</td>
<td>3.4 ± 0.81‡</td>
<td>3.29 ± 1.06‡#</td>
<td>3.19 ± 1.1</td>
<td>0.003*</td>
</tr>
<tr>
<td>Overall mean score</td>
<td>53.1 ± 13.5</td>
<td>54.9 ± 15.4‡</td>
<td>53.1 ± 11.4‡</td>
<td>52.9 ± 12.5</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

Table 6. — Correlation between MRS and QoL and other parameters.

<table>
<thead>
<tr>
<th>WHO QoL BREF</th>
<th>All</th>
<th>Premenopausal (n=503)</th>
<th>Perimenopausal (n=215)</th>
<th>Postmenopausal (n=496)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical domain</td>
<td>-0.4 0.02*</td>
<td>-0.5 0.02*</td>
<td>-0.3 0.02*</td>
<td>-0.5 0.02*</td>
<td>0.001*</td>
</tr>
<tr>
<td>Psychological domain</td>
<td>-0.5 0.01*</td>
<td>-0.4 0.01*</td>
<td>-0.4 0.01*</td>
<td>-0.4 0.01*</td>
<td>0.001*</td>
</tr>
<tr>
<td>Social relationships</td>
<td>0.4 0.03*</td>
<td>0.3 0.03*</td>
<td>0.5 0.03*</td>
<td>0.3 0.03*</td>
<td>0.001*</td>
</tr>
<tr>
<td>Environmental domain</td>
<td>0.6 0.001*</td>
<td>0.7 0.001*</td>
<td>0.4 0.001*</td>
<td>0.5 0.001*</td>
<td>0.001*</td>
</tr>
<tr>
<td>Overall mean score</td>
<td>0.5 0.01*</td>
<td>0.5 0.01*</td>
<td>0.6 0.01*</td>
<td>0.4 0.01*</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

*Statistically significant difference among three. #Statistically significant difference versus other two groups.
Discussion

Menopause is an important phase in women’s life. As mentioned earlier, with increasing life expectancy, more women are expected to spend up to one third of their lives in a menopausal state [11 - 13]. Little data are available about this important phase and its effects on women from Egypt which prompted the authors to carry out this study.

The present study revealed that the mean age at menopause was 48.1 years. Other studies from Egypt reported 46.7 years [15] and 49.2 years [25] as a mean age of menopause among Egyptian women. This slight variation in the mean age of menopause may be due to the different population studied or the sample size of the studies. There is a need for a nation-wide study assessing this issue all over the country. Other studies across the world have revealed slightly different mean age but all of these studies are still within the normal range of menopausal age [1, 8, 28, 29].

In the present study the authors have used the translated MRS for assessment of prevalence and severity of menopausal symptoms. Menopausal symptoms assessment tools are few and MRS is one of the most commonly used ones and has been widely used in many epidemiological and clinical studies. Other surveys have used the same tool as the present [8, 14, 26] while other tools have been used by other studies as Nisar and Sohoo, [13] who have used Menopause-specific QoL questionnaire (MENQoL) to assess the frequency and severity of symptoms.

The present authors have translated and validated the MRS and found that in accordance to the recently published validated Arabic version published by Sweed el al in 2012 [25].

The most prevalent somatic symptoms in our study were joint and muscular pain (84.8%), sleep problems (81.1%) and hot flushes (72.5%). Lack of exercise and inadequate supplementation of calcium will invariably increase the incidence of joint and muscular pains. In addition, a significant proportion of women in our study were overweight/obese which adds further burden on the joints. It should be noted that menopause alone cannot explain all the somatic and psychological changes occurring among menopausal women; age-related changes play a significant role. For example, it is well known that the prevalence of joint pain increases progressively with age in women [30]. Nisar and Sohoo [13] findings were in agreement with the above results.

In agreement with our findings, Sweed et al. [25] have reported that the most prevalent somatic symptoms were joint pain (90.3%), sleep problems (84%), and hot flushes (76.8%). Other studies have reported the menopausal classical symptoms - including hot flushes - to be less prevalent (66.3%) [31]. This variation in the reported prevalence can be attributed to different factors. Hot flushes resolve within few years of menopause in most of women, but some women report symptoms for many years after they cease to menstruate [32, 33]. Menopausal status and symptoms vary across racial/ethnic groups [34, 35]. In Germany, for example, hot flushes was the most commonly reported symptom by 96.4% [36], whereas among Arab and Greek women living in Australia it was 63% and 43%, respectively [30] and the incidence was as low as 3.9% among Singaporean women [31]. In the United States, the prevalence of hot flushes was highest among African Americans (46%), followed by Hispanics (34%), whites (31%), Chinese (21%), and Japanese (18%) [35].

Perimenopausal women were found to have high scores among all subscales of MRS. Consistent with the current study, Nisar and Sohoo [13] have shown that psychological domain scores were significantly higher in the menopause transition group. The association of psychological symptoms with perimenopausal period has been reported also by Rahman et al. [8]. Studies from Thailand and south-east Asian countries showed that many menopausal symptoms such as hot flushes, upset stomach, insomnia, and urinary symptoms are significantly related to menopausal transition period [37, 38].

Unlike the present study, several previous papers have reported higher scores of urogenital subscale among postmenopausal women compared to pre- and perimenopausal women [1, 29, 31]. The urogenital symptoms including sexual problems, bladder problems, and dryness of vagina were less frequent; the individual and overall scores of MRS were also low for urogenital domain and this was consistent with Nisar et al. study [39].

QoL of postmenopausal women were found to be the most affected compared to premenopausal and perimenopausal women. The present findings in terms of QoL is consistent with Elsabagh et al., [14] however, unlike the present findings they did not report significant difference as regard social domain of WHOQUOL-REF questionnaire. These results support the results by Nisar and Sohoo [13] who highlighted that there was a negative correlation between MRS scores and WHOQOL-BREF scores in all domains for postmenopausal women. Moreover, Yakout et al. [40] emphasized that a negative significant relation was demonstrated between QoL and postmenopausal symptoms, where quality of life was adversely affected by postmenopausal symptoms among the postmenopausal Saudi women in the study subjects.

Other previous researches have reported different results inconsistent with the present study. Ozkan et al. [41] and Satoh and Ohashi [42] reported that there was no significant difference in the mean scores in the all domains and the total score of the quality of life.
The present authors have found significant negative correlation between total MRS score and all subscales of WHOQOL-BREF questionnaire. The present findings are supported by results reported by multiple previous studies who found that the severity of menopausal symptoms is negatively correlated with QoL of studied women [13, 14, 40, 43].

With regards to relation between QoL and socio-demographic characteristics, the present study have shown that QoL is significantly related to age, educational level, and socioeconomic status of women as older women with lower educational level and low socioeconomic status are more liable to have poor quality of life and vice versa. This is consistent with results reported by Elsabagh et al. [14], who reported significant correlation of QoL with age, educational level, and also family income. Other factors as family size and gravidity have been evaluated by other authors and were found to have significant relation with QoL [21, 40].

The main limitation of the present study is the cross-sectional nature of the study that might not reflect the situation of the whole community. Also, the authors did not exclude other confounding factors that influence women’s physical and psychological health in this age group.

MRS was established to be a self-reporting questionnaire but the authors used face-to-face interview to collect data due to relatively high percentages of illiteracy. Women were asked to provide some retrospective information such as climacteric symptoms experienced in the preceding weeks, regularity of menstruation, and last menstrual period, hence recall bias is unavoidable especially in some elderly women.

Conclusion

Postmenopausal women have higher prevalence of menopausal symptoms that significantly affect their QoL more than pre- and perimenopausal women. Those in the transition period (perimenopausal) have higher prevalence of psychological symptoms with higher impact on their psychological welfare.

Recommendations

Further wider scale community-based surveys are required for more detailed addressing of women’s health and impact of menopausal symptoms on QoL of women. It is recommended that health education programs should be directed toward premenopausal women for adequate understanding of the physiological changes accompanying the menopausal period and how to adapt with the new physiological status and avoid adverse effects on their psychological health. Improving sleep and joint problems will have good impact on QoL.

Acknowledgments

The authors are grateful to the medical and nursing staff at the Gynecology Department, Suez Canal University Hospital for their help and support throughout the conduction of the study.

References

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Genetic variation in COX-2 -1195 and the risk of endometriosis and adenomyosis

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Summary

Aim: This study aims to explore the relationship between COX-2 gene polymorphism and the hereditary susceptibility of endometriosis and adenomyosis. Materials and Methods: Gene polymorphism in COX-2 gene was genotyped in 170 cases of endometriosis, 150 cases of adenomyosis, and 240 matched non-endometriosis and non-adenomyosis controls. Results: Genotypic frequencies of GG, AG, and AA in COX-2 locus in endometriosis and adenomyosis were 16.5%, 51.2%, 32.4% and 16.0%, 49.3%, 34.7%, respectively. They were both significantly different from those in the control group (24.6%, 53.3%, and 22.1%) (p < 0.05). An allele frequency in endometriosis and adenomyosis were significantly higher than that in the control group. The risk of endometriosis or adenomyosis for those carrying two A alleles were 2.19 and 2.41 times to non-A genotype. Conclusion: Genetic variation of G to A at -1195 locus in the promoter region of COX-2 gene increases the risk of endometriosis and adenomyosis, and the genetic susceptibility of these two diseases are similar.

Key words: Endometriosis; Adenomyosis; COX-2; genetic susceptibility; Single nucleotide polymorphisms (SNPs).

Introduction

Endometriosis and adenomyosis are two common gynecological diseases that usually manifest dysmenorrhea and infertility clinically [1, 2]. Their incidences in women in reproductive age are more than ten percent. To date, the exact etiology and pathogenesis of these two diseases are still not clear. Although both the etiology and pathological mechanisms are not similar in these two diseases, a certain genetic predisposition does exist indeed [3, 4]. In recent years, it is very enthusiastic to the polymorphism studies on these two diseases, and a lot of relationships between some genetic variants and these two diseases have been revealed. For example, Juo et al. found neither the CYP1A1 nor CYP17 genes, estrogen-metabolizing genes, had no significant association with either of the two diseases [5], meanwhile, Govindan et al. indicated a significant association of C allele of estrogen receptor (ER) alpha gene with endometriosis [6]. Liu et al. reported -1154G/A and -2578C/A in the vascular endothelial growth factor (VEGF) gene maybe decreased risk of endometriosis in Chinese women [7]. Still some other cytokine-related genes, such as TNF and IL [8-10], and matrix metalloproteinase gene family, such as MMP-2, MMP-7 and MMP-9 [11, 12] were investigated, and some certain relationships have been revealed. However, up to now, the study on genetic variants in cyclooxygenase-2(COX-2) gene in endometriosis and adenomyosis is relatively rare.

COX-2 is an important inducible enzyme in the inflammatory process. It is an important rate-limiting enzyme in the synthesis of prostaglandin (PG), which is an important mediator in the inflammatory process [13]. Normally, COX-2 does not express in most tissues. However, if the cells receive a variety of stimuli, such as inflammatory mediators, growth factors, cytokines and tumor promoters, COX-2 will be quickly synthesized and involved in the inflammatory processes and tumor’s occurrence [14]. COX-2 overexpression has been confirmed in eutopic and ectopic endometrium of patients affected by endometriosis and/or adenomyosis in previous studies [15]. Therefore COX-2 is regarded as an important factor in the development of endometriosis and/or adenomyosis and its mechanism is that the two diseases are estrogen-dependent. Estrogen promotes the production of PG through the upregulation of COX-2, and establishes a positive feedback loop that the high concentration of peritoneal prostaglandin E2 (PGE2) increases the cyclic adenosine monophosphate (cAMP) level in cells. cAMP-dependent alternative pathway stimulates the production of P450 aromatase in ectopic endometrial cells and regulates the synthesis of estrogen and play an important role in the occurrence and development of endometriosis and adenomyosis [16, 17]. Recently, The Korean scholars Kim et al. reported the relationship between the COX-2 -765 G>C genetic variation and endometriosis and concluded that C allele may be a protective factor from endometriosis [18]. In this...
study, a case-control analyzing method was used to explore the distribution of the SNP locus at -1195bp in the promoter region of COX-2 gene in the Han women with endometriosis and adenomyosis in Tangshan, China, with the aim to supply some molecular theoretical basis for revealing the pathogenesis of endometriosis and adenomyosis.

Materials and Methods

Subjects

The study included 170 cases of endometriosis, 150 cases of adenomyosis, and 240 matched non-endometriosis and non-adenomyosis controls that were enrolled. Patients with endometriosis or adenomyosis enrolled were from the Tangshan Han women hospitalized in the Department of Obstetrics and Gynecology of Tangshan Workers’ Hospital and underwent a laparoscopy or laparotomy treatment from January 2007 to March 2011. All post-operative specimens were confirmed pathologically as ovarian chocolate cysts, pelvic endometriosis or adenomyosis and were classified as Stage II-IV using the revised American Fertility Society (AFS) classification of endometriosis. Patients in the control group were randomly selected from the non-endometriosis and non-adenomyosis patients treated in the same hospital during the same period. The age, menstrual history, reproductive history, family history, and other basic information of each subject was recorded. Patients complicated with other medical, surgical or endocrine diseases were excluded in this study. All subjects had not been treated with hormone therapy in the latest three months. Four ml peripheral venous blood sample from each subject was collected in a sodium citrate anticoagulant tube and stored at -80°C. This study was conducted in accordance with the declaration of Helsinki and with approval from the Ethics Committee of Tangshan Worker’s Hospital. Written informed consent was also obtained from all participants.

Genomic DNA extraction

Genomic DNA was extracted from blood samples using proteinase K digestion and saturated phenol-chloroform extraction method and dissolved in TE buffer. The DNA concentration was measured with a spectrophotometer.

Polymerase chain reaction (PCR)

PCR-based restriction fragment length polymorphism (PCR-RFLP) was used for genotyping. The following specific gene primers pair was used: forward: 5’-CCC TGA GCA CTA CCC ATC AT-3’ and reverse: 5’-GCC CTT CAT AGG AGA TAC TGG-3’. The PCR product size was 273 bp. The PCR reaction system contained 100 ng DNA template, 0.1 mM primer, 0.2 mM dNTP, 1.0 IU Taq DNA polymerase, 1× buffer and 1.5 mM MgCl₂. The reaction was run in the program of 95°C pre-denatured for two minutes, 35 cycles of 94°C 30 s, 60°C 30 s, and 72°C 45 s, and another seven minutes extending at 72°C. Then the PCR products were kept in 4°C for the next experiment.

Enzyme digestion

One mg of the purified PCR production was used for enzyme digestion. The reaction also required two ml 10×buffer, 0.25 IU restriction enzyme PvuII and double-distilled water to a total volume of 20 ml. Enzyme digestion was performed at 37°C for four hours and then the production was analyzed with 2% agarose gel electrophoresis. Gel imaging system determined the digesting results.

Sequence analysis

Some of the PCR products were purified by agarose gel extraction and sequenced by an ABI 377 automatic sequencer in order to verify the mutations at the COX-2 -1195 locus. AA was homozygous, GA was heterozygous, and the allele frequency = (2 × AA+GA) / (2×total cases). Genotyping was carried out blinded in order to ensure its reliability. In addition, repeated experiments were carried out by another researcher using 10% of the specimens randomly selected. The results were consistent with the first experimental results.

Statistical analysis

SPSS v17.0 software was used for statistical analysis in this work. Comparison of the age was carried out with analysis of variance. Comparison of genotypes was performed with Chi-square test. The odds ratio (OR) and 95% confidence interval (CI) calculated with non-conditional logistic regression model were used to indicate the strength of the association of genotypes with endometriosis and adenomyosis.

Results

Clinical characteristics

The age of each group showed no statistical difference (Table 1).

PCR-Restriction fragment length polymorphism (RFLP)

COX-2-1195 genotypes of the three groups were analyzed by PCR-RFLP. Genotype GG presented two bands of 200 bp and 73 bp, genotype GA presented three bands of
Genetic variation in COX-2 -1195 and the risk of endometriosis and adenomyosis

273, 200, and 73 bp, and genotype AA presented only a 273 bp band (Figure 1). The sequence analysis of some PCR products randomly selected from the three groups confirmed the results obtained from PCR-RFLP (Figure 2).

Relationship between COX-2 gene and endometriosis disease

Genotypic frequencies of GG, GA, and AA at -1195 bp in the promoter region of COX-2 gene of the control group were 24.6%, 53.3%, and 22.1%, respectively. However, in the cases group including endometriosis and adenomyosis, their genotypic frequencies were 16.3%, 50.3% and 33.4%, respectively (Table 2). There were significant differences in the frequencies between the two groups ($\chi^2 =11.235$, $p = 0.004$). According to the Hardy-Weinberg genetic equilibrium law, the distributions of the three genotypes in both the control group and the cases group are in line with the law, indicating that subjects in this study are random in genetics. Genotypic frequency of AG showed no significant difference between the two groups ($p = 0.112$) but genotypic frequency of AA was significantly higher in the case group than in the control group ($p = 0.001$). In the case group, A allele frequency was significantly higher than that in control group. Non-conditional logistic regression analysis showed that the risk of endometriosis was 1.43 (95% CI = 0.92–2.21) for those carrying an A allele and it was 2.29 (95% CI = 1.39–3.77) for those carrying two A alleles compared with GG genotype. It was markedly different between them ($p = 0.001$), indicating that A allele at -1195 bp in the promoter region of COX-2 gene significantly increased the risk of endometriosis disease.

Relationship between COX-2 gene and endometriosis or adenomyosis

The distributions of the three genotypic frequencies in the three groups are in line with the Hardy-Weinberg genetic equilibrium law, indicating that subjects in this study are random in genetics. Genotypic frequencies of GG, GA, and AA at -1195 bp in the promoter region of COX-2 gene were respectively 24.6%, 53.3%, and 22.1% in the control group, 16.5%, 51.2%, and 32.4% in the endometriosis group, and 16.0%, 49.3%, and 34.7% in the adenomyosis group (Table 3). They were dramatically higher in the endometriosis group and adenomyosis group than in the control group ($\chi^2 =7.159$, $p = 0.028$ and $\chi^2 =8.909$, $p = 0.012$, respectively) but showed no significant difference between the endometriosis group and the adenomyosis group ($\chi^2 = 0.192$, $p = 0.908$). Difference in the AG genotypic frequency was not significant, while difference in the AA genotypic frequency was significant between the endometriosis group and the adenomyosis group. A allele frequency in both the endometriosis group and the adenomyosis group were higher than in the control group.
The human COX-2 gene, mapped to chromosome 1q25.2–q25.3, is about 8.3 kilobase pairs in size and contains ten exons [19]. There are about 17 sites of the single nucleotide polymorphisms (SNPs) in COX-2 gene have been studied in some benign and malignant diseases, but most of them are non-functional [20–22]. As for COX-2-1195, a meta-analysis based on 25 case-control studies by Tang et al., including a total of 9,482 cancer cases and 12,206 controls, indicated that the variant of COX-2 -1195G>A moderately increased risk of cancers (AA/AG versus GG, OR = 1.15, 95% CI: 1.02–1.31) [23]. Dasdemir et al. reported COX-2-1195 AG genotype was significantly high in patients with migraine [24]. However, to the authors’ knowledge, the relationship between the G >A genetic variation at -1195 in the COX-2 gene promoter region and endometriosis or adenomyosis has not yet been reported.

In this study, genotypic frequencies of GG, GA, and AA at -1195 bp in the promoter region of COX-2 gene were 24.6%, 53.3%, and 22.1% in the control group, 16.5%, 51.2%, and 32.4% in the endometriosis group, and 16.0%, 49.3%, and 34.7% in the adenomyosis group. The genotypic frequencies in the control group were consistent with the literature reported by Zhang et al. [11]. The present authors found that COX-2-1195G>A and A allele frequencies in -1195 AA genotypic frequency and A allele frequencies in the adenomyosis group. The genotypic frequencies of GG, GA, and AA at -1195 bp in the control group were 22.5%, 53.4%, and 24.1% in the control group, 16.5%, 53.3%, and 22.1% in the adenomyosis group. The genotypic frequencies in the control group were consistent with the literature reported by Zhang et al. That the distribution frequencies of GG, GA and AA at -1195 bp in the promoter region of COX-2 gene were 22.5%, 53.4% and 24.1% in Han people [25]. The present authors found that COX-2 -1195 AA genotypic frequency and A allele frequencies in the case group were significantly higher than those in the control group, but they were not quite different between the endometriosis group and the adenomyosis group. Carrying A alleles would increase the risk of adenomyosis disease, which was consistent with the functions of -1195 G>A polymorphism. According to the previous investigations, polymorphisms of -1195G>A can form a binding site for c-Myb and increases the COX-2 gene promoter activity significantly, just as its carcinogenesis, regulate the balance among cell division, survival, and differentiation [26, 27], resulting in endometriosis. So the authors conjectured that -1195 G>A genetic variation may play an important role in the occurrence of endometriosis and adenomyosis, which have a similar pathogenesis.

Altogether, COX-2 -1195 A allele would significantly increase the risk of endometriosis and adenomyosis, which may be an important factor that affects the individual genetic susceptibility to endometriosis and adenomyosis, whose genetic susceptibility is similar.

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Genetic variation in COX-2 -1195 and the risk of endometriosis and adenomyosis


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IVF/ICSI frozen replacement cycles; every cycle?
Opinion expressed after a systematic review of the literature

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Summary
Objective: To determine whether in vitro fertilization (IVF), frozen replacement cycles offer better outcomes than fresh cycles in order to support, or not, a possible shift towards total replacement of fresh IVF/intracytoplasmic sperm injection (ICSI) cycles from frozen elective transfers (FETs). Study design: Systematic review; opinion paper. Results: Initial results seem to support a shift in current practice towards frozen cycles. Conclusion: Initial results may support replacement all fresh IVF/ICSI cycles with FETs, as this could be a safer and equally effective strategy. However, robust evidence from randomized controlled trials is needed if this will be generally applied.

Key words: In vitro fertilization (IVF); Intracytoplasmic sperm injection (ICSI); Frozen elective transfers (FET).

Introduction
Assisted reproduction technology (ART), through in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), has offered a happy family to millions of couples since its first implementation in the 1970’s [1]. Close to the increased demand for ART, nowadays lies the need for fetal and maternal safety [2-5].

Worldwide, the majority of IVF/ICSI cycles are “fresh” treatment cycles; any embryos left from them, remain frozen in storage for future use.

The first ever live birth after transfer of a thawed cryopreserved embryo took place in 1984 [6]. Since then, freezing-thawing technology has advanced greatly; so have number of frozen embryo transfers (FETs) and live births associated with them [7]. While having already accepted FET safety, in terms of offspring health [8] and obstetric outcome [9], it seems that efficacy in terms of live birth, is also comparable [10-12].

With the present study, the authors attempted to summarize currently available evidence examining FETs in order to support, or not, a possible shift towards total replacement of fresh IVF/ICSI cycles from FETs.

Methodology
Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews were followed. A systematic literature search was conducted using two standard electronic databases (Pubmed and Embase) plus Cochrane database of Systematic Reviews. All computerized searches were performed using the following medical subject heading terms: ‘frozen embryo transfer’, ‘IVF’, ‘perinatal’, ‘obstetric’, ‘outcome’, ‘fresh’. Publication type was either ‘randomized controlled trial’ or ‘systematic review’. There was no language restriction.

The search was performed between December 1, 2012 and January 31, 2013 for all available papers that had to be written in English. All papers’ reference lists were checked in order to identify additional studies. From this search the authors identified two RCTs examining fertility outcomes in women undergoing either fresh or elective frozen embryo transfers [10-11]. Moreover, they report the outcomes of a meta-analysis of observational studies examining obstetric and perinatal outcomes of either frozen or fresh embryo transfers [9].

Pregnancy rates after fresh cycles and FETs: is there a biological mechanism behind these?
Results of the two randomized controlled trials are presented in Table 1. They both present much higher clinical pregnancy rates in the FET group: 39 vs. 27.8% [10] and 84 vs. 54.7% [11], respectively. Aflatoonian et al. included 374 women aged under 38 years while Shapiro et al. included 137 women under 41 years old with an expected normal response to ovarian stimulation.

The biological mechanism behind these differences is not clearly defined. Several researchers have suggested better endometrial receptivity and higher embryonic-endometrial synchronization in FET cycles [13-16].

Hormonal profile in fresh cycles [very high E2 levels in proliferative phase causes upregulation of endometrial progesterone receptors [15], as well (along with high prog-
Estradiol (estrogen) as alteration in endometrial gene expression profiles [16]) is considered responsible for that decreased receptivity.

Molecular pathways responsible involve the complement, the transforming growth factor beta (TGFβ) signaling pathway, the “coagulation cascade” and the leukocyte transendothelial migration [10]. Thus, as progesterone’s role is recognized, in FET cycles, embryonic and endometrial synchronization can be achieved better by timing progesterone administration [10]. Therefore, the proposed “freeze-all embryos” cryopreservation and their transfer in a subsequent cycle, may increase endometrial receptivity and, therefore, implantation rate and live-birth outcome. Thus, it provides clinical benefits, including the increase of cumulative pregnancy and reducing the risk of ovarian hyperstimulation syndrome (OHSS [10].

Close to the increased endometrial receptivity, Shapiro et al. [11] suggested a different mechanism for the better results of the cryopreservation group. They suggested that the freeze–thaw procedure preferentially “selects” and rules outlawed embryos. Therefore, it results in a greater proportion of better quality, viable blastocysts being transferred in the cryopreservation group, and thus pregnancy rates are indirectly increased.

Results of both studies are encouraging. Nevertheless, both trials have some methodological limitations. Shapiro et al. [11] study was underpowered (required sample size 411) [17], with co-interventions (such as dual trigger for final oocyte maturation) and its pregnancy rates (84% vs. 54.7%) were far higher than those reported in worldwide available registries.

Results of both studies are encouraging. Nevertheless, both trials have some methodological limitations. Shapiro et al. [11] study was underpowered (required sample size 411) [17], with co-interventions (such as dual trigger for final oocyte maturation) and its pregnancy rates (84% vs. 54.7%) were far higher than those reported in worldwide available registries.

None of these RCTs provide live birth rates or cost-effectiveness and patients’ acceptability data [17]. Different types of freezing (Aflatoonian et al. [10]: vitrification / Shapiro et al. [11]: slow freezing) had been used and embryos were replaced in hormonally mediated cycles on Day-3 (Aflatoonian et al. [10]) or at blastocyst-stage (Shapiro et al. [11]).

The total number of 511 women remains far from the projected total number of 918 (459 in each group) to show a difference of 10% in pregnancy rates (between 25 and 35%) with 90% power and 95% as Maheswari and Bhattacharya reports [17].

Obstetric – perinatal results after fresh IVF cycles and FETs

The most reliable available meta-analysis [9] showed that in pregnant women after IVF, the relative risks of preterm birth, small for gestational age, low birth weight, perinatal mortality, and antepartum hemorrhage were significantly lower in those after FET than in those getting a fresh embryo transfer. Nevertheless, this meta-analysis has a number of limitations. Firstly, it examines only singleton pregnancies. Moreover, aggregated data cannot be adjusted for confounders (such as age, smoking, etc) whereas significant statistical heterogeneity (population, design of studies, and freezing-thawing protocols) exists.

Clinical implications

From the initial available results, it seems that the strategy of elective cryopreservation of all fresh embryos achieved in a fresh IVF/ICSI cycle and their transfer in a subsequent frozen (perhaps downregulated) cycle could offer pregnancy rates close to those of fresh embryo transfer. If we add evidence that show better results regarding obstetric safety, then a shift to ART practice may become a reality. Nevertheless, proper, robust randomized trials that will eliminate the flaws of those currently available, need to take place in order to boost that change in everyday clinical practice in ART.

References


Table 1. — Fertility outcomes after fresh cycles and FETs.

<table>
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<tr>
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<td>Elective FETs</td>
<td>Fresh embryo transfer</td>
<td>Clinical pregnancy</td>
<td>Higher pregnancy rates in FETs (39% vs. 27.8%)</td>
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<tr>
<td>Shapiro [11] RCT</td>
<td>137 women &lt;41 years old, with expected normal ovarian response</td>
<td>Elective FETs</td>
<td>Fresh embryo transfer</td>
<td>Clinical</td>
<td>Higher pregnancy rates in FETs (84% vs. 54.7%)</td>
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Table 2. — Obstetric outcomes following fresh IVF cycles and FETs. Relative risk, 95% confidence interval, FET vs. fresh embryo transfer.

<table>
<thead>
<tr>
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<th>Low birth weight</th>
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A pilot survey on obstetric complications in pregnant women with a history of repeated embryo implantation failure and those undergoing single local endometrial injury

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Summary

Purpose of Investigation: To assess if a history of repeated implantation failure (RIF) or local endometrial injury (LEI) for RIF affects the pregnancy course in women who conceived in the subsequent in vitro fertilization (IVF)-embryo/blastocyst transfer (ET/BT) cycle. Materials and Methods: Of 42 pregnant women with a history of three consecutive failed ET/BT cycles with negative pregnancy tests, 11 patients had a clinical pregnancy in the immediate subsequent ET/BT cycle following (the RIF group), whereas 31 patients had a clinical pregnancy in the subsequent ET/BT cycle following single curettage LEI in the proliferative phase of the preceding spontaneous cycle (the RIF/LEI group). Information on the obstetric complications were retrieved from medical records and compared with that of women who had a live birth in the first ET/BT attempt (the control group). Results: The clinical pregnancy rate, ongoing pregnancy rate, and live birth rate were significantly higher in the RIF/LEI group than in the RIF group (p < 0.010). There were no significant differences in the incidence of pregnancy of unknown location, ectopic pregnancy, miscarriage, stillbirth, preterm birth, premature rupture of the membranes, placenta previa, placental abruption, preeclampsia, pregnancy-induced hypertension, gestational diabetes, fetal growth restriction, caesarean section, and blood transfusion similar between the three groups (p > 0.31). Conclusion: In this pilot survey, neither a history of RIF nor LEI intervention for RIF increased the incidence of obstetric complications in the women who conceived in the subsequent ET/BT cycle.

Key words: Local endometrial injury; Repeated implantation failure; Obstetric complications.
progestogens was continued until nine weeks of gestation. RIF was defined as a history of three consecutive negative pregnancy tests following transfer of high-grade early cleavage embryos and/or blastocysts [9, 10]. Based upon the treatment preferences of the patients, hysteroscopy and single LEI was or was not performed once between the sixth and 12th day in the spontaneous cycle as previously described [11]. The patients with endometrial micropolyps, submucosal fibroids, and intrauterine septa/adhesion were excluded from the study. The patients with normal hysteroscopic findings proceeded subsequent ET/BT cycle. Information on pregnancy course was retrieved from medical records.

The continuous variables were analyzed using Tukey-Kramer test for multiple comparisons or Dunnet’s test for comparisons with the control group. The proportional data sets were compared using Pearson’s chi-square test, Fisher’s exact test, or Ryan’s multiple comparison method. A \( p \) value less than 0.05 was considered significantly different.

**Results**

From January 2010 to March 2012, a total of 789 infertile women underwent IVF-ET with short or gonadotropin-releasing hormone antagonist flexible protocol. Of them, 207 (26.2%) had a clinical pregnancy in the first transfer cycle of morphologically good embryo/blastocyst and live birth (the control group). One hundred and eighty-five patients (23.4%) had RIF despite three transfer cycles of morphologically good embryos/blastocysts. Of them, 171 patients preferred further infertility treatment. While 79 patients continued ET/BT cycle (the RIF group), 92 patients opted for single curettage LEI in the proliferative phase of the subsequent spontaneous cycle (the RIF/LEI group).

There were no significant differences in age and body mass index between the RIF group (36.9 ± 3.3 years, 20.6 ± 1.7 kg/m²), RIF/LEI group (37.8 ± 3.8 years, 20.8 ± 2.5 kg/m²), and the control group (36.1 ± 4.2 years, 20.5 ± 2.3 kg/m²) (\( p > 0.41 \)). Information on the pregnancy course was available in all patients in the RIF/LEI group and RIF group, and 191 out of 207 (92.3%) patients in the control group (Table 1). There were no reports on fatal obstetric complications in the patients in each group. The clinical pregnancy rate and ongoing pregnancy rate and live birth rate were significantly higher in the RIF/LEI group and control group than in the RIF group (\( p < 0.010 \)). Meanwhile, the incidence of pregnancy of unknown location, ectopic pregnancy, miscarriage, stillbirth, premature rupture of the membranes, placenta previa, placental abruption, preeclampsia, pregnancy-induced hypertension, gestational diabetes, fetal growth restriction, preterm birth, caesarean section, and blood transfusion were similar among the three groups (\( p > 0.31 \)).

**Discussion**

Studies demonstrated that IVF-ET pregnancy is a risk factor of obstetric complications [12]. Several researchers hypothesized that defective blastocyst implantation may be the initial step that lead to some obstetric complications such as preeclampsia or gestational hypertension [13]. In this pilot survey, the authors found that past history of RIF does not increase the onset of obstetric complications in the subsequent IVF-ET pregnancy. Moreover, LEI for infertile women suffering from RIF did not have a negative impact on the gestational course and outcome of these patients.
LEI was shown to upregulate the local expression of the embryo implantation-associated molecules including chemokines (CCL4 and CXCL1), cytokines (tumor necrosis factor-a and interleukin-15), adhesion molecules (transmembrane mucin-1, laminin 4, and integrin 6), and membrane-bound proteins (uroplakin 1b, adipose differentiation-related protein, and lysosomal associated membrane protein-2). These findings support the idea that LEI is capable of inducing mucosal inflammatory responses required for migration, attachment, and invasion of blastocysts [4, 6, 7, 14, 15]. The current findings implicate that these local inflammatory responses induced by mechanical scratches do not negatively influence intrauterine environment during the pregnancy course.

Early studies adopted multiple LEI in the preceding cycle [2-6]. However, considering the pains of the patients and the onset of the complications, it is conceivable that less invasive approach is more acceptable in the clinical practice. In this regard, the present authors previously demonstrated that the ongoing pregnancy rate following single-time LEI by curettage biopsy in the proliferative phase of the preceding spontaneous cycle is comparable to that following multiple LEI [8]. In combination with the results of the current study, the present authors suggest single LEI by curettage biopsy in the proliferative phase of the preceding spontaneous cycle as a safe and effective medical intervention to treat unexplained RIF.

References


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Introduction

Fear of childbirth (FOC) is a significant problem during pregnancy and in prenatal and the postnatal periods [1]. FOC may cause an increase in the rate of cesarean section on the mother’s request due to the fear of labour pain, baby’s death, woman’s death herself, losing control during labour, vaginal instrumental birth, and third-degree perineal tear [2]. Its prevalence differs based on maternal factors such as parity, maternal age, delivery method, educational level, history of complicated pregnancy, and whether there are psychological problems [3, 4]. Due to these factors, prevalence of FOC in women has been reported to vary from 5% to 20% [5-7].

Experienced traumatic delivery (e.g. emergency cesarean section, vacuum extraction) has been found as a risk factor for the development of FOC in multiparous women [3, 8, 9]. Nilsson et al. [4] reported that a negative birth experience was the most important factor for explaining FOC during pregnancy and one year after birth. Although Nieminen et al. [8] found that nulliparous women had higher mean FOC scores compared to parous women. In another study, Fenwick et al. [10] showed that nulliparous women experienced more fear than parous women before birth, and there was no difference in postpartum fear levels between nulliparous and parous women.

The authors investigated whether FOC may occur in multiparous women with previously uncomplicated vaginal delivery or elective cesarean delivery. The primary aim of this study was to evaluate FOC prevalence in multiparous women with a positive birth experience. The secondary aim of this study is to detect the relationship among FOC, previous delivery method, planned pregnancy, preferred method of delivery in multiparous women with no history of negative delivery, and pregnancy experiences.

Materials and Methods

This descriptive study was approved by the Ethics Committee of the Medical Faculty, Ataturk University. This study was conducted at the Obstetrics Department of Nenehatun Hospital (mean annual delivery rate: 6,000 deliveries), Erzurum, Turkey, from February 2012 to May 2013. Initially, obstetric examination was performed and whether there was a maternal or fetal problem was detected. Women with first pregnancy, complicated pregnancies (e.g. placenta previa, oligohydramnios, and fetal congenital abnormalities), medical disease (e.g. hypertension, diabetes mellitus), psychiatric illness, multiple pregnancies, a complication in previous pregnancies (e.g. miscarriage, abortion), experienced traumatic delivery (e.g. emergency cesarean section, forceps or vacuum extraction), and using assisted reproductive technologies to become pregnant were excluded from the study. Patients were questioned about their birth experience and their answers analysed according to previous studies [4, 6].
Patients with numeric rating scale score (NRS) ≥ 9 were defined as a negative birth experience [6] and they were excluded from the study. Patients who had undergone previous cesarean section because of maternal request were also excluded. The inclusion criteria composed of multiparity, pregnancy between 35 and 37 weeks gestation, uncomplicated pregnancy, history of traumatic pregnancy or delivery and history, and no severe FOC in previous pregnancies.

After written informed consent was obtained from women, the data were collected with a questionnaire form. The questionnaire included women’s demographic-obstetric information and the Wijma Delivery Expectancy/Experience Questionnaire (W-DEQ) form A. W-DEQ form A measures FOC level with 33 items in pregnant women [11]. In this study, FOC was assessed with the Turkish form of W-DEQ version A that has been established as reliable and valid to measure the level of FOC among Turkish women by Korukcu et al. [12]. This form includes 33 items regarding women’s cognitive appraisal and expectancies of childbirth. Answers are given on six scale steps per item ranging from 0 (not at all) to 5 (extremely) and the FOC level is detected according to total W-DEQ scores. W-DEQ scores ≥ 85 is defined as FOC and W-DEQ≥100 is defined as severe FOC or phobic fear [6]. Participants completed W-DEQ form A and maternal age, gestational week, parity, educational level, previous delivery methods, whether planned pregnancy, and preferable delivery method for the current pregnancy were recorded.

A power analysis was calculated for this study using Russ Lenth’s Power and sample size calculation application [13]; 323 patients are needed to calculate the probability of a condition with 95% confidence intervals (CI). A p < 0.05 was considered significant.

### Statistical analysis

SPSS 14 for Windows was used for statistical analysis of data. Data was initially assessed for normality using the Kolmogorov-Smirnov test. The analysis of participants for differences in demographic and obstetric characteristics was assessed with the unpaired t test. Presence (W-DEQ score ≥ 85) was analyzed with the unpaired t test. The unpaired Wilcoxon test was conducted to compare FOC scores, previous delivery method, parity, planned pregnancy, and preferred delivery method for the current pregnancy in two groups. In group 2, comparison of W-DEQ scores of the patients according to used anaesthetic technique were made with unpaired t test. The findings were calculated as mean ± standard deviation and odds ratios (OR) with 95% confidence intervals (CI). A p < 0.05 was considered significant.

### Results

During the study period 2,300 multiparous women attended the clinic for antenatal control, of whom 2,100 agreed to participate. Among these women 1,000 were excluded from the study due to history of experienced traumatic pregnancy (emergency cesarean section ‘n = 300’; forceps or vacuum extraction ‘n = 100’; history of miscarriage, abortion, and fetal malformation ‘n = 300’, severe FOC in previous delivery ‘n = 200’, and deep perineal laceration ‘n = 100’). Women who had become pregnant with assisted reproductive techniques (n = 150) were excluded from the study. Ten women with placenta previa, three women with twin pregnancies, five women with suspected fetal abnormality, ten women with gestational diabetes, and five women with psychiatric disease were also excluded. The remaining 917 patients were questioned about their previous birth experience and 100 patients were diagnosed as having had a negative birth experience (NRS score ≥ 9) were excluded from the study.

Eventually, the study sample consisted of 817 women who had completed the questionnaire form. Two groups were formed: group 1: women with a previous uncomplicated vaginal delivery (n = 472) and group 2: women with a previous elective cesarean section delivery (n = 345). Indications for cesarean section in group 2 were cephalopelvic disproportion (n = 70), previous cesarean section (n = 200), repeated cesarean (n = 50), non-cephalic presentation (n = 22), and genital herpes (n = 3). The demographic and obstetric characteristics of women are presented in Table 1. The total number of women with FOC in both groups (W-DEQ score ≥ 85) was 128 (15.6%). Women in group 1 had

### Table 1. — The demographic and obstetric characteristics of women participating in the study.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 (n = 472)</th>
<th>Group 2 (n = 345)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>28.74 ± 4.93</td>
<td>29.35 ± 4.39</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Maternal BMI (kg/m²)</td>
<td>29.28 ± 3.40</td>
<td>28.93 ± 2.98</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Parity</td>
<td>2.45 ± 0.79</td>
<td>2.37 ± 0.63</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Weeks of gestation</td>
<td>35 ± 4.34</td>
<td>36 ± 2.68</td>
<td>&gt; 0.05</td>
</tr>
</tbody>
</table>

Group 1: Women with a previous uncomplicated vaginal delivery. Group 2: Women with a previous elective cesarean section delivery.

### Table 2. — Some factors associated with FOC and mean W-DEQ scores of women.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 (n=472)</th>
<th>Group 2 (n=345)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fear of childbirth during pregnancy (W-DEQ score≥85)</td>
<td>75, 15.9</td>
<td>70.42±12.67</td>
<td></td>
</tr>
<tr>
<td>W-DEQ scores (mean±SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women with age ≥ 35 (n=125)</td>
<td>31, 24.8*</td>
<td>75.70±10.20*</td>
<td></td>
</tr>
<tr>
<td>Women with age &lt; 35 (n=692)</td>
<td>97, 14.0</td>
<td>69.86±12.44</td>
<td></td>
</tr>
<tr>
<td>University graduates (n=129)</td>
<td>21, 16.3</td>
<td>70.73±12.42</td>
<td></td>
</tr>
<tr>
<td>Non-university graduates (n=688)</td>
<td>107, 15.6</td>
<td>70.75±12.29</td>
<td></td>
</tr>
<tr>
<td>Pregnant (n=576)</td>
<td>69, 11.9</td>
<td>68.34±11.72**</td>
<td></td>
</tr>
<tr>
<td>Unplanned pregnancy (n=241)</td>
<td>59, 24.4</td>
<td>76.52±1.73</td>
<td></td>
</tr>
<tr>
<td>Women who previously had elective cesarean section with regional anaesthesia (n=204)</td>
<td>24***, 11.7</td>
<td>70.42±11.44</td>
<td></td>
</tr>
<tr>
<td>Women who previously had elective cesarean section with general anaesthesia (n=141)</td>
<td>26, 18.4</td>
<td>72.56±11.82</td>
<td></td>
</tr>
</tbody>
</table>

Group 1: Women with a previous uncomplicated vaginal delivery. Group 2: Women with a previous elective cesarean section delivery.

*p < 0.001, compared to women with age < 35 years. **p < 0.0001, compared to unplanned pregnancy.
similar mean W-DEQ scores to group 2 (70.42 ± 12.67, 71.21 ± 11.79, respectively, p > 0.05). The percentage of women with FOC was found to be higher in women who previously had elective caesarean section with general anaesthesia (18.4%) than women with regional anaesthesia (11.7%) (p < 0.05, OR1.87, 95% CI 1.02 - 3.43) (Table 2).

There was no correlation among FOC level and educational level (p > 0.05) (Table 2). Lower mean W-DEQ scores was found in women who had planned their pregnancy (68.34 ± 11.73) than unplanned pregnancy (76.52 ± 1.73), (p < 0.0001) (Figure 1). FOC was associated with pregnancy planning status (OR 2.4, 95% CI 1.66 - 3.58). Fifty-three women (41.4%) with FOC and 360 women without FOC (81.2%) preferred vaginal delivery for their current pregnancy and difference was significant (p < 0.001). Fear of labour pain was found as the major cause for preferring caesarean section (73.5%). The women who desired caesarean section (n = 204) had similar W-DEQ scores to the women who desired vaginal delivery (n = 613) for current pregnancy (72.55 ± 11.19, 70.51 ± 12.45, respectively, p > 0.05). FOC was associated with preferring delivery methods (OR 5.91, 95% CI 3.96 - 8.84) (Table 3). W-DEQ scores were found to be higher in participants over 35 years of age compared with the others (75.70 ± 10.20, 69.86 ± 12.44, respectively, p < 0.001) (Figure 2, Table 2). The odds ratio of FOC was 1.99 (95% CI 1.28 - 3.16) for age. In both groups, none of the patients had severe FOC (W-DEQ score ≥ 100). Women with W-DEQ score ≥ 85 referred to a specialist for psycho-education and psychosomatic support.

Table 3. — Distribution of women according to preferred delivery methods for their current pregnancy and causes for preferring delivery methods.

<table>
<thead>
<tr>
<th></th>
<th>Women who desired cesarean section for their current pregnancy (n=111)</th>
<th>Women who desired vaginal delivery for their current pregnancy (n=706)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women with FOC</td>
<td>75, 58.6%</td>
<td>53, 41.4%</td>
</tr>
<tr>
<td>in both groups (n=128)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women without FOC</td>
<td>129, 18.7%</td>
<td>560, 81.2%</td>
</tr>
<tr>
<td>in both groups (n=689)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean W-DEQ scores</td>
<td>72.55 ±11.19</td>
<td>70.51 ±12.45</td>
</tr>
<tr>
<td>(mean±SD)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Women’s reasons for preferring vaginal delivery (n=613)
- Post-delivery recovery is easier 100, 16.3
- It is a natural way 400, 65.2
- It is safer for the baby and mother 80, 13.0
- It is my doctor’s advice 33, 5.38

Women’s reasons for preferring elective cesarean section (n=204)
- Fear of labour pain 150, 73.5
- Wanted control of delivery time 20, 9.8
- Fear of vaginal lacerations 30, 14.7
- Tubal ligation request 4, 1.96

*p < 0.005, compared to the women with FOC who desired cesarean section for their current pregnancy. **p < 0.001, compared to the women without FOC who desired cesarean section for their current pregnancy.
from patients who previously had spontaneous vaginal delivery, vacuum extraction delivery, and emergency or elective cesarean section delivery. In the current study, FOC was observed in 128 of 817 women, and the study sample was created using patients with a positive birth experience who previously had elective cesarean or uncomplicated vaginal delivery. FOC was reported in 61 of 1,179 patients with positive birth experience by Storksen et al. [6]. However, there were no inclusion criteria in their study. Although women with previous complicated pregnancies or deliveries and obstetric complications for their current pregnancy were excluded from the present study, FOC prevalence was found higher in this study than in the studies of Nilsson et al. [4] and Storksen et al. [6]. The most important reason for this result may be lack of information regarding the delivery of Turkish women because of inadequate prenatal education. Another factor is that regional anaesthesia methods for labour pain relief are not used routinely in the present clinic. Also, Turkish women had insufficient support from their partner during pregnancy [14].

Rouhe et al. [3] found that severe FOC (W-DEQ scores > 100) was more common in nulliparous women than parous women. Additionally, they reported that incidence of severe FOC was more in women beyond 21 weeks of gestation compared with those before. None of the women had severe FOC in the present study. This reveals the importance of positive birth experience to reduce the level of FOC. Indeed, it was reported that for explaining subsequent FOC, women's negative overall birth experience was a more important factor than the delivery method [4]. The present authors found higher W-DEQ scores in participants over the age of 35 compared to participants under the age of 35. In contrast to these results, Nilsson et al. [4] found no association between FOC and maternal age during pregnancy or one year after childbirth.

In another study, it was shown that women with an unplanned pregnancy experienced had more depressive symptoms during pregnancy than women with a planned pregnancy [15]. The present authors have previously reported a higher rate of hyperemesis in patients with an unplanned pregnancy compared to patients with a planned pregnancy [16]. In the current study, W-DEQ scores were found to be significantly lower in women with planned pregnancy than unplanned pregnancy.

Previously studies showed that patients with FOC had preferred cesarean section for current pregnancy [17, 18]. The present results supported these findings; cesarean section delivery was chosen by most women with FOC. Fear of labour pain was the most significant reason the preference for cesarean section delivery. It has been revealed that the request for cesarean section due to fear may be reduced by psychological support, psycho-education, and relaxation exercises [19].

Regarding the limitations of this study, the authors did not establish a group of patients with a negative birth experience...
for comparison to patients with positive birth experience. Another limitation is the failure to include patients with first pregnancy. A comparison may be done in terms of FOC level between primiparous and multiparous Turkish women.

**Conclusion**

FOC may be seen to some extent in women with a positive birth experiences; however women’s positive birth experience is important to avoid severe FOC. Pain relief methods in labour should be effectively implemented to reduce the cesarean section rate due to maternal request. In addition, pregnancy planning status should be evaluated in the early stages of pregnancy and maternal education programs may be offered to support their psychological health and to reduce FOC. To reduce the prevalence of FOC, women may be encouraged to complete their family before the age of 35. Larger population studies are needed to identify the underlying causes of fear of childbirth in women with a positive birth experience.

**References**


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Fetal loss after amniocentesis: analysis of a single center’s 7,957 cases in China

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Summary

Purpose of investigation: The fetal loss rate after amniocentesis was different in previous reports. Instead of using the fetal loss rate reported by others when facing the counseling couples, the present authors sought to estimate our institution-specific fetal loss rate after amniocentesis. Materials and Methods: The study included 7,957 Chinese women in singleton pregnancy that had an amniocentesis in mid-trimester between 18-26 weeks of gestation in Shengjing Hospital for any indication. All clinical data, fetal karyotype, and pregnancy outcome were collected for analysis in the present study. Results: The number of abnormal karyotypes detected in this study were 436 (5.48%). The loss follow-up rate was 0.45%. The total fetal loss rate after amniocentesis was 4.09% including 3.23% elective termination of pregnancy and 0.86% unintended fetal loss. The potentially procedure-related fetal loss rate was lower than 0.59%. The potentially procedure-related fetal loss rate was found to be significantly associated with maternal age (> 35 years), previous fetal loss history, and abnormal vaginal bleeding in this pregnancy. Conclusion: 5.48% of women with amniocentesis have abnormal karyotypes and the proportion of women with major chromosomal abnormalities was even 2.20%; on the contrary, the fetal loss rate related to the procedure was lower than 0.59%.

Key words: Amniocentesis; Abnormal karyotypes; Fetal loss.

Introduction

Amniocentesis was first introduced in the 1950s for sex determination, and was applied in clinical practice in 1966 to obtain fetal cells for karyotyping [1]. Now amniocentesis is an invasive prenatal diagnostic examination widely performed for screening fetal karyotypic abnormalities early in the second trimester of pregnancy in clinical practice. Before amniocentesis, as with any procedure, informed consent must include a complete and accurate discussion. The counseling discussion includes the risks of the procedure, the limitations, and accuracy of the laboratory testing, the risk and burden of the disease(s) that might be diagnosed, the utility of the diagnostic information, and the fetal loss. In the end the couples’ decision depends on simply the outcomes: the risk of having a child with a chromosomal abnormality or a specific genetic disease compared with the risk of losing a normal pregnancy as a result of the procedure.

The incidence of pregnancy loss following mid-trimester amniocentesis has traditionally been estimated to be 0.5%, which is based on recommendations by the Centers for Disease Control and Prevention (CDC) and endorsed by the American College of Obstetricians and Gynecologists (ACOG) [2,3]. During two past decades, advances in ultrasound imaging technology and developments in molecular biology have led to an increase in new indications for amniocentesis. The loss rates reported in these more recent studies [4, 5] are different from those reported in previous reports [6, 7]. There is a wide variation in the reported incidences regarding the fetal loss rate after amniocentesis. It ranges form 0.06% [4] to 1.4% [8]. Comparing rates between these studies is difficult because of their differences relative to exclusion criteria, gestational age range at amniocentesis, and follow-up period used to calculate fetal loss rates. Instead of using the fetal loss rate reported by others when facing the counseling couples, the present authors sought to estimate their institution-specific fetal loss rate after amniocentesis.

Materials and Methods

To estimate the present institution-specific fetal loss rate, the present authors collected the data of 7,957 Chinese women in singleton pregnancy who had mid-trimester amniocentesis between 18-26 weeks of gestation in Shengjing Hospital of China Medical University between January 2007 and December 2011. They excluded all second amniocenteses, for any reason. The research protocol was approved by the ethics committee of the Shengjing Hospital of China Medical University. All pregnant women who had amniocentesis indications were referred to the obstetric clinic for further counseling. At the time of counseling all referred patients received an ultrasound examination to confirm gestational age. An amniocentesis was arranged for those women who elected to have the procedure after the procedure itself and related risks were thoroughly explained to the couple and written consent was obtained in all cases.
Table 1. — The indications for amniocentesis.

<table>
<thead>
<tr>
<th>Indications</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased risk of serum biochemical screening for Down syndrome (&gt; 1/270)</td>
<td>3,677</td>
<td>46.21</td>
</tr>
<tr>
<td>Advanced maternal age (&gt; 35 years)</td>
<td>2,662</td>
<td>33.45</td>
</tr>
<tr>
<td>Previous abnormal baby history</td>
<td>779</td>
<td>9.79</td>
</tr>
<tr>
<td>Positive sonographic markers for aneuploidies</td>
<td>343</td>
<td>4.31</td>
</tr>
<tr>
<td>Maternal anxiety</td>
<td>236</td>
<td>2.97</td>
</tr>
<tr>
<td>Drug use and environmental factor</td>
<td>166</td>
<td>2.09</td>
</tr>
<tr>
<td>Abnormal karyotype in either of couples</td>
<td>67</td>
<td>0.84</td>
</tr>
<tr>
<td>Consanguineous marriage</td>
<td>27</td>
<td>0.34</td>
</tr>
<tr>
<td>Total amniocentesis</td>
<td>7,957</td>
<td>100</td>
</tr>
</tbody>
</table>

Amniocentesis was usually arranged to be performed for all cases in mid-trimester between 18-26 weeks of gestation. Six senior operators used the same facilities and had the same objectives. Amniocentesis was performed with a 22-gauge needle as a sterile procedure under continuous ultrasound guidance. Operators made every effort to avoid transplacental insertion. The first one ml of amniotic fluid was discarded and another 20 ml were aspirated for culture and chromosomal assessment. When bleeding occurred within the last two weeks prior to scheduled amniocentesis, the procedure was postponed for another two weeks. The result of chromosomal karyotyping was available at four weeks after the amniocentesis. Fetal sex would not be revealed in the result.

All clinical data was collected by an experienced medical secretary in the interview including maternal age, gestational age, positive obstetric history, abnormal vaginal bleeding in this pregnancy, amniotic fluid color, the number of insertion, fetal karyotype, and pregnancy outcome. Gestational age was calculated from the first day of the last menstrual period and confirmed or corrected by a first-trimester ultrasonography in all cases. Fluid samples were classified as clear, tinged, blood-tinged, and bloody. The data was updated if the patients had any complication after amniocentesis. After delivery, the relevant information about mother and neonate were collected via telephone.

Statistical analyses were all done with SPSS for Windows (version 13.0). Chi-square (x²) test was used to analyse the difference of proportion. A p < 0.05 was defined significant.

Results

The women who had amniocentesis in the present hospital were 7,957. The median maternal age was 32.24 ± 5.53(18 - 49) years, the median gestational age was 20.79 ± 1.44 (18 - 26) weeks. Table 1 lists the indications for amniocentesis. The principal indication in the present study was increased risk of serum biochemical screening for Down syndrome (> 1/270) (46.21%) and advanced maternal age (> 35 years) (33.45%). Adequate amniotic fluid was obtained after one puncture in 7,818 (98.25%) procedures, two punctures in 123 cases (1.55%) and three punctures in 16 cases (0.2%). Transplacental insertion of the needle was required in 246 (3.09%) cases. Fluid was clear in 7,628 cases (95.86%), abnormally colored in 329 cases (4.14%), including tinged in 126 cases (1.58%), blood-tinged in 112 cases (1.41%) and bloody in 91 cases (1.14%).

A total of 7,957 results of fetal karyotype were collected in the present study. There were 436 abnormal karyotypes (5.48%) in this study. The abnormal karyotypes included 175 major chromosomal abnormalities and 261 minor chromosomal abnormalities, judged to be of no clinical significance. The major chromosomal abnormalities included 79 cases of Trisomy 21, 30 Trisomy 18, 22 other trisomies, and 44 sex chromosomal abnormalities including 32 45 XO, 6 47 XXX, 6 47 XXY. Minor abnormalities included 60 balanced inversion, 33 balanced translocation, 13 46 XY Y bigger or smaller than 22,18 unbalanced Robertsonian translocations, and 137 pseudomosaicism (Table 2).

The number of complete follow-up information regarding pregnancy outcome was 7,921 collected in all 7,957 women. The loss follow-up rate was 0.45%. There were 256 (3.23%) elective termination of pregnancy and 68 (0.86%) unintended fetal loss. The total fetal loss rate after amniocentesis was 4.09 %. In 256 elective pregnancy termination cases, none was performed as a consequence of a complication due to amniocentesis. The unintended fetal loss rate after amniocentesis was 0.86%. All unintended fetal loss rate was considered as potentially procedure-related, except the eight neonatal deaths with major structural abnormalities, and the 13 cases with strong obstetric or non-obstetric causes. The cumulative fetal loss rates, including only these
47 potentially procedure-related cases (0.59%), were 0.08% within the first week of the amniocentesis, 0.23% within two weeks, 0.40% within four weeks, 0.48% within six weeks, and 0.53% within ten weeks (Table 3). The fetal loss rate up to 24 weeks and 28 weeks of gestation was 0.35% and 0.45% respectively.

The potentially procedure-related fetal loss rate was found to be significantly associated with maternal age (> 35 years) [0.84% (25 / 2988) vs 0.45% (22 / 4933), p = 0.028], previous fetal loss history [1.44% (10 / 696) vs 0.42% (37 / 7225), p = 0.002] and abnormal vaginal bleeding in this pregnancy [1.05% (15 / 1426) vs 0.49% (32 / 6495), p = 0.00]. However, the same difference was not detected in the number of punctures (p = 0.78), a transplacental insertion of needle (p = 0.64), or a discoloured amniotic fluid (p = 0.32).

Discussion

In the present study, the authors collected the data of 7,957 Chinese women who had an amniocentesis in the present hospital for any reason and pregnancy outcome of 7,921 women were also gathered. With the spread use of serum triple test screening for Down syndrome in clinic of China, the first indication of amniocentesis was the increased risk of serum biochemical screening for Down syndrome (> 1 / 270) instead of advanced maternal age, which was different from in western countries. In the present study, the median maternal age was 32.24 ± 5.53 years and 62.28% of the women were younger than 35 years. The authors took amniocentesis from 18 weeks to decrease the risk of fetal loss after amniocentesis [9], hence the median gestational age was 20.79 weeks. Of the women studied, 5.48% were found to have abnormal karyotypes. The proportion of women with major chromosomal abnormalities was 2.20%. The proportion of abnormal karyotypes was significantly higher in women with indication of abnormal karyotyping in either of couples (35.82%, 24 / 67) and positive sonographic markers for aneuploidies (13.12%, 45 / 343) than with other indications.

Follow-up information regarding the pregnancy outcome was gathered in 99.55% of 7,957 women in this study. The lost follow-up rate was only 0.45%. The total fetal loss rate was 4.09%, which included 3.23% elective pregnancy termination and 0.86% unintended fetal loss. In 68 unintended fetal losses, the authors found the accurate cause in eight neonatal deaths with major structural abnormalities and the 13 cases with strong obstetric or non-obstetric causes. Forty-seven unintended fetal loss cases were considered as potentially procedure-related. The fetal loss rate was 0.59% and 0.59% fetal loss rate after amniocentesis was not all actually attributable to the procedure, which also included some background fetal loss and some other reason for the loss. In general, to calculate the fetal loss rate attributable to the procedure, the background fetal loss and other reason loss rate must be subtracted; however the accurate background fetal loss rate cannot currently be gathered, because it requires a large randomized controlled trial. There was no control group, matched by age and previous obstetric history with the study group, in which an amniocentesis was not performed and such a trial could not be performed today because it would not be considered ethical, which could result in the failure to identify some cases with abnormal karyotype and thus the continuation of unwanted pregnancies. For these reasons the present authors could not give a precise fetal loss rate after amniocentesis only attributable to the procedure.

From the previous study, ultrasound-based studies have shown that the spontaneous fetal loss rate, assessed without considering maternal age and ethnicity, is approximately 1% after 16 weeks of gestation [10]. Seeds [7] analyzed first 15 studies with a total number of 6,457 controls without amniocentesis and second 14 studies with a total number of 12,097 controls without amniocentesis. The background fetal rate was 1.4% and 1.08%, respectively. From these background fetal loss rates, the present authors found that the fetal loss rate in this study was lower than those background fetal loss rates. Although initially surprising, the explanation is simple. Because these women with amnio-centesis had prenatal diagnosis, aneuploid pregnancies were identified and could thus be terminated. The higher background fetal loss rate in control group which did not undergo amniocentesis likely resulted from the spontaneous loss of undiagnosed aneuploid fetuses. It was impossible to gather the accurate background fetal loss rate after excluding the elective pregnancy termination and the accurate fetal loss rate after amniocentesis simply attributable to the procedure could not be gathered, but it was not important. Because the couples’ decision depended on simply the outcomes: the risk of having a child with a chromosomal abnormality or a specific genetic disease compared with the risk of losing a normal pregnancy as a result of the procedure. From the present study, the authors discovered that 5.48% of all women with amniocentesis were found to have abnormal karyotypes and the proportion of women with major chromosomal abnormalities was 2.20%; on the contrary the fetal loss rate after elective pregnancy termination related to the procedure was lower than 0.59%. It was without a doubt that amniocentesis brought benefits for women who needed amniocentesis with the correct indication.

In the present study, unintended fetal loss rate after amniocentesis was lower than the other previous reports [11-15]. The reasons may include: (a) six operator was experienced and all the procedure was under continuous ultrasound guidance and the needle was 22-gauge; (b) because the increased risk of serum biochemical screening for Down syndrome (> 1 / 270) became the first indication instead of advanced maternal age, the median maternal age was younger in the present study. It is well known that fetal loss rate is higher in older women [16-18] as also proven by the present study outcome; (c) the median gestational age was 20.79 weeks in the present study which was later than
other reports. The fetal loss after amniocentesis was correlated with the gestational age [9, 12, 19]; (d) the elective pregnancy termination rate was 3.23%, which was higher than other reports. In the present study, virtually almost all Chinese women with a prenatal diagnosis of major chromosomal abnormalities and 20% of those with minor chromosomal abnormalities chose to terminate their affected pregnancies. This choice was different from reports from western societies [5, 20].

Conclusion

When an invasive amniocentesis is required, the couples will face a difficult choice: the risk of having a child with a chromosomal abnormality or a specific genetic disease compared with the risk of losing a normal pregnancy as a result of the procedure. The present study gave them the answer: 5.48% of all women with amniocentesis were found to have abnormal karyotypes and the proportion of women with major chromosomal abnormalities was even 2.20%; on the contrary the fetal loss rate related to the procedure was lower than 0.59%. Therefore amniocentesis should be recommended to all women who require it.

References

Epidemiological, clinical, and virological characteristics of women with genital warts in Greece

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Summary
This is a prospective study of the epidemiological, clinical, and virological characteristics of cases of genital warts in a Greek University Hospital. The women completed a questionnaire regarding their medical and sexual history and underwent cervical cytology, HPV DNA typing, mRNA testing, colposcopy, Chlamydia testing, and proctoscopy. Univariate and multivariate analyses were performed. The most commonly detected types were type 6 (36.1%) and 16 (24.3%). E6/E7 mRNA testing was positive in 21.5%. Concurrent cervical intraepithelial neoplasia grade 2 or worse was found in 11.1% and intra-anal warts in 10.4%. For chlamydial infection the number of sexual partners was a significant predictor. Women with warts infected with types 6 and 11 constituted only 37.5% of the total. This could have a negative effect on the efficacy of vaccination in reducing the incidence of the disease. Based on the present findings the authors recommend cytology and colposcopy for all women with genital warts.

Key words: Genital warts; Condylomata acuminata; Human papillomavirus; DNA; Fingerprinting; Chlamydia.

Introduction
Genital warts is caused by infection by human papillomavirus (HPV) mostly of low-risk types (6 and 11) and is a common disease, with 4% of the female population having been diagnosed with the disease in the UK [1]. In the UK 80,000 and in the USA over 300,000 diagnoses are made annually. The condition does not usually cause major morbidity or mortality, but has serious aesthetic and psychosexual sequelae. Studies have shown that women with genital warts have worse body image than women without or have high anxiety levels and more commonly have conflicts with their partners [2]. Also genital warts in pregnancy have been associated with juvenile respiratory papillomatosis through vertical viral transmission to the newborn [3] and obstruction of respiratory tract. All these issues make women seek treatment. Given that genital warts is a common disease and that recurrence following treatment is frequent, the financial burden for the healthcare system increases considerably. A single successful episode of treatment of genital warts has been estimated to cost approximately 400 USD. The high healthcare costs have created an argument for the use of the quadrivalent HPV vaccine which aims to prevent not only cervical cancer but also the acquisition of genital warts.

Given the importance of this condition and because the lack of detailed data in Greece, the authors undertook this study in order to address the local epidemiological and molecular issues of this disease.

Materials and Methods
All women that presented to the colposcopy department of the University Hospital of Ioannina with genital warts from February 2010 until May 2011 were asked to participate in this study which had ethical approval from the University of Ioannina. In their initial visit, each woman had a cervical smear taken which was placed in ThinPrep medium. This sample was used for the following tests:

a. Liquid based cytology (LBC) which was reported according to the Bethesda system;
b. HPV DNA testing with a genotyping test for detection of 35 HPV genotypes; the test was considered positive for high-risk types when at least one of the following types was detected: 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82, and 85.
c. Flow cytometric evaluation of E6/E7 mRNA of high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82) with an HPV detection kit. The test was considered positive if the result was >1.5%.

In women with symptoms suggestive of possible chlamydial infection such as vaginal discharge, postcoital bleeding or pelvic pain, an endocervical swab was taken for Chlamydia testing by PCR.

Once the samples were taken, a detailed colposcopic examination of the whole lower genital tract was performed and any lesions were recorded with biopsy if necessary. Colposcopically directed biopsy was done in patients, who aside from the genital warts, colposcopy raised the suspicion of a high-grade cervical lesion. If perianal warts were evident, or if the patient requested,
proctoscopy was also performed. The treatment choice for the warts was individualized with usual treatment options including prescription of podophyllotoxin or imiquimod or laser ablation at the same or a subsequent visit. At the end of the visit, the women were asked to complete a questionnaire regarding their medical and sexual history. The univariate statistical analysis was done with the Fisher’s exact test and the multivariate by logistic regression.

### Results

A total of 144 women with genital warts were included in this study. The mean age was 25.7 years. The demographic characteristics are given in Table 1.

HPV DNA genotyping of the cervical smear revealed the following: Single type HPV infection in 43/144 (29.86%), multiple type infection in 66/144 (45.83%), negative test in 15/144 (10.41%), and in 20/144 (13.88%) women genotyping was not performed either due to lost sample or lack of reagents or because a sample was not taken. The most common detected HPV types were type 6 (36.1%) and 16 (24.3%). The distribution of the various HPV types is shown in Table 2.

<table>
<thead>
<tr>
<th>TEST</th>
<th>Outcome</th>
<th>Result (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV DNA typing</td>
<td>Single infection</td>
<td>29.86</td>
</tr>
<tr>
<td></td>
<td>Multiple infection</td>
<td>45.83</td>
</tr>
<tr>
<td></td>
<td>No type</td>
<td>10.42</td>
</tr>
<tr>
<td></td>
<td>Invalid result or no test</td>
<td>13.89</td>
</tr>
<tr>
<td>HPV mRNA testing</td>
<td>Positive</td>
<td>21.53</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>55.55</td>
</tr>
<tr>
<td></td>
<td>Invalid result or no test</td>
<td>22.92</td>
</tr>
<tr>
<td>Pap test</td>
<td>WNL</td>
<td>15.28</td>
</tr>
<tr>
<td></td>
<td>ASCUS</td>
<td>10.42</td>
</tr>
<tr>
<td></td>
<td>LSIL</td>
<td>53.47</td>
</tr>
<tr>
<td></td>
<td>HSIL</td>
<td>5.55</td>
</tr>
<tr>
<td></td>
<td>Invalid result or no test</td>
<td>15.28</td>
</tr>
<tr>
<td>Chlamydia PCR</td>
<td>Positive</td>
<td>5.55</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>29.17</td>
</tr>
<tr>
<td></td>
<td>No test</td>
<td>65.28</td>
</tr>
<tr>
<td>Colposcopy + biopsy</td>
<td>CIN2+</td>
<td>11.11</td>
</tr>
<tr>
<td></td>
<td>Intra-anal warts</td>
<td>10.42</td>
</tr>
</tbody>
</table>

HPV mRNA testing with flow cytometry results were the following: positive result in 31/144 (21.52%), negative in 80/144 (55.55%), no result due to lost sample or lack of reagents or because of failure to take a sample in 32/144 (22.22%), and invalid result in 1/144 (0.69%).

The results of the LBC Papanicolaou test were: within normal limits (WNL) in 22/144 (15.27%), atypical cells of undetermined significance (ASCUS) in 15/144 (10.41%), low-grade squamous intraepithelial lesion (LSIL) in 77/144 (53.47%), high-grade squamous intraepithelial lesion (HSIL) in 8/144 (5.55%), and no data in 22/144 (15.27%).

The histology results showed that 16/144(11.11%) had cervical intraepithelial neoplasia grade 2 or worse (CIN2+). Intra-anal warts were detected in 15/144 (10.41%).

PCR for Chlamydia was positive in 8/144 (5.55%), negative in 42/144 (29.16%), and 94/144 (65.27%) were not tested. Test results are summarized in Table 3.

**Univariate analysis**

A positive flow result was significantly associated with high-risk type HPV DNA presence ($p = 0.008$) but not with age or parity. Multiple type HPV infection was significantly associated with nulliparity ($p = 0.033$) but not with smoking or age at first sexual intercourse, however the association with over five sexual partners marginally failed to reach significance ($p = 0.059$). Chlamydial infection was not associated with smoking, number of partners, age or parity. Presence of CIN2+ was only associated with HSIL cytology ($p < 0.001$).

**Multivariate analysis**

Chlamydial infection and high-grade histology were studied dependent variables. Age, smoking, parity, age at first intercourse, and number of sexual partners were the independent variables. For chlamydial infection, the number of sexual partners was a significant predictor with odds
ratio 1.25 (95% CI 1.05-1.48) for every additional partner. For CIN2+ histology, no predictor was found.

Discussion

Genital warts are not only caused by low-risk types. A proportion will have high-risk type leading to E6 and E7 expression (21%) and CIN2+ (11%). This should not be overlooked. Therefore, all women should have cervical cytology and colposcopy. If a possible high-grade lesion is seen on the cervix at colposcopy, it is recommended to not to use laser vaporization of cervical condylomas, before the biopsy of the suspicious region. As 10% of women have intra-anal warts, proctoscopy should be discussed in the women with relevant sexual history [4].

Even though positive flow cytometry result was not associated with the finding of CIN2+ in this study, it is known that E6 and E7 mRNA expression is a key step to cervical carcinogenesis [5]. It may be that these women in this study with a positive flow result but no CIN2+ on histology are at risk of high-grade lesions in the future.

Studies have shown that 90% of genital warts are cause by types 6 and 11 with up to 50% of lesions containing co-infections with other types [6-8]. In this study the frequency of women with genital warts who were infected with types 6 and 11 was 37.5%. The percentage of HPV 11 was only 1.388%. There is a recent male study in which the genotypes most commonly detected in genital warts were HPV 6 (43.8%), HPV 11 (10.7%), and HPV 16 (9.8%) [9]. The cost of care of genital warts in England exerts a considerable impact on health services which clearly demonstrates the importance of immunization using the HPV vaccine [10]. Not taking into consideration the issue of crossreactivity with types not included in the vaccine, immunization by the quadrivalent vaccine would have prevented at most 60.5% of the cases and by the bivalent 30.5% of the cases even though the bivalent vaccine is not aimed at prevention of genital warts. The present data suggest that the vaccine may not be as effective in preventing genital warts in particular population.

Simultaneous Chlamydial infection was found in 5.6% of women with genital warts. The percentage is not high enough to warrant testing for all women with warts. As no reliable predictors were found for positive Chlamydia result, the authors cannot recommend Chlamydia testing in only a small subgroup of patients with specific epidemiological characteristics. Given the serious effects of Chlamydia infection on fertility, the authors would encourage clinicians to have a high degree of suspicion in nulliparous women especially when they report multiple sexual partners.

References


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Vaginal bilateral cervical lips suture in combination with intrauterine Foley catheter to arrest postpartum hemorrhage

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Summary

Vaginal bilateral cervical lips suture allows retention of intrauterine Foley catheter in women with a dilated cervix. This novel indication for vaginal bilateral cervix suture may be a useful adjunct to intrauterine balloon tamponade in the management of postpartum hemorrhage. Objective: To describe an effective, minimally invasive surgical technique for avoiding intrauterine balloon tamponade prolapse. Materials and Methods: This procedure was performed in the delivery room with or without bladder retraction. The cervix was grasped with two ring forceps and firmly pulled outward, two cm horizontal suture of the cervical lips was made at both the three and nine o’clock positions, which were placed two cm as close to the cervix external os, without transversing the cervicovesical reflection anteriorly and the pouch of Douglas posteriorly, then one or more Foley catheters were inserted through the cervix and inflated with saline 60-80 ml each. Results: The balloons remained in place and hemorrhage abated in all nine cases. Conclusion: Vaginal bilateral cervical lips suture can prevent intrauterine balloon prolapse, which may be a useful adjunct to intrauterine balloon tamponade in management of postpartum hemorrhage.

Key words: Intrauterine balloon tamponade; Postpartum hemorrhage; Prolapse, cervix.

Introduction

In case of postpartum hemorrhage, first-line treatment includes uterotonic agents with or without procedures aimed at achieving uterine tamponade. However, a problem often encountered is prolapse of the balloon through a dilated cervix [1-3]. Thus, there is a need to establish an adjunct to intrauterine balloon to control postpartum uterine hemorrhage.

Materials and Methods

DaLian Maternity Hospital is a very busy maternity unit where about 13,000 deliveries are held annually. The intrauterine Foley balloon tamponade was used in 56 cases from August 2003 to April 2013. However, in nine cases the balloon prolapsed and the present team adopted the vaginal bilateral cervical lips suture combined with balloon replacement through the cervix and controlled the bleeding. In three cases this technique was not applied and resulted in hysterectomy as the only way to control bleeding. Therefore the current authors presented all the cases where the technique was successfully used.

Once consent had been obtained, the procedure was performed without delay after the prolapse of Foley balloon catheter. Transfer to an operating room was unnecessary and took time, regional anesthesia or pudendal or cervical block could be administered. The patient was placed in the lithotomy position, with or without bladder retraction. Visualisation of the full circumference of cervix was accomplished by application of firm upward pressure on vaginal anterior wall while the operator firmly exerted an outward traction on the lips of the cervix with two ring forceps. A 2-0 delayed absorbable Vicryl suture was selected as suture material.

The needles were passed from posterior to anterior at both the three and nine o’clock positions of the cervix with transversing the cervical lips (including myometrium) two cm horizontally, two cm to the external os, and the sutures were securely tied laterally. Additional one or two ligatures, depending on the length of the cervix, were applied cephalad to secure the ligation, using the same technique. Attention was paid to avoid damaging the bladder anteriorly, the rectum posteriorly, or major vessels laterally by straying outside of limits of the cervical stroma (Figures 1 and 2).

One or more 24 Foley catheters were inserted through the cervix and carefully pulled from the vagina by an assistant; each balloon was infused with 60-80 ml saline, a plastic bag was tied to the distal end of each catheter, and hung over the patients bed in order to observe the drainage.

Postoperatively, oxytocin infusion was continued for 12 hours and a single dose of a second generation cephalosporin was administered for 24 hours. The balloon was left in situ, usually for 18-24 hours, and withdrawn gradually if haemostasis was achieved.

Patients admitted to the present unit provided written consent to use their clinical data for research purpose, provided that anonymity was maintained.

Results

The first patient in whom this technique was used was a 32-year old woman, gravida 3, para 1. At 38 weeks gestation, she underwent emergency cesarean section and diagnosed with “dystocia and intrapartum fever” at the second stage of labor. The operation processed smoothly, but when the operators prepared to send her back, they found heavy
and continuous uterine bleeding. The uterus was well contracted using uterotonic agents, including oxytocin, prostaglandin F2 alpha, there was no retained placental tissue left in the uterus, no vaginal or cervix laceration inspected, and the estimated blood loss was 1,500 ml. Two 24 Foley balloon catheters were inserted through the cervix into the uterine cavity under ultrasonographic guidance, each catheter was distended with 80 ml saline. The balloons temporarily stopped the bleeding, but the balloons prolapsed through the dilated cervix shortly. Because the likely cause of failure of the balloon catheter was the dilated cervix, the bilateral cervical lips was sutured at three and nine o’clock positions, two Foley balloons were gradually replaced into the uterine cavity, inflated with 80 ml of saline each. The balloons remained in place and the hemorrhage abated.

The same technique was used for another eight patients with the same history with Foley balloon that had fallen off, whose clinical characteristics are included in Table 1.

Table 1. — Clinical data and variables of the patients.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Parity</th>
<th>Gestational weeks</th>
<th>Delivery mode</th>
<th>Foley number</th>
<th>Suture number</th>
<th>Total transfusion</th>
<th>Risk factors</th>
<th>Hb (g/dl)</th>
<th>Blood loss (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28</td>
<td>1</td>
<td>38+3</td>
<td>Cesarean delivery</td>
<td>1</td>
<td>2</td>
<td>6 PRBC</td>
<td>Intrapartum sepsis</td>
<td>4.9</td>
<td>3600</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
<td>1</td>
<td>38+1</td>
<td>Cesarean delivery</td>
<td>2</td>
<td>2</td>
<td>4 PRBC</td>
<td>Twins, placenta low lying</td>
<td>5.2</td>
<td>2000</td>
</tr>
<tr>
<td>3</td>
<td>32</td>
<td>1</td>
<td>41+5</td>
<td>Cesarean delivery</td>
<td>2</td>
<td>2</td>
<td>6 PRBC</td>
<td>___</td>
<td>5.0</td>
<td>3000</td>
</tr>
<tr>
<td>4</td>
<td>32</td>
<td>1</td>
<td>39+2</td>
<td>Vaginal delivery</td>
<td>4</td>
<td>4</td>
<td>3 PRBC</td>
<td>Placenta previa</td>
<td>6.1</td>
<td>1500</td>
</tr>
<tr>
<td>5</td>
<td>35</td>
<td>1</td>
<td>37+5</td>
<td>Vaginal delivery</td>
<td>3</td>
<td>4</td>
<td>2 PRBC</td>
<td>Placenta low lying</td>
<td>7.2</td>
<td>1200</td>
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<td>6</td>
<td>34</td>
<td>1</td>
<td>40+6</td>
<td>Vaginal delivery</td>
<td>3</td>
<td>4</td>
<td>Macrosomia</td>
<td>8.0</td>
<td>1200</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>22</td>
<td>1</td>
<td>36+1</td>
<td>Vaginal delivery</td>
<td>2</td>
<td>2</td>
<td>4 PRBC</td>
<td>twins</td>
<td>6.0</td>
<td>1800</td>
</tr>
<tr>
<td>8</td>
<td>30</td>
<td>2</td>
<td>40+5</td>
<td>Vaginal delivery</td>
<td>3</td>
<td>4</td>
<td>Placenta residue</td>
<td>8.3</td>
<td>1200</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>34</td>
<td>2</td>
<td>26+3</td>
<td>Top</td>
<td>1</td>
<td>2</td>
<td>6 PRBC</td>
<td>Placenta previa</td>
<td>3.5</td>
<td>3500</td>
</tr>
</tbody>
</table>

Top: termination of pregnancy; Hb: hemoglobin; PRBC: packed red blood cells; FFP: fresh frozen plasma.
The mean gestational age was 37 weeks and the mean age was 30.4 years. Estimated blood loss ranged from 1,200-3,600 ml (mean 2,100 ml) and patients received mean 3.6 units of packed red blood cells and mean 1.5 unit of frozen plasma. The mean hemoglobin level before transfusion was 6.1 mg/dl. The mean Foley catheter number placed into the uterus was two and the mean suture number of the cervix lips was two.

Three of the patients had a cesarean delivery, two of them after a trial of labor, four of the patients after a vaginal delivery, and one of the patients after the second trimester termination of pregnancy because of trisomy 21. No medical complications occurred in the study group. Five patients were admitted to the intensive care unit for postoperative surveillance.

In five cases, there was bleeding from what was described as the previous placental site (two cases with placenta previa, one with placenta increta, one with a low lying placenta, and one with placenta bipartite). In three cases, postpartum hemorrhage was due to uterine atony, which was unresponsive to oxytocin or analogs of prostaglandin E1 or E2.

Bilateral cervix lips suture combined Foley catheter was effective in all cases. Furthermore, it was successful after a combination with square sutures in one case after cesarean section. In the overall group, the present authors did not observe surgical complications directly related to the technique. All patients were discharged five days after surgery, and none presented with further bleeding. At the routine six-week follow-up no abnormality was detected on transvaginal ultrasound scanning of the pelvis. After completion of breastfeeding, all women resumed their normal amount of menstrual flow.

Discussion

Postpartum hemorrhage is the leading cause of maternal deaths worldwide [4]. If management with uterotonics fails to control the hemorrhage, intrauterine balloon tamponade can be an appropriate first line intervention for most women with postpartum hemorrhage [5]. There is ample evidence that balloon tamponade is highly effective for postpartum hemorrhage using various types of balloon catheters, such as Foley catheters, Bakri balloon, Rusch balloon, and condom catheters [5,6]. The main advantage of the Foley catheter is its availability and cheapness, it can be introduced easily with minimal skill and without any anaesthesia or sophisticated equipment [7]. The present authors usually use 24 Foley balloon catheters.

Although balloon tamponade is successful for postpartum hemorrhage in most cases, failures sometimes occur primarily due to displacement of balloon into the vagina through a dilated cervix [6-8]. The use of a vaginal pack has been described elsewhere, but often fails to maintain the balloon within the uterine cavity [6]. To the authors’ knowledge, there are few reports that present unique methods to keep a balloon within the uterus. Jain used a cervical cerclage [9], Khalil et al. made a traction stitch of a balloon through the uterine cavity and the abdominal wall during cesarean section [10], Kawamura et al. used forceps to clamp the cervix, but the safety are needed to elucidate [8]. Unlike their methods, the present authors employed bilateral cervix suture to prevent the balloons’ prolapse. Their approach is quick, safe, and readily available in cases where a balloon protrudes through the cervix. The threads need not be removed, so this was a successful maneuver in maintaining the intrauterine placement of the balloon and there was ultimate success in managing the postpartum hemorrhage.

The haemostasis mechanism of the present authors’ technique is unclear. Perhaps the suture ligated some descending branches or vaginal branches of the uterine artery, made the uterus ischemic to increase uterine contraction, contract the cervix thereby closing the cervical os and retaining the catheter balloon. Or during the process, holding the cervix stimulated the contraction of the uterus [11, 12], but when the balloon is expelled repeatedly despite the technique presented here, obstetricians should not persist in the use of balloon.

The suture of the cervix may raise a concern regarding the potential ischemic changes or ultimate necrosis with substantial cervical damage [11]. In the current case, the suture remained in place without any complications, because the hemodynamic circulation and collateral pathway of the cervix. The duration of balloon tamponade varies considerably (range one to 82 hours) and there has been no consensus on how long intrauterine balloon should be kept in place.

In conclusion, the use of bilateral cervix suture to retain the balloon may be a worthwhile, readily available approach to consider when an intrauterine balloon is likely to be extruded through the cervix.

References


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The importance of size of cervical ectopy to predict postcoital bleeding: is there any cut-off value?

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Summary
Objective: To investigate the relationship between size of cervical ectopy and existence of postcoital bleeding (PCB) in non-symptomatic women. Materials and Methods: Study population were recruited from women ages 18-65 years, sexually active who applied to the present outpatient department. They were asked whether they had had postcoital bleeding in the last three months. After full visualization of the cervix, the existence of ectopy was noted and measured. The smears were taken from all patients with endobrushes. Results: The authors found a relationship between the size of ectopy and PCB. In the prediction of PCB, the lesion’s size (of both antero-posterior and transverse diameters) of 3.5 mm as the cut off level, sensitivity, and specificity were found to be 70% and 76%, respectively. Conclusion: The full visualization of the cervix is important because of the relationship between the existence of ectopy and PCB.

Key words: Ectopy; Postcoital bleeding.

Introduction
Reddish patches on the cervix are a common clinical finding in daily gynecological examination, however, there is no unique term to define this lesion. In medical terminology, it can be named as ectropion, erythroplakia, macula rubra, and erosion [1-4]. Among them, erosion is an inspectional term during gynecologic examination which is commonly used in literature apart from underlying pathology to describe red areas within cervix around the external orifice [5].

There are many underlying pathologies resulting in reddish appearance of the cervix. One of the most commonly seen underlying reasons of the reddish patches of cervix can be ectopy (also called ectropion), erosion, cervical precancerous lesions, or even cervical cancer. Ectopy occurs when the columnar epithelium of the endocervical canal extends outwards into the ectocervix, which is normally covered by stratified squamous epithelium. It appears as a single layer of glandular cells that reside in close association with the underlying vascular cervical stroma [6]. Due to its thin and vascularized epithelium, ectopic tissue is fragile. The prevalence of ectopy ranges from 17% to 50% [7]. It is common in adolescents, pregnant women, and those taking hormonal contraceptives due to physiologic cervical changes [8, 9]. Exact underlying pathogenesis of ectopy is not well known but there is an association with the effects of estrogen [2, 10, 11]. Ectopy is a rare occurrence beyond menopause and frequent during the reproductive ages. It has higher prevalence during pregnancy [2] and also among users of estrogen-based contraceptives [11, 12].

Postcoital bleeding (PCB) is a common gynecologic symptom and it is defined as bleeding during or just after sexual intercourse, independent from menstruation [13]. It can be a source of stress for the patient if it is in excessive amount or frequently seen. The underlying etiology may be due to benign or malignant pathology. In a systematic review, the prevalence of PCB among women in their reproductive ages was reported to be in the range of 0.7 - 9% [14].

The aim of the present study was to investigate the importance of diameter of cervical ectopy in women with PCB and to detect the possible cut-off value to predict possibility of PCB.

Materials and Methods
After approval of the medical ethics committee, this cross-sectional study was conducted at a high-volume center between January 2012 and June 2012. The study population was recruited from sexually-active women aged 18-65 years. All women in this study had no gynecologic complaint and they were admitted to the outpatient clinic due to routine annual gynecologic examination. Study population included women having cervical ectopy during gynecologic examination. Exclusion criteria of the study were pregnant women, previous diagnosis of preinvasive or invasive cervical lesions, patients with active vaginal bleeding, presence of visible cervical polyps, previous history of abnormal smear pathology, and intensive purulent vaginal discharge. Patients were asked whether they had PCB in the last three months.
or not and the patients were grouped into two on the basis of existence of PCB.

After complete abdomino-pelvic ultrasonography and routine biochemical tests, all patients were examined in the lithotomy position by using disposable speculum which was applied gently. Ectopy was noted and measured during the complete visualization of the cervix if it existed. Then, widest transverse and antero-posterior diameters of the ectopy were measured and recorded (Figure 1). After, cervical smears were collected from all patients with endobrushes and the Bethesda System was used for the evaluation of cytological diagnosis (revised in 2001). Existence of cervical ectopy, and dimensions of the ectopy were compared between PCB (+) and PCB (–) groups. Also, the authors detected any cut-off value between diameter of cervical ectopy and possibility of PCB.

The Female Sexual Function Index (FSFI) was used to evaluate the female sexual dysfunction for all patients.

Statistical analyses of data including demographic properties of women, measurement records, and pathology results, were performed using 17.0 SPSS program. Chi square and t test were used to compare the results of the groups. The receiver operating characteristics (ROC) curve was used to establish cut-off values for the sizes of the cervical lesions. A $p < 0.05$ was considered to be statistically significant.

### Results

During this cross-sectional study, 656 women without clinical complaint were evaluated for the study. After exclusion criteria, a total of 187 women had cervical ectopy in their routine gynecologic examination. Forty-four of them reported PCB in last three months. The demographic characteristics of the patients in PCB (+) and PCB (–) are shown on Table 1. The mean age, number of gestation, and smoking did not differ significantly between groups (Table 1).

Similarly, types of birth control methods did not show statistical significance between PCB (+) and PCB (–) women.

<table>
<thead>
<tr>
<th>PCB (+) (n = 44)</th>
<th>PCB (–) (n = 143)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 38.8 ± 10.1</td>
<td>37.9 ± 12.3</td>
<td>0.751</td>
</tr>
<tr>
<td>Gravidity 3.11 ± 1.1</td>
<td>3.22 ± 1.6</td>
<td>0.922</td>
</tr>
<tr>
<td>Smoking 9/44 (20.4%)</td>
<td>29/143 (20.2%)</td>
<td>0.918</td>
</tr>
<tr>
<td>OC pill 4/44 (9.1%)</td>
<td>15/143 (10.5%)</td>
<td>0.124</td>
</tr>
<tr>
<td>IUD 8/44 (18.2%)</td>
<td>27/143 (18.8%)</td>
<td>0.861</td>
</tr>
<tr>
<td>Other 32/44 (72.7%)</td>
<td>101/143 (70.7%)</td>
<td>0.677</td>
</tr>
<tr>
<td>Nulliparity 13/44 (29.5%)</td>
<td>39/143 (27.2%)</td>
<td>0.162</td>
</tr>
<tr>
<td>Mutiparity 31/44 (70.5%)</td>
<td>104/143 (72.8%)</td>
<td>0.279</td>
</tr>
<tr>
<td>Vaginal delivery 30/44 (68.2%)</td>
<td>100/143 (69.9%)</td>
<td>0.438</td>
</tr>
<tr>
<td>Cesarian section 14/44 (31.8%)</td>
<td>43/143 (30.1%)</td>
<td>0.214</td>
</tr>
</tbody>
</table>

FSFI 26.37 ± 6.21 31.26 ± 7.13 <0.001

PCB: postcoital bleeding; OC pills: oral contraceptive pills; IUD: intrauterine device; FSFI: Female Sexual Function Index.
The importance of size of cervical ectopy to predict postcoital bleeding: is there any cut-off value?

(Table 1). Percentage of nulliparity and multiparity, and the percentage of types of delivery among PCB (+) and PCB (–) women were also compared with their counterparts. No statistical significance was noted between groups (Table 1).

Lower FSFI score was noted in PCB (+) group ($p = 0.02$). The ROC analysis was performed to show the sensitivity and the specificity of the diameter of cervical ectopy to predict the postcoital bleeding (Figures 2, 3). According to ROC curve analysis, 3.5 mm was found to be the cut-off size for both transverse and antero-posterior diameter of ectopy that had a sensitivity of 70% and a specificity of 76% for prediction of PCB.

Discussion

Although most of the cervix abnormalities such as leukoplakia or polyp are well-defined, there is still ongoing debate in terminology of red lesions of the cervix. Morphophysiological changes which take place in the transformation zone of the cervix, is that the term cervical erosion is an anachronism. This term should therefore be abandoned. In literature, authors stated that more appropriate terms for the clinical appearance of the cervix are ectopy or ecropion before proven pathological diagnosis [5]. In present study, only histological proven cervical ectopy was included and the relation between its diameter and PCB was investigated.

Cervical ectopy is a commonly seen pathological findings in routine gynecologic examination. Its exact prevalence is not well known, however it is logic to expect that the prevalence of cervical ectopy can vary among clinically symptomatic or asymptomatic women. In the present series, approximately 28.5% of 656 women with no clinical symptoms had cervical ectopy in their vaginal examination. This result was comparable with the literature. Some authors reported the prevalence of cervical ectopy approximately 25% in a family planning polyclinic [7].

Up to now, most of the studies in literature were concentrated on different treatment modalities and the success of the treatment fashion of the cervical ectopy. To the present authors’ knowledge, this is the first study of association between size of cervical ectopy and PCB. They found positive relation between the size of ectopy and PCB. As the size of ectopy increases, possible existence of PCB also increases. In the prediction of PCB, 3.5 mm of largest diameter of cervical ectopy was a cut-off value (both for antero-posterior and transverse diameters) in this study and sensitivity and specificity were found to be 70% and 76%, respectively.

It is known that cervical ectopy can be seen in clinically symptomatic or asymptomatic women. Its existence is independent from clinical symptoms and its own clinical symptom are various. However in clinical practice, it is
generally underestimated by both women as well as gynecologists unless it is associated with malign lesion or clinical findings such as PCB or dyspareunia, etc. In the present study, initially all of women stated that they had no gynecologic complaint. However, the present authors found that 23.5\% of them reported PCB in last three months in their detailed history. Ignoring of PCB by women in this study might be due to infrequent and small amount of PCB. The results of this study showed that cervical ectopy may be more symptomatic than expected. Therefore, careful and detailed history taking is important to reveal existence of associated symptoms.

PCB can occur due to various underlying reasons. Although it is commonly seen symptom in daily gynecologic practice, most of the women may underestimate it if it is not too much or too frequent. There is no data in literature to detect the relationship between PCB and female sexual function. However, it can potentially be a stress factor on woman’s quality of life. In present study, it was shown that existence of PCB, even if it was in small amount, can potentially affect female sexual function. Because, the women in PCB (+) group had lower FSFI score than their PCB (−) counterparts. This result also shows the possible importance and impact of cervical ectopy on female sexual function. In this regards, the cut-off value of diameter of cervical ectopy may be helpful to estimate possible post coital bleeding and consequently female sexual function.

The present study has some limitations. Small number of the groups is main limitation of the study. Secondly, it was also difficult to measure the largest diameter of cervical ectopy. Attempting to measure the largest diameter of cervical ectopy may prolong gynecologic examination time and it may lead to compliance problem of the women. Lastly, some of the women in this study had low socio-economic status. Therefore it was difficult for those women to answer FSFI questionnaire exactly. A relative of the women helped to answer FSFI questionnaire. This also may cause some divergence in exact FSFI score. However in the absence of such data in literature, the present results give an idea regarding the cut-off value of cervical ectopy to predict the possibility of PCB.

As a conclusion, complete visualization of the cervix is an important part of the pelvic examination to exclude malign, premalign, as well as benign lesions. Although cervical ectopy is a benign pathology, it may potentially affect women sexual life even if the women have no obvious complaint. According to the present results, whether the largest diameter of cervical ectopy is larger than 3.5 mm, there is a high possibility of PCB. Therefore, detailed history taking may helpful to identify occult PCB history in those women.

References

Efficacy of chlortetracycline treatment on vulvar non-neoplastic epithelial disorders

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Summary
Objective: To observe the effectiveness of chlortetracycline (aureomycin) treatment on vulval white lesions and to explore its possible pathogenesis. Materials and Methods: From January 2001 to April 2011, 194 patients with vulvar non-neoplastic epithelial disorders were divided into three groups according to therapy regimens received, i.e., chlortetracycline treatment group (72 cases), chlortetracycline + beclomethasone treatment group (66 cases), and beclomethasone treatment group (56 cases); their local changes of vulvar lesions were observed and efficacy of these treatment profiles was evaluated after one year. Results: Effective rates of chlortetracycline group, chlortetracycline + clobetasol group and clobetasol groups were 86.1% (62/72), 87.9% (58/66), and 62.5% (35/56), respectively. There was a significant difference among these three groups (Hc = 10.7766, p = 0.0046), the curative rate of clobetasol group was markedly lower than that of the former two groups (p = 0.0072 and p = 0.0019), but was not statistical significant (p = 0.6077) when compared between the former groups. Conclusion: The occurrence of vulvar non-neoplastic epithelial disorders may be associated with chlamydia and mycoplasma infection, the chlortetracycline is an effective drug for this illness, the mechanism of which might be related to killing pathogens directly and inhibiting inflammatory mediators.

Key words: Vulvar white lesions; Squamous cell hyperplasia; Lichen sclerosis; Chlortetracycline.

Introduction
Vulvar white lesions, also known as vulvar non-neoplastic epithelial disorder, is a group of chronic diseases of degeneration and pigment change in female genital skin and mucosal tissue, which features local skin’s intractable itching, hypopigmentation, atrophy, even adhesions, and cicatrice with the disease progression, that seriously affect the patient’s quality of life. Because the exact cause of the disease is currently unknown, there is no ideal method of treatment to cure this disease [1-3]. In 2001, the authors began applying the chlortetracycline (aureomycin) to treat it and had achieved good results.

Materials and Methods
General Information
From January 2001 to April 2011, the authors observed 194 cases of vulvar non-neoplastic epithelial disorders, including 30 cases in adolescent girls, 58 in reproductive-age women, and 106 in postmenopausal women. All patients had to undergo a vulvar lesions biopsy to get a conformed pathological diagnosis. Histological types included squamous cell hyperplasia, lichen sclerosis, and mixed type (Table 1). Median age of the patients was 42.2 years (17 to 73 years). Patients were randomly divided into the chlortetracycline treatment group (72 cases), chlortetracycline + clobetasol (propionate clobetasol) group (66 cases) and clobetasol group (56 cases). There were no significant differences (p > 0.05) among the three groups in age, pathological type, severity of symptoms, and duration of disease.

All patients were followed up once monthly for one year. Efficacy after treatment was assessed by rank of cure: 1) resolved: the symptoms disappeared, the elasticity and pigmentation of the genital skin and mucosa were basically recovered to normal, the chapped ulcers and atrophy were healing; 2) obviously improved: the symptoms disappeared and lesions restored as described above by more than 80%; 3) slightly improved: itching relieved and lesions restored as described above by more than 50%; 4) no change: no change between before and after treatment.

Determine the efficacy
All patients were followed up once monthly for one year. Efficacy after treatment was assessed by rank of cure: 1) resolved: the symptoms disappeared, the elasticity and pigmentation of the genital skin and mucosa were basically recovered to normal, the chapped ulcers and atrophy were healing; 2) obviously improved: the symptoms disappeared and lesions restored as described above by more than 80%; 3) slightly improved: itching relieved and lesions restored as described above by more than 50%; 4) no change: no change between before and after treatment.
Vulvar non-neoplastic epithelial disorders in three groups.

Table 1 — Histological types of vulvar non-neoplastic epithelial disorders in three groups.

<table>
<thead>
<tr>
<th></th>
<th>Chlortetracycline</th>
<th>Chlortetracycline + clobetasol</th>
<th>Clobetasol</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous epithelial hyperplasia</td>
<td>22</td>
<td>18</td>
<td>14</td>
<td>54</td>
</tr>
<tr>
<td>Lichen sclerosis</td>
<td>20</td>
<td>26</td>
<td>24</td>
<td>70</td>
</tr>
<tr>
<td>Mixed type</td>
<td>30</td>
<td>22</td>
<td>18</td>
<td>70</td>
</tr>
<tr>
<td>Total</td>
<td>72</td>
<td>66</td>
<td>56</td>
<td></td>
</tr>
</tbody>
</table>

\[ p = 0.4550 \]

Results

The three groups were comparable in effective rate (Table 2). The number of both cured and obviously improved cases were 62 in the chlortetracycline treatment group (86.1%), 58 in chlortetracycline + clobetasol group (87.8%), and 35 in clobetasol group (62.5%) respectively. The difference was statistically significant between the former two groups and the clobetasol group \(( p = 0.0072 \) and \( p = 0.0019 \)), but no significant difference was showed when comparing the chlortetracycline group with the chlortetracycline + clobetasol group \( ( p = 0.6077 \)).

In the chlortetracycline group, two patients appeared with obvious vulvar itching and lesions relapse within six months after treatment, of which one case was squamous cell hyperplasia and the other lichen sclerosis. In the chlortetracycline + clobetasol group, one patient’s squamous epithelial hyperplasia recurred in six months after treatment. The clobetasol group also showed good mitigation by treatment, but one year later ten cases recurred, including five cases with squamous cell hyperplasia, two with lichen sclerosis type, and three with mixed type.

Discussion

Vulvar non-neoplastic epithelial disorder is a gynecological disease that is difficult to treat and often recurs, causing great physical or mental pain to the patient. One of reasons difficult to treat is uncertain in etiology. It is supposed that genetics, autoimmune, local irritation, hormone metabolism, and local chronic injury might be the cause of this disease [2,3]. Therefore, its treatment methods are diverse, such as hormones (triamicinolone acetonide, flucinolone acetonide, testosterone propionate, progesterone, etc.), vitamins, lasers, high-intensity focused ultrasound, traditional Chinese medicine, and others. Propionate clobetasol ointment treatment achieved good results. It is a potent topical corticosteroid preparations, which can effectively penetrate into skin corneum, and works well as anti-inflammation, anti-allergy, anti-proliferation, anti-itch immune-suppression, and vasoconstriction. However, it’s long-term side effects, such as the topical vulvar skin’s telangiectasia, hirsutism, atrophy, infection, and prolonged unhealed chaps, as well as a higher recurrence rate, have repeatedly been brought to attention [2-5].

Over nearly three decades, the authors observed chlortetracycline treatment had positive effects treating vulvar non-neoplastic epithelial disorders. In this study, the authors compare the curative effect among three treatment groups, chlortetracycline, clobetasol, and chlortetracycline + clobetasol, attempting to find a more efficacious regimen. The results revealed the improvement rate of the chlortetracycline treatment group (86.1%) was a little lower than that of chlortetracycline + clobetasol group (87.8%), but no statistical difference was found between these two groups. Nevertheless, the efficiency rates of these two groups to treat vulvar non-neoplastic epithelial disorders were higher than that of clobetasol group (62.5%, \( p = 0.0072 \) and \( p = 0.0019 \)). In addition, the relapse cases in the clobetasol group were also higher when compared with the former two groups. In view of the above the authors conclude that chlortetracycline preparation is an effective drug to treat white lesions of vulva.

The chlortetracycline belongs to the class of tetracycline antibiotics, a broad-spectrum antibacterial agent family, the antibacterial mechanism of which is that they can specifically combine with the bacterial position A of 30S ribosomal subunit, to prevent the linking of the aminoacyl-tRNA in this position, consequently inhibiting bacterial protein synthesis. In addition to inhibiting gram-positive, gram-negative, and anaerobes, they can effectively kill most Rickett genera, the genus Mycoplasma, Chlamydia, atypical Mycobacterium genus, spirochetes, and some protozoa. The tetracycline has a higher concentration in the organization of human body, especially in stomach, lung, bladder, oral mucosa, and other parts. Cancer tissue has a strong affinity to it and can quickly take it into cells [6, 7].

The mechanism of chlortetracycline treating vulvar non-neoplastic epithelial disorders effectively may be related to killing chlamydia and mycoplasma. The present authors speculate that occurrence of vulvar non-neoplastic epithelial disorders is most likely due to infection of chlamydia mycoplasma. Chlamydia and mycoplasma often exist in specific organs, such as eyes, nostrils, anus, mouth, vagina, etc. When mycoplasma or chlamydia infects humans, the first invasion place is epithelial cells, in which they begin to grow and reproduce quickly then enter the monocyte-macrophage

Table 2 — Clinical efficacy of three treatment groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Resolved</th>
<th>Obviously improved</th>
<th>Slightly improved</th>
<th>No change</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlortetracycline</td>
<td>72</td>
<td>32</td>
<td>30</td>
<td>6</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Chlortetracycline + clobetasol</td>
<td>66</td>
<td>32</td>
<td>26</td>
<td>6</td>
<td>2</td>
<td>Hc=10.7766, df=2</td>
</tr>
<tr>
<td>Clobetasol</td>
<td>56</td>
<td>17</td>
<td>18</td>
<td>11</td>
<td>10</td>
<td>p=0.0046</td>
</tr>
</tbody>
</table>

\[ 1<->2 \ p = 0.6077 \begin{array}{c} 1<->3 \ p = 0.0072 \end{array} 2<->3 \ 0.0019 \]
system to proliferate, resulting in the death of infected cells. Meanwhile, they are also capable of evading the host immune defense function and get intermittent protection. The pathogenic mechanism of mycoplasma and chlamydia is to inhibit the metabolism of the infected cells, leading to the release of dissolved enzymes and the cytotoxicity of metabolites, causing local or systemic allergy, and autoimmunity [8-12]. Chlamydia species can produce a similar endotoxin to the that of gram-negative bacteria. The lipopolysaccharide and protein in the exterior of the endotoxin can induce chlamydia to adsorb in susceptible cells, promoting the susceptible cell endocytosis to chlamydia, and preventing the fusion of phagosomes and lysosomes, so that chlamydia can multiply inside the phagocytic vesicle and suppress cell metabolism until it is eventually destroyed [8-10]. Toxic substances of mycoplasma metabolism, such as dissolved nerve mycoplasma producing neurotoxins, cause nerve cell membrane damage. Mycoplasma urealyticum producing urea can bring large amounts of ammonia to damage cells [11, 12]. The present authors speculated that genital epithelial cell destruction, allergy, and autoimmunity, for the pathogenic mechanism of chlamydia and mycoplasma in vulvar nonneoplastic epithelial disorders, may be the important reasons for local itching, depigmentation, atrophy, scarring, and adhesion.

Chlortetracycline, in addition to killing chlamydia and mycoplasma, also play an important role in suspension of further damage to the epithelial cells, especially blocking or repairing local inflammation and clearing inflammatory mediators. Existing data found that the tetracycline could restrain activity of matrix metalloproteinase (MMP) and phospholipase A2 (PLA2), as well as strongly clean out oxygen free radicals [13-18]. These inflammatory cytokines, such as oxygen-free radicals, have been found to have a concerning relationship with the white lesions of the vulva [19].

In summary, the authors believe that chlortetracycline eye ointment for external use is an effective drug to treat vulvar non-neoplastic epithelial disorders, whose possible main mechanism may be its resistance to chlamydia and mycoplasma. The latter two are perhaps the prime suspect of vulvar nonneoplastic epithelial disorders. The present study group is carrying out an experiment on local histological pathogens of vulvar non-neoplastic epithelial disorders in order to obtain a clear conclusion.

Acknowledgments

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References

A new surgical approach for the management of severe postpartum hemorrhage due to uterine atony: preliminary results in 27 cases

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Summary

Purpose of investigation: To demonstrate a new suturing technique that effectively reduces severe postpartum hemorrhage secondary to uterine atony. Materials and Methods: The study consisted of 27 patients with persistent postpartum bleeding due to uterine atony which was unresponsive to medical treatment. The patients were treated with ∞ compression sutures that passed through entire uterine wall on which the placenta was located and were knotted within uterine cavity. Demographic properties, complications, operative results are demonstrated. Results: Uterine bleeding was controlled in 26 of 27 cases (%96.3). Total abdominal hysterectomy was performed in only one patient who had persistent incision site bleeding and disseminated intravascular coagulation. Conclusion: Uterine atony is an emergency and early intervention is necessary. As indicated by the preliminary results, the new technique effectively stopped bleeding in 96.3% of cases; no other techniques were carried out additionally. The technique is promising with properties as easy applicability, safety, and absence of major complications. A larger study is needed for further comparison of operative results.

Key words: Postpartum Hemorrhage; New Surgical Approach; ∞ Compression suture.

Introduction

Postpartum hemorrhage (PPH) still remains to be one of the most serious health problems related to maternal mortality worldwide, accounting for 25–30% of all maternal deaths [1]. PPH complicates up to 18% of all deliveries [1]. In addition, 64.7% of severe maternal morbidity is the result of obstetric hemorrhage most of which is the result of uterine atony (UA) [2].

Management of UA begins with intravenous and urinary catheterization. Uterine massage, uterotonic agents with bimanual uterine compression, volume replacement (crystalloid or if needed blood products) should be maintained in order to prevent coagulopathy. Besides uterine tamponade, compression sutures and in selected cases embolization or hypogastric artery ligation is applied. Hysterectomy is the last opportunity in order to supply homeostasis. Due to recent advances in effective medical and surgical interventions, need for emergent hysterectomy is highly decreased. In a report, emergent per partum hysterectomy incidence was reported as 0.2–0.5% [3].

Uterine compression sutures are successful in avoiding hysterectomy in 82% of these women [4]. Of the several different techniques noted in the literature, the B-Lynch suture, which was first reported in 1997, has gained the most popularity, with a number of subsequent publications attesting to its efficacy [5]. Although compression sutures are highly efficient in the management of uterine atony, persistent bleeding still remains as a fear for obstetricians.

In Literature, new methods and investigations are being reported and continued in the management of uterine atony. Several concerns about the current compression sutures have been raised since they may lead to occlusion of the uterine cavity and blood entrapment. As the other is relatively new, data on the safety and efficacy of the new uterine compression suture techniques and efficacy are limited [6].

In this paper, the authors describe another simple variation of uterine compression suture technique (∞ suture) that is applied over placental bed by transmural suturing of the uterine wall on which the placenta was located for which the preliminary results appear to be effective and safe.

Materials and Methods

The present study is a retrospective review of cases at Necmettin Erbakan University Meram Faculty of Medicine, Obstetrics Department between January 2010 and March 2013. This study was approved by the Institutional Review Board of Necmettin Erbakan University Meram Faculty of Medicine.

Meram Medical Faculty serves as a referral hospital in a geographic area which has four million inner lands. The mean birth rate regarding last five years is 2,915 per year. Besides, it is the re-
ferral center of the complicated obstetrical cases. The demographic data: age, parity, gravidity, and gestational week were all recorded. The comorbidities with UA were also recorded.

In this report, the preliminary operative results of 27 cases with UA who were treated with transmural suturing of the uterine wall on which placenta was located were demonstrated.

The new surgical approach was carried out by the same operator (AA) in all cases. The technique was applied through pfannenstiel incision site. Laparotomy was performed through pfannenstiel incision for the patients who had UA after normal spontaneous delivery. Uterus was taken out of abdominal cavity.

Unless disseminated intravascular coagulopathy developed, bleeding occurred only from placental side, thus the placental side was the targeted area of the suturing technique. The placental detachment site was palpated and the interior uterus was tamponed from uterine incision site in order to visualize the bleeding placental area on which the suturing technique would be applied.
A new surgical approach for the management of severe postpartum hemorrhage due to uterine atony: preliminary results in 27 cases

The suturing of entire uterine wall objected to block the circulation within arcuate, radial, basal and spiral arteries, especially the anastomoses among these. This was the initial hypothesis of the study (Figure 1).

Placental detachment region (Figure 2) was outlined and inspected by low segment uterine incision. No. 1 sized 50 mm long semicircular needle was used and the needle was inserted from interior uterine cavity and passed through entire uterine wall (endometrium, myometrium, and serosa) towards serosa (first exit). The needle was then inserted from serosal surface just three to four cm lateral to first exit towards uterine cavity (first entry). After that, needle was inserted for the third time three to four cm cross downwards from first entry inside uterine cavity towards serosal surface (second exit). On the next step, the needle on the serosal surface was inserted from three to four cm lateral to second exit just parallel to the first suture towards uterine cavity (second entry). By the help of these moves, both ends of the suture were kept ready within uterine cavity to be tied. The end of suture at first exit and the other on second entry were tightened correspondingly in balance and tied (Figure 3-4-5). To prevent loosening suture was tied twice. At the same time, uterine wall being sutured was approximated manually from serosal site. Same procedure was repeated for each repeats of suture. When needed, two or more sutures were applied on placental area and bleeding was observed from incision site. In cases of placenta previa, following the appropriate reduction of bladder, the technique was applied on each bleeding areas all around cervix (Figures 6-7). Sutured areas could be observed for persistent bleeding intraoperatively and sutures could be repeated (Figures 8-9).

Figure 6. — The anterior view of the last state of knotting in case with placenta previa.

Figure 7. — The posterior view of the last state of knotting in case with placenta previa.

Figure 8. — Two repeats of technique in a case with placenta previa, posterior view.

Figure 9. — Multiple repeats of technique in a case with anteriorly located placenta.
The patients were observed for 60 minutes in intensive care unit postoperatively. The transfused blood products were recorded. The intraoperative and postoperative complications, the duration of hospital stay were all recorded. The study results were analyzed by SPSS version 13 and reported as mean ± standard deviation.

Results

Eighteen of 27 patients (66.6%) had UA after caesarean section and nine (33.3%) had UA after vaginal delivery. All cases received antibiotic prophylaxis. Mean age of cases was 28.5 ± 2.3 (21-33) years, mean gravidity was 3.2 (1-5), and mean parity was 2.7 (1-6). Twelve of 27 patients (44.5%) were primiparous and 15 of 27 (55.5%) patients were multiparous. Mean gestational week was 35.5 ± 2.1 (32-39) weeks. Eleven of 27 (32.6%) cases had placenta previa coexisting with uterine atony.

Total abdominal hysterectomy was performed in only one patient who had persistent bleeding and disseminated intravascular coagulation. This patient was urgently referred to the present clinic for UA developed after cesarean delivery. At admission, patient hemoglobin level was four g/dl. It was learned that Bakri postpartum balloon had been inflated at an outside center. Since patient's bleeding had continued, laparotomy was planned. The new technique was applied; afterwards bilateral internal iliac artery ligation was achieved. Due to continuation of bleeding, total abdominal hysterectomy was performed. Two patients had wound infection postoperatively. Two patients remained vaginal bleeding (five pads/day), but these patients did not require additional transfusion; the remaining patients had insignificant vaginal bleeding.

Twenty-seven patients were operated by new suture technique. Bleeding was controlled in 26 patients (96.2%). Total abdominal hysterectomy was performed in only one patient who had persistent bleeding and disseminated intravascular coagulation.

The sutures were repeated in necessary cases, and the mean suture number/case was 2.3 ± 1.1 (1-5). The mean blood loss in the series during operations was 1,650 ± 950 cc (600-5,000). Four patients (14.8%) did not require blood transfusion postoperatively; on the other hand mean transfusion rate in the series was four units (2-15). Mean operation time was 75 ± 10 minutes (60-100 minutes). Routine controls on 40th day were normal.

Discussion

UA is one of the most important obstetric emergencies that cause maternal mortality and morbidity. It may occur in cases even without risk factors (elderly maternity, history of cesarean section, history of postpartum hemorrhage, multiple pregnancy, polihydramnios, prolonged labor, and tired uterus). Mortality and morbidity decrease with early intervention [2].

Options for the management of postpartum hemorrhage resulting from uterine atony include uterotonics, selective devascularization by suture ligation or angiographic embolization, uterine compression sutures, intrauterine packing, and hysterectomy. All of these therapies are objected to diminish blood loss, preserve fertility, and avoid life-threatening complications.

When conservative medical treatments fail to control hemorrhage, surgical options are considered. Hysterectomy is one of these surgical approaches for the management of uterine atony, but is a radical option and is not appropriate for patients who desire further fertility. Regarding this fact, in recent years compression sutures have been introduced into literature for the management of UA. Initially in 1997, B-Lynch et al. applied a surgical approach in five cases and reported successful management of hemorrhage [5]. Afterwards several modified techniques were reported [7-11]. In severe and persistent hemorrhage, Lynch compression suture together with balloon tamponade was defined [12].

All of these techniques puncture the uterine walls. Most of them directly define the suturing of the anterior and posterior uterine walls, which result in obliterated uterine cavity. The reported complications of these sutures were reported as such as pyometrium, uterine synechiae, uterine necrosis, partial ischemic necrosis and, in a few of the procedures, the sutures slid off at the uterine fundus [13-19]. Multiple square sutures described by Cho et al. that target placental area in severe postpartum hemorrhage were found to be efficient and safe. In some cases, moderate to severe adhesions were reported, and those adhesions were reported to be resected by hysteroscopic approaches [7].

The present authors’ new technique is a compression suture but targets the placental bed. (The suture passes through entire uterine wall on which the placenta is located and the suture is placed on the bleeding part of uterine cavity). It can be predicted that the technique may have some complications, but similar to other compression sutures, it is predicted to be free of great vessel and ureter injury.

In the literature, Wohlmuth et al. in their series achieved blood stoppage in 85% of 22 cases [20]. Mostfia et al. described a needle suture that compresses the uterus in a different way without opening the uterine cavity and reported success in 12 patients out of 13 [21]. In the present series, the authors have succeeded homeostasis in 26 cases (96.2%).

In 1991 Cho et al. described interrupted circular suture (one cm frequently) around of the bleeding lower uterine segment with zero chronic suture [22]. They described a suturing technique which was placed on serosal face of uterus.

Druzin described four cases in which bleeding stopped by hard buffering of lower uterine segment [23]. In literature, it is also reported that Bakri balloon application stopped active hemorrhage in cases with placenta previa without any need for hysterectomy [24, 25].
In a study in which 70 cases with postpartum hemorrhage were investigated, it was reported that hemorrhage was controlled in 75% of cases by balloon and Lynch suture, and in 24% of cases hysterectomy was carried out. Sixteen percent of cases suffered from organ dysfunction, and one patient died. Though promising developments are reported in the management of postpartum hemorrhage, it retains its importance and severity [26].

Later on, in 2000 Cho et al. reported square sutures at cesarean delivery that approximated anterior and posterior walls of the uterus in order to compress the bleeding site of the uterus. They have also reported that their technique was applicable in cases with placenta previa [7].

The present technique offers suturing of entire thickness of the uterine wall on which placenta had been located, beginning from endometrial cavity towards serosa, placing the knot of suture within endometrial cavity. By this way, the uterine cavity is not totally collapsed and this may be an advantage in the future for preventing complications related to compression suture techniques. Similarly, the present technique also provides alternative for cases with placenta previa, which in turn is another advantage in cesarean deliveries. By the present method, bleeding areas can be observed intraoperatively and repeated sutures can be applied. The present authors can predict that their technique may lead to complications, but they believe in that a few infinite sutures applied only on to the placental bed without interfering other sites on endometrial cavity (uterine cavity is not totally collapsed) is an advantage to prevent complications and it also provides to detect the cessation of hemorrhage during operation. The suturing of entire uterine wall objected to block the circulation within arcuate, radial, basal, and spiral arteries spiral, especially the anastomoses of these. The suturing of entire wall and the placement of the knot within the cavity objected to decrease the uterine volume, thus to help uterine contraction.

In cases with fundal localization of placenta, in order not to traumatize the adjacent tissue, the needle was straightened and protruded towards uterine fundus by the guidance of finger tip. The needle was inserted from uterine cavity, traversed entire uterine layers and reinserted from serosal site towards uterine cavity, thus all these maneuvers achieved the suturing of uterine fundus which remains as a closed area. It might be much easier to suture with 80-mm sized needle, but it would also be more traumatic, so the present authors preferred to use 50-mm sized needle. Since, atonic uterus is soft, 50-mm sized needle is appropriate in each case even when placenta was located on fundus. No other interventions such as Lynch suture, ligation of uterine, and hypogastric arteries other than this method were applied in this series.

Conclusion

The present new technique is a placental side compression suture rather than a uterine compression suture, thus preventing obliteration of uterine cavity. The authors believe that this intervention only on placental bed without interfering other sites on endometrial cavity (uterine cavity is not totally compressed) is an advantage to prevent complications. However, this theory should be supported by further studies with further studies that included larger case series.

The authors succeeded to control uterine bleeding in 26 cases out of 27 (96.2%), thus it may be offered as an alternative approach in the management of uterine atony.

References


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Introduction

A urinary tract infection (UTI) is an infection that affects any part of the urinary tract. UTI is not only frequent but the range of clinical effect varies from asymptomatic bacteriuria (AB) to acute pyelonephritis. Symptomatic UTI refers to patients whose urine is teeming positive cultures (≥ 10^5 CFU/ml) and who have symptoms that can be related to problems in the urinary tract. Asymptomatic bacteriuria (ASB) refers to the presence of two consecutive clear-voided urine specimens both yielding positive cultures (≥ 10^5 CFU/ml) of the same uropathogen, in a patient without urinary symptoms [1, 2]. UTI is very common during pregnancy [3]. Pregnant women are more sensitive to UTI when compared to non-pregnant ones due to changes in sex hormone levels, vesicoureteral reflux caused by uterus pressure to adjacent organs, and glycosuria that is very common in pregnancy and suitable for bacterial growth [4]. Asymptomatic bacteriuria and UTIs carry risks of adverse pregnancy outcomes and can have far-reaching consequences for the woman and neonate. Pregnant women with AB are more likely to deliver pre-mature or low-birth-weight infants and to develop pyelonephritis comparing with those without bacteriuria [5]. In addition acute pyelonephritis has been associated with anaemia, pre-eclampsia, and chronic renal disease (that has been cited as significant adverse obstetric outcome and medical conditions) and with increased neonatal mortality, particularly with Gram negative sepsicaemia [6-8].

The factors contributing to bacteriuria are age, parity, frequent intercourse during pregnancy, diabetes mellitus, and sickle cell anemia, anomalies of urinary tract, inadequate hygiene of intimate organs, earlier infections, and lower educational and income level [9].

Prenatal care has the potential to address many pregnancy complications, concurrent illnesses, and health problems [10]. An essential aspect of prenatal care models concerns the content of prenatal care, which is characterized by three main components: 1) early and continuing risk assessment, 2) health promotion (and facilitating informed choice), and 3) medical and psychosocial interventions and follow-up [11].

Prenatal care consists of medical checkups and screening tests which are designed to keep mother and baby healthy during pregnancy. It also involves education and counseling about how to handle different aspects of pregnancy. During these visits many issues are discussed, such as healthy lifestyle, diet, exercise, and stress management.

Summary

Purpose of investigation: To investigate how the regularity of checkups in pregnancy influences maternal behavior regarding habits in prevention of urinary tract infection (UTI), the level of information, and finally the prevalence of asymptomatic bacteriuria (AB). Materials and Methods: This study included 223 women with regular and 220 women with irregular checkups in pregnancy were given the questionnaire on the following issues: frequency of sexual intercourses during pregnancy, the regularity of bathing and changing of underwear, the direction of washing the genital region after urinating, the regularity of antenatal visits to gynecologist, and the subjective experience concerning the quality of the information received by the healthcare provider. Results: AB was present significantly more frequent in group of participants with irregular controls during pregnancy compared to group with regular checkups in pregnancy. The prevalence of AB was higher in those women who had irregular prenatal checkups. Maternal behaviors related with the risk of urinary infections are more frequent among women with irregular prenatal care. Conclusion: Results of the present study emphasize the importance of regular prenatal care in AB prevention.

Key words: Asymptomatic bacteriuria; Urinary infection; Checkups; Behavior; Pregnancy.
and desirable maternal behavior and screening tests. Thus, maternal behavior in prevention of urinary infections is discussed and screening for AB is performed (among other things) during these visits. As long as the pregnancy is straightforward, women should have ten antenatal appointments. The pregnant women are seen once a month during the first and second trimesters. Pregnant women are asked to give a urine sample at antenatal appointments. The urine is checked for several things, including bacteriuria, protein or albumin. If the bacteriuria is found in urine, it may indicate that one has an infection that needs to be treated.

The aim of the study was to investigate how the regularity of checkups in pregnancy influences the maternal behavior regarding desired habits in prevention of UI, the level of information regarding these desirable habits obtained during a visit to a doctor, and finally the prevalence of AB.

Materials and Methods

The present prospective cohort study involved pregnant women screened for AB in the Institute of Gynecology and Obstetrics, Clinical Center of Serbia, during the study period of February 1st, 2010 to February 1st, 2013. Eligibility criteria for study participants were: single pregnancy, primiparity, and second trimester of pregnancy, aged between 18 and 38, and no family history of diseases or chronic illnesses. Women with urinary symptoms, frequent urinary infections, renal calculosis, urinary tract anomalies, gynecological diseases, history of surgical procedures, abortions, antibiotic or immunosuppressive therapy in the last six months, and those with conditions related to high risk for AB (such as gestational diabetes and sickle cell anemia) were excluded. Women who require more-frequent checkups in pregnancy, such as those at higher risk of complications (high risk pregnancies, women who had had difficulty conceiving or carrying a baby, had a higher risk of birth defects) were excluded from the study.

After signing informed consent, each participant had an individual conversation with investigator and had to fill the questionnaire. The first part of the survey consisted of questions about age, educational (elementary school, high school, college), and income level (average, below or above the average). In the second part of the questionnaire, participants filled out the survey about following habits: the frequency of sexual intercourses during pregnancy, the regularity of bathing and changing of underwear, and about the direction of washing the genital region (forward to backward or backward to forward) after urinating. The third part comprised the questions related to the regularity of antenatal visits to gynecologist and the subjective experience concerning the quality of the information provided by the healthcare provider related to recommended behavior during pregnancy, particularly associated with the issues addressed in the second part of the questionnaire.

Pregnant patients were divided into two groups: group A involved women who were regularly controlled during pregnancy and group B with irregular checkups in pregnancy. Regular controls were defined according to the standard protocol for pregnancy checkups in Serbia, which imply monthly visits to caregiver during the first and second trimester.

Afterwards, the following tests were done for each participant: urine analysis and urine culture. Morning urine samples were collected from each patient and sent to laboratory for analyses. Samples with over than 100,000 colonies per ml were considered positive.

Statistical analysis

SPSS software package 15.0 was used for statistical data analysis. The authors used descriptive statistical methods and χ square test to compare regularly and irregularly controlled groups. They calculated and estimated the odds ratio (OR) and confidence interval (CI = 95%). Comparison of sexual intercourse frequencies among the subgroups is calculated using the χ square test. Value $p < 0.05$ was considered statistically significant.

Results

During the study period, 443 pregnant women were enrolled to study, 223 in group A and 220 in group B. The main characteristics of study participants are presented in Table 1.
The prevalence of AB in the present study population was 7.22% and AB was present significantly more frequent \( p = 0.0000001 \) in group of participants with irregular controls during pregnancy (20 participants) comparing with group with regular checkups in pregnancy (12 patients) (Figure 1).

Escherichia coli were the primary urinary tract pathogen found in AB. The list of other uropathogens discovered in AB participants and their prevalence are presented in Table 2. The difference in frequency of AB among study group was significant \( p < 0.01 \). AB was present in 12 group A participants and in 20 group B participants.

The survey about habits of interest regarding conditions associated with an increased prevalence of asymptomatic bacteriuria in pregnancy, revealed differences among the groups of study participants (Table 3). These differences were significant, with the exception of sexual intercourse frequencies during pregnancy.

### Discussion

In the present study population, pregnant women who went to regular controls were significantly different in terms of age, education, income and smoking status compared to those who did not regularly visited the obstetricians. Despite universal healthcare insurance coverage due to constitutional and legislative provisions in Serbia, women with younger age, especially those with lower level of education and lower income level, tended to less of the health services system. Explanation of this phenomenon could be found in the fact that Serbia is a non-western developing country, where the poverty and lack of education are the social roots of morbidity [12]. It has been demonstrated that the health cannot be achieved without addressing these social determinants of health, and the answer does not exist only in the health sector [13]. Overcoming barriers to health service access is likely to be more difficult for the poor and other vulnerable groups (for example young people) as lack of information and cultural barriers impede them from benefiting from public healthcare system. Even in most industrialized western countries, studies have shown that non-western women make inadequate use of prenatal care. They are less likely to attend all prenatal care appointments [14].

The prevalence in the entire present study population was in line with literature data [15, 16]. Furthermore, the authors examined the association between the regularity of checkups in pregnancy and AS measured through the prevalence of AB. The prevalence ranged from 5.69% in group A to 10% in group B. The present study showed that women with the irregular checkups in pregnancy were more likely to have AB \( p < 0.001 \).

Regarding bacteriologic isolates from pregnant women with AB in the present study, the etiologic agent Escherichia coli was the most frequent, which is in agreement with similar reported studies [16, 17].

The regular bathing and changing of underwear and forward to backward direction of washing the genital region after urinating as desired habits in terms of prevention of urinary infections in pregnancy were more frequent among group A participants. This is in agreement with other authors who have shown that unsatisfying genital hygiene in-
fluences the rate of further infections in pregnancy [16]. From this the we might conclude that women with regular examinations during pregnancy have more opportunities to obtain information on proper behavior during pregnancy. This is supported by the fact that the study demonstrated that women who went for regular checkups were significantly more satisfied in relation to the quality and quantity of information provided by gynecologists about the proper actions and habits during pregnancy. A variety of maternal behaviors and practices are linked with adverse health outcomes for both the mother and the infant [18]. Information regarding maternal manners and experiences is required to observe trends, to improve the understanding of the relations between behaviors and health outcomes, to plan and evaluate programs, to direct policy decisions, and to monitor progress towards improving health [19]. AB is one of the five areas of antenatal care where studies have shown that screening and appropriate management improves outcomes [20]. Bearing in mind the presented results of this study, we have to underline the importance of regular prenatal care in prevention of AB.

**Conclusion**

In spite of near universal coverage for antenatal visits in Serbia, younger women, women with lower levels of education and lower income levels, tend to less use of the health services system. The prevalence of AB is higher in those women who had irregular prenatal checkups. Maternal behaviors related with the risk of urinary infections are more frequent among women with irregular prenatal care. Results of the present study emphasize the importance of regular prenatal care in prevention of AB.

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**References**


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Introduction

Violence against women is the most widespread yet under-recognized human rights violation in the world [1]. It is an important global health problem and particularly women of reproductive age [2, 3]. According to the United Nations Declaration on the Elimination of Violence Against Women of 1993, violence against women is defined as “any act of gender-based violence that results in, or is likely to result in, physical, sexual, or psychological harm or suffering to women, including threats of such acts, coercion, or arbitrary deprivation of liberty, whether occurring in public or private life” [4]. Violence can take many forms including psychological, physical, and sexual nature and it can occur within the context of family or even the general community [5]. The World Health Organization’s (WHO) 2002 World Report on Violence and Health defines intimate partner violence (IPV) as “any act of behavior within an intimate relationship that causes physical, psychological, or sexual harm to those in the relationship” [6]. Studies regarding violence against women in Egypt show that this problem is widespread. According to the Egyptian Demographic and Health Surveys (EDHS) conducted in 1995, about (32%) of women reported been beaten during pregnancy [7]. WHO 2001 review of national studies on women subjected to physical violence by an intimate partner showed that 34.4% of Egyptian women have been subjected to this form of abuse [8].

The available reports about maternal and neonatal adverse outcomes due to violence during pregnancy are not conclusive. Some studies have shown positive associations between different forms of abuse and birth outcomes [9–12] but others did not [13–15]. The effect of violence on pregnancy is thought to be due to either direct (blow to the abdomen) or indirect (psycho-somatic consequences) mechanisms [16]. The understanding of close relationship between violence during pregnancy and adverse maternal and neonatal consequences could have important clinical and public health effects.

The current study aims to evaluate the incidence of violence during pregnancy among women in Ismailia city – North Eastern part of Egypt – and to evaluate the maternal, fetal, and neonatal health consequences associated with this problem.

Materials and Methods

The study protocol runs in compliance with the Helsinki Declaration and approved by ethical committee of Suez Canal University Hospital (SCUH). This prospective cohort, hospital-based study was conducted among all pregnant women attending the Obstetrics...
outpatient clinic of SCUH during any period of pregnancy. Women were followed up until delivery and for one month thereafter for assessment of neonatal outcome. The study was performed during the period from first of January 2010 until the end of December 2012. The study included only women with singleton pregnancy aged 18 – 43 years. Women were approached by members of the nursing staff in the clinic after reassuring them about the confidentiality of the study and the information it contains, then an informed written consent was obtained from all participants. A total of 2,193 women were recruited and a total of 1,857 completed the study. Written consent was obtained from all participants. A total of 2,193 women were recruited and a total of 1,857 completed the study. The studied women were interviewed using a questionnaire that contained initially the demographic characteristics of women, intimate partner characteristics, and assessment of IPV during the current pregnancy. Data were then placed in a sealed envelope and kept in the records. The studied women were also examined to identify injuries and other signs of violence. Immediately after delivery, any adverse maternal or fetal outcomes are added to the questionnaire. Women were seen again at the end of puerperium and any adverse neonatal outcomes were recorded. Contact details including telephone numbers were obtained to communicate with the patients if they were lost at follow up.

WHO defined intimate partner as intimate partners who may or may not be cohabitating, and the relationship need not involve sexual activities [18]. It includes current or former spouses (legal and common-law), and non-marital partners (boyfriend, girlfriend, same-sex partner, dating partner). In the current study and due to social considerations, intimate partner was defined as the current or ex-husband (whether women was married or divorced) and whether the women was living or used to live with him.

In the present study the authors used the NorVold Domestic Abuse Questionnaire (NORDAQ) [19]. Arabic translation was used. The translation was based on the original NORDAQ questionnaire and was validated before the study population was recruited. Validation was done to ensure that the questions were reliably conveyed to women and that they carried the intended meaning they were devised for. In addition, the questionnaire matched the Arabic validated version that was described by Haddad et al. [20].

Table 1. — Socio-demographic characteristics of the studied women classified by exposure to violence.

<table>
<thead>
<tr>
<th>Women’s characteristics</th>
<th>Exposed to violence (n=818) 44.1%</th>
<th>Not exposed to violence (n=1039) 55.9%</th>
<th>Total</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 –</td>
<td>206 (25.2%)</td>
<td>85 (8.2%)*</td>
<td>291 (15.7%)</td>
<td>3.8 (2.9 – 5.02)</td>
</tr>
<tr>
<td>25 –</td>
<td>300 (36.7%)</td>
<td>234 (22.5%)*</td>
<td>534 (28.8%)</td>
<td>1.9 (1.6 – 2.5)</td>
</tr>
<tr>
<td>30 –</td>
<td>280 (34.2%)</td>
<td>271 (26.1%)*</td>
<td>551 (29.6%)</td>
<td>1.5 (1.2 – 1.8)</td>
</tr>
<tr>
<td>35 –</td>
<td>20 (2.4%)</td>
<td>278 (26.8%)*</td>
<td>298 (16.1%)</td>
<td>0.07 (0.04 – 0.1)</td>
</tr>
<tr>
<td>40 – 43</td>
<td>12 (1.5%)</td>
<td>171 (16.4%)*</td>
<td>183 (9.8%)</td>
<td>0.08 (0.04 – 0.1)</td>
</tr>
<tr>
<td>GA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First trimester</td>
<td>371 (45.4%)</td>
<td>189 (18.2%)*</td>
<td>560 (30.2%)</td>
<td>3.7 (3.01 – 4.6)</td>
</tr>
<tr>
<td>Second trimester</td>
<td>291 (35.5%)</td>
<td>307 (29.5%)*</td>
<td>598 (32.2%)</td>
<td>1.3 (1.08 – 1.6)</td>
</tr>
<tr>
<td>Third trimester</td>
<td>156 (19.1%)</td>
<td>543 (52.3%)*</td>
<td>699 (37.6%)</td>
<td>0.2 (0.1 – 0.3)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Divorced</td>
<td>100 (12.2%)</td>
<td>34 (3.3%)*</td>
<td>134 (7.2%)</td>
<td>4.1 (2.7 – 6.3)</td>
</tr>
<tr>
<td>Married</td>
<td>718 (87.8%)</td>
<td>1005 (96.7%)*</td>
<td>1723 (92.8%)</td>
<td>0.9 (0.8 – 1.0)</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>118 (14.4%)</td>
<td>460 (44.3%)*</td>
<td>578 (31.1%)</td>
<td>0.2 (0.1 – 0.3)</td>
</tr>
<tr>
<td>Para 1-2</td>
<td>409 (50%)</td>
<td>512 (49.3%)</td>
<td>921 (49.6%)</td>
<td>1.03 (0.9 – 1.2)</td>
</tr>
<tr>
<td>≥ Para 3</td>
<td>291 (35.6%)</td>
<td>67 (6.4%)*</td>
<td>358 (19.3%)</td>
<td>8.01 (5.9 – 10.8)</td>
</tr>
<tr>
<td>Educational level</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illiterate</td>
<td>281 (34.4%)</td>
<td>108 (10.4%)*</td>
<td>389 (20.9%)</td>
<td>4.5 (3.5 – 5.8)</td>
</tr>
<tr>
<td>&lt; 12 years</td>
<td>306 (37.4%)</td>
<td>95 (9.1%)*</td>
<td>401 (21.6%)</td>
<td>5.9 (4.6 – 7.7)</td>
</tr>
<tr>
<td>≥ 12 years</td>
<td>231 (28.2%)</td>
<td>836 (80.5%)*</td>
<td>1067 (57.5%)</td>
<td>0.09 (0.08 – 0.1)</td>
</tr>
<tr>
<td>Job (current/previous)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Housewife</td>
<td>595 (72.7%)</td>
<td>113 (10.9%)*</td>
<td>708 (38.1%)</td>
<td>21.8 (16.9 – 28.3)</td>
</tr>
<tr>
<td>General worker</td>
<td>90 (11%)</td>
<td>76 (7.3%)*</td>
<td>166 (8.9%)</td>
<td>1.6 (1.1 – 2.2)</td>
</tr>
<tr>
<td>Semi-professional</td>
<td>103 (12.6%)</td>
<td>550 (52.9%)*</td>
<td>653 (35.2%)</td>
<td>0.1 (0.09 – 0.2)</td>
</tr>
<tr>
<td>Professional</td>
<td>30 (3.7%)</td>
<td>300 (28.9%)*</td>
<td>330 (17.8%)</td>
<td>0.09 (0.06 – 0.1)</td>
</tr>
<tr>
<td>Socio-economic status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>342 (41.8%)</td>
<td>241 (23.2%)*</td>
<td>583 (31.5%)</td>
<td>2.4 (1.9 – 2.9)</td>
</tr>
<tr>
<td>Moderate</td>
<td>383 (46.8%)</td>
<td>731 (70.4%)*</td>
<td>1114 (59.9%)</td>
<td>0.43 (0.3 – 0.5)</td>
</tr>
<tr>
<td>High</td>
<td>93 (11.4%)</td>
<td>67 (6.4%)*</td>
<td>160 (8.6%)</td>
<td>1.8 (1.3 – 2.6)</td>
</tr>
<tr>
<td>Duration of marriage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5 years</td>
<td>289 (53.3%)</td>
<td>403 (38.8%)*</td>
<td>692 (37.3%)</td>
<td>0.9 (0.7 – 1.05)</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>347 (42.4%)</td>
<td>444 (42.7%)*</td>
<td>791 (42.6%)</td>
<td>0.9 (0.8 – 1.2)</td>
</tr>
<tr>
<td>Pregnancy intent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unwanted</td>
<td>296 (36.2%)</td>
<td>85 (8.2%)*</td>
<td>381 (20.3%)</td>
<td>6.4 (4.9 – 8.4)</td>
</tr>
<tr>
<td>Wanted</td>
<td>522 (63.8%)</td>
<td>954 (81.8%)*</td>
<td>1476 (79.5%)</td>
<td>0.7 (0.6 – 0.8)</td>
</tr>
<tr>
<td>Smoking, addiction/alcohol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>801 (97.9%)</td>
<td>1036 (99.7%)*</td>
<td>1837 (98.9%)</td>
<td>7.3 (2.1 – 39.1)</td>
</tr>
<tr>
<td>Yes</td>
<td>17 (2.1%)</td>
<td>3 (0.3%)*</td>
<td>20 (1.1%)</td>
<td>0.09 (0.06 – 0.1)</td>
</tr>
</tbody>
</table>

*Statistically significant difference; OR: odds ratio; CI: confidence interval; GA: gestational age.
basic needs (such as food, shelter, and medical care) and deprivation of liberty [19]. Physical violence comprised use of physical force or weapons in attacks that injured or harmed a woman, including beating, kicking, pulling hair, biting, burning, attacks with weapons and objects, and murder [19]. Sexual violence comprised actions that forced the woman to engage in sexual acts against her will, without her consent; it included administering drugs to the women. The authors excluded the section of healthcare system violence as it was beyond the scope of the present study.

The adverse maternal outcomes in the present study included threatened abortion (< 20 weeks), complete abortion, placental abruption, preterm labor defined as a live birth before 37 completed weeks of gestation, and premature rupture of the membranes. Adverse fetal outcomes included, fetal distress, fetal death, and small-for-gestational age (SGA) defined as the sex- and gestational age-specific birth weight below the 10th percentile [21]. Adverse neonatal outcomes included neonatal death and low birth weight (< 2,500 kg).

**Results**

A total of 1,857 pregnant women completed the study and were divided into two groups; those exposed to any form of violence (n = 818, 44.1%) and those not exposed (n = 1,039, 55.9%). A total of 336 women did not complete the study for different reasons.

Tables 1 and 2 present the socio-demographic characteristics of the studied women and their intimate partners. The mean age was 28.6 years with 37.6% of women presented in the third trimester. Only 7.2% of the women were divorced.

### Table 2. — Socio-demographic characteristics of the intimate partners classified by commission of violence.

<table>
<thead>
<tr>
<th>Intimate partner's characteristics</th>
<th>Commit violence against wives</th>
<th>Don't commit violence against wives</th>
<th>Total</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age difference</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5 years</td>
<td>386 (47.2%)</td>
<td>469 (45.1%)</td>
<td>855 (46.1%)</td>
<td>1.09 (0.9 – 1.3)</td>
</tr>
<tr>
<td>5 – 10 years</td>
<td>283 (34.6%)</td>
<td>513 (49.4%)*</td>
<td>796 (42.8%)</td>
<td>0.5 (0.4 – 0.7)</td>
</tr>
<tr>
<td>&gt; 10 years</td>
<td>149 (18.2%)</td>
<td>57 (5.5%)*</td>
<td>206 (11.1%)</td>
<td>3.8 (2.8 – 5.4)</td>
</tr>
<tr>
<td>Educational level</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illiterate</td>
<td>197 (24.1%)</td>
<td>78 (7.5%)*</td>
<td>275 (14.8%)</td>
<td>3.9 (2.9 – 5.2)</td>
</tr>
<tr>
<td>&lt; 12 years</td>
<td>438 (53.5%)</td>
<td>261 (25.1%)*</td>
<td>699 (37.6%)</td>
<td>3.4 (2.8 – 4.2)</td>
</tr>
<tr>
<td>≥ 12 years</td>
<td>183 (22.4%)</td>
<td>700 (67.4%)*</td>
<td>883 (47.6%)</td>
<td>0.13 (0.11 – 0.2)</td>
</tr>
<tr>
<td>Job (current/previous)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General worker</td>
<td>308 (37.7%)</td>
<td>223 (21.5%)*</td>
<td>531 (28.6%)</td>
<td>2.2 (1.8 – 2.7)</td>
</tr>
<tr>
<td>Semi-professional</td>
<td>291 (35.6%)</td>
<td>498 (47.9%)*</td>
<td>789 (42.6%)</td>
<td>0.6 (0.4 – 0.7)</td>
</tr>
<tr>
<td>Professional</td>
<td>219 (26.7%)</td>
<td>318 (30.6%)</td>
<td>537 (28.9%)</td>
<td>0.8 (0.6 - 0.3)</td>
</tr>
<tr>
<td>Smoking, addiction/alcohol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>209 (25.6%)</td>
<td>1009 (97.1%)*</td>
<td>1218 (65.6%)</td>
<td>98.1 (65.9 – 145.6)</td>
</tr>
</tbody>
</table>

*Statistically significant difference; OR: odds ratio; CI: confidence interval.

### Table 3. — Prevalence and severity of intimate partner violence during pregnancy.

<table>
<thead>
<tr>
<th>Exposure to intimate partners’ violence</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1039</td>
<td>55.9%</td>
</tr>
<tr>
<td>Total number of women exposed to any type of violence</td>
<td>818</td>
<td>44.1%</td>
</tr>
<tr>
<td>Physical violence alone</td>
<td>73</td>
<td>3.9%</td>
</tr>
<tr>
<td>Sexual violence alone</td>
<td>41</td>
<td>2.2%</td>
</tr>
<tr>
<td>Emotional violence alone</td>
<td>455</td>
<td>24.5%</td>
</tr>
<tr>
<td>Physical and sexual violence</td>
<td>98</td>
<td>5.3%</td>
</tr>
<tr>
<td>Physical and emotional violence</td>
<td>104</td>
<td>5.6%</td>
</tr>
<tr>
<td>Sexual and emotional violence</td>
<td>25</td>
<td>1.3%</td>
</tr>
<tr>
<td>Physical, sexual and emotional</td>
<td>22</td>
<td>1.2%</td>
</tr>
<tr>
<td>Total exposure to physical violence</td>
<td>297</td>
<td>15.9%</td>
</tr>
<tr>
<td>Total exposure to sexual violence</td>
<td>186</td>
<td>10%</td>
</tr>
<tr>
<td>Total exposure to emotional violence</td>
<td>606</td>
<td>32.6%</td>
</tr>
</tbody>
</table>

**Severity of different types of violence**

**Physical violence (n = 297)**

| Mild abuse                      | 103   | 34.7% |
| Moderate abuse                 | 139   | 46.8% |
| Severe abuse                   | 55    | 18.5% |

**Sexual violence (n = 186)**

| Mild abuse; no genital contact | 20    | 10.7% |
| Mild abuse; emotional/sексual humiliation | 79 | 42.5% |
| Moderate abuse; genital contact | 36    | 19.4% |
| Severe abuse; penetration       | 51    | 27.4% |

**Emotional violence (n = 606)**

| Mild abuse                      | 140   | 23.1% |
| Moderate abuse                 | 352   | 58.1% |
| Severe abuse                   | 114   | 18.8% |

*N.B: total physical violence = physical violence only + physical and sexual violence + physical and emotional + physical, sexual and emotional (and so on for other types).*

About half of the studied women were para 1-2 (49.6%). The pregnancy was unplanned among 20.5% of the cases. Regarding the intimate partners, in about half of the cases, the age difference between the woman and her partner was less than five years (46.1%) and more than ten years in 11.1%;

34.3% of the partners were smokers, addicts or drinking alcohol. Evaluation of risk factors for exposure to intimate partner’s violence during pregnancy, the authors found that most of women exposed to violence were aged 25 – 30 years (70.9%), presented during first trimester, ≥ para 1-3, had lower educational level with low socio-economic status. Unwanted pregnancy was significantly associated with higher prevalence of exposure to intimate partners’ violence (36.2% vs 8.2%). Regarding the partners’ characteristics, it was found that partners of most women exposed to violence had wider age difference to their wives (from 5 to > 10 years), lower educational level, and addicted to drugs or alcohol. The most common drugs abused by the partners according to report of women were cannabis, rohypnol, parkinol, seconal, and tramadol. These drugs have common names among abusers and can be easily identified through their public label.

According to the NORAQ, a total of 44.1% of studied women was exposed to IPV during pregnancy. The most common type was emotional violence that was reported among 32.6%. About (15.9%) of studied women had been exposed to physical violence while 10% had been exposed to sexual violence (Table 3).

Assessment of adverse maternal outcomes showed that 5.1% of women had threatened abortion, 2.7% had an-

Table 4. — Adverse maternal and neonatal outcomes among the studied participants classified by exposure to any type of violence.

<table>
<thead>
<tr>
<th>Maternal adverse outcomes</th>
<th>Exposed to violence (n=818)</th>
<th>Not exposed to violence (n=1039)</th>
<th>Total</th>
<th>RR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threatened abortion</td>
<td>61 (7.5%)</td>
<td>32 (3.1%)*</td>
<td>93 (5.1%)</td>
<td>2.4 (1.6 – 3.7)</td>
</tr>
<tr>
<td>Complete abortion</td>
<td>30 (3.7%)</td>
<td>7 (0.7%)*</td>
<td>37 (1.9%)</td>
<td>5.4 (2.4 – 12.3)</td>
</tr>
<tr>
<td>Placental abruption</td>
<td>9 (1.1%)</td>
<td>21 (2.1%)</td>
<td>30 (1.6%)</td>
<td>0.5 (0.3 – 1.2)</td>
</tr>
<tr>
<td>Placenta previa</td>
<td>6 (0.7%)</td>
<td>13 (1.3%)</td>
<td>19 (1.1%)</td>
<td>0.6 (0.2 – 1.5)</td>
</tr>
<tr>
<td>Preterm labor</td>
<td>49 (5.9%)</td>
<td>26 (2.5%)*</td>
<td>75 (4.1%)</td>
<td>2.4 (1.5 – 3.8)</td>
</tr>
<tr>
<td>Premature rupture of Membranes</td>
<td>108 (13.2%)</td>
<td>43 (4.1%)*</td>
<td>151 (8.1%)</td>
<td>3.2 (2.3 – 4.5)</td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>360 (44%)</td>
<td>436 (41.9%)</td>
<td>796 (42.9%)</td>
<td>1.04 (0.9 – 1.2)</td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>286 (34.9%)</td>
<td>332 (31.9%)</td>
<td>618 (33.3%)</td>
<td>1.09 (0.9 – 1.2)</td>
</tr>
<tr>
<td>Post partum Hemorrhage</td>
<td>98 (11.9%)</td>
<td>104 (10%)</td>
<td>202 (10.9%)</td>
<td>1.1 (0.9 – 1.5)</td>
</tr>
</tbody>
</table>

*Statistically significant difference; RR: Relative risk; CI: confidence interval.

Table 5. — Adverse maternal and neonatal outcomes among the studied participants classified by exposure to physical violence.

<table>
<thead>
<tr>
<th>Maternal adverse outcomes</th>
<th>Exposed to physical violence (n=297)</th>
<th>Not exposed to physical violence (n=1560)</th>
<th>Total</th>
<th>RR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threatened abortion</td>
<td>56 (18.9%)</td>
<td>37 (2.4%)*</td>
<td>93 (5.1%)</td>
<td>7.9 (5.3 – 11.8)</td>
</tr>
<tr>
<td>Complete abortion</td>
<td>25 (8.4%)</td>
<td>12 (0.8%)*</td>
<td>37 (1.9%)</td>
<td>10.9 (5.6 – 21.5)</td>
</tr>
<tr>
<td>Placental abruption</td>
<td>8 (2.7%)</td>
<td>22 (1.4%)*</td>
<td>30 (1.6%)</td>
<td>1.9 (0.9 – 4.2)</td>
</tr>
<tr>
<td>Placenta previa</td>
<td>5 (1.7%)</td>
<td>14 (0.9%)*</td>
<td>19 (1.1%)</td>
<td>1.8 (0.7 – 5.2)</td>
</tr>
<tr>
<td>Preterm labor</td>
<td>39 (13.1%)</td>
<td>36 (2.3%)*</td>
<td>75 (4.1%)</td>
<td>5.7 (3.7 – 8.8)</td>
</tr>
<tr>
<td>Premature rupture of Membranes</td>
<td>74 (24.9%)</td>
<td>77 (4.9%)*</td>
<td>151 (8.1%)</td>
<td>5.1 (3.8 – 6.8)</td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>137 (46.1%)</td>
<td>659 (42.2%)</td>
<td>796 (42.9%)</td>
<td>1.1 (0.9 – 1.3)</td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>110 (37.1%)</td>
<td>508 (32.6%)</td>
<td>618 (33.3%)</td>
<td>1.1 (0.9 – 1.3)</td>
</tr>
<tr>
<td>Postpartum hemorrhage</td>
<td>42 (14.1%)</td>
<td>160 (10.3%)</td>
<td>202 (10.9%)</td>
<td>1.3 (1 – 1.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fetal/neonatal adverse outcomes</th>
<th>Exposed to physical violence (n=297)</th>
<th>Not exposed to physical violence (n=1560)</th>
<th>Total</th>
<th>RR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal distress</td>
<td>148 (49.8%)</td>
<td>150 (9.6%)*</td>
<td>298 (16.1%)</td>
<td>5.2 (4.3 – 6.3)</td>
</tr>
<tr>
<td>Fetal death</td>
<td>6 (2.1%)</td>
<td>3 (0.2%)*</td>
<td>9 (0.5%)</td>
<td>10.5 (2.6 – 41.7)</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>41 (13.8%)</td>
<td>89 (5.7%)*</td>
<td>130 (7.1%)</td>
<td>2.4 (1.7 – 3.4)</td>
</tr>
<tr>
<td>Neonatal death</td>
<td>7 (2.4%)</td>
<td>12 (0.8%)*</td>
<td>19 (1.1%)</td>
<td>3.1 (1.2 – 7.7)</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>78 (26.3%)</td>
<td>89 (5.7%)*</td>
<td>167 (8.9%)</td>
<td>4.6 (3.5 – 6.1)</td>
</tr>
</tbody>
</table>

*Statistically significant difference; RR: Relative risk; CI: confidence interval.
terpartum hemorrhage, 4.1% had preterm labor, 10.9% had postpartum hemorrhage, and 8.1% had premature rupture of membranes. The most common adverse fetal outcome was fetal distress that was reported in 16.1% of cases, 7.1% of fetuses were small for gestational age, and after delivery low birth weight was evident among 8.9% of neonates. Women exposed to IPV during pregnancy showed significantly higher incidence of threatened abortion (7.5% vs 3.1%), complete abortion (3.7% vs 0.7%), preterm labor (5.9% vs 2.5%), and premature rupture of membranes (13.2% vs 4.1%). As regarding fetal and neonatal outcomes, fetal distress, fetal death, and low birth weight were significantly more common among women subjected to violence during pregnancy (Table 4).

As shown in Table 5, there was an increased risk of most of adverse maternal outcomes and all of adverse fetal outcomes among women who were exposed to physical violence versus those who did not. Abortion had the highest relative risk (10.9 for complete abortion and 7.9 for threatened abortion) with exposure to physical violence. Cesarean delivery and postpartum hemorrhage were more prevalent among women exposed to physical violence but without statistically significant difference. All adverse fetal outcomes showed significant increased risk with exposure to physical violence.

The total number of cases who were exposed to physical form of violence was 297 (15.9%). The most prevalent form of physical violence among these cases was kicking (30.3%) and punching (17.8%); 39 (13.1%) women were exposed to whipping, 14 women (4.7%) were exposed to stab wound, four cases have been exposed to firearm shooting (1.3%), and nine women (3.0%) were exposed to burns (Table 6).

By examining the inflicted wounds among the total 297 women exposed to physical violence, it was found that contusions were the most common type of wound (43.1%). Most of the wounds were induced by a heavy blunt object (64.3%) while rough objects were used with 26.6% of cases to induce abrasions. Contused wounds represent 19.5% of all wounds. Four women had firearm injuries (one had inlet

### Table 6. — Frequency and pattern of physical violence among studied women exposed to physical violence.

<table>
<thead>
<tr>
<th>Form of physical violence</th>
<th>Number</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slapping</td>
<td>42</td>
<td>14.1%</td>
</tr>
<tr>
<td>Punching</td>
<td>53</td>
<td>17.8%</td>
</tr>
<tr>
<td>Kicking</td>
<td>90</td>
<td>30.3%</td>
</tr>
<tr>
<td>Hitting by blunt object</td>
<td>46</td>
<td>15.5%</td>
</tr>
<tr>
<td>Shooting</td>
<td>4</td>
<td>1.3%</td>
</tr>
<tr>
<td>Stabbing</td>
<td>14</td>
<td>4.7%</td>
</tr>
<tr>
<td>Whipping</td>
<td>39</td>
<td>13.1%</td>
</tr>
<tr>
<td>Burning</td>
<td>9</td>
<td>3.0%</td>
</tr>
<tr>
<td>Total</td>
<td>297</td>
<td>100%</td>
</tr>
</tbody>
</table>

### Table 7. — Types of wounds and weapons used among the studied women exposed to physical violence (n = 297).

<table>
<thead>
<tr>
<th>Types of wounds</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contusions</td>
<td>128</td>
<td>43.1%</td>
</tr>
<tr>
<td>Contused wounds</td>
<td>58</td>
<td>19.5%</td>
</tr>
<tr>
<td>Abrasions</td>
<td>79</td>
<td>26.6%</td>
</tr>
<tr>
<td>Stab wounds</td>
<td>14</td>
<td>4.7%</td>
</tr>
<tr>
<td>Inlet of firearm wound</td>
<td>1</td>
<td>0.3%</td>
</tr>
<tr>
<td>Inlet and exit of firearm wounds</td>
<td>3</td>
<td>1%</td>
</tr>
<tr>
<td>Dry burn</td>
<td>2</td>
<td>0.7%</td>
</tr>
<tr>
<td>Scalds</td>
<td>7</td>
<td>2.4%</td>
</tr>
<tr>
<td>Fractures</td>
<td>5</td>
<td>1.7%</td>
</tr>
<tr>
<td>Total</td>
<td>297</td>
<td>100%</td>
</tr>
</tbody>
</table>

### Weapons used in inducing wounds

| Heavy blunt object | 191 | 64.3% |
| Sharp object       | 14  | 4.7%  |
| Firearm weapon     | 4   | 1.3%  |
| Dry fire           | 2   | 0.7%  |
| Hot fluid          | 7   | 2.4%  |
| Rough object       | 79  | 26.6% |

Discussion

IPV against women is difficult to measure for different reasons; including the lack of uniform definition and that some women are reluctant to disclose violence as a result of social shame or cultural considerations [21].

The present study has shown that 44.1% of women were subject to different forms of violence during pregnancy inflicted by their partners. There are many reports – both national and international – confirming the widespread occurrence of this problem albeit with variable rates. Studies have shown great variability of prevalence of IPV from country to country and even among studies within the same country. Findings from 80 population-based studies carried out in 50 countries show that 10% to 60% of women who had ever been married or partnered had experienced at least one incident of physical violence from a current or former intimate partner [22].

Nationally, the Egyptian Centre for Women’s Rights in 2008 suggested that violence against women was on the rise [23], and according to a United Nations Children’s Fund (UNICEF) study in 2000, 35% of Egyptian women were beaten by their husbands [24]. In the 2005 Egyptian Demographic and Health Survey (EDHS), 47% of ever-
married women reported ever having experienced physical violence since the age of 15 years [25]. In the present study, although 44.1% of studied women had been exposed to violence during pregnancy, only 16% had been subjected to physical violence.

However, a comparative analysis of the 1995 and 2005, EDHS suggests that there may have been a decrease in the prevalence of more severe forms of physical abuse along with an increase in overall reporting of violence [24]. In the 1995 survey, 35% of married women reported exposure to physical violence by their current husbands [26]. However, in the 2005 survey, a significant decrease of physical and sexual violence rates to 22% was noted [25].

Internationally, a recent study by Urquia et al., [27] have found that among 8,400 Canadian women, 10.9% have reported exposure to any violence during the two-year period preceding the postpartum interview and among them only 3.3% were exposed during pregnancy.

Previous comprehensive review of the literature by Gazmararian et al., [28] have found that the prevalence of IPV in pregnancy ranged from 1% – 20%. A population-based study in New Zealand revealed a prevalence of 9% of IPV during pregnancy [29].

With regards to the type of IPV, the most common reported type in the present study was emotional violence (32.6%). Sexual violence was reported among 10% of the studied women. This is consistent with previous two studies of sexual abuse of married Egyptian women. These studies showed that 12% of women in Lower Egypt and 17% of women in Cairo reported being forced to engage in sex by their partners [26, 30]. The term marital rape is not legally, socially or culturally accepted in conservative societies like Egypt. However, studies in Jordan and Morocco have shown that an overwhelming majority of women ascertain the right to refuse sex with their husband under certain circumstances [3]. In an Iranian study by Faramarzi et al., [31], the prevalence of physical, sexual, and emotional domestic violence was respectively 9.1%, 30.8%, and 19.2%.

Previous studies have shown lower percentage of physical violence during pregnancy (9.1% in study of Faramarzi et al., [31] vs 16% in the present study). The most common form of physical violence reported in the present study was kicking followed by punching and slapping. In their study Faramarzi et al., [31] have shown that the most prevalent form of physical violence was slapping and punching.

Assessment of risk factors for IPV revealed that the probability of exposure to IPV during pregnancy is increased among younger divorced women, women of higher parity, lower educational level, lower socioeconomic status, wider age difference with husband, lower educational level of husband, and husband’s addiction to drugs and alcohol. Similar findings have been reported by previous studies [25, 32].

In this study, younger aged women were exposed to IPV more than older women; similar results were found in the study carried out among Australian women reporting that 19% of 6,300 women aged 18–24 years were exposed to violence in the preceding year, compared with 10% of women aged 25–30 years, 6.8% of women aged 35–44, and 1.2% of women aged 55 and over [33]. Employment and the socio-economic status have the potential to impact IPV, as IPV is shown to be associated with unemployment and underemployment [34].

In the present study, there was a wide distribution of drug abuse among husbands who committed different forms of violence against their wives during pregnancy; the most common drugs abused according to says of women were cannabis, rohypnol, parkinol, seconal, and tramadol. Other studies have shown a strong relation between violence during pregnancy and the use of illicit drugs by the male partner [35]. In general, among men who assaulted their female partners, substance use has been found to frequently accompany beating [31].

Consistent with the present finding, a previous review of national surveys in nine countries found a consistent association of an increased risk of partner abuse for women with low educational attainment, being under 25 years of age and having low socioeconomic status [25]. Also another multi-national study found significant association between physical IPV and several characteristics including regular alcohol consumption by the husband and poor family work status [36].

In a comparative analysis of the 1995 and 2005 EDHSs, there was a decrease of the association between socio-demographic variables and physical violence. However, high educational level was still associated with lower rates of IPV [37] and even some research suggests that education has a protective effect on women’s experience with violence, even when controlling for age and income [38].

The present study has shown that compared to non-exposed women, women who had been exposed to IPV during pregnancy had higher odds of miscarriage, preterm labor, and premature rupture of membranes. Concerning birth outcomes, the present study has shown that there was significant association between fetal distress, fetal death and low birth weight, and exposure to intimate partner violence. Associations between IPV and adverse maternal and neonatal outcomes have been supported by multiple previous studies [10-13, 27, 31]. However, in one meta-analysis assessing abuse as a risk factor for low birth weight that included eight studies, seven of them reported non-statistically significant associations [9]. A causative relation between IPV and adverse maternal and fetal/neonatal outcomes cannot always be explained. Some outcome such as miscarriage and placental abruption can be explained by the direct effect of trauma. Others such as low birth weight and fetal distress could not be simply explained.

In conclusion, intimate partner violence during pregnancy is widespread public health issue in Egypt and is associated with multiple socio-demographic determinants as
younger age, lower educational level, poverty, inadequate antenatal care, and partners’ addiction. The burden of the problem on maternal and neonatal health is great and it is associated with increased risk for multiple significant health issues as miscarriage, preterm labor, premature rupture of membranes, and low birth weight.

The present study has few limitations. The prospective cohort hospital-based nature is one to bear in mind and hence results cannot be extrapolated to the whole Egyptian community; therefore community based study is recommended. Despite this, the study addresses an important health issue that is not widely studied in the country. Another possible limitation would be the potential under-reporting of female-related or male-related data as a result of shame. All efforts were made to acquire as much complete data as possible. The study used a structured interview to obtain data regarding issues such as addiction, alcohol, etc. Answers to these questions may be quite subjective and probably need further tools and documentations to assess accurately. The interviewers attempted to adhere to the definitions of such conditions and maximize the data obtained in the context of such a short structured interview process.

The authors recommend that further wider scale population-based surveys are required for more detailed addressing of intimate partner violence during and away from pregnancy among Egyptian women. Increasing public and political interest in such a problem should be a global aim for national and international health and women’s organizations.

References


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Plasma pentraxin 3 levels in preeclamptic patients

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Summary

The authors evaluated plasma pentraxin 3 (PTX 3) levels in preeclamptic patients and determined the relationship between albuminuria and plasma PTX 3 levels. During a period of one year, 29 patients with severe or mild preeclampsia and 49 healthy pregnant women were included in the cross-sectional study. The two groups were compared each other with PTX 3 levels. The relationship between PTX 3 levels and urea, creatinine, AST, ALT, CRP, LDH, platelet count, and spot urine protein/creatinine rate was evaluated. PTX 3 level was significantly high in the preeclamptic group (p < 0.05). No significant correlation was found between serum PTX 3 level and urea, creatinine, AST, ALT, CRP, LDH, platelet, and spot urine protein/creatinine rate (p > 0.05). PTX 3 is a biochemical parameter that shows endothelial dysfunction. The authors believe that PTX 3 can be a valuable parameter to predict preeclampsia according to the significantly high PTX 3 levels in preeclamptic patients.

Key words: Pentraxin 3; Preeclampsia; Albuminuria.

Introduction

The etiology of preeclampsia remains unclear despite its association with significant maternal and fetal morbidity. Disorders of trophoblastic development, endothelial dysfunction, angiogenesis, and abnormal oxidative stress may contribute to the pathophysiology of preeclampsia [1]. The maternal serum markers related to these mechanisms have been evaluated for the early identification of women at high risk developing preeclampsia [2].

Pentraxin 3 (PTX 3), which belongs to the same family as C-reactive protein (CRP), is expressed in response to inflammatory stimuli by a variety of cells, including endothelial cells, monocytes, macrophages, and fibroblasts [3]. Previous studies have shown that maternal PTX 3 levels are significantly higher in women with preeclampsia when compared to those in normal pregnancies [4]. As PTX 3 is expressed from inflammatory tissue, it is mainly related to endothelial dysfunction [5].

The aim of this study was to evaluate PTX 3 levels at preeclamptic patients and to show the relationship between proteinuria and PTX 3 levels as being the marker of endothelial dysfunction.

Materials and Methods

This cross-sectional study was carried out in women with preeclampsia and healthy pregnant women. They were recruited 12 months from the maternal–fetal medicine services at the present hospital. The study group consisted of 29 women with mild or severe preeclampsia at third trimester. The control group was made up of 49 women with uncomplicated pregnancies at third trimester, selected by simple random sampling using a table of random numbers.

The study protocol conformed to the Helsinki Committee requirements and was approved by the Ethics Committee of the present hospital. Written informed consent was also obtained from all subjects before the study.

All participants were non-smokers, had not received any medication, and had no clinical evidence of cardiovascular, metabolic, or inflammatory diseases. Exclusion criteria were smokers, confirmed diabetes mellitus, chronic hypertension, renal diseases, connective tissue diseases, inflammatory or infective disorders, and heart diseases, as well as treatment with aspirin and non-steroidal anti-inflammatory drugs.

The two groups were compared to each other with PTX 3 levels, urea, creatinine, AST, ALT, CRP, LDH, platelet count, and spot urine protein/creatinine rate. The relationship between PTX 3 levels and mentioned biochemical parameters were evaluated.

Maternal age, gestational age, gravid, parity, and systolic and diastolic blood pressure were recorded. Mild preeclampsia was defined as a systolic blood pressure of at least 140 mmHg or a diastolic blood pressure (BP) of at least 90 mmHg recorded on two occasions at least six hours apart in association with new onset proteinuria. Proteinuria was defined as +1 or greater on dipstick on at least two occasions. The present authors defined severe preeclampsia as having a BP of at least 160 mmHg systolic or at least 110 mmHg diastolic on at least six hours apart or if proteinuria of five grams or more in 24 hours. Women with symptoms of end-organ involvement (persistent headache, disturbance in vision, protracted nausea and vomiting, or epigastric pain) were considered to have severe disease. The present definition of severe preeclampsia also included those with laboratory abnormalities of complete or limited hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome (total bilirubin of 1.2 mg/dl or more, lactate dehydrogenase (LDH) of 600 U/l or more, aspartate aminotransferase (AST) of 72 U/l or more, or platelet

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count of no more than 100,000/mm³) [6]. Eclampsia was considered as the occurrence of convulsion in preeclamptic cases, not attributable to other causes.

**Biochemical Analyses**

After maternal blood samples were collected, they were centrifuged and serum was stored at -80°C to record their urea, creatinine, AST, alanine aminotransferase (ALT), CRP, LDH, platelet count. Sandwich enzyme-linked immunosorbent assay (ELISA) for PTX 3 was performed. The PTX 3 ELISA system had a detection limit of 0.02 ng/ml with an intra-assay and inter-assay coefficient of variation (CV) of % 4-6 and % 8-10, respectively. Serum levels of CRP were measured using the ultrasensitive latex immunoassay CRP Vario with the intra- and inter-assay CV both <10%. Spot urine protein and creatinine were analyzed. Spot urine protein/creatinine rate was calculated.

**Statistical analyses**

All data were analyzed with Number Cruncher Statistical System (NCSS) 2007 and Power Analysis and Sample Size (PASS) 2008 Statistical Software. Descriptive statistics are reported as mean ±SD and percentage. Unpaired Student’s t test, Mann–Whitney U test, v² test, or Fisher’s exact test was used for intergroup comparisons. Statistical significance was defined as \( p < 0.05 \). Correlations between variables were evaluated with Pearson’s correlation coefficient.

**Results**

All 29 women (100%) in the preeclampsia group met the criteria for the diagnosis of severe preeclampsia. Of those women, seven women had developed severe preeclampsia. Demographic and pregnancy characteristics are shown in Table 1. Serum urea, creatinine, LDH, AST, and protein/creatinine rate were found significantly high at the preeclamptic group \( (p < 0.05) \). The present authors also found PTX 3 levels significantly high in the preeclamptic group \( (1.01 ± 1.00 \text{ ng/ml vs. } 0.58 ± 0.39 \text{ ng/ml}) \ (p < 0.05) \). The level of
PTX3 in women with severe preeclampsia was higher than women with mild preeclampsia ($p < 0.05$, Figure 1). No significant correlation was found between serum PTX3 level and urea, creatinine, platelet, LDH, AST, ALT, CRP, and spot urine protein/creatinine rate ($p > 0.05$).

**Discussion**

PTX3 is a member of the pentraxin family, which includes CRP and serum amyloid P component (SAP). The cross-species evolutionary conservation of PTX3, in contrast to CRP and SAP, suggests an important role for this molecule. PTX3 appears to have a major role in resistance against selected pathogens by acting as a predecessor of antibodies, recognizing microbes, activating complement, and facilitating pathogen recognition by phagocytes. The abnormal pro-inflammatory maternal status, pre-existing endothelial damage, and excess of oxidized LDL seen in women who subsequently develop preeclampsia may all induce PTX3 elevation [6, 7]. Vascular endothelial growth factor (VEGF) has the major role in the microcirculation of the renal glomerulus. It is shown that VEGF is excreted from both glomeruli endothelium and podocytes. Any abnormality of the excretion of the VEGF causes fenestration loss and proteinuria [8]. PTX3 reduces excretion of VEGF by inhibiting FGF2, therefore PTX3 causes antiangiogenic situation and damages microcirculation at the glomerular endothelium [9].

Zhou et al. searched the expression of PTX3 in placentas from patients with severe preeclampsia and evaluate the relationship between PTX3 and the pathogenesis of severe preeclampsia. They found that PTX3 level was higher in severe preeclamptic patients [10]. Hamad et al. searched endothelial function in relation to anti-angiogenic biomarkers and the inflammatory process in preeclampsia [11]. They found that PTX3 was higher in women with preeclampsia especially in women with early-onset preeclampsia. In the present study, the authors found PTX3 levels in preeclamptic group higher than control group, especially in severe preeclamptic patients.

Durnwald et al. found that there was no significant correlation between protein/creatinine rate in spot urine and proteinuria in 24-hour urine. They found that looking for proteinuria in 24-hour urine is much more significant [12]. However, Kuang et al. evaluated the clinical application of protein/creatinine rate in spot urine samples in order to check whether it can replace urine protein excretion in 24-hour collections for the diagnosis and screening of preeclampsia. They found that the protein/creatinine in spot urine samples can replace urinary protein excretion in 24-hour collections [13]. In the present study no significant correlation was found between PTX3 levels and proteinuria. The reason of this uncorrelation may be detecting proteinuria by calculating protein/creatinine rate in spot urine instead of proteinuria in 24-hour urine.

Caterino et al. searched acute phase proteins in preeclampsia. They found the concentrations of CRP is significantly higher in preeclamptic patients [14]. Kucuoz et al. also found that CRP and D-dimer levels were significantly higher in preeclamptic patients in their study [15]. In the present study the authors found no significant difference in CRP levels between control group and preeclamptic patients. CRP levels were normal in both groups and also no significant correlation between PTX3 and CRP levels was found in this study. The authors believe that the reason of low CRP levels in preeclamptic patients is due to the very limited amount of severe preeclamptic patients in this study. Jaiswar et al. evaluated LDH as a biochemical marker of preeclampsia in their research [16]. They found LDH significantly higher in preeclamptic patients. In the present study, LDH levels were also significantly higher in preeclamptic patients. However, there was no significant correlation between LDH and PTX3 levels. The authors believe that this uncorrelation is because of the limited number of severe preeclamptic patients. Sibai determined that with severe preeclampsia/eclampsia, elevated liver enzymes are seen because of the fibrin deposits at hepatic sinusoids according to the endothelial dysfunction [17]. In the present study, similar elevated AST levels were found in preeclamptic patients.

The small amount of the severe preeclamptic patients is one of the limitations of the present study. Another limitation of this study is that the population of the study included only the patients in their third trimester. It would have been better if the patients were selected from the beginning of the pregnancy for early prediction of preeclampsia. Another limitation was the determining of proteinuria in preeclampsia by calculating protein/creatinine ratio in spot urine instead of proteinuria in 24-hour urine. However there is no significant consensus for the spot urine protein/creatinine ratio to determine proteinuria, hence further studies should be designed with 24-hour urine collection for proteinuria.

As a conclusion, PTX3 level is higher in preeclamptic patients. PTX3 can be used to predict preeclampsia due to its evidence of endothelial dysfunction. The present authors can recommend to clinicians that PTX3 can be a valuable parameter to predict preeclampsia.

**References**


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Levonorgestrel-releasing intrauterine device use as an alternative to surgical therapy for uterine leiomyoma

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Summary

Objective: To evaluate the efficacy of the levonorgestrel-releasing intrauterine system (LNG-IUS) in the treatment of leiomyoma-related menorrhagia and to assess the effect of LNG-IUS on uterine, leiomyoma, and ovarian volume. Materials and Methods: In this prospective before and after study, LNG-IUS was inserted in 38 women with myoma-related menorrhagia. The patients were evaluated for serum levels of hemoglobin, hematocrit and uterine, leiomyoma, and ovarian volume at the time of insertion and at six months. Results: Significant reduction in the Pictorial Blood Loss Assessment Chart (PBAC) score and increases in serum hemoglobin levels and in amenorrhea was observed within three months. However, there was no statistically significant reduction in the myoma and uterine volume. Ovarian volume, also, did not changed significantly. Conclusion: The use of LNG-IUS is effective in reducing menorrhagia associated with leiomyomas with improvement in hemoglobin levels and may be a simple and effective alternative to surgical treatment of leiomyoma-related abnormal uterine bleeding (AUB-L) without significant influence on the volume of leiomyoma and ovarian and uterine volume.

Key words: Leiomyoma; Levonorgestrel; Intrauterine device; Menorrhagia.

Introduction

Uterine leiomyomas are the most common premenopausal benign uterine tumours, account for up to 40 percent of all hysterectomies in premenopausal women [1]. There are well established options for nonsurgical treatment include danazol, gonadotropin releasing hormone agonist (GnRH), uterine artery embolization, mifepristone (RU 486) [2]. However, their use is not widespread. Danazol is associated with marked androgenic side-effects and liver dysfunction [3]. GnRH analogues are expensive and associated with hypoestrogenism leading to hotflushes, vaginal dryness, and bone loss [4]. Uterine artery embolization has potential risks of premature ovarian failure and uterine synechia [5]. Compared to GnRH analogues, mifepristone is associated with less hypoestrogenic side effects. However, it was not found to reduce fibroid volume [6].

The levonorgestrel-releasing intrauterine system (LNG-IUS) is a widely used, highly effective contraceptive method [7]. In addition, there are many other non-contraceptive beneficial effects of LNG-IUS such as the reduction of excessive menstrual blood loss and therefore this system is now used for dysfunctional uterine bleeding [8]. Furthermore, the use of LNG-IUS has been considered specifically for the treatment of abnormal uterine bleeding (AUB) caused by leiomyoma, which is classified by the International Federation of Gynecology and Obstetrics (FIGO) as leiomyoma-related abnormal uterine bleeding (AUB-L) [9]. While LNG-IUS was shown to be effective in the management of AUB related to leiomyoma, studies concerning the effect of LNG-IUS on myoma size and uterine size have been published in recent years. Grigorieva et al. [10] reported that the use of LNG-IUS resulted in a reduction in myoma volume and total uterine volume. However, Maruo et al. [11] concluded that the use of levonorgestrel does not always lead to a reduction in the volume of leiomyomas and may even stimulate the proliferative potential of the leiomyoma cells. A recent study by Naki et al. has also supported findings of Maruo et al. [12]. Additionally, Inki et al. [13] suggested that LNG-IUS use in the treatment of menorrhagia is associated with the development of ovarian cysts. Therefore, the present study was designed to evaluate the effect of LNG-IUS on uterine volume, ovarian volume, and volume of leiomyomas.

Materials and Methods

This was a prospective before and after study. In total, 38 women of reproductive age (35-50 years) attending the present clinic because of menorrhagia associated with uterine myomas were enrolled into the study during 2009. Approval for the trial protocol and written informed consent of all patients were ob-
tained. Size of the uterus estimated to be less than 12 weeks of gestation by pelvic and ultrasonographic examination and presence of one type II myoma (according to ESH) at least three cm in diameter or multiple myomas in which each one was greater than one cm in diameter measured by transvaginal ultrasonography were eligibility criteria.

Exclusion criteria were: 1) any concomitant medical disorder that may be a contraindication to LNG-IUS’ use (e.g., congenital uterine anomaly, acute pelvic inflammatory disease (PID), abnormal cervical cytology, pregnancy); 2) type 0 or type I submucous myoma (European Society of Hysteroscopy classification); 3) myomas greater than five cm; 4) adenomyosis; 5) premenopausal or malignant uterine and breast diseases; 6) use of oral contraceptives or oral progesterone during the previous three months; 7) the presence of an ovarian cyst or tumor.

Uterine bleeding was quantitatively assessed by a validated pad scoring method known as Pictorial Blood Loss Assessment Chart (PBAC). A PBAC score of 100 or more was considered to be a diagnostic of menorrhagia with a specificity and sensitivity of above 80% [14]. Complete physical, routine laboratory evaluation examination including hemoglobin, total leukocyte count, platelet count, thyroid profile, fasting blood sugar, transvaginal ultrasonography, and probe curettage was performed before insertion of LNG-IUS to exclude the possible underlying causes for hemorrhagia other than leiomyoma. The uterus, leiomyoma, and each ovary was measured in three dimensions and the uterine volume, the volume of the leiomyomas and ovarian volume was calculated using the formula for ellipsoid mass (4/3 x π x D1 x D2 x D3). In cases with multiple leiomyomas, total leiomyoma volume was calculated by the summation of each leiomyoma.

Follicular cysts were not included in the calculation of ovarian volume. All transvaginal ultrasonography examination were performed with eight MHz probes by the same examiner, at the beginning of the study, also at the third and sixth months of LNG-IUS insertion. An IUS releasing 20 µg/day of levonorgestrel was inserted into the uterine cavity during days 5-7 of the menstrual cycle. Follow-up visits were scheduled at three and six months after insertion of the LNG-IUS. At these visits, the changes in bleeding pattern, assessed with the PBAC and hematocrit were considered. Additionally, transvaginal sonography was carried out for evaluation of the uterine volume, volume of the leiomyomas, and ovarian volume. Absence of uterine bleeding for over three months was interpreted as amenorrhea, while infrequent uterine bleeding with intervals longer than 38 days was considered to be oligomenorrhea. The statistical analysis was done using statistical software (SPSS 10.0 for Windows) and Student’s t-test, McNemar’s test, and Friedman variance analysis were used, as appropriate. Significance level was defined as 0.05. Data were expressed as mean ± SD and percentage (%), where appropriate.

Results

Table 1 shows the clinical and sonographic characteristics of pretreatment and posttreatment. The mean age of the patients was 41.43 ± 4.859 years. An evaluation of the patients revealed significant increases in the serum levels of hemoglobin and hematocrit (p < 0.05 for each) and increase in amenorrhea incidence (p < 0.01, Table 2). After the third and sixth months, the PBAC score was reduced by 91.2% and 95.1%, respectively. Compared with preinsertion values, there were no statistically significant changes in uterine and ovarian volumes and the volumes of leiomyomas (Table 1). Unexpectedly, in 18 patients, increases in the volume of leiomyomas were observed. No early complications were observed following the insertion of the IUS.

Discussion

The present study confirmed that LNG-IUS is statistically effective in reducing PBAC scores and in increasing hemoglobin values in women with AUB-L. The impact of treatment in terms of PBAC scores and hemoglobin values was observed three months following insertion of the LNG-IUS. Furthermore, over half of the patients had amenorrhea by the end of this study. However, there was no reduction in the volume of the leiomyomas and in the uterine volume. Even an increase in uterine fibroids volume was observed in 47% of the patients, at six months after the insertion of LNG-IUS. The present findings are in line with previous studies which the effectiveness of the LNG-IUS for reduction of menstrual blood loss in leiomyomas has been confirmed [10, 12, 13, 15-17, 18, 19]. Although LNG-IUS has proven its success in reducing bleeding, there has been much debate about the effect of LNG-IUS on leiomyoma and uterine volumes. Grigorieva et al. [10] demonstrated that LNG-IUS use among women with myomas resulted in a reduction in the volume of the myomas and in total uterine volume at 12 months. Size reduction, however, has not been consistent across studies listed in Table 3. In their study, Magalhes et al. [20], Socolov et al. [21] and Kriplani et al. [22] found that uterine volume had decreased

<table>
<thead>
<tr>
<th>PBAC score</th>
<th>410 ± 21</th>
<th>40 ± 17</th>
<th>20 ± 3.0*</th>
<th>20 ± 3.0*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin, g/dL</td>
<td>10.7 ± 1.2</td>
<td>11.5 ± 0.9*</td>
<td>12.3 ± 0.8*b</td>
<td>12.3 ± 0.8*b</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>32.9 ± 2.9</td>
<td>35.3 ± 2.5*</td>
<td>36.9 ± 2.6*b</td>
<td>36.9 ± 2.6*b</td>
</tr>
<tr>
<td>Uterine volume, mm³</td>
<td>487,818.6 ± 487,176.8 ± 488,962.8 ±</td>
<td>352,724.0 ± 353,724.6 ± 359,641.6 ±</td>
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<td></td>
</tr>
<tr>
<td>Myoma volume, mm³</td>
<td>22,367.0 ± 22,025.5 ± 21,624.2 ±</td>
<td>21,879.1 ± 21,556.5 ± 21,090.6 ±</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovarian volume, mm³</td>
<td>52,796.05 ± 52,744.74 ± 52,230.00 ±</td>
<td>45,093.173 ± 43,972.322 ± 43,414.368 ±</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Data are shown as n (%) or mean ± SD.

* p < 0.05, compared with third month values.

p < 0.001, compared with baseline scores.

p < 0.05, compared with baseline scores.
significantly 12 months after insertion of LNG-IUS, whereas changes in leiomyoma volume were not significant. Considering the 30% natural growth rate per year of leiomyomas, it seems reasonable to suggest that LNG-IUS inhibits their growth [20]. The growth of leiomyomas rely on the ovary steroid hormone and is regulated by local growth factors. A research study found that after treatment with 25 mcg/ml LNG for 72 hours, in vitro, the IGF-1 mRNA level of fibroid cells was decreased remarkably, thus IGF-1 downregulation could induct cell growth inhibition and apoptosis on the uterine leiomyoma [23]. However, Naki et al. [12], demonstrated that leiomyomas increased by 23% at six months.

Studies evaluating the effects of LNG-IUS on ovarian function showed a weak relationship while LNG-IUS causes high levonorgestrel levels in endometrial tissue but low levels in the systemic circulation [18, 24]. However, LNG-IUS use in the treatment of AUB-L was found to be associated with the development of ovarian cysts at six months, but these were symptomless and showed a high rate (94%) of spontaneous resolution [13]. Few studies evaluated the effect of LNG-IUS use in AUB-L on ovarian function and volume and no significant change was found after 12 months follow up [13, 18]. Supporting this data, the present authors observed no significant change in ovarian volume at six months.

Twelve months follow up was suggested to reveal significant reduction in uterine and leiomyoma volumes [10, 18]. Therefore, lack of long-term follow up (> one year) is a recognized limitation of the present study, which otherwise might be beneficial in terms of a more accurate assessment of volumetric alterations related to insertion of LNG-IUS. However, it is proposed that three months follow up might be sufficient to observe a reduction in the incidence of bleeding disturbances [19].

In conclusion, the present study demonstrated that the use of LNG-IUS is effective in reducing menorrhagia associated with leiomyomas with improvement in hemoglobin levels and may be a simple and effective alternative to surgical treatment of AUB-L without significant influence on the volume of leiomyoma and ovarian and uterine volume. Additional trials are needed to define LNG-IUS’ role in the treatment of symptomatic leiomyomas.

References

Table 3. — Evidence for LNG-IUD use in patients with AUB-L.

<table>
<thead>
<tr>
<th>Author and year of publication</th>
<th>Number of cases with leiomyoma</th>
<th>Follow-up time</th>
<th>Hemoglobin</th>
<th>Menstrual blood loss</th>
<th>Uterine volume</th>
<th>Volume of the leiomyomas</th>
<th>Ovarian volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inki et al., 2002 [13]</td>
<td>119</td>
<td>12 months</td>
<td>-</td>
<td>-</td>
<td>No change was observed</td>
<td>No change was observed</td>
<td>Association with the development of ovarian cysts</td>
</tr>
<tr>
<td>Soysal et al., 2005 [16]</td>
<td>32</td>
<td>12 months</td>
<td>Increased[^1]</td>
<td>PBAC score reduced[^2]</td>
<td>No change was observed</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Magalhães et al., 2007 [20]</td>
<td>27</td>
<td>36 months</td>
<td>-</td>
<td>-</td>
<td>Decreased[^2]</td>
<td>No change was observed</td>
<td>-</td>
</tr>
<tr>
<td>Gunes et al., 2008 [17]</td>
<td>21</td>
<td>12 months</td>
<td>Increased[^1]</td>
<td>The mean number of pads used daily during menstruation decreased[^3]</td>
<td>Decreased</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tasci et al., 2009 [18]</td>
<td>25</td>
<td>12 months</td>
<td>Increased[^1]</td>
<td>-</td>
<td>No change was observed</td>
<td>Decreased[^2]</td>
<td>No change was observed</td>
</tr>
<tr>
<td>Naki et al., 2010 [12]</td>
<td>60</td>
<td>6 months</td>
<td>Increased[^1]</td>
<td>A decrease in VBS[^4] score</td>
<td>No change was observed</td>
<td>Increased</td>
<td>-</td>
</tr>
<tr>
<td>Socolov et al., 2011 [21]</td>
<td>96</td>
<td>12 months</td>
<td>-</td>
<td>PBAC score reduced[^2]</td>
<td>Decreased[^2]</td>
<td>No change was observed</td>
<td>-</td>
</tr>
<tr>
<td>Xie et al., 2012 [19]</td>
<td>29</td>
<td>12 months</td>
<td>Increased[^1]</td>
<td>PBAC score reduced[^2]</td>
<td>No change was observed</td>
<td>No change was observed</td>
<td>-</td>
</tr>
<tr>
<td>Present study, 2013</td>
<td>38</td>
<td>6 months</td>
<td>Increased[^1]</td>
<td>PBAC score reduced[^2]</td>
<td>No change was observed</td>
<td>No change was observed</td>
<td>No change was observed</td>
</tr>
</tbody>
</table>

[^1] p < 0.05, *VBS: Visual Bleeding Score.


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Scorpion stings in pregnant women: an analysis of 11 cases and review of literature

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²Mustafa Kemal University, School of Medicine, Department of Internal Medicine, Antakya (Turkey)

Summary
Scorpion sting is one of the most important public health problem in many regions of the world. But there is not enough medical data about scorpion stings in pregnant women in the literature. The aim of this study was to describe the clinical findings and treatment modalities of scorpion stings in pregnant women. This study was performed in the Southeast Region of Turkey, retrospectively. Eleven pregnant women were studied, totally. All of the patients were detected as class 1 according to the scorpion envenomization system. They were in different weeks of gestation. Local pain, hyperemia, swelling, and itching were the most frequent complaint in these cases. None of our patients received antivenom, and all of them were treated, symptomatically. Complication of pregnancy was observed in none of them.

Key words: Scorpion sting, pregnancy, treatment.

Introduction
Scorpions are arthropods of the arachnid class and they are one of the most important public health problems in many countries, especially Africa, South India, the Middle East, and South Latin America. Throughout the world, 3,250 deaths from scorpion stings occur per year. Therefore, the most of scorpion stings have local symptoms [1]. There are approximately 1,500 types of scorpions in the world but 50 types are dangerous for humans especially Buthus, Prabuthus, mesobuthus, Tityus, Androstonus, and Centruroides family of Buthidae. However Androctonus Crassicauda, Leiurus quinquestriatus, Mesobuthus gibbosus, and Mesobuthus eueus are important types of scorpions in Turkey [2]. Different clinical presentations, from severe local skin reactions to neurologic, respiratory, and cardiovascular collapse are caused by scorpion stings. Simple local skin reactions can be treated with analgesics, antihistamines, and supportive care. However, severe systemic conditions must be treated with a multidisciplinary approach in intensive care unit.

The epidemiologic features of a patient who has been envenomed show a disposition in rural areas during the summer and the victims are generally adults. However envenomation is more dangerous in children. Several authors have reported the complications and epidemiology of scorpion stings in humans, but medical data about scorpion stings in pregnant women is not common in literature.

This study aimed to describe clinical characteristics and treatment modalities of scorpion envenomization in pregnant women.

Materials and Methods
This retrospective study was performed in the Obstetrics and Gynecology Department of the Adiyaman University between January 2010 and January 2013. Clinical and treatment data were obtained from medical records of the hospital. Initial evaluation and management were performed by the obstetric and gynecology staff. Laboratory investigations were performed in the emergency department. Clinical symptoms, vital signs, complications, and the period until the hospital after scorpion sting were recorded. The patients were classified depending on the severity of the symptoms. (Table 1) [3]. After being discharged, obstetric follow-up of patients were performed by clinicians. The delivery records were obtained by clinicians.

Results
Eleven pregnant women were studied, and their medical data records were analysed. Demographic characteristics, clinical stage, treatment modalities, and mode of delivery are shown in Table 2. Gestational age of patients were detected in ultrasonographic evaluation. Mean age and gestational age of patients 27.8 ± 4.9 (19-35), 23.4 ± 9.2 (10-35) respectively. The admission time was 8.4 ± 1.1 (0.5-36) hours after being stung.

There were no detected laboratory anomalies in all patients. Intravenous hydration, analgesic agent, and cold pack was applied in patient as a first treatment. The additional treatment was not needed for all of patients. The patients were discharged according to clinical severity in six to 24 hours. Patient’s follow-up performed by clinicians. In delivery records, there were no observed abnormalities. Four patients had performed a cesarean section because of obstetric indications.
The mortality rate in all age groups. Therefore, unborn baby is at the greatest risk for envenomization. This increased rate is caused by the delay in receiving medical assistance due to a longer travel time to medical centers and the lack of advanced medical treatment. However, advances in public health education, social status, treatment modalities, and intensive care units have decreased mortality and morbidity from scorpion envenomization [4, 5].

Several studies have shown a varied age or medical status distribution for scorpion stings, but there is not enough study on scorpion sting in pregnant women. Scorpion envenomization during pregnancy is generally studied on pregnant rats. On the other hand, only case reports have been reported on pregnant women. The results of these studies have shown that scorpion stings are associated with miscarriage, preterm birth, and placental abruption [6]. Limited available literature suggests that adverse outcomes are primarily related to venom effects on the mother. In the literature, some types of scorpion venoms were tested on the isolated rat uterus and its effects were obtained. An amount of venom caused a contraction of the uterus [7]. The teratogenicity of the venom on fetus is unknown. The teratogenic effect of the venom appears to be the results of its metabolic effect and action on body electrolytes of the maternal animal, rather than to a direct effect on the fetuses [8]. On the other hand, the several studies in the animals observed that some types of scorpion venoms cause a high fetal resorption rate (especially during the 9-11 gestational age), vertebral and ossification defects, and fetal weight loss [8,9].

In this study, 11 pregnant women were evaluated retrospectively. All of patients clinical stage were defined as stage I including local pain, erythema, and local paresthesia. Gestational age of the patients distribution are shown in Table 2. When the present authors investigated the total number of cases, there was a difference in gesta-

### Table 1. — Clinical class of scorpion envenoming.

<table>
<thead>
<tr>
<th>Class</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Local pain (sometime associated with local paresthesia, erythema, ecchymosis, blisters)</td>
</tr>
<tr>
<td>II</td>
<td>Mild systemic envenoming: Idem grade I + hyperthermia + cardiovascular and respiratory symptoms: tachycardia, arrhythmia, dysnea, hypertension/hypotension, electrocardiographic abnormalities, priapism</td>
</tr>
<tr>
<td>III</td>
<td>Life-threatening envenoming: idem grade II + multiserial failure</td>
</tr>
</tbody>
</table>

### Table 2. — Demographic characteristics, clinical stage, and treatment modalities of patients.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Gestational age</th>
<th>Sting site</th>
<th>Admission time after sting (hour)</th>
<th>Envenomation severity</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19</td>
<td>24</td>
<td>LE</td>
<td>6</td>
<td>Class I</td>
<td>Supportive</td>
</tr>
<tr>
<td>2</td>
<td>24</td>
<td>31</td>
<td>UE</td>
<td>6</td>
<td>Class I</td>
<td>Supportive</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>26</td>
<td>UE</td>
<td>3</td>
<td>Class I</td>
<td>Supportive</td>
</tr>
<tr>
<td>4</td>
<td>27</td>
<td>11</td>
<td>LE</td>
<td>2</td>
<td>Class I</td>
<td>Supportive</td>
</tr>
<tr>
<td>5</td>
<td>32</td>
<td>28</td>
<td>LE</td>
<td>3</td>
<td>Class I</td>
<td>Supportive</td>
</tr>
<tr>
<td>6</td>
<td>35</td>
<td>12</td>
<td>UE</td>
<td>6</td>
<td>Class I</td>
<td>Supportive</td>
</tr>
<tr>
<td>7</td>
<td>34</td>
<td>34</td>
<td>UE</td>
<td>1</td>
<td>Class I</td>
<td>Supportive</td>
</tr>
<tr>
<td>8</td>
<td>31</td>
<td>35</td>
<td>LE</td>
<td>0.5</td>
<td>Class I</td>
<td>Supportive</td>
</tr>
<tr>
<td>9</td>
<td>30</td>
<td>18</td>
<td>LE</td>
<td>5</td>
<td>Class I</td>
<td>Supportive</td>
</tr>
<tr>
<td>10</td>
<td>23</td>
<td>29</td>
<td>LE</td>
<td>3</td>
<td>Class I</td>
<td>Supportive</td>
</tr>
<tr>
<td>11</td>
<td>26</td>
<td>10</td>
<td>LE</td>
<td>6</td>
<td>Class I</td>
<td>Supportive</td>
</tr>
</tbody>
</table>

*: LE: Lower extremity; UE: Upper extremity.
Scorpion stings in pregnant women: an analysis of 11 cases and review of literature

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Scorpion stings are frequent during the summer months. This result is agreement with previous studies [10, 11].

Number of patients is not enough for suggestion of treatment modalities in pregnant women. Clinical presentation of patients depend on scorpion species. Hemoglobin, hematocrit, white blood cell, and biochemical problems according to excessive sweating, vomiting, and stimulation of autonomic nervous system have detected in advance stage of scorpion stings. Fortunately, this situation was not encountered in the present patients. Especially, hyperglycemia associated with inhibition of insulin secretion is important in pregnancy. Hyperglycemia might be responsible for fetal mortality or impaired neuronal development [8]. Scorpion envenomization treatments have no scientific basis. First medical aid and knowledge for patients is essential. The aim of the treatment of scorpion stings in pregnant women must be protection of women’s health, because if the pregnant women’s health is good, the baby’s health is also good.

Conclusion

The present study showed that supportive treatment is enough in class I scorpion envenomization in pregnant women. Pregnancy related complications were not detected in this class. When the scorpion envenomization in pregnant women is in class II or class III, antivenom or additional treatment agents are used for women’s health, since it is necessary for the health of babies. Because only class I patients were detected in this study, further studies are needed in the class II and III pregnant women with scorpion stings.

References


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Microparticles hyperactivity in a case of intrauterine growth restriction

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Summary
A case of a residual intrauterine fetal growth is described in a primiparous woman, aged 33 years, undergoing the 37th week of pregnancy. The patient was admitted to the outpatient department of the present clinic complaining of decreased fetal movement in the past few days. The cardiotocography (CTG) was non reactive, with reduced variability for a period of more than 30 minutes. The evaluation of the activity of microparticles (MPs) showed a value of 48.90 nM, which was 21.26 times higher than the mean of normal women of comparable pregnancy age (2.31 ± 1.95 nM) and 18.11 times higher than that of the average women who had intrauterine growth retardation (2.70 ± 2.63 nM). The reasons for this increase in the activity of the MPs are discussed in this case report.

Key words: Microparticles; Pregnancy complications; Intrauterine growth restriction.

Introduction
The term intrauterine growth restriction (IUGR) refers to a fetus, who presents a lower growth rate than normal. The development of the fetus is considered restricted when the fetal weight is below the 10th percentile for the pregnancy age. The frequency of IUGR ranges from 4% to 7%. The diagnosis of IUGR, which is divided into symmetrical and asymmetrical, is done via ultrasound, by assessing the biparietal diameter (BPD), the head circumference (HC), the abdomen circumference (AC), the femur length (FL), and by estimating the fetal’s weight EFW [1-3].

The microparticles (MPs) are vesicles with a diameter less than one mm, which derive from the cytoplasmic membrane of various cells (endothelial, monocytes, platelets) during the activation or their programmed cell death. Women during pregnancy show an increase in the activity of the MPs, compared with healthy non-pregnant women [4, 5]. Complications of pregnancy such as premature rupture of fetal membranes, pre-eclampsia, miscarriage, and IUGR, are believed to be associated with placental dysfunction and could provoke significant maternal and fetal morbidity and mortality, resulting in increased activity of the MPs [6].

The presentation of this case was motivated by the unusual finding of very high potency of MPs and its possible correlation with the pathogenesis of this complication.
The measurement of procoagulant activity of MPs (platelet, leukocytes, endothelial) in plasma was carried out after exposure of amniotic phospholipids, with main representative the phosphatidylserine, bounded by the annexin V (Zymaphen MP - Activity).

Results
The measurement of procoagulant activity of MPs showed that their levels were 21.26 times higher than the mean of women with comparable age normal pregnancy (2.31 ± 1.95 nM) and 18.11 times higher than the mean of women with IUGR (2.70 ± 2.63 nM). The list of the pregnant women with asymmetrical type of IUGR included eight patients with mean (3.27).

Discussion
IUGR is related to considerable maternal and fetal morbidity and mortality. Etiology is partly understood and it is widely known that during the first half of pregnancy, trophoblastic invasion participates to the remodeling of the spiral arteries into dilated, inelastic vessels, converting them to low-resistance vessels capable of supplying large amounts of blood to the placenta and the developing fetus. Consequently, a functional uteroplacental circulation is the result of this physiological process [7-9].

Impaired remodeling due to deficient trophoblastic invasion is associated with maintenance of high resistance and low flow spiral arteries, related to possible subsequent development of IUGR. Various studies have been reported, connecting restricted invasion of the trophoblastic cells to the decidual segments leaving the myometrial segment of the spiral arteries unchanged [10, 11]. IUGR is a multi-system disorder and may be identified as symmetrical or asymmetrical. Causes of symmetrical IUGR are: genetic including chromosomal, constitutional and single gene defects, inborn errors of metabolism, smoking, heroine, therapeutic irradiation and/or accidental exposure, sickle cell anemia, and infections (toxoplasma, rubella, cytomegalovirus, herpes - T.O.R.C.H.).

Factors like gene defects and chromosomal anomalies seem to be responsible for this complication. Fetuses with chromosomal disorders (trisomy 13, 18, and 21) and other autosomal abnormalities (various deletions and ring chromosome structure alterations) have suboptimal growth. Congenital malformations, and chromosomal disorders are responsible for approximately 20% of IUGR fetuses, and that percentage is substantially higher if growth failure is detected before 26 weeks gestation [12, 13]. Maternal nutritional abnormalities lead to reduced fetal growth if substrate deprivation is severe. IUGR fetuses are not common in heavier woman (> 68.03 kg prepregnancy weight).

Fetal infections consist 5%-10% of all causes of IUGR, like T.O.R.C.H. with cytomegalovirus, rubella, herpes (H. Simplex), syphilis, and also parvovirus has been reported to impair fetal growth. Cytomegalovirus seems to affect fetal development before 20 weeks of gestation. The viruses that infect the trophoblast alter trophoblast gene expression, and this alteration reduces trophoblast invasive activity, leads to apoptotic cell death, impairs trophoblast function and induces IUGR.

Maternal smoking and drugs consumption such as cocaine, heroin, alcohol, anticonvulsants, and warfarin’s derivatives may also influence fetal development. There are also reports that 15%-30% of multiple gestations, especially monochorionic twins with the fetal transfusion syndrome, are associated with IUGR [13-16].

Causes of asymmetrical IUGR are: preeclampsia, anemia, vasculopathies, hemoglobinopathies, chronic hypertension, extensive placental infarctions, abruptio placenta, multiple gestations, and severe renal and cardiovascular pathology.

Maternal vascular disease, with its deficiency in uteroplacental perfusion, is related to 25%-30% of all IUGR infants while chronic hypertension and superimposed preeclampsia usually have the most profound effect on fetal growth [17]. One more risk factor seems to be the thrombophylic disorders and preliminary evidence show that the prothrombin gene mutation may be a cause. The antiphospholipid syndrome has also been associated with IUGR and a wide spectrum of pregnancy complications [18]. There is also a relation between abnormal size and function of placenta and IUGR infants, such that when gestational age was used as a covariant, 24% were found to have smaller placenta [19].

The presented case had the characteristics of the asymmetrical type of IUGR. Specifically, the biometrical results of the fetus showed a restriction of abdominal circumference (AC: 28w+1d), which was significantly increased in relation to other biometrical measurements. Inflammatory markers like leucocytes, neutrophils, and C-reactive protein (CRP) were high, and this may be the evidence of inflammation and placenta deficiency. The authors’ previously described patient had pathological increased procoagulant activity of MPs. This finding may be the evidence of macroscopical appearance of calcifications at the uterine side and the low weight of placenta.

Cell-derived MPs are small vesicles released from cells upon activation or apoptosis. MPs seem to play a role in inflammatory processes by altering or activating the function of various cells types like monocytes, endothelial cells, or neutrophil granulocytes. This process is being conducted via the transfer of bioactive molecules, or ligand-receptor interactions. It has been shown in vitro by Nauta et al. and Gasser et al., that MPs may also play a role in complement activation via the classical pathway, (C1q binding to MPs and the deposition of C3, C4 components of the complement activating surfaces). Elevated platelet-derived MP/ (PDMP), monocyte-derived MP/ (MDMP), and endothelial cell-derived MP/ (EDMP) concentrations are documented in almost all thrombotic diseases including both arterial and venous beds. Conclusively, elevated levels of MPs have been found in a number of conditions associated with inflammation, cellular activation and dysfunction, angiogenesis and transport [20, 21].
During normal pregnancy multiple changes occur in the vascularization, and the balance of haemostasis shows an effect on procoagulant state. Coagulation factors are elevated in the preeclamptic state and recurrent pregnancy loss in comparison to normal pregnancy and uteroplacental thrombosis. Thus, haemostatic imbalance and vascular dysfunction may have a role in both these pregnancy complications [4,22]. There are not many studies (PubMed and Medline) valuating the levels of MPs in IUGR and particularly the diversification between asymmetrical and symmetrical type of IUGR [23].

In the present case, very important point is the over increase of procoagulant activity of MPs. The levels of MPs were 21.26 times higher of the mean of normal women with comparable age pregnancy (2.31±1.95 nM) and 18.11 times higher of the mean of women with IU/GR (2.70 ± 2.63 nM).

The interpretation of these findings may be strong evidence of inflammation confirmed by increased leucocytes, neutrophils, and CRP. In the present case, the macroscopical observation of placenta showed low weight and bold calcification on the uterine side of it. This may be connected with the elevation of MPs, which are released from the surface of cells following cell activation or apoptosis, including chemical stimuli, (cytokines, thrombin, and endotoxin), or physical stimuli (shear stress or hypoxia).

Following cell apoptosis, MPs formation depends on an elevation in the cytosolic calcium concentration, with consequent activation of calpain and protein kinases and inhibition of phosphatase. These changes may have a direct effect to cytoskeletal reorganisation, membrane blebbing, and the formation of MPs. Secondary activation of the coagulation mechanism may correlate MPs to the development of platelet and fibrin rich thrombi, through the recruitment of cells and the accumulation of tissue factor (TF), or via both factor VII (FVII)/TF which participates to dependent and independent pathways [4, 24].

Conclusion

It seems that there is a possible correlation between inflammation, placental insufficiency, and IUGR. In the present case, intrauterine inflammation seems to be the main cause of IUGR, followed by secondary activation of coagulation, while these warrant increased expression of MPs. Further studies are needed to clarify this correlation and the probable difference in expression of MPs in the two types of IUGR.

References


A case of prenatally diagnosed Uhl’s anomaly

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Summary

Background: Uhl’s anomaly is an extremely rare cardiac defect characterized by absence of the myocardium of the right ventricle. Until now, only three cases have been diagnosed or have showed suspicious diagnosis in prenatal period. Case: A 28-year-old nulliparous woman was referred to the present hospital for counseling the risk of drug medication. The authors found dilatation of the right ventricle and thinning of the right ventricular wall in the fetus at 25 weeks gestation. No other structural abnormalities were found concerning the great arteries and all heart valves demonstrated normal function. Uhl’s anomaly was suspected on fetal echocardiography and it was confirmed postnatally by echocardiography and computed tomography (CT). The infant showed stable condition during neonatal period and is doing well in the ambulatory care after three-years follow up. Conclusion: Although the outcomes of Uhl’s anomaly are generally unfavorable, the duration of survival shows wide variation according to the cardiac function. To estimate the postnatal outcomes, it is highly recommended to perform the accurate differential diagnosis by using fetal echocardiography during pregnancy.

Key words: Echocardiography; Uhl’s anomaly.

Introduction

Uhl’s anomaly is characterized by absence of the myocardium of the right ventricle. It is a very rare cardiac dysplasia first reported by Henry Uhl in 1952. The missing myocardial layer results in the formation of a very thin ventricular wall, also described as “parchment” heart, where there is no interposing adipose tissue and also no evidence of inflammation or necrosis [1]. Approximately 100 studies have been published in PubMed, but only three cases were diagnosed or showed suspicious diagnosis in prenatal period [2-4]. In the present case the authors found dilatation of the right ventricle and thinning of the right ventricular wall in the fetus at 25 weeks. Uhl’s anomaly was suspected on fetal echocardiography and it was confirmed postnatally by echocardiography and computed tomography (CT).

Case Report

A 28-year-old nulliparous woman was referred to the present hospital at ten weeks for counseling regarding pregnancy related risks due to the consumption of two tablets of trimebutine maleate consumed at week 6. Two tablets of trimebutine maleate (FDA category D) were administered at six weeks of pregnancy. Quad test showed low risk at 16 weeks of pregnancy and no abnormal cardiac findings were observed. At 25 weeks of pregnancy, however, the dilatation of the right ventricle was marked on the targeted sonography with diameter of 1.44 cm, while diameter of the left ventricle was 0.86 cm. Apical trabeculation was observed, but the lateral wall of the right ventricle was much thinner than that of the left ventricle (Figure 1). No other structural abnormalities were found concerning the great arteries and all heart valves demonstrated normal function. Uhl’s anomaly was suspected. Pre- and post-natal complications such as arrhythmia, heart failure, and sudden cardiac arrest were explained to the patient. The patient wanted to prolong the pregnancy, and there were no other interval changes during sonographic examinations timely performed every two weeks. In order to provide the best possible intensive care for the newborn, the labor was induced using prostaglandin E2 pessary and oxytocin at 38+3 weeks. The patient delivered a 2,670 g female with Apgar score of 8 at one minute and 9 at five minutes. No abnormal cardiopulmonary symptoms or signs were found during the postnatal intensive care. An initial chest radiograph noted marked cardiomegaly. Echocardiography of the newborn immediately after birth verified the prenatal findings: moderately dilated right inlet and wall thickness of the right ventricle was 2.8 mm. Ostium secundum type atrial septal defect with diameter of eight mm was also observed and cone-shaped patent ductus arteriosus in 1 x 2 x 3.4 mm size was found. Regurgitation of the tricuspid valve or any other cardiac dysfunction was not found. Pro-BNP (brain natriuretic peptide) was increased to 3,426 pg/ml in the blood test. A chest CT was carried out on the third day post-partum. Dilatation of the right ventricle and myocardial thinning of the lateral wall were observed. Size of the right atrium was adequate and no other unexpected cardiac abnormality was found. Diagnosis of Uhl’s anomaly was confirmed by echocardiography and chest CT (Figures 2, 3). The infant showed stable condition in general and was discharged from the hospital at seven days after birth. The infant showed normal weight increase and stable body condition in the ambulatory care after three years.

Discussion

Uhl’s anomaly is an extremely rare cardiac dysplasia that may cause a sudden death. Only 84 cases had been reported...
until 1993, and its etiology is not yet clearly determined. It is characterized by absence of the myocardium in the right ventricular lateral wall. The right ventricle is composed of apposing endocardial and epicardial surfaces with thin wall and ventricular cavity dilatation. Apart from the absence of myocardium in the right ventricle, the septomarginal trabeculation and papillary muscles of the tricuspid valve are normal. Patients’ age at the time of death ranged from one day after birth to 84 years with an average of 15 years. No difference of incidence was found between males and females [5].

Majority of the cases are known to be sporadic but some cases were familial. The underlying cause is not yet determined, but some hypothesize that it is caused by primary agenesis or selective apoptosis of the cell, while others hypothesize that it is caused by recessive heredity of damaged genes or by incomplete expression of dominant genes. Exposure of toxic substances or infection sources may be another cause of the disease as well. It is important to distinguish between Uhl’s anomaly and arrhythmogenic right ventricular dysplasia (ARVD). In ARVD, myocardium of the right ventricle is partially replaced with fibrofatty layer and endocardium and epicardium appear separate. Contrary to Uhl’s anomaly which is mostly diagnosed in infancy, majority of ARVD cases are diagnosed in adulthood. The typical symptoms of ARVD are palpitation, syncope, ventricular tachycardia, cardiac arrest, and sudden death often related with exercise [5]. Uhl’s anomaly should also not be confused with hypoplasia of the right heart. Uhl’s anomaly is rarely associated with other congenital cardiac malformations, and arrhythmias or heart block is not the general symptom of this disease.

In the past, Uhl’s anomaly was mainly diagnosed by autopsy. However, prenatal and postnatal diagnoses have been increasing due to the recent development of ultrasonography and echocardiography. Total of three cases have reported the prenatal diagnosis or suspicion of the prenatal diagnosis (Table 1). In the first case on prenatal diagnosis reported by Wager et al., the high similarity of Uhl’s anomaly and Ebstein’s anomaly were shown in which pulmonary atresia was also present. However, the tricuspid valve in Wager’s case was normally located in the atrioventricular groove [2]. It is uncertain whether the thinning of the right ventricular wall is prior to or a secondary reaction resulted by the dysplastic tricuspid or pulmonary valve. Some suggest to watch for the secondary reaction and not to diagnose it as an original Uhl’s anomaly if other cardiac

![Figure 1. — Fetal echocardiography at 25 weeks gestation shows moderately dilated right ventricle and thin right ventricular wall.](image1)

![Figure 2. — Postnatal CT findings confirm very thin lateral wall of the right ventricle in a transverse cardiac image (arrow).](image2)

![Figure 3. — Postnatal CT findings confirm very thin lateral wall of the right ventricle in a three-dimensional image (asterisk).](image3)
malformations are associated [5]. There is another case reported on Uhl’s anomaly diagnosed at 31 weeks of pregnancy. Unlike the previous cases, their case showed no dilatation of the right atrium, but excessive tricuspid regurgitation with pericardial effusion and thrombus was found. Heart failure at the time of birth was treated by dopamine and heparin, and further evaluation was followed for a year. No unexpected outcome was revealed [4].

The present case is the only report among the prenatal diagnosed cases that has not shown any abnormal cardiopulmonary symptoms or signs and stayed in subclinical condition. Follow-ups on this case are still ongoing. The possible reasons for this are; firstly, unlike the other previous cases, this case showed the typical signs of Uhl’s anomaly such as occurrence of dilatation or wall thinning only in the right ventricle without any other dysfunctions in the tricuspid valve or the pulmonary valve. Secondly, no dilatation was found in the other right atrium. This supports the earlier study of Benson et al. describing dilatation of the right atrium and level of the cardiac compromise as the key factors for outcome of the Uhl’s anomaly [3]. Thirdly, the reason for maintenance of the ventricular function may be because it involved only the partial region of the lateral wall in the right ventricle. Virtually, the apical trabeculations observed in prenatal period persisted even in the postnatal period.

The main cause of sudden death in Uhl’s anomaly is either congestive heart failure or critical ventricular arrhythmia. Therefore, periodical observation and conservative treatment on the congestive heart failure should be performed. Implantable cardioverter defibrillator is recommended to prevent sudden death and heart transplantation should be considered when Fontan-type circulation has developed. A successful treatment in emergency situation has been reported using the following procedures: the tricuspid valve closure and a bidirectional Glenn shunt with atrial septectomy combining a partial right ventriculectomy, namely, “one-and-a-half ventricular repair” [6]. The outcomes of Uhl’s anomaly are generally unfavorable. However, if it is a single lesion and only partial loss is suspicious, similar to the present case, it can be in the subclinical phase even at maturity [7]. Therefore, in order to estimate the postnatal outcomes, it is highly recommended to perform the accurate differential diagnosis by using fetal echocardiography at pregnancy.

References


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Table 1. — Cases of Uhl’s anomaly which were diagnosed or showed suspicious diagnosis in prenatal period.

<table>
<thead>
<tr>
<th>Name of Authors</th>
<th>GA (weeks)</th>
<th>RV</th>
<th>RA</th>
<th>TV</th>
<th>PV</th>
<th>Associated anomalies</th>
<th>Prenatal diagnosis</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wager et al. 1988</td>
<td>24</td>
<td>Large, thin</td>
<td>Large</td>
<td>Dysplastic</td>
<td>Atresia</td>
<td>None</td>
<td>Ebstein’s Anomaly</td>
<td>Expired at 1st postpartum day</td>
</tr>
<tr>
<td>Benson et al. 1995</td>
<td>18+5</td>
<td>Large, thin</td>
<td>Large</td>
<td>TR</td>
<td>Normal</td>
<td>None</td>
<td>Ebstein’s Anomaly</td>
<td>Termination at 21+4 weeks</td>
</tr>
<tr>
<td>Cardaropoli et al. 2006</td>
<td>31</td>
<td>Large, thin</td>
<td>Normal</td>
<td>TR</td>
<td>Normal</td>
<td>Pericardial effusion, hydramnios</td>
<td>Uhl’s anomaly</td>
<td>Neonatal resuscitation, Asymptomatic for 1 year</td>
</tr>
<tr>
<td>This case</td>
<td>25</td>
<td>Large, thin</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>None</td>
<td>Uhl’s anomaly</td>
<td>Asymptomatic for 6 months</td>
</tr>
</tbody>
</table>

Increased nuchal translucency and diaphragmatic hernia.  
A case report

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Summary
Increased nuchal translucency (NT) thickness is present in 40% of fetuses with diaphragmatic hernia, including 80% of those that result in neonatal death and in 20% of the survivors. A 33-year-old nulliparous woman had first trimester scan at 12 weeks. The fetus had a NT of 2.3 mm, normal ductus venous (DV), and tricuspid doppler and present nasal bone. Pregnancy-associated plasma protein A (PAPP-A) was 0.59 MoM and beta-human chorionic gonadotropin (b-hCG) 2.56 MoM. The couple did not opt for chorionic villous sampling (CVS) and repeat ultrasound examination was advised. At 18 weeks, ultrasound revealed left sided diaphragmatic hernia. The couple consented for termination of the pregnancy. The molecular test showed normal karyotype and male gender. In such cases with intrathoracic herniation of abdominal viscera, the increased NT may be the consequence of venous congestion due to mediastinal compression. The prolonged compression of the lungs causes pulmonary hypoplasia. Increased NT with normal fetal karyotype is associated with structural fetal anomalies like diaphragmatic hernia and screening at 16-18 weeks is imperative.

Key words: Nuchal translucency; Diaphragmatic hernia; Congenital diseases; Fetal ultrasound scan; Serum screening.

Introduction
Congenital diaphragmatic hernia occurs in approximately one in 4,000 births. Development of the diaphragm is usually completed by the ninth week of gestation. In the presence of the defective diaphragm, there is a herniation of the abdominal viscera into the thorax at about ten to 12 weeks of gestation, when the intestines return to the abdominal cavity from the umbilical cord. However, at least in some cases, intrathoracic herniation of viscera may be delayed until the second or third trimester of pregnancy. When diaphragmatic hernia is present, there is a reduction of the available thoracic space to the developing lungs and thus, a reduction of the airways, alveoli, and arteries. Furthermore, there is an increase in arterial medial wall thickness, and there is also an extension of muscle distally into the small pre-acinar arteries. Although an isolated diaphragmatic hernia is an anatomically simple defect, which might be correctable, the mortality rate is about 50%. The main cause of death is hypoxemia due to pulmonary hypertension, resulting from the abnormal development of the pulmonary vascular bed. In fetuses with a diaphragmatic defect, which allows the intrathoracic herniation of abdominal viscera only after mid-gestation, prenatal correction, by allowing further development of the alveoli and intra-acinar vessels, may well prevent pulmonary hypoplasia and neonatal death [1-4].

The authors present an interesting case of a fetus with increased nuchal translucency (NT), normal karyotype, and left-sided diaphragmatic hernia diagnosed by ultrasound at 18 weeks of gestation. They also present a brief review of the literature about occurrence, follow up, and diagnosis of increased NT normal karyotype, and isolated structural fetal abnormalities.

Case Report
A 32-year-old nulliparous pregnant woman attended the present outpatient department for her routine 1st trimester ultrasound screening for Down’s syndrome. On ultrasound assessment the fetus was found to have a NT of 2.3 mm, normal ductus venosus (DV) doppler and present nasal bone (Figure 1). No anatomical abnormalities were identified at the time of the examination. Pregnancy associated placenta protein A (PAPP-A) was 0.59 MoM and beta-human chorionic gonadotropin (b-hCG) 2.56 MoM, whereas the total risk for trisomy 21 was calculated 1/269, by using the Astraia risk calculation system. The couple was offered, but did not opt for chorionic villous sampling (CVS). Therefore, a repeat ultrasound examination was advised. At 18 weeks, she had a repeat ultrasound which revealed a left sided diaphragmatic hernia, with prolapsing stomach, and bowel into the thoracic cavity, pushing the heart and the mediastinum towards the right side (Figures 2, 3).
Results

The couple was counseled about the poor prognosis of the fetus and they were offered a medical termination. The molecular test of fetal tissue showed a normal karyotype and male gender.

Discussion

Diaphragmatic hernia is usually a sporadic abnormality. However, in about 50% of affected fetuses, there are associated chromosomal abnormalities – usually trisomy 18, 13 – mainly craniospinal defects, including spina bifida, hydrocephalus, and rarely encephaly, cardiac abnormalities, and some genetic syndromes such as Marfan, Fryns, and De Lange. If a large defect is present, the fetus may suffer from a severe cardiac failure which leads to ascites, accompanied by severe pulmonary hypoplasia and respiratory insufficiency, causing death in newborns. Mortality rates of the sole cardiac failure are about 60-80%, whereas if accompanied by pulmonary hypoplasia, the rates rise up to 100%. The earlier in gestation the abnormality is present, the poorer the outcome for the fetus [5-8].

Diaphragmatic hernia can be diagnosed by demonstrating the stomach and intestines in 95%, or the liver in 50% of cases protruding in the thorax, and by the mediastinal shift to the opposite side. Herniated abdominal contents associated with a left sided diaphragmatic hernia, are usually easy to demonstrate because of the characteristic imaging of the echo-free fluid filled stomach and the small bowel contrast to the a more echogenic fetal lung. On the contrary, the diagnosis of a right-sided hernia is more demanding, since the echogenicity of the fetal liver is similar to that of the lung, and the visualization of the gall bladder in the right side of the fetal chest, may be the only marker which can lead to the diagnosis. Polyhydramnios, is usually found only after 25 weeks of gestation, in about 75% of the cases, as a consequence of impaired fetal swallowing due to compression of the esophagus by the herniated abdominal organs. If much of the bowel is in the fetal chest, this can result in a reduced abdominal circumference measurement, giving the impression of asymmetrical growth restriction. However, serial measurements, usually demonstrate normal growth velocity. Diagnosis at 18 weeks as in the present case in quiet demanding and difficult since the herniated mass is usually small and there are no clinical suspicious signs, like polyhydramnios at this stage of pregnancy [9-12].

When there is increased NT but the karyotype is normal, the pregnancy remains as high risk for further non chromosomal anomalies and a detailed ultrasound at 18 and 22 weeks should be offered in these cases [2,6,11].
Conclusion

Increased NT with normal fetal karyotype is associated with increased structural fetal anomalies like diaphragmatic hernia and screening for these at 16-18 weeks is imperative.

References


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Sonographic diagnosis of complete uterine inversion:
an unusual case

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Summary
Complete puerperal uterine inversion is an uncommon but potentially life-threatening obstetric emergency. It generally occurs as an obstetrical complication in the postpartum period and can present in acute, subacute, and chronic forms depending on the time interval after delivery. Maternal mortality has been reported to be as high as 15%, mainly because of life associated threatening blood loss and shock. Early diagnosis and treatment are essential, but diagnosis of this is not simple. This is a report of unusual case of complete uterine inversion diagnosed by accurate ultrasound leading to prompt potentially life-saving treatment.

Key words: Puerperal uterine inversion; Prompt diagnosis; Ultrasound examination.

Introduction
Puerperal uterine inversion is a rare but potentially life-threatening obstetric complication in the postpartum period. Earlier diagnosis is very critical to the therapy, the misdiagnosis based on symptoms and physical examination often led to delayed treatment. Sonographic findings were crucial to assist a prompt diagnosis. Several cases of uterine inversion were reported in the literature, with 15% of morbidity [1]. Unfortunately in some cases, hysterectomy was performed. The present authors report a subacute complete uterine inversion diagnosed by accurate ultrasound. Orthometria was performed successfully through the uterine isthmus incision and hysterectomy was avoided.

Case Report
A 27-year-old Chinese woman (gravida 1, para 1) was admitted to the present hospital due to profuse vaginal bleeding for three successive days after spontaneous vaginal delivery. She vagnally delivered a full-term female infant three days prior at a local hospital. The infant weighed 3,850 g with good Apgar scores. The first stage of labor lasted about five hours. Pressure was applied at delivery of the infant. When the placenta was delivered by controlled cord traction, the patient passed approximately 500 ml fresh blood. Vaginal examination revealed non palpable uterus with a shaggy appearing globular mass of 8×9×10 cm protruding from the os into vagina. A diagnosis of submucous myoma was made at the peripheral hospital. Pitocin (10 U) was injected into the uterus and 400 μg misoprostol suppository was given rectally. Uterine bleeding was still intermittent. Blood loss was approximately 1,700 ml in two hours. Then three PVP were inserted into vaginal to decrease bleeding, and cefuroxime and metronidazole were administered to prevent infection. Total blood loss was approximately 2,600 ml in 16 hours. The patient was given eight units of blood transfusion and fresh frozen plasma 1,200 ml then. After two days, PVP were taken out of the vagina. Vaginal bleeding decreased, but still remained intermittent and more than usual lochia. Then she was admitted to the emergency department of the present hospital. She did not appear well, but the blood pressure and pulse were normal. Abdominal examination was pained and rebound tenderness noted in the lower abdomen. The fundus of uterus was not palpable.

A transabdominal ultrasound examination revealed an enlarged uterus at 12 week size. Longitudinal image revealed that the long axis of uterus turned 180 degrees (Figure 1). As is shown in Figure 1, the fundus of uterus lay in the vagina and the cervix lay at the top of pelvic cavity. The endometrium lined the periphery of the inverted fundus and perimetrium lay in the center of the inverted uterus. The uterus appeared as a mirror image of a normally situated uterus. The two opposed serosal surfaces simulated the appearance of an endometrial stripe or “pseudostripe.” Transverse image showed the uterus appeared as a “target sign” with a hyperechoic fundus surrounded by a hypoechoic rim, representing fluid within the space between the inverted fundus and the vaginal wall (Figure 2). Transabdominal imaging showed the obvious position change of two ovaries (Figure 3). The two ovaries appeared to be attached to each other and retracted to the midline as “kissing ovaries”; and were close to the top of cervix. Based on ultrasound findings, a diagnosis of a complete uterine inversion was made.

Vaginal exploration was performed by an obstetrician. Mucosal surface measuring 8 × 9 cm was seen at the top of vagina, with obvious congestion and edema. Cervix and vaginal fornix were not found. The diagnosis of complete uterine inversion was confirmed.

The patient was immediately taken to the operating room. Attempts to replace uterine inversion with intravaginal pressure under the epidural anesthesia were not successful. Then exploratory laparotomy was performed, confirming a complete uterine inversion. The cervix lay at the top while the corpus turned down. Rough endometrium was seen outside which showed spherical inversion of uterus. It confirmed the diagnosis by ultrasound. Manual repositioning was attempted without success because the cervix was tight around the uterus. Hysterotomy was performed. Uterine isthmus was longitudinally incised from an-
Metrorrhosis was performed successfully through the incision.

Three days later, the patient was re-examined by ultrasound. The position of womb was normal. Two ovaries lay on either side of the womb. There had been a successful replacement of uterine inversion. The postoperative period was uncomplicated. The patient fully recovered and was discharged from hospital. Findings on follow-up examinations two weeks later were unremarkable.

Discussion

Puerperal uterine inversion is considered one of the most serious complications in obstetrics. A few case reports of puerperal uterine inversion have been published; they are extremely rare [2]. Unfortunately in some cases, hysterectomy was performed.

Complete puerperal uterine inversion has been classified into acute, subacute, and chronic on the basis of the chronologic diagnosis. Acute, within 24 hours of delivery; subacute, 24 hours to 30 days postpartum; and chronic, greater than 30 days postpartum. Most of postpartum uterine inversion occurred within 24 hours of delivery, occurred usually early in the third early stage of labor. On the basis of clinical history and sonographic findings, the presented patient had subacute uterine inversion.

It is unclear why inversion occurs. The most likely cause is strong traction on the umbilical cord in the third stage of labor particularly if the placenta is fundal in position. Other related factors include Crede’s method of placental delivery, excessive fundal pressure, relaxed uterus, morbidly adherent placenta especially involving the fundus, a short umbilical cord, congenital weakness of the uterus, and antepartum use of magnesium sulphate or oxytocin. Some intrinsic risk factors such as primiparity, pauciparity uterine hypotonia secondary to twin pregnancy, betamimetic, fundic or accrete placenta, fundic myoma and short umbilical cord have been reported too [3]. In the present case, the reason for the inversion may have been related to fundal pressure applied to the uterus for the delivery of the infant and umbilical cord traction.

The most common symptoms of uterine inversion are abnormal vaginal bleeding and low abdominal pain. Atypical symptoms render the diagnosis more difficult [4]. In the present case, the main symptom was intermittent vaginal bleeding. The prolonged treatment results from misdiagnosis based on symptoms and physical examination. Thus sonographic findings were crucial to assist in a prompt diagnosis.

Puerperal uterine inversion can easily be confused with a submucous myoma due to the similar symptoms. For example, there was uterine bleeding and the cervix could not be touched by vaginal exams in both diseases. It is dangerous as misdiagnose may lead to incorrect treatment, threatening the life of the patient. Ultrasound imaging showed that the position of the fundus of uterus and the cervix re-
versed in the puerperal uterine inversion, while the fundus of uterus and the cervix was eutopic in submucous myoma, and the position of two ovaries obviously changed, appearing to be attached to each other and retract to the midline as “kissing ovaries” in the puerperal uterus, while the two normal ovaries lay in bilateral iliac fossa, far away from each other in submucous myoma.

Puerperal uterine inversion can be differentiated from a markedly retroflexed uterus when the transducer abuts the normal-appearing cervix, whereas in complete uterine inversion, the transducer abuts the fundus, and a normal cervix is not shown, while the position of the fundus of uterus and the cervix reversed in the puerperal uterine inversion. In a markedly retroflexed uterus, ultrasound imaged that the two normal ovaries lie in normal position, far away from each other. The present case testified that preoperative ultrasonographic diagnosis of complete uterine inversion was feasible.

Treatment methods vary due to the time of occurrence of uterus inversion. As far as in the present case is concerned, oxytocin should not be used before the successful reset of the uterus because cervical contractile ring led by oxytocin was adverse for orthometria. Orthometria through the uterine isthmus incision successfully repositioned the uterine and avoided hysterectomy.

Prompt diagnosis of uterine inversion and immediate treatment are necessary because it can cause life-threatening hemorrhage. In the present case, the patient had subacute uterine inversion. Some cases reported that the uterine inversion was life threatening and diagnosis was difficult [5-7]. In cases of chronic uterine inversion, hysterectomy was performed as the optimal method for management. These patients had psychological issues later.

The present case alludes that it might be possible and feasible to avoid hysterectomy if uterine inversion is diagnosed earlier. The ideal result might be obtained in the acute and subacute uterine inversion. Ultrasound evaluation facilitates the assessment of clinically undetectable uterine inversion and should always be performed as soon as possible in cases of unexplained postpartum hemorrhage. Most important in the proper management of this obstetric emergency is rapid recognition and prompt attempts in resuscitation and reposition of the inverted uterus.

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References


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Viper bite during pregnancy: case report

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Summary

Viper bites in pregnant women have rarely been reported thus far. Moreover, there is no consensus regarding the treatment of such cases. In this paper, the authors report the successful treatment of viper bite during pregnancy without using antivenom.

Key words: Viper; Venomous snakebite; Pregnant woman; Antivenom.

Introduction

Viper bite during pregnancy appears to be uncommon, and such cases have been rarely reported thus far. Venomous snakebite in pregnant women may lead to poor outcomes for both the mother and fetus. For cases of venomous snakebite during pregnancy, previous literature reviews report a fetal death rate ranging from 38% to 43% and a maternal death rate of approximately 10% [1, 2]. Here, the authors present the case of a pregnant woman who was bitten by a viper who was successfully treated with good maternal and fetal outcomes without using antivenom. The authors obtained the approval of the submission by written consent.

Case Report

A 34-year-old gravida 1, para 1 woman at 36 weeks of gestation was bitten by an unknown snake on the road near her house and was transferred to the present emergency department. The snake was considered to be a viper since vipers were known to be present in that area.

The patient presented with one small puncture wound over at the first finger of the right foot (Figure 1). She complained of localized pain, and swelling was noted around the wound, however, no erythema, ecchymosis, or systemic symptoms were observed. The vital signs at admission were as follows: temperature, 37.4°C; pulse, 90 beats/min; respiration rate, 16 breaths/min; and blood pressure, 117/69 mmHg. The puncture wound was dissected and washed with saline water. Laboratory investigations showed normal bleeding and clotting times but with low levels of hemoglobin. The coagulation profile and renal function tests were also within the normal range (Table 1). An obstetrics and gynecology consultation was obtained for the patient’s pregnancy and the condition of the fetus. Obstetric ultrasonographic results showed no abnormal findings. Fetal well-being was evaluated as normal by the biophysical profile score, and vaginal examination revealed a normal cervix for 36 weeks of gestation. The patient was administered prophylactic antibiotic therapy, but antivenom therapy was not initiated.

At six hours after the patient was admitted to the intensive care unit (ICU), examination revealed edema and ecchymosis throughout the bitten area extending up to popliteal fossa, however, there was no change in the reported pain and observed swelling. Since fetal well-being and the coagulation profile continued to be normal, the patient was scheduled for follow-up visits without further treatment.

At 24 hours after admission, the edema and ecchymosis had progressed up to the groin (Figure 2) but the pain remained unchanged; subsequently, it began to recede. At three days after admission, the patient began to stand up by herself but was unable to walk due to severe pain. At six days after the bite, she could walk slowly although some pain and edema persisted. Further recovery was uneventful, and the patient gave birth to a healthy male infant weighing 3,118 g by spontaneous vaginal delivery at 11 days later after hospitalization. The Apgar scores were 9 and 10 at one and five minutes, respectively. Neither the mother nor the infant experienced any postpartum complications.

Discussion

Snakebite envenomation is not common in pregnancy. In the event of a viper bite in pregnancy, patients should be transported emergently to a facility with the appropriate obstetrical and emergency capabilities.

It is often difficult to accurately identify the species of snake. In the present case, the snake bite was diagnosed as a viper bite on the basis of the injury occurring in a place where vipers were frequently seen, the presence of fang marks, and localized swelling and pain. The fang marks were obviously confirmed. Typically, two fang marks are observed in viper bites. However, the patient showed only a single fang mark, which possibly resulted in a relatively favorable clinical course.

Definitive medical treatment for venomous snakebite should include an evaluation of the severity of the envenomation. The leading edge line of the swelling should be recorded initially and every 30–60 minutes thereafter (Figure 2). Laboratory values that should be monitored include coagulation, chemistry, and renal profiles along with a complete blood count. These should be repeated
every few hours if there is any suggestion of envenomation. In general, the best chance to ensure fetal survival is to guarantee maternal survival and health [1]. Accordingly, maternal cardiorespiratory and renal functions and the coagulation profile must be routinely monitored. It is important to recognize and treat shock as soon as possible. Fetal heart rate and fetal movements should be followed continuously to ensure early recognition of fetal distress [3].

Table 1. — Laboratory values and coagulation parameters of the patient.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>At admission</th>
<th>6 hours later</th>
<th>12 hours later</th>
<th>24 hours later</th>
<th>48 hours later</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>9,900</td>
<td>15,700</td>
<td>12,400</td>
<td>13,200</td>
<td>10,000</td>
</tr>
<tr>
<td>Hb</td>
<td>10</td>
<td>9.9</td>
<td>9.6</td>
<td>9.1</td>
<td>8.5</td>
</tr>
<tr>
<td>Ht</td>
<td>31.4</td>
<td>31.1</td>
<td>30.1</td>
<td>28.5</td>
<td>27.6</td>
</tr>
<tr>
<td>PLT</td>
<td>36.7</td>
<td>32.8</td>
<td>27</td>
<td>27.9</td>
<td>22.4</td>
</tr>
<tr>
<td>APTT</td>
<td>25.7</td>
<td>27</td>
<td>27.8</td>
<td>27.4</td>
<td>29.1</td>
</tr>
<tr>
<td>PT%</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>89.6</td>
<td>98.6</td>
<td>85.7</td>
</tr>
<tr>
<td>Fib</td>
<td>504</td>
<td>457</td>
<td>459</td>
<td>445</td>
<td>459</td>
</tr>
<tr>
<td>AT III</td>
<td>107</td>
<td>100</td>
<td>92</td>
<td>94</td>
<td>87</td>
</tr>
<tr>
<td>CRP</td>
<td>0.38</td>
<td>0.38</td>
<td>1.34</td>
<td>3.08</td>
<td>5.68</td>
</tr>
<tr>
<td>CK</td>
<td>111</td>
<td>104</td>
<td>95</td>
<td>98</td>
<td>94</td>
</tr>
<tr>
<td>BUN</td>
<td>8</td>
<td>7</td>
<td>6</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Cr</td>
<td>0.4</td>
<td>0.44</td>
<td>0.47</td>
<td>0.51</td>
<td>0.47</td>
</tr>
</tbody>
</table>

WBC: white blood cell (μl), Hb: hemoglobin (g/dl), Ht: hematocrit (%), Plt: platelets (μl), APTT: activated partial thromboplastin time (seconds), PT: prothrombine time (%), Fib: Fibrinogen (mg/dl), ATIII: antithrombine III (%), CRP: C-reactive protein (mg/dl), CK: creatine kinase (U/l), BUN: blood urea nitrogen (mg/dl), Cr: creatinine (mg/dl).

maternal deaths were reported; moreover, in the pregnant patients who did not receive antivenom, seven (6.6%) maternal deaths were reported [4]. Whereas acute adverse effects from the use of antivenom have been reported in mothers, only one case of serum sickness has been reported in a pregnant person [5]. Based on the limited number of cases reported, it appears that antivenom is effective in preventing maternal deaths. However, the safety of antivenom with regards to the fetus remains unclear. Antivenin crotalidae polyvalent (ACP), an equine-derived immune globulin antivenom, causes acute allergic reactions in up to 23% of patients and serum sickness in 50% [6]. A less antigenic ovine-derived antivenom, crotalidae polyvalent immune fab (CroFab), received FDA approval in 2000. A prospective trial reported a 14% incidence of acute reactions, of which nearly all were mild to moderate in nature [7]. Both products are included in the Pregnancy Category C by the FDA. Antivenom use in pregnancy is further complicated by the content of ethylmercury in the thimerosal preservative used in antivenoms. Fetuses exposed to organic mercurials have been well documented to display severe psychomotor retardation, cerebral palsy, and microcephaly after exposure to high doses. Therefore, ideally, physicians should refrain from using any antivenom in pregnant women as much as possible. In the present case, good maternal and fetal outcomes were obtained without using antivenom. However, if their use is essential, sufficient informed consent must be taken before their administration.

Prophylactic antibiotics were administered to the present patient because many types of bacteria are known to be present in the oral cavity of a viper. Although such prophylactic antibiotic administration in pregnant women remains controversial [8], the authors considered that the possibility of a bacterial infection was high in the present patient, based on the increased WBC and CRP counts at
24 hours after admission. The infection may have been severe if the authors had not administered the antibiotics. Therefore, they consider that prophylactic antibiotic administration was the correct treatment in this case.

No prophylactic administration of tetanus toxoid or antivenom was performed in the present case due to the problem of teratogenicity. Many authors have reported a favorable short-term prognosis in newborns following the administration of antivenom to pregnant women [7, 9]. However, no information is available concerning the long-term prognosis of such newborns.

In the present case, the authors treated the patient in cooperation with the departments of disaster and emergency medicine, pediatrics, and anesthesiology for ensuring complete care.

Conclusions

Pregnant patients who suffer viper envenomation should receive supportive care irrespective of the severity of the bite. The use of antivenom must be individualized, and the patient must be informed of the potential risks of antivenom administration to herself and to the fetus. It is necessary to establish a guideline for the management of venomous snakebite in pregnant women in order to avoid complications and to ensure good maternal and fetal outcomes.

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Successful management of a second-trimester post-abortion hemorrhage with the Bakri balloon tamponade

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Summary
Hemorrhage after abortion is rare but it is a significant cause of abortion-related mortality and morbidity. Conservative management of hemorrhage is gaining popularity. The authors describe a case which a uterine tamponade balloon which was successfully used to control second-trimester post-abortion hemorrhage.

Key words: Hemorrhage; Abortion; Bakri balloon tamponade.

Introduction
Hemorrhage after abortion is rare, occurring in less than one percent of abortions [1], but its associated morbidity may be clinically significant. Current recommendations regarding the risk factors and treatment of post-abortion hemorrhage are based on extremely limited evidence. The management of these complications depends on the causative factors and can include uterotonics, re-aspiration, Foley or intrauterine balloon tamponade, uterine artery embolization, hemostatic sutures, or hysterectomy. Here, the authors present a case of massive hemorrhage, due to a second-trimester abortion, successfully controlled by using a Bakri balloon catheter.

Case Report
A 35-year-old woman, who had a 19-week pregnancy, was admitted to the present emergency department due to premature rupture of membranes. It was her third pregnancy; she had undergone two prior vaginal deliveries. She had a blood pressure of 120/80 mmHg, pulse rate of 80/min, and cervix dilation of five cm. She experienced a spontaneous abortion five hours after her admission (baby’s weight 0.4 kg; Apgar score 0/0). An ultrasonography examination indicated the presence of some retained placental tissue in the uterine cavity and curettage was performed under intravenous sedation. Uterine bleeding occurred during removal of the placenta. The patient’s hemoglobin level and hematocrit value during admission were 12.8 g/dl and 36.9%, respectively. After evacuation of the uterus, bimanual uterine massage was performed and 0.2 mg of methylergonovine was administered intramuscularly to improve uterine tone and decrease uterine bleeding. However, after two minutes, uterine bleeding increased, and therefore, misoprostol (800 µg) was administered rectally. Ultrasonography examination indicated that the uterine cavity appeared normal and a physical inspection showed no apparent cervical lacerations. Her post-procedure control hemoglobin level was 7 g/dl. Hemorrhage continued, and she experienced tachycardia (128/min); subsequently, two units of red blood suspension were administered. To manage the hemorrhage in first instance, the authors used a G16 Foley catheter balloon tamponade. However, it was unsuccessful in controlling the hemorrhage and vaginal bleeding continued. A Bakri uterine balloon tamponade was then inserted under intravenous sedation. The anterior and posterior lips of the cervix were grasped with ring forceps and the catheter was inserted into the uterine cavity under sonographic guidance. After catheter insertion, the balloon was inflated with 200 ml warm sterile normal saline until the uterine fundus was firmly palpable or until the bleeding was controlled. After the balloon was inflated, it filled the uterine cavity and bleeding was arrested by the tamponade. Gentle traction was applied on the catheter to ensure that the balloon was firmly fitted in the uterine cavity. Broad-spectrum antibiotics were administered until the catheter was removed on the following morning. The patient’s vaginal bleeding was minimal. Her postoperative hemoglobin level was 8.7 g/dl and was asymptomatic. She was discharged in a stable condition on her post-procedure first day.

Discussion
The most important complication after second-trimester abortions is massive uterine hemorrhage. Treatment for this condition should be carefully performed in order to preserve fertility since several patients are of reproductive age, and wish to remain fertile. For the management of hemorrhage, the successful utilization of tamponade techniques has been well described and for many years, uterine packing was the primary technique employed [2]. The Bakri intrauterine balloon tamponade method, which was developed in 1999, has been used specifically for the treatment of postpartum hemorrhage [3]. Cengiz et al. [4] and Aibar et al. [5] described the use of the Bakri balloon for the successful management of postpartum hemorrhage. In
the literature, only two reports have been described to use of the Bakri intrauterine balloon to control refractory bleeding after a first-trimester and second-trimester abortion, respectively [6, 7]. The present case appears to be the second case in which the Bakri intrauterine balloon was used to manage second-trimester post-abortion hemorrhage. In this case, the authors first used a Foley catheter because they had no previous experience with the Bakri balloon in post-abortion hemorrhage. The size of the uterus may permit the insertion of a large tamponade; however, the Foley tamponade could be inflated with only 30 cc of saline, which may not be sufficient to significantly compress the inner uterus. Moreover, unlike the Bakri balloon, when filled with fluid, the Foley catheter balloon tamponade cannot adapt to the shape of the intrauterine cavity. Thus, the Foley tamponade was not successful in terminating the bleeding in our case.

Thus far, no study has specified the exact quantity of fluid that should be used to fill the balloon for the management of post-abortion hemorrhage. Bakri et al. [3] have suggested the balloon should be inflated with 500 cc saline and placed in the uterus for 20–24 hours. In the present case, the authors filled the balloon, under sonographic guidance, with 200 cc saline until a slight resistance was encountered, and the bleeding reduced and finally stopped.

The authors believe that cervicovaginal bacteria may enter the uterus during the introduction of a balloon catheter; the surface of the catheter is a potential site of microbial adherence and retention, and the endometrium is a good target site for infection. Therefore, they administered broad-spectrum antibiotic prophylaxis while the balloon was still in place, as described by Nelson et al. [8]. The balloon was removed from the uterus after 24 hours (Figure 1). The manufacturers’ instructions state that the indwelling time should be ≤ 24 hours due to the risk of infection and tissue necrosis; however, this time interval is not based on any published data. The Bakri device does not contain latex, and once inflated, it conforms very closely to the shape of the entire uterine cavity. The authors experienced no complications related to Bakri tamponade insertion in the presented case.

**Conclusion**

Uterine balloon tamponade is a fertility-sparing treatment option for second-trimester post-abortion hemorrhage. It can be used not only to manage uterine atony, but also in any situation in which hemorrhage should be conservatively managed. However, randomized trials are needed to compare the effectiveness of balloon tamponade with other conservative modes of treatments, such as arterial embolization, surgical ligation of uterine arteries, or uterine compression sutures.

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The outcome of pregnancy in a woman affected by Takayasu arteritis: case report and review of literature

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Introduction

Idiopathic inflammation of the main arteries (aorta, pulmonary, and coronary) leads to progressive and often occlusive inflammation. Hence, it also known as Takayasu arteritis (TA), pulseless disease, or obliterative inflammation. The cause is not very clear and it often occurred in females. The average age of this disease is about 22 years old. Disease prognosis is poor and the risk during pregnancy is high. The present hospital successfully treated a pregnancy with TA as well as term delivery.

Case Report

This study was conducted in accordance with the declaration of Helsinki and with approval from the Ethics Committee of Capital Medical University Affiliated Beijing Friendship Hospital. Written informed consent was also obtained from the patient. The patient is 27-years-old and her condition during pregnancy is as follows. She had regular menstrual cycles of 7 days / 30 days. The urine HCG test was positive after 40 days of amenorrhea. At six weeks of pregnancy nausea and vomiting occurred. The pregnancy then continued normally; however, upper limb blood pressure could not be determined during pregnancy and lower limb blood pressure is normal. No headache, nausea, and other discomfort, occasional dizziness, fatigue, abdominal pain, vaginal bleeding, and vaginal fluid flow were present in the third trimester of pregnancy. Therefore, the patient was referred to the present hospital. Past medical history: suffering from TA since 2000, from optic atrophy since 2003, and had had eye cataract surgery with intraocular lens replacement surgery in 2004.

Discussion

TA is a chronic non-specific inflammatory disease, mainly affecting the aorta and its main branches, such as the brachiocephalic trunk, carotid, vertebral, renal, coronary, and pulmonary arteries [1, 2].

Epidemiology

The disease is more common in Asia, Latin America, North America, and in Europe. The annual incidence rate of
this disease is 1.2 to 2.6 per million [3]. The disease occurs in women of childbearing age, but in recent years the incidence in men has increased. Male to female ratio is approximately 1:8, with an average age of diagnosis at 29 years of age. Infants and young children to middle-aged patients have also been reported. Furthermore, three out of four patients experience the onset during their adolescence [4, 5].

Etiology and pathogenesis
The etiology and pathogenesis of TA is unclear and involves heredity, infection, cellular and humoral immune mechanism, sex hormones and other factors. At present, genetic factors, immune mechanisms, and infection are object of study. TA is related to other inflammatory disease may be due to the following: Firstly, there are common or related antigens between TA and other inflammatory diseases. Secondly, inflammatory disease may stimulate the immune system therefore leading to an autoimmune mechanism. Thirdly, inflammation may directly damage blood vessels and produce auto-antigen. TA and other coexisting autoimmune diseases indicate that the immune system is abnormal: its unbalance caused by bacteria or viral infection may be accompanied by the morbidity and progress of TA [6].

Clinical characteristics and classification
The clinical feature of TA is not obvious. From the onset of symptoms to the clinical diagnosis, several months or even years on average may be required. More than half of patients suffer from systemic inflammation at first instance, such as fever, dizziness, fatigue, night sweats, and weight loss. After ruling out infections and tumoral diseases, TA should be considered in young women who have an unexplained fever. Earlier diagnosis is difficult, because the early symptoms of TA are non-specific [7]. As the illness progresses, the lesions begin to block blood vessels that cause organ problems and many clinical manifestations such as dizziness, headache, dizziness, fainting, vision loss, hemiplegia, aphasia, tachycardia, vascular murmur, myocardial ischemia, kidney disease, and other manifestations [8]. Not being able to assess the upper pulse, 50% ~ 60% of patients complicate with hypertension. One of the main complications is congestive heart failure, which accounts for about 28%. It is mainly induced by high blood pressure and in few cases it is caused by aortic regurgitation. Angina pectoris or myocardial infarction can appear if the coronary artery is involved. Proximal pulmonary involvement may have similar symptoms as pulmonary embolism. As a late complication, pulmonary hypertension is one of the factors influencing the prognosis [9]. According to clinical manifestations, TA can be divided into five groups [10]: Type I: cerebral ischemic type; Type II: hypertensive type; Type III: limb ischemic type; Type IV: aneurysm type; Type V: cardiopulmonary vascular and visceral vascular type.

The early pathology of TA mainly include active granulomatous inflammation of artery and its branches, and intimal hyperplasia, degeneration in the middle membrane, and fibrosis in the outer membrane occurs in its late stage (hardening) which will result in the occlusion of the aorta and other affected arteries; 85% ~ 96% patients suffering from TA are at the hardening stage after diagnosis. Ischemic symptoms of upper limb are common, but symptoms due to lower limb ischemia are few. Differential blood pressure of bilateral limbs is more than four kPa in the majority of patients. These patients suffer from orthostatic dizziness or fainting. Carotid artery is involved in about a quarter of the patients with retinal disease.

Diagnoses
The diagnosis of TA is mainly based on clinical symptoms, signs, laboratory examination, and radiographic inspection.

The circulating endothelial cells in the blood tested by serological examination can be used as indicator of the active stage. They have good correlations with the blood sedimentation [11]. The rapidly increasing white blood cells and platelets, mild anemia, CRP or ESR may emerge during the acute phase, which is normal in the silent period. IgG, IgM, and aortic antibodies may be increased in some patients, but the specificity of the relationship between these factors and TA is not strong, hence the diagnostic value is insufficient [8].

Currently, angiography is recognized as the gold standard in the diagnosis of TA. Typical angiographic aspects include unsmooth lining surface of the aorta and its branches, expansion after stenosis, aneurysm, artery occlusion or “shape like rat tail” of the thoracic aorta. The comparison of several non-invasive tests showed that ultrasonic, MRI, CT vessel three-dimensional reconstruction can detect thickness changes in the vessels’ wall during the early stage of TA. The combination of the angiography and the aforementioned can be found as early-stage TA lesions [12].

Therapies
Early stage of TA, hormone is preferred as the drug treatment. Japan’s recommendation is the combined utilization of hormone and small doses of antplatelet drugs such as aspirin, etc. [1]. The therapy of high-dose glucocorticoid has been approved which can obviously improve systemic symptom, prevent the progress of TA in its systemic inflammatory phase, and reduce blood sedimentation.

The patients with side-effects to hormone therapy also require to immune inhibitors. Cyclophosphamide is effective for some patients. Small doses of methotrexate (about 0.3 mg/kg, once a week) can increase the curative effect of hormone and reduce the dose used of the latter [2]. Preventing infection is conducive to controlling the disease if early infection lesions are found in respiratory system or
other parts of body. Although medications successfully improved symptoms in the majority of patients, more study is required to assess whether long-term complications can be prevented or if survival can be prolonged.

The indications include high blood pressure caused by renal vascular stenosis, patients who cannot take care of themselves on a daily basis due to motor dysfunction, cerebral ischemia, aortic regurgitation, and myocardial ischemia [7]. In recent years, percutaneous transluminal angioplasty (PTA) has been attempted to treat the obstructive vasculopathy of TA. Tyagi et al. have treated aortic stenosis with PTA. The pressure gradient of the narrow parts of the vessel and the high blood pressure decreases after the period of expansion in 94% patients. Symptoms are significantly improved in patients successfully treated.

The following aspects should be considered: Firstly, the blood pressure must be closely monitored. If the blood pressure of the brachial artery in patients cannot be measured, the popliteal artery should be utilized. Blood oxygen and ECG should be monitored contemporarily. Secondly, appropriate low epidural block should be adopted. The dosage of local anesthetics should be reduced as much as possible, but effective anesthesia still needs to be achieved because both pain and contractions could stimulate vasospasm. After childbirth, the blood flows to the internal viscera due to reduced abdominal pressure; if returned blood volume decreased dramatically, the blood supply of important organs may be compromised and can lead to loss of consciousness or heart failure. Therefore, it is important to maintain stable blood pressure, avoiding large fluctuations. Thirdly, dexamethasone needs to be preventative used to strengthen the symptomatic treatment of arterial inflammation. Drugs which can cause the blood vessels to constrict should be avoided. Oxytocin should be directly injected to the corpus uteri and the intravenous route must be avoided. Vaginal delivery is difficult and the cesarean section should be adopted to effect the delivery.

Because the arterial intima involved in these patients often show diffuse or localized thickening, hardening, and rigidity, their lumens include different degrees of narrowing, also according to pathological changes. Thrombosis can easily occur and induce embolism due to the high coagulative properties of blood during later pregnancy; hence all types of embolisms should be considered.

If antibiotics are used to prevent infection after the surgery, breastfeeding after delivery is unfavorable. Pregnancy is contraindicated in TA patients due to associated serious complications. In this study, the patient had a strong desire to become pregnant and therefore refused its termination. Therefore the full-term pregnancy was maintained under strict monitoring. Natural childbirth was obviously not suitable. In addition, at 36-37 weeks, the cervical conditions and cardiac function of patient were poor, and the success rate of induced labor was low. Strong uterine contractions and pain could have caused vasocostric-

tion and aggravated the illness. Therefore a cesarean section is relatively safe for both mother and baby.

As the number of reported cases as the present are few, more obstetric experience needs to be attained in order to more effectively treat this vascular disease.

Conclusion

TA is a severe vascular disease. The patients with this kind of disease are advised against pregnancy as it can seriously affect both mother and child. For the patient who insists on pregnancy, precautions should be taken to intensify mother and fetal care throughout pregnancy and periparative hemodynamic changes should also be assessed; these are effective methods to prevent heart failure, embolism, and thrombosis.

References


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Live birth after transfer of vitrified-warmed blastocyst derived from ICSI with frozen-thawed sperm: case report

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Summary

Objective: A live birth after transfer of vitrified-warmed blastocyst derived from intracytoplasmic sperm injection (ICSI) with frozen-thawed sperm of a male cancer patient is described. Materials and Methods: A case report from a tertiary center for assisted reproductive technologies. The 35-year-old male patient had been diagnosed with testicular tumor nine years ago. He had unilateral orchectomy operation after the diagnosis. Four years after the first operation, he was diagnosed with another testicular tumor in the other testis. He admitted to our center with the demand of sperm preservation before the second surgery. The sperm samples were cryopreserved and stored in liquid nitrogen until required. The patient had no chemotherapy or radiotherapy after the operations. After he completed his oncologic follow up, ICSI was decided with his frozen samples. Although the couple failed to conceive with the fresh cycle, the remaining embryos were frozen and revealed a pregnancy in the subsequent frozen-thawed cycle. Results: A healthy female infant with a birth weight of 3,700 g was born by cesarean section at 38th weeks of the gestation. Conclusion: Giving detailed information about fertility-saving management in male patients is important in those who wish to bear children. However, both the patients and physicians should be cautious that preservation should be performed before surgery and/or adjuvant therapy. In this respect, assisted reproductive technology (ART) and related facilities yield chance of pregnancy in such population.

Key words: Blastocyst; Vitrification; Sperm; Cryopreservation; Testicular cancer; Assisted reproductive techniques.

Introduction

Male cancer patients will be faced with compromised fertility as a result of their cancer treatments. Iatrogenic sterility after chemo/radio therapy in these patients might be avoided by the cryopreservation of sperm cells. Although the studies on the spermatogonial stem cells appear promising, they are still experimental. Nowadays, sperm cryopreservation has become an important part of fertility preservation for those of cancer patients. [1-3].

Cryopreservation of embryos has become a necessary part of assisted reproductive technology (ART) that helps to prevent multiple pregnancies and wastage of supernumerary embryos. This technique may also contribute to increase cumulative pregnancy rates in ART cycles. In this manner, vitrification is a simple technique and gradually replacing slow freezing due to a higher survival rate after thawing. Most infertility units use vitrification technique particularly for oocyte and blastocyst cryopreservation, as both structures did not perform well with slow freezing technique [4].

In the present case, we aim to report the management of a male patient who had been diagnosed with testicular malignancy and demanded to preserve his fertility. Although the couple failed to conceive with the fresh cycle, the remaining embryos were frozen and revealed a pregnancy in the subsequent frozen-thawed cycle.

Case Report

The 35-year-old male patient had been diagnosed with testicular tumor nine years ago. He had unilateral orchectomy operation after the diagnosis. Four years after the first operation, he was diagnosed with another testicular tumor in the other testis. He admitted to our center with the demand of sperm preservation before the second surgery. His semen sample was frozen in our IVF clinic with freezing medium test yolk buffer with glycerol just before the operation. The sperm samples were preserved in liquid nitrogen until required. After he completed his oncologic follow up, ICSI was decided with his frozen samples. Although the couple failed to conceive with the fresh cycle, the remaining embryos were frozen and revealed a pregnancy in the subsequent frozen-thawed cycle.
guided puncture of follicles 36 hours after hCG administration. Twelve oocyte–cumulus complexes were retrieved of which 11 were in metaphase II suitable for ICSI. On the next day, nine of them were fertilized. Eight of the embryos cleaved and a single fresh blastocyst evaluated as 4BB (Gardner’s criteria) was transferred four days after oocyte retrieval [6]. A single surplus blastocyst (4CB) was vitrified using cryotip. However the couple failed to conceive in the fresh cycle and a thawed cycle was decided four months later. The patient was prepared using down regulation with leuprolide acetate and artificial preparation of the endometrium using exogenous estrogen and progesterone. A single blastocyst was thawed and transferred following two-hours of incubation. The serum β-hCG test 14 days after the transfer was 265 mIU/ml. A singleton pregnancy with positive fetal heart activity was noted at the seventh week of gestation by transvaginal ultrasonography. Finally, this resulted in a birth of a healthy female infant weighing 3,700 g at 38 weeks of gestation by cesarean section.

Discussion

New technologies in assisted reproductive treatments have created opportunity for fertility preservation in young male cancer patients. Sperm cryopreservation before cancer treatment is the best available way to enable these patients to achieve parenthood. At the same time, ICSI with frozen-thawed sperm is feasible and potentially successful technique in that group of patients. On the other hand, blastocyst culture and transfer is now common in most of the IVF centers. So, this selection process has reduced the number of embryos transferred per cycle and increased implantation rates. As a result of this, embryo cryopreservation has become a routine procedure to increase cumulative pregnancy rates and to prevent wastage of surplus embryos.

Vitrification of human blastocyst is a feasible and viable option to slow freezing method. In recent years, this technique has become superior to slow freezing as it eliminates ice crystals formation and is very easy to perform [7-9].

To our knowledge, a live birth achieved by frozen-thawed blastocyst derived from ICSI with frozen-thawed testicular sperm from a man with non-mosaic Klinefelter’s syndrome is reported by Rosenlund et al. [10]. In that case, they used slow freezing technique for blastocyst cryopreservation instead of vitrification.

Although Kyono et al. [11] were the first to describe a birth of male infant after transfer of vitrified-warmed blastocysts derived from ICSI with vitrified-warmed oocytes and frozen-thawed spermatozoa, donor sperm was used in that study. Differently from the case by Kyono we injected fresh oocytes with frozen-thawed patient’s own sperm to achieve a pregnancy.

In conclusion, this is a rare case of a live birth after transfer of vitrified-warmed blastocyst obtained from ICSI with frozen-thawed sperm of male testicular cancer patient. This report highlights the effective use of cryopreservation techniques to overcome infertility problems in young cancer patients.

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Abdominal wall desmoid tumor during pregnancy: case report and literature review


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Summary

Desmoid tumors are fibromatous lesions that are the result of abnormal proliferation of myofibroblasts. Despite its benign microscopic appearance and non-metastasizing behavior, tumor infiltrates surrounding tissues and has a high risk of recurrence. Pregnancy-associated desmoid tumors are very rare and optimal management of this tumor is not well established. The authors report a case of a 31-year-old pregnant woman with a large desmoid tumor, which increased rapidly in size and caused worsening symptom of dyspnea. The tumor was successfully removed during a caesarian section, which resulted in an anterior abdominal wall defect. Reconstruction of the abdominal wall defect was performed with a polypropylene mesh. The postoperative recovery of the patient was uneventful. After a follow-up of 44 months, the patient was found to be well and there was no evidence of local recurrence. The authors also reviewed the literature on the world’s experience with this tumor and its management during pregnancy. Twelve desmoid tumors arising during pregnancy were reported in the existing literature; the managements were varied and has yet to be defined.

Key words: Desmoid tumor; Pregnancy; Abdominal wall.

Introduction

Desmoid tumors, also known as aggressive fibromatosis or musculo-aponeurotic fibromatosis, are uncommon, benign, soft tissue neoplasms which comprise 0.1% of all the tumors and 3.5% of fibrous tissue neoplasms [1]. These rare tumors can develop in any musculo-aponeurotic structure and can be found in all regions of the human body. They may rise sporadically or in patients with familial adenomatous polyposis (FAP). The incidence of sporadic desmoid tumors has been estimated to be two to five per million people per year; however, it increases almost 1,000 times in patients with FAP [1, 2]. The precise etiology of desmoid tumor is undefined, however, trauma, surgical history, and estrogen hormone levels have been reported to play a crucial role in the pathogenesis, and genetic factors have also contributed [3]. Pregnancy-associated desmoid tumor is even rarer, and there is very limited published research available in this case. The optimal management of this tumor during pregnancy has yet to be defined.

The authors hereby report a large desmoid tumor that was diagnosed and resected successfully within the caesarian section. Previous reports have documented successful surgical management of these tumors during pregnancy with uneventful delivery, however, the size of the specimens they reported are much smaller than in the present case. A caesarian section followed by a successful complete resection of the tumor, with uneventful postoperative recovery as well as longer-term follow-up. The authors also reviewed published literatures and management experience of this tumor during pregnancy.

Case Report

A 31-year-old woman (gravida 2, para 1) at 34 weeks of estimated gestation was transferred to the present department because of difficult breathing. The symptom was mainly caused by an abdominal mass that had grown very rapidly. At 21 weeks gestation, in a primary hospital, it was misdiagnosed to be a uterine leiomyoma by ultrasound examination. The ultrasonography revealed a solid hypo-echoic mass measuring 12×15 cm in the anterior wall of the uterus. Seven weeks later, another ultrasonography was performed and it indicated that the mass had grown to 23.3×11.4×17.6 cm. The fetus was also evaluated and noted to be viable. The doctor advised her to receive a mass removal, however, the patient refused to undergo surgery. She began to experience symptoms of increased dyspnea. The symptoms were very severe at her 34 weeks of estimated gestation. Ultrasonic evaluation showed a large mass of 36×19.5×33 cm in size. From this result, there was a rapid growth of the mass, almost tripled in size compared to the prior result at 13 weeks gestation. This patient was transferred to the present department because of the limited medical resources at the primary hospital.

The patient was admitted, an ultrasonography confirmed a 35×35×14 cm mass located in the abdominal cavity anteriorly to the uterus. The myometrium of the anterior wall was measured to be six mm in thickness. The evaluation of the fetus showed that the baby was in a good condition. The authors suspected the mass to be a large leiomyoma or a sarcoma of the uterus. Given the

*Contributed equally to this work and considered senior authors.
rapid growth of this tumor and the worsened symptoms of dyspnea, a decision was taken to resect the tumor within the caesarian section and not to wait until the pregnancy came to term spontaneously. The surgery was performed at 35 weeks of estimated gestation.

A vertical incision of the lower abdominal was chosen. The authors found a large, hard, incompressible tumor in front of the peritoneum. The tumor seemed to originate from the anterior abdominal wall muscles and covered the uterine corps and the lower uterine segment. No adhesions were found between the tumor and the uterus. The tumor was so large that its superior border reached the xiphoid process, while its right side reached the right posterior axillary line and its left side reached the left anterior axillary line. The inferior border of the tumor reached the pubic symphysis.

Many vessels were found in the surface of the tumor. The authors used retractors to expose the lower uterine segment and then successfully preceded with caesarean section. A normal male infant with an Apgar score of 10 and a body weight of 2,300 g was extracted. After successful child delivery and closure of the uterine tissue, the authors extended the incision to the xiphoid process. However, due to the large tumor size, it was difficult to expose the entire tumor, so they made another transverse incision, from the upper side of the umbilical round to the left anterior axillary line. Then, a local complete resection with a macroscopically tumor-free margin was performed. The peritoneal and rectus abdominis involved were also dissected during the operation that resulted in an anterior abdominal wall defect measuring 10×5 cm in size. Reconstruction of the abdominal wall defect was performed.
with a polypropylene mesh, which was sutured to the excision edge of the anterior abdominal wall fascia and muscles. Intraoperative blood loss was approximately 2,500 ml, thus, the patient received blood transfusion (Figures 1-3).

The pathological report demonstrated that the specimen measuring 35×30×14 cm in size and 7.1 kg in weight. The tumor was encapsulated and margin-free. The histologic specimens consisted of interlacing bundles of fibrous tissues and benign fibroblasts with moderate cellularity. The appearance of which was consistent with desmoid tumor (Figure 4).

The postoperative recovery of the patient was uneventful. She was discharged ten days after the surgery. However, the infant was transferred to neonatal intensive care unit because of hyaline membrane disease caused by preterm labor. The patient was noted to be well and there was no evidence of local recurrence after 44 months of follow-up.

**Discussion**

Desmoid tumor is a benign, locally aggressive neoplasm that arises from fascial or musculo-aponeurotic tissue. It is characterized by proliferation of fibroblasts but without the cytological feature of malignancy [4]. Although these tumors are benign, they can infiltrate the surrounding vital structures or organs, which may result in significant local morbidity and even death [5]. This tumor was first described by MacFarlane in 1832, and the term of “desmoid” was applied by Muller in 1838 [6]. Most of them occur sporadically, while 5% arise in association with FAP [7]. The incidence in the general population is two to five cases per million people. Patients with FAP have a 1,000-fold increase risk for desmoid tumors as compared to the general population [1, 2]. Desmoid tumor may occur in the extremities (most commonly around limb girdles), the abdominal wall (most frequently diagnosed in women), and bowel mesentery (most commonly associated with FAP)[7].

The definitive etiology of desmoid tumors is currently unknown; however, endogenous or exogenous estrogen exposure has been shown to be a risk factor regarding the pathogenesis of this tumor. First, women are more frequently affected with an incidence ratio of female to male of 5:1 [2, 8]. Second, women during their reproductive age, pregnancy, and those taking contraceptive pills have a higher incidence of desmoid tumors [9]. Third, spontaneous regression of this tumor has been observed in women after menopause or oophorectomy [4, 10]. Finally, anti-estrogens agents such as tamoxifen have been reported to be effective in vitro [11, 12] and in vivo [13-15]. Risk factors like prior trauma or surgery and genetic pre-
disposition are also contributed to the pathogenesis of this tumor [3, 16].

Pregnancy-associated desmoid tumor is even less common. By now, the available literatures, reporting desmoid tumor during pregnancy, are sporadic case reports (Table 1). There is a lack of general recommendations for the treatment of pregnancy-associated desmoid tumor because of the small number of cases available in literature, as well as the lack of randomized and prospective studies concerning the direct comparisons of different treatment approaches. Management of patients with desmoid tumor during pregnancy is complicated and some issues remain controversial. It is not only due to the tumor itself, but also because of confounding obstetrical considerations. Embryo safety has to be considered while deciding therapeutic approaches during pregnancy. Currently, the main controversies focus on the role and timing of surgery, and the safety and value of non-operative therapies.

A simple observation is a reasonable management option for selected patients. According to the literature, 10\% of desmoid tumor resolved spontaneously, 30\% underwent cycles of progression and regression, 50\% remained stable after diagnosed, and 10\% progressed rapidly [6, 17]. Given its inherent morbidity, some authors suggested a wait-and-see policy for suitable patients. A number of reports regarding conservative management for desmoid tumor during pregnancy have been published. De Cian et al. documented a case where an abdominal wall desmoid tumor was diagnosed in a 42-year-old woman at 12 weeks of gestation. The tumor measured 8×5 cm in size. The patient was examined clinically every month, while the tumor was carefully measured every two months by ultrasonography and remained unchanged during the last six months of gestation. At last, the tumor was resected via a Pfannenstiel incision during concomitant caesarean section at 37 weeks gestation [18]. Molelekwa et al. reported a case in which a desmoid tumor was diagnosed in a 42-year-old woman during her first trimester. The tumor measured 3.2×6.5 cm in size. Regular fortnightly scans were performed and showed no significant growth of the tumor. The tumor was excised with clear margins one month after caesarean delivery [19]. Arshad et al. reported three patients who presented with a large anterior abdominal wall desmoid tumor diagnosed during their pregnancy. All three patients received a “wait-and-see” policy until the tumors were excised successfully postpartum [20]. Viriyaroj et al. reported a 17-year-old woman presenting with a desmoid tumor at her suprapubic region during the fifth month of gestation. She completed a full-term pregnancy and delivery by caesarean section. The tumor had grown very rapidly after delivery and was finally completely excised. In these cases, the patients were asymptomatic or with few or mild symptoms and the tumors were not so large. Most important, the conditions of the fetus were not influenced by the tumor. Therefore, patients with small desmoid tumor which is not encroaching on any nearby structures, especially not compressing the gravid uterus and endangering the fetus could be observed closely to complete a full-term pregnancy. These patients should be followed clinically and with modern imaging methods to assess the increase of size of these tumors. Ultrasonography and magnetic resonance imaging (MRI) are usually recommended. Different treatment approaches should be considered after successful delivery depending on the risk factors like age, tumor size, and location.

Surgery has a key role in the management of abdominal desmoid tumors. Wide radical local excision has been described as the optimal primary treatment. The role of surgical management for desmoid tumor has been questioned because of its inherent morbidity and its biological behavior. Desmoid tumor with a lack capsule or displays non-palpable spread along muscles and fascial planes makes it difficult for surgeons to estimate the tumor extent at operation. It can result in microscopic positive surgical margins and incomplete tumor removal, which possibly explains their high recurrence rate even after a presumably adequate resection [17, 21, 22]. The timing of the surgery is also controversial. Early surgical intervention entails risks to the fetus and potential obstetric problems related to resection and reconstruction of the abdominal defect. Severe pain had been reported during pregnancy due to shearing of an abdominal wall mesh graft [23]. Furthermore, a caesarean section would be technically troublesome in such a case, and vaginal delivery would be considered inadvisable within one or two years after the prosthetic implant [24]. To date, most of the literature has documented the diagnosis and resection of an abdominal desmoid tumor during caesarean section or postpartum [3, 18-20, 25-27]. However, only few reports regarding desmoid tumor resection during pregnancy have been published in the recent literatures. Gherman et al. reported a case of desmoid tumor of the larynx complicating pregnancy, which caused a symptom of progressively worsening vocal hoarseness and subtotal excision was performed at 21 weeks gestation. The residual tumor was monitored until the labor was induced at 36 weeks gestation because of oligohydramnios. Endoscopic evaluation and biopsy at nine weeks postpartum revealed regression of tumor [28]. Firoozmand et al. described an abdominal tumor in a pregnant woman, which caused worsened symptoms of difficult defecation and interference with fetal growth. The pelvic desmoid tumors measuring 17×14×10 cm was successfully excised at 23 weeks gestation, but the patient required a diverting ileostomy, and she subsequently entered preterm labor at 27 weeks [29]. Durkin et al. documented a case where a desmoid tumor was diagnosed at the first trimester. The tumor increased significantly in size and worsened the patient’s symptoms of pain and abdominal fullness. The patient un-
derwent a successful en bloc resection of her desmoid tumor as well as abdominal wall reconstruction with polytetrafluoroethylene mesh during her 22nd week of gestation. Subsequent to her surgery, the patients completed a full-term pregnancy without complication and proceeded with an uneventful transvaginal delivery at 39 weeks [9]. These reports demonstrated that symptomatic desmoid tumors can be resected during pregnancy, even those requiring abdominal reconstruction. Surgical intervention has to be the first choice in desmoid tumors that cause significant symptoms, increased rapidly in size, compressing the uterus, and interfering with fetal growth. The decision to subject the mother and fetus to the potential morbidity of immediate surgery was weighed against the potential circumstance that further delay in treatment may have resulted in an inability to achieve tumor-free margin.

Radiation therapy had been used as an adjuvant treatment for patients with positive surgical margin as well as those who are poor candidates for surgery or with unresectable disease. Some investigators [30-32] reported better control of recurrent disease in patients with no residual tumor treated with adjuvant radiation therapy while some other groups [33, 34] failed to make similar observations. However, radiation therapy is contraindicated during pregnancy because it can lead to abortion, stillbirth and fetal malformation. The role of radiotherapy postpartum has yet to be defined.

A variety of systemic therapies have been investigated in non-pregnant patients. The aim is to induce remission, to prevent complications and disease recurrence, and to reduce morbidity [6]. Non-steroidal, anti-inflammatory drugs such as indomethacin, sulindac, and anti-estrogens such as tamoxifen have been considered as first line pharmacological therapies [26, 35, 36]. Cytotoxic drugs such as doxorubicin, dacarbazine, actinomycin-c, methotrexate, vinblastine, and vinorelbine have been found to have some activities in symptomatic patients, unresectable and clinically aggressive desmoid tumors which do not respond to conventional treatment [37-39]. Nevertheless, a medical intervention exposes the fetus to the potentially harmful effects of drugs, it is also contraindicated during pregnancy. To the knowledge of the present authors, there are no pregnant patients with desmoid tumor who have been treated with these drugs during pregnancy. The role of pharmacological therapy in postpartum period has yet to be established. Early delivery of the fetus may be necessary to facilitate tumor regression or to allow a treatment with radiotherapy or pharmacological therapies in selected patients.

Desmoid tumors are reported to have a high recurrence rate even after radical surgical excision due to the infiltrative growth pattern. The recurrence rate following resection of abdominal wall desmoid tumors are approximately 50% [40]. There is an increased risk of recurrence after a primary operation in patients with positive surgical margins of resection, whereas age, sex, site, size, or number of previous recurrences had no significant value on the likelihood of recurrence [37, 41, 42]. Unfortunately, there are no literatures, which have evaluated the recurrence rate of pregnancy-associated desmoid tumors following surgical excision specifically. However, based on reviewed documents, it was noticed that abdominal wall desmoid tumors that arise during pregnancy seemed to have a lower recurrence rate compared with the other types of desmoid tumor. The reasons are not clear yet it may be associated with the postpartum drop of estrogen level.

Conclusion

Desmoid tumor that arises during pregnancy is rare and the optimal management has not yet been well established. Simple observation is a reasonable management option for asymptomatic patients while surgical intervention has to be the first choice for patients who have significant symptoms or tumors increased rapidly in size, compressing the uterus and interfering with fetal growth. However, radiotherapy and pharmacological therapy are contraindicated during pregnancy, the role of postpartum radiotherapy, and pharmacological therapy remains controversial. The management of desmoid tumors diagnosed during pregnancy is complicated and the treatment must be individualized.

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