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Serum markers of oxidative stress and endometriosis

J.C. Rosa e Silva, V. Ferreira do Amaro, J.L. Mendonça, A.C. Japur de Sá Rosa e Silva, L.S. Nakao, O.B. Poli Neto, R.A. Ferriani

Purpose of investigation: To assess the changes secondary to chronic inflammation in women with and without pelvic endometriosis by the determination of serum thiols and carbonyls. Materials and Methods: Sixty-seven women with endometriosis consecutively submitted to laparoscopy and 41 women without endometriosis consecutively submitted to tubal ligation (control group) were selected. Serum levels of total thiols and carbonyls were determined in both groups. Results: Patients with endometriosis had significantly lower thiol levels than controls (342.37 ± 142.09 µM vs 559.60 ± 294.05 µM) (p < 0.001), as well as significantly lower carbonyl levels (8.97 ± 3.76 µM vs 16.40 ± 9.26 µM) (p < 0.001). Other clinical characteristics were not associated with changes in marker levels. The cutoff point established by the ROC curve was 396.44 µM for the thiols, with 73.1% sensitivity and 80.5% specificity, and 14.9 µM for the carbonyls, with 94% sensitivity and 51.2% specificity. Conclusions: The serum thiol levels revealed an increase in oxidative stress related to the development of pelvic endometriosis.

Key words: Endometriosis; Oxidative stress; Serum markers; Thiols; Carbonyls.

Introduction

Pelvic endometriosis is a benign gynecologic affection in which endometrial glands and/or stroma develop outside the uterus. The prevalence of endometriosis is ten to 15% among the female population of reproductive age and 20% to 50% among infertile women [1, 2]. Classic clinical signs and symptoms are dysmenorrhea, dyspareunia, acyclic chronic pelvic pain, and infertility [3].

The presence of endometrial cells in the peritoneal cavity leads to the recruitment of monocytes that provoke the release of cytokines, consequently favoring a pelvic inflammatory reaction [4]. On this basis, endometriosis can be considered to be a disease of an inflammatory nature, as confirmed by evidence showing elevated levels of cytokines and growth factors present in peritoneal fluid. Changes in B lymphocyte activity and increased antibody production are detected in women affected by this disease [1]. The inflammatory process is associated with elevated levels of oxidative stress [4].

Oxygen free radicals have been suggested to be involved in the pathogenesis of endometriosis and in the association of the disease with infertility [5]. Oxidative stress is induced when there is an imbalance between oxidant and antioxidant substances. This phenomenon is caused by overproduction of reactive oxygen species (ROS) associated with depletion of the antioxidant system [4]. ROS and reactive nitrogen species produced in vivo, which are not adequately metabolized by the antioxidant system may cause alterations in proteins, lipids, carbohydrates, and nucleic acids. The oxidative modification of these molecules by toxic levels of these species may have deleterious consequences. The production of subtoxic ROS levels can lead to a change in the intra- and extracellular redox state and has been demonstrated to signal changes in cellular functions. Thiols and carbonyls are recognized as key components of many of these events [6]. Thiols are a class of organic derivatives with a critical intra- and extracellular function as equilibrators of the redox state through the thiol/disulfide protein. Extracellular thiols are an important component of the antioxidant defense with relevance for cardiovascular diseases, representing a direct measurement of the in vivo redox state. In addition, they also reflect the ability of DNA repair or the possible accumulation of genetic damage to cells [7, 8].

ROS induce lipid peroxidation and modify amino acid and carbonyl derivatives, with the latter, in turn, reflecting protein oxidation [9]. Carbonyl concentration is important in the pathogenesis of atherosclerosis and its formation is a subproduct of phagocyte-derived reactions. Thus, carbonyl concentration is a marker of both phagocyte activation and inflammation [7].

Free radicals and oxidative stress are being extensively studied in different diseases and are believed to participate in their etiology and prognosis. Endometriosis is one of these diseases and the demonstration of a positive relationship between this disease and oxidative stress may provide a definitive, sensitive, and non-invasive method for the determination of its diagnosis [10-12].

The objective of the present study was to evaluate the changes secondary to chronic inflammation in women with...
and without pelvic endometriosis by means of the determination of serum thiols and carbonyls, as well as the influence of clinical characteristics on these determinations. The cut-off points for these serum markers with better sensitivity and specificity was determined by a ROC curve.

Materials and Methods
The authors selected 83 women of fertile age consecutively submitted to laparoscopy due to suspected endometriosis and with histologic confirmation of endometriosis in the endometriosis outpatient clinics of the Department of Gynecology and Obstetrics, Faculty of Medicine of Ribeirão Preto, and of “Santa Casa de Misericórdia” of Curitiba. Exclusion criteria were smoking, the use of anti-inflammatory medications up to two months before surgery, patients presenting ovarian tumor, pelvic inflammatory disease, myomas and adenomyosis as intraoperative or ultrasonographic findings, patients who had received hormonal therapy (oral contraceptives, progestogens or GnRH analogues) during the preceding three months, pregnant patients or patients who refused to participate in the study. The authors selected as controls 55 women of fertile age consecutively submitted to bilateral tubal ligation and attended in the family planning sector of the Maternity Victor Ferreira do Amaral and in the family planning outpatient clinic of the Department of Gynecology and Obstetrics, Faculty of Medicine of Ribeirão Preto. These women had no endometriosis as determined by laparoscopy and the same exclusion criteria as cited above were applied to this group. Ten ml blood were collected in each venipuncture and centrifuged at 5,000 rpm for ten minutes and the serum obtained was frozen at -80°C until the time for analysis. Some samples were discharged because of hemolysis or high lipid concentration in the centrifuged serum, what could interfere in the markers’ measurement and consequently could constitute a bias. Therefore, the number of analyzed patients was 67 and 41 in the endometriosis and control groups, respectively.

The project was approved by the Research Ethics Committees of the participating institutions and all patients gave written informed consent to participate in the study.

Analysis of thiol concentration
Thiols were determined using the dithiobis 2-nitrobenzoic acid (DTNB) method [13]. The samples were thawed and immersed in ice. The standard curve used for the calculations of unknown concentrations was obtained using glutathione at concentrations from 0.2 to 2 mM. Samples were analyzed in duplicate on 96-well microplates. Ten µl serum plus 190 µl of the DTNB solution and of diethylenetriamine-penta-acetic acid (DTNB) were added to each well. The plates were incubated for ten minutes at room temperature and the absorbance of the samples was read at 405 nm. The concentration (in µM) was calculated for each patient using a specific equation.

Analysis of carbonyl concentration
The analysis was carried out by the 2,4 dinitrophenyl hydrazine (DNPH) method [14]. Two test tubes per patient were used. Serum (200 µl) and one ml DNPH (one mM in two M HCl) were added to the tube identified as the sample, and 200 µl of serum in one ml two M HCl were added to the tube identified as the blank. All tubes were left in a water bath at 37°C for 90 minutes. After cooling, each tube received one ml 28% trichloroacetic acid (w/v) and the tubes were vortexed for three minutes and then centrifuged at 6,000 rpm for an additional three minutes. The supernatant was discarded and one ml ethanol: ethyl acetate (1:1) was added to the pellet. The material was again homogenized in a vortex for two minutes and the tubes were once again centrifuged at 6,000 rpm for six minutes. The procedure was repeated one more time.

The supernatant was discarded and one ml of six M guanidine was added to the pellet. Homogenization was carried out for one minute and the content of each tube was then transferred to microtubes which were centrifuged for three minutes at 6,000 rpm in a microcentrifuge. The absorbance of each sample was read at 360 nm and carbonyl concentration was obtained by a specific equation.

Statistical analysis
The GraphPad Prism 4.0 32-Bit Executable software and MedCalc statistical software, Version 7.2.1.0 were used for statistical analysis. The clinical variables were analyzed by the Fisher exact test. The nonparametric Mann-Whitney test was used for the evaluation of the serum markers and the cut-off points with highest sensitivity and specificity for these markers were determined by the ROC curve. The level of significance was set at p < 0.05 in all tests. Results of thiol and carbonyl levels were expressed in median (minimum-maximum).

Results
The mean age of the two groups was similar (33.22 ± 6.22 years for the endometriosis group and 32.49 ± 4.74 years for the control group). The endometriosis group had a greater prevalence of dyspareunia (p < 0.001), chronic pelvic pain (p = 0.015), infertility (p < 0.001), dysmenorrhea (p < 0.001), menstrual irregularity (p = 0.001), and cyclic intestinal changes (p = 0.001). There was no significant difference regarding the presence of midcycle pain, post-coital bleeding or cyclic urinary changes between groups.

The patients with endometriosis presented significantly lower serum thiol levels compared to control (median 325.25 (103.89 – 828.22) µM vs 530.29 (133.86 – 1892.00) µM) (p < 0.001) (Figure 1), as well as lower carbonyl levels (median 8.00 (1.10 – 20.60) µM vs 15.61 (5.23 – 44.13) µM) (p < 0.001) (Figure 2).

The presence of dysmenorrhea, midcycle pain, infertility, dyspareunia, post-coital bleeding, menstrual irregularity, and cyclic urinary or intestinal changes, when evaluated separately in each group, was not associated with significant changes in the levels of any marker.

The cut-off point suggested by the ROC curve for the thiols was 396.44 µM, with 73.1% sensitivity and 80.5% specificity, and the area under the curve equal to 0.806 (Figure 3). For the carbonyls, the suggested cut-off point was 14.9 µM, with 94% sensitivity and 51.2% specificity, and the area under the curve equal to 0.768 (Figure 4).

Discussion
The complaints and clinical symptoms observed in endometriosis were confirmed in the current study and, as expected, the presence of the tetrad dysmenorrhea, dyspareunia,
infertility, and chronic pelvic pain was prevalent in many of the women with the disease.

The markers chosen for the present investigation have already been extensively studied in other diseases, such as diabetes, chronic renal failure, atherosclerosis, hypertension, and psoriasis, having proved to be good markers for these diseases. However, they have not been studied previously in endometriosis.

Several studies have shown an association between endometriosis and oxidative stress. Jackson et al. [15] used four markers of oxidative stress to compare women with and without endometriosis on the basis of thiobarbituric acid reactive substances and detected an increase in these markers in women with pelvic endometriosis. In two different studies, Zhao et al. [16] and Sczepanska et al. [17] observed that the antioxidant status was reduced in women with pelvic endometriosis. Liu et al. [5] used peritoneal fluid as the biological medium to be evaluated and detected higher levels of oxidative stress in women with endometriosis [5]. de Foyouzi et al. [18] suggested that reactive oxygen species can modulate the growth of the endometrial stroma. In pathological conditions such as endometriosis, high levels of these unstable molecules and antioxidant depletion may contribute to the excessive growth of cells of the endometrial stroma [18]. Oner-Iyidogan et al. [19] concluded in their study that several factors, such as the cytokines released by macrophages activated in peritoneal fluid and hormones synthesized by the ovary, may locally affect the antioxidant status of the ectopic endometrium.

Figure 1. — Thiol levels in the endometriosis and control groups (p < 0.001).

Figure 2. — Carbonyl levels in the endometriosis and control groups (p < 0.001).

Figure 3. Sensitivity and specificity for cut-off point of thiols.

Figure 4. Sensitivity and specificity for cut-off point of carbonyls.
These results demonstrate the participation of oxidative stress in the development of the disease and suggest that treatment with antioxidant substances could be of benefit to women with endometriosis and protect healthy women against the disease.

However, some investigators did not detect oxidative stress in women with endometriosis. Ho et al. [20] compared women with and without endometriosis in terms of total antioxidant status and of the levels of nitric oxide-derived products and found no significant differences in these levels between the groups with and without the disease. Polak et al. [21] also did not obtain a positive result regarding the association of oxidative stress markers with the presence of endometriosis.

The carbonyl levels detected were lower in the endometriosis group, although, in contrast to the thiol, the higher the levels of this marker, the lower the oxidative stress, with these levels proving not to be good markers of oxidative stress in women with endometriosis.

It should be pointed out that the sensitivity and specificity of the two serum markers evaluated here were not high, that indicates a limitation of their use in clinical practice as serum markers of this disease when compared to other markers such as CA125 [22, 23].

Conclusion

Based on the present data, we conclude that oxidative stress seems to play a role in the genesis of pelvic endometriosis, considering mainly the serum thiol levels. Nevertheless, its levels should be evaluated with caution when used as a marker of the disease. Anyway other studies with bigger casuistic may be developed in order to definitely prove this relation.

References

Pregnancy outcome after laparoscopic myomectomy

S. Fagherazzi, S. Borgato, M. Bertin, A. Vitagliano, L. Tommasi, L. Conte
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Summary

Purpose of investigation: Main purpose of this study was to analyze the reproductive and obstetrical outcome as delivery mode and incidence of major complications (uterine bleeding and uterine rupture) after laparoscopic myomectomy. Materials and Methods: The authors conducted an observational study in patients who underwent laparoscopic myomectomy. Inclusion criteria were: surgery performed for single and or multiple myomas sized between five and 15 cm and pregnancy desire. Exclusion criteria were: surgery for pedunculated myomas and male or tubal infertility. Collected data on pregnancy desire, success in obtaining pregnancy surgical interval time before pregnancy, performing assisted reproductive medicine, gestational weeks, mode of delivery, indicating a possible cesarean section, and complications. On collected data the authors calculated pregnancy and abortion rates. Results: Among patients aged between 19 and 42 years who answered a telephonic questionnaire, the authors selected 185 patients with pregnancy willing. A total number of 426 myomas were removed; 115 (62.2%) patients reported 151 pregnancies, nine in a total of 17 patients achieved it with reproductive assistance, 38 pregnancy ended in abortion, and two had an ectopic implantation. The authors finally reported 111 successful pregnancy, with seven preterm deliveries (6.3%). Mode of delivery had been cesarean section in 69 cases (63.4%) and vaginal delivery in 42 cases (36.6%), with a respective mean interval time between surgery and delivery of 24.6 ± 20.0 months and 19.2 ± 13.3 months. Conclusion: Laparoscopic myomectomy proved to be an effective procedure feasible for women who wish to become pregnant with a subsequent good reproductive outcomes, both in terms of pregnancy and abortion rates that were comparable with the literature. If laparoscopic suturing of the fovea myometralis is adequate, there are no contraindications for vaginal delivery, regardless of the patient’s age, the number, size, and location of the myomas removed.

Key words: Fibroids; Laparoscopic surgery; Pregnancy outcome.

Introduction

Uterine fibroids (also called leiomyomas) represent the most common neoplastic disease in women. They affect the functions of the uterus producing uterine bleeding, anemia, defective implantation of an embryo, recurrent pregnancy loss, preterm labor, obstruction of labor, pelvic discomfort, and urinary incontinence. Among middle-aged women the incidence of fibroids nearly reached 70% of white women and more than 80% of black women. Incidence of symptoms, moreover, affect 15% to 30% of this patient cohort. Approximately 200,000 hysterectomies, 30,000 myomectomies, and thousands of selective uterine artery embolizations and high-intensity focused ultrasound procedures are performed annually in the United States to remove or destroy uterine fibroids [2, 3].

As compared with other fibroids, submucous fibroids that extend into the uterine cavity are the most disruptive to endometrial integrity, implantation, and the capacity of the myometrium to contract and stop menstrual bleeding from the endometrial blood vessels; thus, even small submucous fibroids are associated with excessive or irregular bleeding, infertility, and recurrent pregnancy loss [4].

Regardless of their size or location, fibroids may have paracrine molecular effects on the adjacent endometrium that are extensive enough to cause excessive uterine bleeding or defective implantation [5, 6].

Surgery is the mainstay of therapy for leiomyomas and hysterectomy is the definitive procedure [7, 8]. In order to preserve patients fertility, however, there are other surgical techniques such as hysteroscopic or laparoscopic myomectomy [9-11]. While it is well established that hysteroscopic myomectomy improves long term outcome, reported as quality of life and reproductive result reported as pregnancy rate [12, 13], a debate remains in laparoscopic myomectomy, if this will affect in some way the outcome of patients eager to have children who underwent previous myomectomy [14]. Main purpose of this study was hence to analyze the reproductive and obstetrical outcome as delivery mode and incidence of major complications (uterine bleeding and uterine rupture) after laparoscopic myomectomy.

Materials and Methods

The authors conducted an observational study in which they selected patients admitted at Department of Women’s and Children’s Health, University of Padua between January 1996 and December 2010 and who underwent laparoscopic myomectomy. Surgery was performed by the same experienced operator in gynecological laparoscopic surgery.

Inclusion criteria were: surgery performed for single and or multiple myomas sized between five and 15 cm, and pregnancy desire. Exclusion criteria were surgery for pedunculated myomas and male or tubal infertility.

Among the entire sample of patients, the authors selected women aged between 19 and 43 years to which had been admin-
istered a telephone questionnaire. They collected general features
data on age, weight, and parity indication for intervention. They also
collected surgical data as myomas location, diameter, and
number, (according to Munro’s classification) [15] surgical duration,
blood loss, complication occurrence, hospitalization days, and
general satisfaction.

A telephone questionnaire collected data on pregnancy desire,
success in obtaining pregnancy surgical interval time before preg-
nancy, performing assisted reproductive medicine, gestational
weeks, mode of delivery, indicating a possible cesarean section, and
complications. On collected data the authors calculate preg-
nancy and abortion rate.

Patients’ satisfaction about surgical intervention was evaluated
with a verbal numeric scale from 0 to 10, where 0 represented the
worst possible satisfaction and 10 the highest degree of satisfac-
tion. The degree of satisfaction was then categorized from 0 to 3
as poor, from 4 to 7 as good, and > 7 as excellent. Data on surgi-
cal procedure were hence grouped according to the patients’ mode
of delivery and had been compared in term of age, fibroids diam-
eter, number and location, and type of myomectomy.

Surgical technique

All laparoscopic myomectomies took place under general anes-
thesia through a 10-mm telescope 0 ° 30 ° videolaparoscope. Umbi-
bilical trocar was placed through the umbilicus and ancillary
trocars were placed two fingers above the anterosuperior iliac
spines, the left one was size 12 mm permitting the procedures of
myoma drilling and morcellation. Central and right lateral trocars
were five mm in size. In enucleating myomas a harmonic scalpel
(ten mm in size) was used. Correct hemostasis was performed
through the same surgical instrument. According to type and size
of myomas uterine wall was sutured, in one, two, or three layers
with using a monofilament absorbable 0 PDS (PDS II, 3.5 Ph)
plus CT-1 needle (36 mm, ½ circle) with interrupted sutures and
intracorporeal knots. Particular attention was posed during the su-
turing time in order to avoid areas of excessive or low voltage.
Myomas were extracted by a tissue morcellator (12 mm).

Statistical analysis

Statistical analysis were performed SPSS Statistics for Win-
dows, version 21.0. Results were expressed in absolute number and
percentage for categorical variables, average, and standard
deviation for continuous variables. Categorical variables were
compared using the Chi-square test or Fisher’s exact test when
necessary. Continuous variables were compared using the Mann-
Whitney U test. The level of significance was set at p < 0.05.

Results

Among patients aged between 19 and 42 years who an-
swered the telephone questionnaire, the authors selected
185 patients with pregnancy desire. At the time of surgery
they reported a mean age of 34.7 ± 4.1 years and a mean
BMI of 24.9 ± 3.5 kg/m². Data regarding parity showed 135
(73.0%) women without previous pregnancy, 29 (15.7%) with
history of a previous pregnancy but with no children,
16 (8.6%) with only one previous child, and five (2.7%)
with more than one previous child.

A total number of 426 myomas were removed, 89
(48.1%) patients underwent single myomectomy, 96
(51.9%) underwent multiple myomectomy, 30 (16.2%) had
two fibroids removed, 42 (22.7%) had three to five fibroids
removed, and 24 (13.0%) had six to 11 fibroids removed.
No intraoperative complications were reported. Detailed data
about surgical procedure are shown in Table 1.

Concerning patients’ satisfaction degree of surgical inter-
vention, the authors found only one case of low satisfac-
tion (0.7%), five cases (2.8%) with mild satisfaction,
while 179 patients (96.5%) reported high level of satisfac-
tion.

Overall in the sample, 115 (62.2%) patients achieved
pregnancy after surgery with a total number of 151 preg-
nancies, nine of which were achieved by assisted medical
reproductive techniques over a total number of 17 patients
that underwent the same procedure; 38 pregnancies ended
in abortion and two had an ectopic implantation. Pregnancy
rate (calculated as total number of obtained pregnancies /
total number of desiring pregnancy patients) hence resulted
in 80.6%, while abortion rate (total number of abortion oc-
curred / calculated as total number of desiring pregnancy
patients) result in 20.5%. The average interval time be-
tween surgery and pregnancy was 23.4 ± 17.9 months.

The authors finally reported 111 successful pregnancies,
with seven preterm deliveries (6.3%). Mode of delivery
was cesarean section in 69 cases (63.4 %) and vaginal de-
delivery in 42 cases (36.6 %), with a respective mean interval

<table>
<thead>
<tr>
<th>Year</th>
<th>Number Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>185 34.7 (4.1)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>185 54.9 (7.5)</td>
</tr>
<tr>
<td>Parity</td>
<td>Nulligravid 135 (73%)</td>
</tr>
<tr>
<td></td>
<td>Nulliparous 29 (15.7%)</td>
</tr>
<tr>
<td></td>
<td>Primiparous 16 (8.6%)</td>
</tr>
<tr>
<td></td>
<td>Multiparous 5 (2.7%)</td>
</tr>
<tr>
<td>Surgical indication</td>
<td>Voluminous myoma 65 (35.1%)</td>
</tr>
<tr>
<td></td>
<td>Menorrhagia 51 (27.6%)</td>
</tr>
<tr>
<td></td>
<td>Infertility 24 (13.0%)</td>
</tr>
<tr>
<td></td>
<td>Chronic pelvic pain 34 (18.4%)</td>
</tr>
<tr>
<td>Myoma site</td>
<td>6-7 72 (38.9%)</td>
</tr>
<tr>
<td></td>
<td>4 106 (57.3%)</td>
</tr>
<tr>
<td></td>
<td>classified by Munro et al. [15]</td>
</tr>
<tr>
<td></td>
<td>8 6 (3.3%)</td>
</tr>
<tr>
<td></td>
<td>2-5 1 (0.5%)</td>
</tr>
<tr>
<td>Blood loss (ml)</td>
<td>185 183.7 (233.7%)</td>
</tr>
<tr>
<td>Myoma weight (g)</td>
<td>185 158.2 (145.1%)</td>
</tr>
<tr>
<td>Surgery lasting (min)</td>
<td>185 81.2 (39.6%)</td>
</tr>
<tr>
<td>Hospitalization lasting (days)</td>
<td>185 1.8 (0.9%)</td>
</tr>
<tr>
<td>Opening endometrial cavity</td>
<td>185 2 (1.1%)</td>
</tr>
<tr>
<td>Postoperative complications</td>
<td>185 7 (3.8%)</td>
</tr>
</tbody>
</table>
time between surgery and delivery of 24.6 ± 20.0 months and 19.2 ± 13.3 months.

The authors registered, as surgical indication for cesarean section, five cases (7.2%) of fetal pathology (one case of IUGR, two cases of acute fetal distress, and two cases with macrosomia), eight cases (11.5%) of previous cesarean section, two cases (2.8%) of placenta praevia, two cases (2.8%) of twin pregnancy, two cases (2.8%) of preeclampsia twins, ten cases (14.4%) of dystocia, and 40 (58.0%) cases of previous myomectomy.

Comparison between cohort of patients divided according to the mode of delivery in term of age, fibroids diameter, number, location, and type of myomectomy showed no significant differences. Detailed data are shown in Table 2.

**Discussion**

Abdominal myomectomy has been the treatment of choice in multiple myoma, where there is a total number > three of leiomyomas sized over five cm, or in a significantly enlarged uterus. Last advances in endoscopic techniques show that operative time, blood loss, and hospital stay are comparable to that with results for abdominal hysterectomy [16, 17]. With advances in laparoscopic suturing technique and instrumentation, most myomectomies can be performed by endoscopic technique, either hysteroscopically or laparoscopically and the results are comparable where they do not result better to those of myomectomy performed by laparotomy. Although the surgical procedure may last longer than laparotomic approach, laparoscopic myomectomy is a safe and effective procedure, even in case of large or multiple myomas or in women who desire future pregnancy [18-20]. Even if laparoscopic approach for fibroids is nowadays recommended, a good clinical practice imposes a correct diagnosis of abnormal uterine bleeding, that is the main fibroid’s symptom, and is important to check, even with hysteroscopy and biopsy or polypectomy performed prior surgery [21, 22].

In the present sample the authors considered 185 women who attempted to get pregnant after a laparoscopic myomectomy. They found that mean duration of surgery was 81.2 ± 39.6 minutes with no intraoperative complications, and 3.8% of minor postoperative complications and overall duration of hospitalization was 1.8 ± 0.9 days. These results are in agreement with the current literature data reporting a surgery lasting of 107.71 ± 43.42 minutes, 1.99 ± 0.87 days of hospitalization, 2.2% of major complications, and 11.1% of minor complications [23-25].

Laparoscopic myomectomy is in fact a minimally invasive procedure with a shorter recovery and a lower overall risk of complications than abdominal myomectomy, and some data suggest that a laparoscopic approach results in less severe adhesive disease, particularly fewer adnexal adhesions, which may impact fertility [24]. The chance of an improved fertility is an important task since leiomyomas are estimated to account for one to two percent of infertility [26], particularly those that impinge upon the endometrium, may affect fertility by interfering with implantation over the myoma site, rapidly distending the uterus in early pregnancy, or impairing uterine contractility [27-29].

Concerning obstetrical outcome, the authors report a total number of 151 pregnancies over 185 patients desiring children, with a calculated pregnancy rate of 81.6% and an abortion rate of 20.5%. These data are in agreement with Campo et al. [30] that report a pregnancy rate of 63.6% and an abortion rate decreased from 61.5% to 13.8% after laparoscopic myomectomy. Theses data are confirmed by many authors [23, 31-35] and they improve the results of laparotomic surgical procedure reported by Li et al. [36] who reported a pregnancy rate of 57% and an abortion rate reduced from 60% to 24% after laparoscopic myomectomy.

The advent of endoscopic surgery hence seems to not have changed the pregnancy and abortion rates following myomectomy, which are comparable with that following laparoscopic myomectomy [37]. The debate is still open on the matter that the woman subjected to certain types of myomectomy (especially intramural) must not give birth vaginally because of the risk of uterine rupture during pregnancy or labor. In a retrospective study performed at the Trinidad Maternity, the observed rate of uterine rupture after laparoscopic myomectomy was 5.3% [38].

The present data report 37 (36.6%) vaginal deliveries and 64 (63.4%) cesarean sections. Intramural myomas were 69.7% among the patients who gave birth vaginally and 57.6% among the patients who gave birth by cesarean section. Comparing the group of women who gave birth vaginally with the group of women who had undergone cesarean section, there were no statistically significant differences between age of patients, number, location and size of removed myomas. Since the present data is in accordance with the literature [39], the present authors analyzed the surgical indication applied in the choice of cesarean section and they found that the main indication was previous myomectomy 40 (58.0%). This seems to be inappropriate because it was well-demonstrated

---

**Table 2. Correlation between surgical and anatomical population features in terms of mode of delivery.**

<table>
<thead>
<tr>
<th></th>
<th>Vaginal Mode of delivery</th>
<th>Cesarean section</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>6.4 ± 2.0</td>
<td>6.5 ± 3.0</td>
<td>0.49</td>
</tr>
<tr>
<td>Number</td>
<td>1.7 ± 0.9</td>
<td>1.9 ± 1.1</td>
<td>0.51</td>
</tr>
<tr>
<td>Age</td>
<td>32.6 ± 3.2</td>
<td>33.5 ± 4.8</td>
<td>0.30</td>
</tr>
<tr>
<td>Single myomectomy</td>
<td>15 (45.5%)</td>
<td>15 (45.5%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Multiple myomectomy</td>
<td>18 (54.5%)</td>
<td>18 (54.5%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Myomas Munro 6-7</td>
<td>23 (69.7%)</td>
<td>19 (57.6%)</td>
<td>0.44</td>
</tr>
<tr>
<td>Myomas Munro 4</td>
<td>10 (30.3%)</td>
<td>14 (42.4%)</td>
<td>0.44</td>
</tr>
</tbody>
</table>
that a woman who underwent previous laparoscopic myomectomy should have the possibility to deliver vaginally. Cesarean section is indicated only in the case of uterine cavity opening during surgical procedure [33, 34]; this is a currently used indication for cesarean section in the present Service. The present authors’ follow up was via telephone and the questionnaire did not include the hospital where the patients gave birth. This may represent a bias in this study because there is not yet a clear agreement and different services may apply different protocols, but at the moment both valid indications for cesarean section. In the present sample the authors report no uterine rupture during pregnancy, labor, and postpartum nor silent dehiscence of sutures in the course of elective cesarean section. These results further confirm that vaginal delivery can be accomplished successfully without uterine rupture in women with a laparoscopic myomectomy history where the myometrial fovea is appropriately sutured regardless of the size, depth, location, and number of myomas removed; an appropriate suturing technique can be considered as equal as laparotomic ones [18,20].

In conclusion, laparoscopic myomectomy has proven to be an effective procedure feasible for women who wish to become pregnant. The study also recorded good reproductive outcomes, both in terms of pregnancy and abortion rates that were comparable with the literature and with the classical surgery [38]. What is important to point out is that an adequate laparoscopic suturing of the fovea myometralis does not represent an absolute contraindication for vaginal delivery, regardless of the patient’s age, the number, size, and location of the myomas removed.

References


Pregnancy outcome after laparoscopic myomectomy


Introduction

Spontaneous abortion is the termination of pregnancy before 28 weeks. The incidence of spontaneous abortion among those with estimated fetal weight < 1,000 g covers about 15% of the total number of pregnancies. The majority of spontaneous abortion occurs before 14 weeks of pregnancy. Spontaneous abortion usually arises within 12 weeks of pregnancy (most within eight weeks) and seldom arises after 12 weeks of pregnancy. Recurrent spontaneous abortion (RSA) refers to two or more consecutive abortions, which has an incidence rate of about one to five percent, and tends to arise within 12 weeks of pregnancy [1-3]. Repeated abortion brings serious adverse effects to women’s physical and mental health. Thus, related research on RSA has become one of the hotspots in reproductive medicine.

Few methods for clinically predicting the pregnancy outcome of patients with RSA during early pregnancy are known. The B-type ultrasonic examination of the fetal heartbeat is a reliable index for predicting a favorable pregnancy outcome. However, the fetal heartbeat is only detectable at a specific stage of pregnancy, thereby limiting the capability of the method to predict the pregnancy outcome during early pregnancy. Nevertheless, previous research on fetal fibronectin (fFN) has provided a new concept for the clinical prediction of pregnancy outcomes of patients with RSA during early pregnancy.

fFN is an isoform of the fibronectin secreted by decidua containing the carcinofetal fragment III-CS and identifiable by the monoclonal antibody FDC-6 in an fFN kit. In the embryonic implantation and placentation process, fFN interacts with its receptor, regulates the activity level of proteolytic enzymes, and functions in the implantation of fertilized eggs and in the connection and adhesion of placental villi and decidua [4]. Immunohistochemical analysis showed that fFN usually exists in the interface of the amnion, placental tissue, chorion, and decidua, is an important extracellular matrix, and can reflect the growth of chorionic trophoblast cells and placenta. Throughout pregnancy, fFN has an important role in maintaining the integrity of the extracellular matrix in the placenta and the stability of the maternal–fetal interface. As an independent predictor, fFN does not depend on gestational weeks and has specific predictive value at different stages of pregnancy [5-7]. However, most studies have focused on the application of fFN in the prediction of premature delivery. Under normal conditions after 24 weeks of pregnancy, fFN should not be detected in the secretions of the posterior fornix (fibronectin < 0.5 μg/ml). A fFN-positive [fFN (+)] result suggests increased risk of premature delivery [8]. Few applications of fFN research during early pregnancy are known.

Summary

Objective: This work aims to investigate the predictive value of fetal fibronectin (fFN) in embryonic loss of patients with recurrent spontaneous abortion (RSA) in early pregnancy. Materials and Methods: Eighty-four patients with RSA in early pregnancy were selected as the test group and 31 healthy women in early pregnancy were selected as the control group. The ages and number of previous abortions, along with other information, were recorded. These patients underwent a fFN test, and their pregnancy outcome was followed up until 14 weeks. Results: The incidence of spontaneous abortion was 20.24% in the test group and 9.68% in the control group. The positive fFN [fFN (+)] rate was 57.14% in the test group and 12.90% in the control group, indicating a statistically significant difference ($p < 0.01, \chi^2 = 17.89$). The incidence of spontaneous abortion was 29.17% (14/48) in the fFN (+) group and 8.33% (3/36) in the fFN (-) group, indicating a statistically significant difference ($p < 0.05, \chi^2 = 5.53$). The sensitivity, specificity, and positive and negative predictive values in the prediction of abortion in fFN (+) patients of the test group were 82.35%, 49.25%, 29.17%, and 91.67%, respectively. Conclusion: If detected at an early stage of pregnancy, fFN in patients with RSA is largely related to the prediction of abortion and facilitates the evaluation of pregnancy outcomes.

Key words: Fetal fibronectin; Recurrent spontaneous abortion; Early pregnancy.

Predictive value of fetal fibronectin on the embryonic loss of patients with recurrent spontaneous abortion in early pregnancy

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Previous studies have shown that the positive rate of fFN is very high in patients with early spontaneous abortion, which is probably due to an immune dysfunction mediated by abundant lymphocytes in decidualized interstitial cells; and by abnormal changes in the decidua and cytokines secreted by the decidua. The latter, in turn, causes proteolytic destruction at the chorion-decidual interface, as well as the release of extracellular matrix protein of the chorion and decidua into the cervical and vaginal secretions [9, 10]. These findings prove the possibility of predicting abortion using fFN. However, previous studies either used a small sample size or lacked a control group, the opposites of which being necessary in further deepening related research. The present research was conducted to investigate the predictive value of fFN on the embryonic loss of patients with RSA in early pregnancy using a control study, thereby providing clinical evidence for early prevention and individualized treatment.

Materials and Methods

Objects and grouping

Eighty-four patients diagnosed with RSA during early pregnancy from August 2008 to February 2009 were selected as the test group. Thirty-one healthy women diagnosed in the present hospital during early pregnancy were selected as the control group. The pregnant women were grouped according to the following criteria: (1) < 12 weeks pregnancy; (2) no symptoms of threatened abortion, such as abdominal pain and colporrhagia; (3) no obvious abnormalities, such as subchorionic hematoma, as observed through B-type ultrasonic examination; (4) no abnormal findings in the bacteriological examination of vaginal secretion; (5) no sexual activity and gynecological examination within 24 hours; (6) no developmental malformation of the genital system; (7) no gynecological diseases, such as chronic cervicitis and cervical polyps; (8) no severe multi-system diseases; (9) no bad habits such as smoking and drinking; and (10) no history of taking prescription medicine. This study was conducted in accordance with the Declaration of Helsinki and with approval from the Ethics Committee of Sun Yat-sen University. Written informed consent was also obtained from all participants.

Sample collection

The vaginas of the pregnant women in lithotomy position were opened with disposable vaginal speculums. A special swab provided in the fFN kit was gently dipped in the cervicovaginal secretions in the posterior fornix for about ten seconds. The swab was removed and its head was inserted and fully mixed into the buffer for ten to 15 seconds. The fFN test bar was removed from the aluminum foil bag and the marking end of the test bar was removed and the results were read. A negative result was indicated by one line, whereas a positive result was indicated by two lines with a deep or shallow color, suggesting that the fFN content in the sample was higher than 50 ng/ml. However, if the quality control line did not appear, the test failed and would have to be repeated.

Index recording

In general, the age, gestational week of sampling, number of pregnancies, and fFN test results were recorded. Pregnancy outcome: all pregnant women were followed up until 14 gestational weeks, and their nuchal translucency (NT) color Doppler ultrasound results for the 12th and 13th gestational weeks were followed up by telephone. A favorable heartbeat obtained during B-type ultrasonic examination suggested that the pregnant women would successfully tide over early pregnancy, and fetal blastoscopy results during B-type ultrasonic examination suggested spontaneous abortion and pregnancy failure. The sensitivity of fFN in predicting abortion in fFN (+) patients (true positive rate) in the test group was determined by calculating the proportion of fFN (+) patients to the total number of abortions. The specificity of predicting abortion in fFN (+) patients (true negative rate) refers to the proportion of fFN (-) patients to the total number of regular pregnant women. The positive predictive value (accuracy of positive predictive results) refers to the proportion of practical abortions to the number of fFN (+) patients. The negative predictive value (accuracy of negative predictive results) refers to the proportion of normal pregnancies to the number of fFN (-) patients.

Statistical analysis

SPSS 13.0 for Windows was used to conduct statistical analysis. The incidence and morbidity rates were expressed as percentages (%). The t-test was used for data measurement; and the chi-square test was used to compare the ratios. A p < 0.05 denoted statistical significance.

Results

General data

Test group: The samples were aged 24 to 43 years, with the average number of pregnancies at 3.57 ± 0.66. The fFN was tested at the gestational age of 35 to 66 days. The control group was composed of patients aged 20 to 39 years, with the average number of pregnancies at 3.24 ± 0.47. The fFN was tested at the gestational age of 39 to 67 days. No statistically significant differences were found for age, gestational age, and number of pregnancies (p > 0.05, Table 1).

Pregnancy outcome and fFN test

Seventeen pregnant women in the test group had spontaneous abortions, which brought the incidence rate to 20.24%. On the other hand, three pregnant women in the control group had spontaneous abortions, bringing the incidence rate to 9.68% in the group. The difference was not statistically significant.

Forty-eight patients (57.14%) from the test group were fFN (+), whereas four patients (12.90%) were fFN (+) in the control group. A statistically significant difference was found between the positive fFN rates in the two groups (p < 0.01, χ² = 17.89).

In the test group, the incidence of spontaneous abortion was 29.17% (14/48) in patients with fFN (+), but only 8.33% (3/36) in patients with fFN (-), denoting a statistically significant difference (p < 0.05, χ² = 5.53). In the control group, the incidence of spontaneous abortion was 25% (1/4) in patients with fFN (+) but only 7.41% (2/27) in patients with fFN (-), as shown in Table 2.
RSA is one of the frequently observed diseases in obstetrics. Multiple previous abortions increase the risk of abortion of the subsequent pregnancy. A recent large sample study on Scottish women showed that the risk of abortion in the present pregnancy is increased among women with one and two previous abortions. On the contrary, the incidence of three previous abortions does not increase the risk of abortion during the next pregnancy [11]. The use of indexes that can effectively predict the risks of embryonic loss will facilitate the clinical diagnosis and treatment of RSA.

Previous studies showed that fFN has a great potential and application value in the prediction of embryonic loss. As an important extracellular matrix secreted by decidualized eggs, as well as in the connection and adhesion of placental villi and decidua [12].

Furthermore, a study found that the dynamic expression of fibronectin presented in early pregnancy plays an important role in the morphological differentiation of the endometrial matrix in mice [13].

In the present study, the positive rate of fFN in patients with RSA in the early pregnancy group was significantly higher than that in the control group. The sensitivity and negative predictive value for predicting abortion among fFN (+) patients were as high as 82.35% and 91.67%, respectively. Consequently, fFN, which has a lower likelihood of providing a missed diagnosis, was used as an index to predict the occurrence of abortion in the next pregnancy of pregnant women with a history of abortion. A negative result has great significance for the exclusion of the probability of abortion. Conducting a fFN test on RSA patients in the early stage of pregnancy, facilitates the assessment of the pregnancy outcome. fFN (+) results during early pregnancy possibly indicate poor uterine receptivity and suggest higher risks of adverse pregnancy outcome.

Previous studies have indicated that the incidence of abortion is related to the age and number of previous abortions of pregnant women. Munnes et al. proved through a multicenter retrospective study of the age and number of abortions of pregnant women that the risk of abortion increases with age [14]. An epidemiological study conducted in Japan also showed that both the age and number of previous abortions of pregnant women affects subsequent pregnancy outcomes [15]. After in vitro fertilization and embryo transplantation, the incidence of early abortion was also found to increase with age [16]. Most scholars consider that age reduces the reproductive capacity of women mainly because of the effect of age on the oocytes [17], namely, 1) the number of oocytes; and 2) the quality of oocytes gradually decreases with age (i.e., the ovum is aging). Furthermore, intracytoplasmic peroxidation is enhanced, and oxygen free radicals increase with age, thereby damaging the nuclear and mitochondrial DNA. This

## Table 1. — Comparison of general clinical data.

<table>
<thead>
<tr>
<th>Items</th>
<th>Test group (n = 84)</th>
<th>Control group (n = 31)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>31.55 ± 5.00</td>
<td>27.90 ± 5.87</td>
<td>0.122</td>
</tr>
<tr>
<td>Gestational age (days)</td>
<td>51.10 ± 11.01</td>
<td>56.0 ± 7.13</td>
<td>0.254</td>
</tr>
<tr>
<td>Number of previous abortions</td>
<td>3.57 ± 0.66</td>
<td>3.24 ± 0.47</td>
<td>0.196</td>
</tr>
</tbody>
</table>

## Table 2. — fFN results and pregnancy outcome in two groups.

<table>
<thead>
<tr>
<th>fFN test result</th>
<th>Abortion ratio in the test group</th>
<th>Abortion ratio in the control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>29.17 (14/48)</td>
<td>25.00 (1/4)</td>
</tr>
<tr>
<td>Negative</td>
<td>8.33 (3/36)</td>
<td>7.41 (2/27)</td>
</tr>
</tbody>
</table>

## Table 3. — Sensitivity and specificity in prediction of early abortion in fFN-positive pregnant women.

<table>
<thead>
<tr>
<th>Group</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive predictive value (%)</th>
<th>Negative predictive value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test group</td>
<td>82.35 (14/17)</td>
<td>49.25 (33/67)</td>
<td>29.17 (14/48)</td>
<td>91.67 (33/36)</td>
</tr>
<tr>
<td>Control group</td>
<td>33.33 (1/3)</td>
<td>89.29 (25/28)</td>
<td>25.00 (1/4)</td>
<td>92.59 (25/27)</td>
</tr>
</tbody>
</table>

## Table 4. — The pregnancy outcome, age, and number of previous abortions in patients with recurrent spontaneous abortion.

<table>
<thead>
<tr>
<th>Items</th>
<th>Number (n)</th>
<th>Abortion ratio (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≤ 35 (years)</td>
<td>70</td>
<td>18.57 (13/70)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Age &gt; 35 (years)</td>
<td>14</td>
<td>28.57 (4/14)</td>
<td></td>
</tr>
<tr>
<td>Number of previous abortions ≤ 2</td>
<td>73</td>
<td>19.18 (14/73)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Number of previous abortions &gt; 2</td>
<td>11</td>
<td>27.27 (3/11)</td>
<td></td>
</tr>
</tbody>
</table>

**Prediction of abortion in fFN (+) patients**

The sensitivity, specificity, and positive and negative predictive values in the prediction of abortion for the fFN (+) early pregnancy group with RSA were 82.35%, 49.25%, 29.17%, and 92.67%, respectively. Those for the normal early pregnancy group were 33.33%, 89.29%, 33.33%, and 92.59%, respectively, as shown in Table 3.

**Relationship between the pregnancy outcome and age and number of previous abortions in patients with RSA**

After a systematic examination of the cause of spontaneous abortion and treatment for the RSA group, no statistically significant difference was found between the incidence of abortion in pregnant women with RSA aged ≤ 35 years and > 35 years (p > 0.05, 18.57% vs. 28.57%, respectively). No statistically significant difference was also observed between the incidences of abortion in pregnant women with two previous abortions and in pregnant women with more than two previous abortions (p > 0.05, 19.18% vs. 27.27%, respectively; Table 4).
process affects meiosis and chromosome assortment, resulting in chromosomal abnormalities in the spermatozoon, ovum, or embryo, as well as increasing the ratio of clinical spontaneous abortions [18-21].

In the present study, the analysis of the age and number of previous abortions of pregnant women showed that after the systematic examination of the cause of abortion and comprehensive treatment of patients with RSA, the abortion ratio of the test group was 18.57% in pregnant women aged ≤ 35 years and 28.57% in pregnant women aged > 35 years, for which no statistically significant difference was found. However, the findings show that the abortion ratio in pregnant women aged > 35 years significantly increased. The incidence of abortion in pregnant women with two previous abortions was 19.18% in pregnant women with two previous abortions and 27.27% for those with more than two previous abortions, suggesting that the risk of abortion slightly increases with age and number of abortions, which is consistent with the findings of previous studies [22].

Acknowledgements

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Microdose flare-up vs. flexible-multidose GnRH antagonist protocols for poor responder patients who underwent ICSI

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Summary

Purpose: To compare the performance of microdose flare-up (MF) and flexible-multidose gonadotropin-releasing hormone (GnRH) antagonist protocols in poor responder patients who underwent intracytoplasmic sperm injection (ICSI). Materials and Methods: One hundred and twelve consecutive patients (217 cycles) suspected to have poor ovarian response were enrolled. Group 1 (MF GnRH agonist group) constituted 64 patients (135 cycles) who underwent MF GnRH agonist protocol. Group 2 (flexible-multidose GnRH antagonist group) constituted 48 patients (82 cycles) who underwent flexible-multidose GnRH antagonist protocol. Results: The duration of stimulation (d) (11.5 ± 2.1 vs. 10.4 ± 2.7, p < 0.01) and the total dose of gonadotropin used (IU) (5,892.9 ± 1,725.7 vs. 4,367.5 ± 1,582.1, p < 0.05) were significantly lower in Group 2 when compared to Group 1. The numbers of retrieved oocyte-cumulus complexes (4.5 ± 3.6 vs. 5.9 ± 4.9, p < 0.05), metaphase II oocytes (3.6 ± 3.1 vs. 4.9 ± 4.2, p < 0.05), two pronucleated oocytes (2.6 ± 3.2 vs. 4.0 ± 3.4, p < 0.05), the number of available embryos at day 3 (2.6 ± 2.2 vs. 4.2 ± 3.2, p < 0.05) and the rate of embryos with ≥7 blastomeres and < 10% fragmentation at day 3 (35.9% vs. 65.1%, p < 0.05) were significantly lower in Group 1 when compared to Group 2. The number of embryos transferred (2.2 ± 1.3 vs. 2.4 ± 0.9), the clinical pregnancy per embryo transfer (16.3% vs. 25.8%), and the implantation rate (8.6% vs. 12.2%) were comparable between groups. Conclusions: Although the flexible-multidose GnRH antagonist protocol produced better oocyte and embryo parameters, the clinical pregnancy rate and the implantation rates were comparable between the flexible-multidose GnRH antagonist and MF protocols in poor responder patients.

Key words: Microdose flare-up; Poor responder; GnRH antagonist; IVF.

Introduction

There is strong evidence that ovarian response is one of the most important prognostic factors for in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) success. Poor ovarian response is associated with a high cancellation rate and low pregnancy rates [1]. However, the debate surrounding which stimulation protocol should be preferred in poor responders is still ongoing. A variety of stimulation regimens have been used, including the use of high doses of gonadotropins, supplementation with exogenous luteinizing hormone (LH), decreased gonadotropin releasing hormone (GnRH) agonist doses, flare regimes, the use of growth hormone or growth hormone-releasing factor, transdermal testosterone, aromatase inhibitors, GnRH antagonists, and microdose flare regimes [2-6].

The microdose flare-up (MF) protocol is one of the stimulation protocols used in poor ovarian responders. The flare effect induced by low-dose GnRH agonist administration in the early follicular phase enhances ovarian response to the subsequent administration of high-dose exogenous gonadotropins. GnRH antagonist protocols are another alternative stimulation protocol for poor responders [7,8]. GnRH antagonists do not suppress endogenous gonadotropin secretion at the stage of follicular recruitment and may increase the ovarian response in patients with diminished ovarian reserve to exogenous gonadotrophins [9].

In this study, the aim was to compare the performance of MF GnRH agonist and flexible-multidose GnRH antagonist protocols in poor responder patients who underwent ICSI.

Materials and Methods

One hundred and twelve consecutive patients (217 cycles) suspected to have poor ovarian response were enrolled from a computerized IVF database during the time period from 2002 to December 2012. Inclusion criteria were: (1) bilateral antral follicle count less than 6; (2) patients who underwent a flexible-multidose GnRH antagonist cycle or MF GnRH agonist cycle; (3) fresh ICSI cycles; (4) cycles in which ejaculate sperm used for ICSI. Assessment of antral follicle count was performed in the early follicular phase without any preceding medical treatment one to three months before the scheduled COH cycle. The total number of follicles in both ovaries, each measuring two to nine mm in diameter at transvaginal ultrasound, was defined as the antral follicle count. The author divided these cycles into two groups according to the pituitary suppression protocol employed. Group 1 (MF GnRH agonist group) constituted 64 patients (135 cycles) who underwent MF GnRH agonist protocol. Group 2 (flexible-multidose GnRH antagonist group) constituted 48 patients (82 cycles) who underwent flexible-multidose GnRH antagonist protocol.

Group 1 (MF GnRH agonist group) patients underwent controlled ovarian hyperstimulation using the microdose leuprolide...
The baseline characteristics of the microdose flare-up protocol (MF) and the flexible-multidose GnRH antagonist protocol.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I (MF)</th>
<th>Group II (GnRH antagonist)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>64</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>No. of cycles</td>
<td>135</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>Rate of first ICSI attempt (%)</td>
<td>47.4</td>
<td>58.5</td>
<td>NS</td>
</tr>
<tr>
<td>No. of canceled cycles (n, %)</td>
<td>31 (23.0)</td>
<td>16 (19.95)</td>
<td>NS</td>
</tr>
<tr>
<td>Female age (y)</td>
<td>35.9 ± 4.3</td>
<td>35.4 ± 4.9</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.8 ± 4.1</td>
<td>26.2 ± 3.9</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of infertility (m)</td>
<td>117.8 ± 81.1</td>
<td>114.6 ± 88.0</td>
<td>NS</td>
</tr>
<tr>
<td>No. of antral follicle count</td>
<td>3.3 ± 1.5</td>
<td>3.5 ± 1.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS: Non-significant

doctor's preference.

The criterion for hCG administration was the presence of three or more follicles exceeding 17 mm in diameter. Oocyte retrieval was carried out under local anesthesia using vaginal ultrasound-guided puncture of follicles 36 hours after hCG administration. Standard procedures were carried out for gamete-embryo handling and cleavage-stage embryo or blastocyst (day 5) embryo transfer was performed under abdominal ultrasonography guidance in all cases using a soft catheter. The luteal phase was supported by daily vaginal progesterone suppositories starting one day after oocyte pick-up.

Clinical pregnancy was defined as the presence of an intrauterine gestational sac by transvaginal ultrasonography. Symptomatic patients with moderate or severe ovarian hyperstimulation syndrome (OHSS) were hospitalized [12].

The statistical analyses were performed using Statistics Package for Social Sciences version 17.0. The chi-squared and Fisher exact tests were used to analyze nominal variables in the form of frequency tables. Normally distributed (Kolmogorov-Smirnov test) parametric variables were tested by student t test. Non-normally distributed metric variables were analyzed by Mann-Whitney U test, and p values of < 0.05 were considered statistically significant. Values were expressed as mean ± SD, unless stated otherwise. The Institutional Review Board of the university approved the study protocol.

Results

Both groups were comparable regarding the women's age, BMI, and the duration of infertility (Table 1). The duration of stimulation (d) (11.5 ± 2.1 vs. 10.4 ± 2.7, p < 0.01) and the total dose of gonadotropin used (IU) (5,892.9 ± 1,725.7 vs. 4,367.5 ± 1,582.1, p < 0.05) were significantly lower in Group 2 when compared to Group 1 (Table 2).

The numbers of retrieved oocyte-cumulus complexes (4.5 ± 3.6 vs. 5.9 ± 4.9, p < 0.05), metaphase II oocytes (3.6 ± 3.1 vs. 4.9 ± 4.2, p < 0.05), two pronucleated oocytes (2.6 ± 2.3 vs. 4.0 ± 3.4, p < 0.05), the number of available embryos at day 3 (2.6 ± 2.2 vs. 4.2 ± 3.2, p < 0.05), and the rate of embryos with ≥ seven blastomeres and < 10% fragmentation at day 3 (35.9% vs. 65.1%, p < 0.05) were significantly lower in Group 1 when compared to Group 2 (Table 2).

The number of embryos transferred (2.2 ± 1.3 vs. 2.4 ± 0.9), the clinical pregnancy per embryo transfer (16.3% vs. 25.8%), and the implantation rate (8.6% vs. 12.2%) were comparable between groups (Table 3).

Discussion

In the current study, although the duration of stimulation (d) (11.5±2.1 vs. 10.4±2.7, p < 0.01) and the total dose of gonadotropin used (IU) (5,892.9 ± 1,725.7 vs. 4,367.5 ± 1,582.1, p < 0.05) were significantly lower in the GnRH antagonist group when compared to MF group (Table 2), the numbers of retrieved oocyte-cumulus complexes (4.5 ± 3.6 vs. 5.9 ± 4.9, p < 0.05), metaphase II oocytes (3.6 ± 3.1 vs. 4.9 ± 4.2, p < 0.05), two pronucleated oocytes (2.6 ± 2.3 vs. 4.0 ± 3.4, p < 0.05), the number of available embryos at day 3 (2.6 ± 2.2 vs. 4.2 ± 3.2, p < 0.05), and the rate of embryos with ≥ seven blastomeres and < 10% fragmentation at day 3 (35.9% vs. 65.1%, p < 0.05) were significantly lower in Group 1 when compared to Group 2 (Table 2).

The number of embryos transferred (2.2 ± 1.3 vs. 2.4 ± 0.9), the clinical pregnancy per embryo transfer (16.3% vs. 25.8%), and the implantation rate (8.6% vs. 12.2%) were comparable between groups (Table 3).
65.1%, \( p < 0.05 \) were significantly higher in the GnRH antagonist group when compared to the MF group (Table 2). However, the clinical pregnancy and implantation rates were comparable between groups. According to the current study, the use of GnRH antagonist may have a possible advantage with regards to the number of oocytes, the number of embryos available at day 3, and the embryo quality when compared to the MF protocol in poor responders. However, this positive effect did not translate into increased clinical pregnancy and implantation rates in the current study.

Scott and Navot [13] first reported the use of the MF agonist protocol in poor ovarian responders (34 patients). The hypothesis was that the flare effect induced by low-dose GnRH agonist administration in the early follicular phase enhances ovarian response to the subsequent administration of high-dose exogenous gonadotropins. They noted a higher number of retrieved oocytes, a lower cancellation rate, and higher pregnancy rates in patients receiving the MF protocol. After this report, Schoolcraft et al. [14], Surrey et al. [15] and Detti et al. [16] reported similar results.

The hypothesis for the usage of GnRH antagonists in the poor ovarian response is that the GnRH antagonists do not suppress endogenous gonadotrophin secretion at the stage of follicular recruitment and may increase the ovarian response in patients with diminished ovarian reserve to exogenous gonadotrophins. Cheung et al. [17] compared the GnRH luteal long protocol (31 patients) with GnRH antagonist fixed multi-dose protocol (32 patients) in poor ovarian responders. There were no significant differences in the cycle cancellation rates, duration of stimulation, consumption of gonadotrophins, and mean numbers of mature follicles, oocytes, and embryos obtained. The implantation rates were similar, but the number of embryos transferred was significantly higher for the antagonist group (2.3 ± 0.6 vs. 1.5 ± 0.8, \( p = 0.01 \)). The pregnancy rates were also higher in the antagonist group, but the difference was not statistically significant.

In a recently published meta-analysis (14 studies included), Pu et al. [18] compared the performance of GnRH antagonist protocols with GnRH agonist protocols in poor ovarian responders. They reported that GnRH antagonist protocols resulted in a statistically significant lower duration of stimulation compared with GnRH agonist protocols, but there was no significant difference in the number of oocytes retrieved or the number of mature oocytes retrieved. Moreover, no significant difference was found in the cycle cancellation rate (odd ratio (OR): 1.01, 95% CI:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I (MF)</th>
<th>Group II (GnRH antagonist)</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of stimulation (d)</td>
<td>11.5 ± 2.1</td>
<td>10.4±2.7</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Total dose of FSH used (IU)</td>
<td>5,892.9 ± 1,725.7</td>
<td>4,367.5 ± 1,582.1</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>( E_2 ) level on the day of hCG administration (pg/mL)</td>
<td>1,334.8 ± 952.2</td>
<td>1,310.3 ± 899.6</td>
<td>NS</td>
</tr>
<tr>
<td>No. of follicles &gt;17 mm in diameter at hCG administration</td>
<td>2.1 ± 1.3</td>
<td>2.2 ± 1.7</td>
<td>NS</td>
</tr>
<tr>
<td>No. of follicles 15–17 mm in diameter at hCG administration</td>
<td>1.5 ± 1.4</td>
<td>1.5 ± 1.7</td>
<td>NS</td>
</tr>
<tr>
<td>No. of follicles 10–14 mm in diameter at hCG administration</td>
<td>2.7 ± 2.6</td>
<td>2.5 ± 3.9</td>
<td>NS</td>
</tr>
<tr>
<td>Endometrial thickness at hCG administration (mm)</td>
<td>9.8 ± 2.6</td>
<td>10.2 ± 2.0</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS: Non significant
vs. 4,200 ± 775, noted that the total gonadotropin used (IU) (3,675 ± 748) was significantly higher in the GnRH antagonist group when compared to MF group. The number of metaphase II oocytes retrieved was significantly lower in GnRH antagonist protocol (4.3 ± 2.1 vs. 3.1 ± 1.1, p < 0.05). They also noted that although the clinical pregnancy rates (28.6% vs. 15%) were comparable between groups, the implantation rates were significantly higher in the MF group (22.1% vs. 11.0%, p < 0.05).

Kahraman et al. recently compared the efficacy of microdose GnRH agonist flare-up (21 patients) and multiple dose GnRH antagonist protocols (21 patients) in patients who have a poor response to a long luteal GnRH agonist protocol. They noted that the mean serum E2 concentration on the day of hCG administration was significantly higher in the microdose GnRH agonist group than in the GnRH antagonist group (1,904.8 ± 768.2 vs. 1,362.5 ± 587.4 pg/ml). The clinical pregnancy rate per started cycle of microdose GnRH agonist and GnRH antagonist groups were 14.2% and 9.5%, respectively (p > 0.05). There were no statistically significant differences in the other ovulation induction characteristics, fertilization, and implantation rates.

Wang et al. [20] in 2008 compared the outcomes achieved by GnRH antagonist (65 patients) and MF (58 patients) in IVF-ET for patients with poor ovarian responses. They noted the total amount of gonadotropin used, the numbers of retrieved oocytes, and the number of embryos transferred were the same between groups. However, the clinical pregnancy rates were comparable between groups. The cycle cancellation rate was lower in the GnRH antagonist when compared to MF groups.

There is no consensus on the definition of poor responders and the test to diagnose it. The basal FSH, E2, inhibit B measurements on day 3 of menstruation, a history of poor ovarian response to controlled ovarian hyperstimulation, anti-Müllerian hormone, ovarian volume measures, and antral follicle count are the most commonly used tests to predict poor ovarian response [21]. Antral follicle count is performed by transvaginal ultrasonography in the early follicular phase and it is considered to have the best discriminating potential for a poor ovarian response compared to the total ovarian volume and basal serum levels of FSH, E2, and inhibit B on day 3 of the cycle [22]. Therefore, the authors only used antral follicle count to predict poor ovarian response in the current study. There is also no clear consensus in the literature on the cut of value for antral follicles count to predict poor ovarian response. However, the majority of the physicians agreed that an antral follicles count of less than six at both ovaries should be considered as a predictor of a poor response to IVF/ICSI.

In conclusion, the current study noted that although flexible-multidose GnRH antagonist protocol produced better oocyte and embryo parameters, the clinical pregnancy rate and the implantation rates were comparable between flexible-multidose GnRH antagonist protocol and MF protocols in poor responder patients.

References

Microdose flare-up vs. flexible-multidose GnRH antagonist protocols for poor responder patients who underwent ICSI


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Computerized in vivo classification of methylene blue stained fallopian tube mucosal damage: preliminary results

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Summary
Objective: Fertiloscopy is a simple minimal invasive method which allows salpingoscopy and microsalpingoscopy in order to examine the mucosa of the fallopian tubes of patients with unexplained infertility. Infectious tubal damage is a common cause of tubal infertility. In 1998 it was demonstrated that nuclear staining of cellular nuclei during microsalpingoscopy with methylene blue provides a simple in vivo method to evaluate cellular damage of the tubal epithelium. The purpose of this study was to introduce and statistically test a new computerized method to objectively evaluate the extent of tubal damage. Design of Retrospective Study: Cooperation of two Departments of Gynecology and Obstetrics (Krankenanstalt Rudolfstiftung, Vienna, Austria and CRES Center, Hôpital Natecia, Lyon, France) with the University of Art and Design, Linz, Austria and University Hospital, Vienna, Austria. Materials and Methods: Microsalpingoscopic images from ten female patients, aged between 18 and 45 years with primary infertility, showing stained nuclei in damaged intrafallopian tubal epithelium were provided by Antoine Watrelot, CRES Center, Hôpital Natecia, Lyon, France. These images were evaluated by an experienced medical expert staff examiner and a computerized standard method called cross-correlation and template matching. The obtained numbers of nuclear stainings were statistically evaluated. Results: Computerized evaluation of nuclear staining of damaged intrafallopian epithelial cells in female patients with infertility obtains similar but more reproducible results compared to manual evaluation \( p = 0.007 \). Conclusion: Normalized cross-correlation can be used to measure tubal damage diagnosed by in vivo methylene blue dyeing during microsalpingoscopy and might facilitate the decision for in vitro fertilisation in patients with unclear unexplained infertility in further studies.

Key words: Infertility; Classification; Image processing; Fertiloscopy; Microsalpingoscopy; Diagnostic Tool; Methylene blue.

Introduction
Hysterosalpingography (HSG) is often used as a diagnostic tool in the workup of female infertility, but studies \([1, 2]\) show low detection rates for tubal pathologies in respect of peritubal adhesions and the grade of inflammatory damaged tubal mucosa. Extrinsic infectious tubal damage, often induced by Chlamydia trachomatis, Neisseria gonorrhoea or multibacterial infections represent a common cause of tubal infertility or repeated tubal pregnancies \([1, 3]\). Until now most of the research with infectious agents has been conducted in epithelial cell lines (e.g. Chlamydia trachomatis in HEp-2 cells and HeLa-229) or in mice \([4]\).

However, greater attention needs to be paid to methods for characterizing infectious in vivo changes to detect tubal infertility or prevent ectopic intrafallopian pregnancies.

Marconi and Quintana demonstrated in 1998 that dye staining of cellular nuclei during microsalpingoscopy with methylene blue provides a simple in vivo method to evaluate cellular damage of the tubal epithelium. Besides the presence of adhesions, it was mainly the dye-stained nuclei of damaged cells in the fallopian tubal mucosa which showed a high correlation with infertility rates \([2]\).

Compared to fertiloscopy, laparoscopy provides another diagnostic and therapeutic possibility to examine unexplained infertility \([5]\). However, fertiloscopy is an easier and less invasive procedure \([6]\). During the last decades, fertiloscopy has been established and has enabled microsalpingoscopy and tubal reconstructive therapy by transvaginal pelvic endoscopy \([7, 8]\).

The object of the present study was to design a simple computerized image processing system of methylene blue stained tubal areas obtained by fertiloscopy to allow a uniform and objective classification of intratubal mucosal damage.

Materials and Methods
Chromopertubation is a standard procedure during laparoscopy and fertiloscopy and is associated with minimal complications. \([9]\) For microsalpingoscopy under fertiloscopy, a rigid endoscope (2.9 mm diameter, with 30 degree lens) type: 26120 BHA, was used. By increasing the magnifying power to 60-fold, nuclear dye staining in damaged tubal epithelial cells can be observed. All fertiloscopy procedures were performed by using two special single-use trocars.

Images from ten patients with stained nuclei in damaged intrafallopian tubal epithelium were provided by Antoine Watrelot, CRES Center, Hôpital Natecia, Lyon, France. Cell nuclei in examined tubal epithelium were stained with 20 ml of methylene blue in vivo.

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dissolved in saline solution (NaCl 10%) by injection through a cervical cannula during fertiloscopy. For better visibility and to wash away excessive dye, saline solution was insufflated through the irrigation sheath of the endoscope used to perform salpingoscopy [2].

These digital color images were then processed with a software the authors developed for methylene blue stained cell recognition. The implemented method was based on template matching, which is a standard digital image processing [10] method to localize a known template in unknown samples. In the present application, the known template was an image clip of a single blue stained cell, which represented typical characteristics of an infectious tubal damage (shape, color, brightness, color of the area surrounding the cell with nuclear staining), as shown in Figure 1.

The authors’ software localizes occurrences of several predefined templates, illustrated in Figure 2, and counts the number in all images per subject. The number of detected methylene blue stained cells was then compared with the number of cells counted by an experienced medical expert staff examiner.

Sharp margined and homogenous stained cells were selected as templates to be counted. Predefined templates used in the present matching procedure in this classification system are shown in Figure 2.

Since the processed images were collected in the prior ten years, informed consent for our retrospective computerized evaluation of the microscopic images sampled during fertiloscopy procedures was not obtained.

For statistical analysis, these images were each evaluated manually (by eye) and under computerized analysis, two times. For each patient, the arithmetic mean and the absolute value of the difference of the two computerized and the two manual counts were calculated. A Pearson correlation coefficient between these mean values and a Wilcoxon signed-rank test for the obtained differences were then performed. Results were considered statistically significant at two-tailed p values < 0.05.

Template matching

Template matching is a standard digital image processing method [10] to localize a known template in unknown samples. The method is used for counting the number of occurrences of several predefined templates in a series of image samples per subject. Since the brightness varies across sample images due to the photo-optical conditions of different camera systems, a normalized cross-correlation (NCC) function as a measure of match is applied. The NCC is calculated for each pixel in the sample image \(i\) with size \(M \times N\) according to the template \(t\) with size \(U \times V\):

\[
NCC(x, y) = \frac{\sum (|i(x + u, y + v) - t(x + u, y + v)|^2)}{\sqrt{\sum (|i(x + u, y + v) - \bar{i}|^2) \sum (|t(x + u, y + v) - \bar{t}|^2)}}
\]

whereby \(x = 0, 1, 2, ..., M-1\), \(y = 0, 1, 2, ..., N-1\), \(u = 0, 1, 2, ..., U-1\), \(v = 0, 1, 2, ..., V-1\), \(\bar{i}\) represents the average of \(i\) and \(\bar{t}\) represents the average of \(t\) at the current location of \(t\) [11]. Figure 3 illustrates the NCC result for a given sample and its template image.

Unprocessed color images and templates were converted into the hue saturation brightness (HSB) color space as a preprocessing step. Template matching was then performed on the brightness channel only. The authors applied the template matching method outlined by Bradski [11] as implemented in OpenCV (Open Source

Figure 1. — The left image (A) shows an unprocessed image sample of a fallopian tube mucosa with methylene blue nuclear staining in vivo, in 60-fold magnification. The green rectangle highlights a single stained cell which is used as search template for the center image (B). The search result is illustrated in the image on the right (C). All occurrences of a stained cell are highlighted with a green rectangle.

Figure 2. — The four images illustrate the criteria the authors defined for selecting the templates on the fallopian tube mucosa. Blue colored spots with sharp margin, round or oval-shaped, and with homogenous staining were counted in the pictures of inflamed fallopian tube mucosa.

Figure 3. — The left image (A) shows the unprocessed sample with three blue stained cells. The center image is the template image to search for in image A. Image C shows the NCC result, which denotes the similarity with the template at the position of each pixel in the sample image. Bright regions indicate a high probability for a template match while dark regions show a high difference to the template.
Computer Vision is a library of programming functions for real time computer vision) according to Rodgers and Nicewander [12].

In order to separate high from low similarity and to allow subsequent counting of similar regions, a threshold is applied to each pixel: the NCC result is converted to a binary image to facilitate the quantification of stained cells as shown in Figure 4. The image is segmented into two regions indicating either a match or no match with the template by applying

\[
b(x, y) = \begin{cases} 
1, & \text{ncc}(x, y) > th \\
0, & \text{ncc}(x, y) \leq th
\end{cases}
\]

where \(th\) is the predefined threshold (0.68 in our case) and the result \(b\) denotes the binary result. Applying the threshold results in a binary image consisting of either 0 (no template match) or 1 (template match).

The authors use an empirically evaluated threshold (0.68) to indicate template matches for two reasons: First of all, the rate of false positive results was reduced when only high probabilities were considered as a match. False negative results were compensated by the use of multiple different templates. Secondly, a higher threshold results in fewer connected regions if the distance of two distinct matches is very small. This is because the probability of an actual match decreases from the center of the comparison region to its boundary.

As mentioned above, multiple templates were used for the identification of stained cell localization. To obtain the final result, all template matching results were merged by

\[
r(x, y) = h_1(x, y) \cup h_2(x, y) \cup \ldots \cup h_n(x, y)
\]

whereby \(h_i \equiv b_i\) denote all \(n\) binary template matching results and \(r\) denotes the merged output. The union operator corresponds to the logical OR function, therefore same regions found by several templates were counted only once and regions found by one template only were considered as well.
As the last step, all localized templates of the result image \( r \) were counted. In order to distinguish distinct regions, a border following the method as implemented in OpenCV after Suzuki et al. [13] was applied.

The number of each, of the two counts obtained by the medical expert staff examiner were denoted as \( m_1 \) and \( m_2 \) and the numbers obtained by the above described computer image processing method \( c_1 \) and \( c_2 \). For each patient the arithmetic mean \( \bar{c} = \frac{c_1 + c_2}{2} \) resp. \( \bar{m} = \frac{m_1 + m_2}{2} \) and the absolute value of the difference \( d_c = |c_1 - c_2| \) resp. \( d_m = |m_1 - m_2| \) for each of the two computerized and the two manual counts are calculated. A Pearson correlation coefficient between these mean values \( \bar{c} \), \( \bar{m} \) and a Wilcoxon signed-rank test for the obtained differences \( d_c \), \( d_m \) was then performed.

Results

Two different characteristic examples of methylene blue stained fallopian tube mucosae are shown in the second row of Figure 5. The first row shows the blue dotted areas with green margins, allowing a numeric value to be attributed to tubal damage under magnified power = numeric amount factor (NAF).

The counts obtained by computerized analysis resulted in the same number for every image. However, the Wilcoxon signed-rank test for the absolute differences was highly significant \( p = 0.007 \), and this can only be due to the variability in manual counting (Figure 6).

Discussion

Until now only a subjective grading of tubal damage exists with respect to nuclear staining. The present results suggest that computerized classification of methylene blue stained fallopian tube mucosal damage is a useful method to objectively evaluate and measure the extent of tubal destruction, as an additional evaluation during laparoscopy and fertiloscopy.

For image processing, a standard method was used (see above) for counting the methylene blue stained cells in the fallopian tube mucosa. The aim was to develop a simple, easy to learn, reproducible tool to evaluate inflammation, independent of the investigator’s experience.

The present study suggests that the computerized evaluation of nuclear staining of destroyed intrafallopian epithelial cells in female patients with primary infertility obtains similar, but more reproducible results, when compared with manual evaluation.

Admittedly, a possible disadvantage of automated pattern recognition is that it is limited by the quality of the images, because the classification system might not recognize blurred areas.

Concerning the methylene blue, the European Medicines Agency (EMA) has approved methylthioninium chloride Proveblue five mg/ml solution for injection for human intravenous therapy of methaemoglobinaemia. This new methylene blue shows increased purity and is especially free of heavy metals and organic impurities. It should be noted that to date methylthioninium chloride has been also used as a standard dye for chromopertubation in diagnostic gynecology. Fertiloscopy was performed by using two special single-use trocars.

Future studies might evaluate to what extent tubal damage could decrease pregnancy rates, and might facilitate the decision whether to perform in vitro fertilisation (IVF). Furthermore, studies should elucidate the relationship between multiple genital tract infections and especially the immunopathogenesis of the common chlamydia trachomatis infections in women and the development of infertility by the correlation of e.g. HLA determinants subtypes, human genetics, cytokine profiles, chlamydial heat shock protein
60, and infectious loads, as well as exact characterizing of in vivo physiological intratubal cellular changes [14-16].

Of course the present results obtained from images of ten patients only can be regarded as preliminary. However, even in this very small sample of patients the authors obtained a significant result. Since it is well known from power analysis that a significant result in a small sample is associated with a high effect size, this small sample might even valorise the present study.

In summary: cost effective computerized classification of methylene blue stained fallopian tube mucosal damage in combination with the simple operative fertiloscopic technique [17], or with laparoscopy, allowing additional procedures such as adhesiolysis and ovarian drilling in cases of polycystic ovarian syndrome (PCOS) might represent an improvement on HSG, and could be performed as a first line diagnostic and therapeutic tool before IVF procedures [18].

Conclusion

The computerized classification of methylene blue stained fallopian tube mucosal damage is an objective grading tool of tubal destruction and might prevent patients with unexplained or unclear infertility from unnecessary IVF in the future.

References


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Study of Urotensin II gene and serum levels in relation to pre-eclampsia

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²Department of Obstetrics and Gynecology, Faculty of Medicine, Alexandria University, Alexandria (Egypt)

Summary
Objective: To verify the relationship between Urotensin II (UII) gene and serum levels and pre-eclampsia (PE). Study Design: Prospective case control study. Setting: Tertiary Obstetric centre and university hospital. Subjects: A total of 80 pregnant women at their third trimester were included, 30 of which were with mild PE, 30 with severe disease and 20 age- and BMI-matched normotensive pregnant women (controls). Materials and Methods: UII gene polymorphism as well as UII serum levels were assessed and compared in patients vs. control. Results: No difference was seen between the groups in terms of age or parity at the time of recruitment. A statistically significant difference in the Urotensin II genotype frequencies between patients and control groups was found. The mean serum UII, also showed a significant difference between the studied groups, and control group. Comparing the observed and expected values of UII genotype frequencies in mild, severe PE, and in controls, no significant difference was noted in the homo-mutant, the hetero-mutant or the wild genotypes. Conclusions: Elevation of UII in the serum of PE patients could be correlated to the severity and/or progression of the disease. The UII genotype frequencies between patients and control groups showed a significant difference, which implies a potential benefit for UII gene or level in serum as a diagnostic or prognostic indicator in pre-eclampsia.

Key words: Pre-eclampsia; Urotensin II.

Introduction
Pre-eclampsia (PE) is a disease of pregnancy resulting from a maternal physiological response to abnormal placentation. It is a multisystem disorder affecting approximately two to seven percent of all pregnancies in the United Kingdom and is a significant cause of maternal and fetal morbidity and mortality [1]. The onset and clinical course are unpredictable. The disease occurs after the 20th week of gestation and is characterized by: hypertension, proteinuria, and/or edema [2]. It has been suggested that PE might originate from an abnormally shallow endovascular cytotrophoblast invasion in spiral arterioles which may lead to relative placental ischemia and increased inflammatory response [3]. A reliable early marker of PE would permit patient identification and possible prophylaxis if available, or at least predicting / avoiding complications. A large number of tests have been proposed to predict PE, beginning from blood pressure measurement and proteinuria determination, to Doppler ultrasound evaluation and/or blood and urine biochemical markers [4]. Urotensin II (UII) is a cyclic peptide of 11 amino-acids that was initially isolated from fish urophysis and subsequently discovered in mammals including humans [5]. The human isoform was identified in 1998. A cyclic hexapeptide region of the molecule is responsible for the biological activity and is absolutely conserved between species [6,7]. The gene for UI is located on chromosome 1 p36–p32 and encodes a peptide that is considered the most potent endogenous vasoconstrictor discovered to date [8]. The UII receptor, also referred to as the hypocretin receptor, is a G-protein coupled receptor which binds the peptide hormone UII [9]. It was originally isolated as an orphan receptor, expressed in neural and sensory tissues and named GPR14, or sensory epithelial neuropeptide-like receptor (SENR), which is widely expressed in cardiovascular, pulmonary, central nervous, renal, and metabolic systems [10]. UII has emerged as a contributor to cardiovascular physiopathology. [11, 12] Higher circulating levels of U-II have been observed in patients with PE, inferring a possible role for this ligand in this disease [13, 14].

In this study, the role of UII gene and serum levels in the development / progression of PE was evaluated.

Materials and Methods
A total of 80 pregnant women were recruited from the hospital’s outpatient clinic during the period of January 2012 to July 2012 and were subdivided on the basis of presence/severity of PE into three groups, mild PE (n=30), severe PE (n=30), and healthy pregnant women as control (n=20). Full history taking and thorough physical examination was done for all subjects. Those with any past or present history of a medical condition (e.g. chronic hypertension, cardiac disease, diabetes mellitus) were excluded. A full informed consent was taken from all subjects before commencement. The medical ethics committee of the faculty of medicine approved the study design. All enrolled subjects promptly received the appropriate treatment according to the standard protocols. For all subjects, eight ml of venous whole blood were withdrawn, where serum urea and creatinine, and enzymatic activity of alanine amino transferase (ALT) and aspartate amino transferase (AST) were measured using a clinical chemistry analyzer.
Table 1. — Comparison between the studied groups according to age, parity, and gestational age

<table>
<thead>
<tr>
<th>UII Gene</th>
<th>Mild PE (n = 30)</th>
<th>Severe PE (n = 30)</th>
<th>Control (n = 20)</th>
<th>Test of sig.</th>
<th>p1</th>
<th>p2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild</td>
<td>9</td>
<td>30.0</td>
<td>5</td>
<td>16.7</td>
<td>11</td>
<td>55.0</td>
</tr>
<tr>
<td>Hetero</td>
<td>14</td>
<td>46.7</td>
<td>11</td>
<td>36.7</td>
<td>7</td>
<td>35.0</td>
</tr>
<tr>
<td>Homo</td>
<td>7</td>
<td>23.3</td>
<td>14</td>
<td>46.7</td>
<td>2</td>
<td>10.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parity</th>
<th>n</th>
<th>%</th>
<th>n</th>
<th>%</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>14</td>
<td>46.7</td>
<td>11</td>
<td>36.7</td>
<td>6</td>
<td>30.0</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>33.3</td>
<td>8</td>
<td>26.7</td>
<td>9</td>
<td>45.0</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>16.7</td>
<td>5</td>
<td>16.7</td>
<td>4</td>
<td>20.0</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>3.3</td>
<td>3</td>
<td>10.0</td>
<td>1</td>
<td>5.0</td>
</tr>
<tr>
<td>&gt;3</td>
<td>0</td>
<td>0.0</td>
<td>3</td>
<td>10.0</td>
<td>0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gestational age (weeks)</th>
<th>n</th>
<th>%</th>
<th>n</th>
<th>%</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min – Max</td>
<td>34.0 – 38.0</td>
<td>32.0 – 38.0</td>
<td>32.0 – 40.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>36.80 ± 1.10</td>
<td>36.20 ± 1.81</td>
<td>37.15 ± 1.60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>37.0</td>
<td>37.0</td>
<td>37.50</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>UII</th>
<th>p</th>
<th>p1</th>
<th>p2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hetero</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homo</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results

There was no difference in terms of age among the studied groups (mild PE: 27.57 (SD 6.06) years, severe PE group: 29.90 (SD 5.82) years, and control: 28.45 (SD 5.42) years). No difference was shown in terms of parity (mild PE: 0.77 (SD 0.86), severe PE group: 1.33 (SD 1.42), and control group: 1.0 (SD 0.86)) nor regarding gestational age at the time of recruitment (mild PE: 36.80 (SD 1.10) weeks, severe PE group: 36.20 (SD 1.81) weeks, and control group: 37.15 (SD 1.60) weeks) (Table 1).

A statistically significant difference in the UII genotype frequencies between patients and control groups was found. (p = 0.0211) The mild PE patients had a higher frequency of the homo-mutant genotype “CC” than controls (23.3 % vs 20 %), a higher frequency of the hetero-mutant genotype “AC” than controls (46.7 % vs 40 %) and a lower frequency of the wild genotype “AA” than controls (30 % vs 40 %). Meanwhile, patients with severe disease had a higher frequency of the homo-mutant genotype “CC” than controls (50 % vs 20 %), a lower frequency of the hetero-mutant genotype “AC” than controls (33.3 % vs 40 %), and a lower frequency of the wild genotype “AA” than controls (16.7 % vs 40 %). (Table 2, Figure 1)

The mean serum UII, however, showed a significant difference between the studied groups (mild PE: 84.10 (SD 6.81) pg/ml, severe PE group: 180.53 (SD 11.27) pg/ml, and control group: 44.10 (SD 6.46) pg/ml). (Table 2, Figure 2)

Comparing the observed and expected values of UII genotype frequencies in patients with mild, severe PE and in controls, no significant difference was noted whether in the homo-mutant, hetero-mutant or the wild
Study of Urotensin II gene and serum levels in relation to pre-eclampsia

This agrees with Hardy-Weinberg equilibrium model (Tables 3, 4, 5).

Discussion

PE and eclampsia may occur in as many as eight percent of pregnancies and remain a leading cause of maternal and fetal morbidity and mortality [20]. It could be argued that screening for hypertensive disorders should be given a higher priority, than the currently screened for conditions at routine antenatal care visits [21]. The maternal and fetal short- and long-term outcomes, however, remain uncertain, thus advocating the search for a reliable, fairly accurate method for early detection and/or prediction of the disease. High-dose UII eventually lead to a series of clinical symptoms of PE. Therefore, the UII could be used as a serologic indicator of disease progression and severity.

The results of this study suggested that UTII single gene (S89N) polymorphism is related to the development of PE, which may be, according to the authors’ knowledge, the first report on this gene polymorphism’s involvement in the development of hypertension with pregnancy. Further studies are needed to investigate the prevalence of other single nucleotide gene polymorphisms in PE [17, 22].

Moreover, UII was also reported to be a proangiogenic agent and, thus, a potential partner in disease pathogenesis. Balat et al. reported a significant increase in the circulating

Table 3. — The observed and expected values of the genotype frequencies among UII gene in mild PE group.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Observed</th>
<th>Expected</th>
<th>$\chi^2$</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference (wild)</td>
<td>9</td>
<td>p2n 8.5</td>
<td>0.117</td>
<td>0.732</td>
</tr>
<tr>
<td>Heterozygote (hetero)</td>
<td>14</td>
<td>2pqn 14.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variant (homo)</td>
<td>7</td>
<td>q2n 6.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4. — The observed and expected values of the genotype frequencies among UII gene in severe PE group.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Observed</th>
<th>Expected</th>
<th>$\chi^2$</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference (wild)</td>
<td>5</td>
<td>p2n 3.3</td>
<td>1.875</td>
<td>0.171</td>
</tr>
<tr>
<td>Heterozygote (hetero)</td>
<td>10</td>
<td>2pqn 13.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variant (homo)</td>
<td>15</td>
<td>q2n 13.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5. — The observed and expected values of the genotype frequencies among gene in control group

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Observed</th>
<th>Expected</th>
<th>$\chi^2$</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference (wild)</td>
<td>8</td>
<td>p2n 7.2</td>
<td>0.556</td>
<td>0.456</td>
</tr>
<tr>
<td>Heterozygote (hetero)</td>
<td>8</td>
<td>2pqn 9.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variant (homo)</td>
<td>4</td>
<td>q2n 3.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
levels of UII in PE, whereas Cowley et al. reported no differences between PE and normal pregnancy [23, 24].

Despite the last two decades of research on this condition, the ability of clinicians to predict PE prior to the onset of symptoms has not improved remarkably. A serum test that directly predicts an impending need for delivery, allowing targeted prenatal care, could offer huge clinical benefits as delivery is currently the only cure for PE [25]. UII, a potent hypertensive agent, has significantly elevated serum levels in numerous disease conditions, including essential hypertension, atherosclerosis, heart failure, diabetes, renal failure, and metabolic syndrome. As such, serum UII may be a useful biomarker in detecting PE onset or progression and the UII gene receptor is emerging as a promising target for therapeutic intervention [26].


Yayan et al. reported a significant difference between PE patients and control groups regarding serum UII levels [28]. Sakamato et al. concluded that UII in serum increases as pregnancy advances, decreases rapidly after delivery, and its concentration during pregnancy correlates with gestational week, thus confirming that UII is derived mainly from the placenta [29]. Our results also agreed with a report by Tan et al. who pointed out an association between the UTS-II 143 G/A polymorphism and gestational diabetes in pregnant Chinese women. Because PE is frequently associated with gestational diabetes, they hypothesized that the UTS-II 143 G/A polymorphism may be associated with PE [30]. Another study done by Gould PS et al. showed that there is an upregulation of UII receptor in PE that causes in vitro placental release of soluble vascular endothelial growth factor [31]. Dikensoy et al. concluded no significant association between the UTS-II S89N polymorphism and PE [32].

Conclusion
UII gene polymorphism and UII serum level may be among very important biomarkers sharing in the pathogenesis, progression, and severity of PE. All results of current and previous studies confirm a promising role of UIII in detection of severity, or prediction of the disease occurrence. The combined screening for both gene polymorphism and serum levels of UIII in pregnant women at risk of developing the disease would be a real value in the management of such a life-threatening condition. Further research is still needed to verify these results.

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The authors wish to thank Dr. Ahmed Gomaa and Dr. Mona Bakir for their sincere effort during most of the steps of this study.

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References
Study of Urotensin II gene and serum levels in relation to pre-eclampsia


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Effect of gestational weight gain as well as rehabilitation training on postnatal pelvic muscle strength


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Summary

Objective: The current study explored the impact of gestational weight gain on postnatal pelvic muscle strength and the effect of low-frequency electrical stimulation combined with biofeedback training on strength recovery. Materials and Methods: A total of 126 mothers six to eight weeks after term delivery were recruited at Peking University Shenzhen Hospital from August 2010 to July 2011. According to gestational weight gain, they were divided into two groups: the < 15 kg (A) and ≥ 15 kg (B) groups. Pelvic floor muscle fibre strength was determined. Target low-frequency electrical stimulation combined with biofeedback training was conducted. After training, pelvic floor muscle fiber strength was determined again for effect evaluation. Results: Before training, types I and II pelvic floor muscle fiber strength of group B was noticeably lower than that of group A (p < 0.05). After rehabilitation, the pelvic floor muscle strength of both groups significantly increased (p < 0.05). However, types I and II pelvic floor muscle fiber strength of group B was still significantly lower than that of group A (p < 0.05). Conclusion: Gestational weight gain negatively influences pelvic floor muscles. Low-frequency electrical stimulation combined with biofeedback training improves postnatal pelvic floor muscle fiber strength. A less gestational weight increase indicates faster postnatal pelvic muscle strength recovery and a better rehabilitative effect.

Key words: Gestational weight gain; Low-frequency electrical stimulation; Biofeedback; Pelvic floor muscle fiber strength.

Introduction

The pelvic floor is composed of multi-layer muscles and fascias close to the pelvic outlet and responsible for maintaining the functions of pelvic organs [1]. Abnormalities in pelvic floor muscles lead to pelvic floor dysfunction, which has become both a social and health problem worldwide. Urinary incontinence and pelvic organ prolapse are two major manifestations of pelvic floor dysfunction, and pregnancy and childbirth are widely-recognized independent risk factors causing such dysfunction. During pregnancy, because of fetal growth and gradual expansion of the uterus, long-term compression of the pelvic floor persists; consequently, such excessive dragging causes the elongation of the pelvic floor muscles and thereby leads to pelvic tissue relaxation and damage [2-8].

To explore the impact of gestational weight gain on pelvic floor muscles and the effect of low-frequency electrical stimulation, combined with biofeedback training on muscle strength recovery, 126 delivery women were recruited in this study.

Materials and Methods

Patients

A total of 126 women for doctors’ office visit six to eight weeks after term delivery at Peking University Shenzhen Hospital from August 2010 to July 2011 were enrolled. Their ages ranged from 24 to 35 years with an average of 29.33 ± 2.77. Their gestational weight gains ranged from six to 30 kg. According to these gains, the patients were divided into two groups: group A (pregnant weight gain < 15 kg; n = 56) and group B (pregnant weight gain ≥ 15 kg; n = 70). The respective average weight gains of the two groups were 11.21 ± 2.34 kg and 19.01 ± 4.04 kg. The inclusion criteria included full-term delivery, free lochia, normal cognition, no serious medical and surgical disease, and no genitourinary infection.

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Peking University Shenzhen Hospital. All patients signed a written informed consent and accepted low frequency electrical stimulation combined with biofeedback training voluntarily.

Methods

An electromyographic (EMG) probe was placed into the vagina with the other end connected to a PHENIX neuromuscular training apparatus.

Types I and II pelvic floor muscle fiber strength [9] Type I pelvic floor muscle fiber strength refers to the maximal strength when pelvic floor muscle contraction reaches 40% within ten seconds. It was determined based on time of duration of the contraction: zero, one, two, three, four, and five seconds were recorded as levels 0, 1, 2, 3, 4, and 5, respectively. Class II pelvic floor muscle fiber strength refers to the maximal strength when pelvic floor muscle contraction and relaxation reach 70%-90% within ten seconds. It was determined based on the numbers of muscle contraction and relaxation satisfying that criterion: zero, one, two, three, four, and five were respectively recorded as levels 1, 2, 3, 4, and 5.

Low-frequency electrical stimulation combined with biofeedback Low-frequency electrical stimulation parameters were individually designed according to determined pelvic floor muscle strength. Further, training was conducted according to effect combined with biofeedback. The training lasted 20-30 min, two times weekly and ten to 15 times in total.

Statistical analysis

Data were analyzed by SPSS 1.19 software. T-tests were performed to compare the effects of different pregnant weight gains

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on pelvic floor muscle strength, and paired-sample t-tests to evaluate the effect of training. A $p < 0.05$ was considered statistically significant.

**Results**

**Weight effect**

Before training, types I and II pelvic floor muscle fiber strength values of group A were $2.75 \pm 1.68$ and $2.18 \pm 1.45$, whereas those of group B were $1.57 \pm 1.67$ and $1.00 \pm 1.32$, showing significant differences ($p < 0.05$; Table 1).

**Muscle fiber strength before and after training**

The mean pre-training I and II pelvic floor muscle fiber strength values of both groups were $2.10 \pm 1.77$ and $1.52 \pm 1.50$. After training, the values significantly increased to $4.35 \pm 1.08$ and $3.70 \pm 1.40$ (both $p < 0.05$). The results are summarized in Table 2.

**Muscle strength comparison after training**

Types I and II pelvic floor muscle fiber strength values of group A were $4.68 \pm 0.60$ and $4.07 \pm 0.97$, respectively, whereas those of group B were $4.09 \pm 1.28$ and $3.40 \pm 1.62$, respectively. Significant differences were observed ($p < 0.05$; Table 3).

**Discussion**

Pelvic floor muscles support pelvic organs. Levator ani muscle, as a major component of the floor, plays a decisive role. During pregnancy, fetal growth and persisting compression weaken the contractility of pelvic floor muscles, especially levator ani muscle. In such a condition, if body weight increases too much and when levator ani muscular tonus damage surpasses 30% of its maximal contractility, muscular ischemia and degeneration will occur; this change causes pelvic floor tissue relaxation and further leads to pelvic floor dysfunction syndrome [10-14].

Anatomically, with gradual pregnant uterine increases in both size and weight, the pelvis becomes more and more vertical. By the third trimester, it has almost become a vertical organ which directly compresses the pelvic floor [15-19]. To full-term gestation, the average increased weight of pregnant women reaches as high as 12.5 kg, which includes the weight of the fetus, placenta, amniotic fluid, uterus, breast, blood, interstitial fluid, and fat deposition; this increased weight directly or indirectly acts on the pelvic floor [20].

In this study, two groups were divided, taking the gestational weight gain of 15 kg as the dividing line (groups A and B). The average weight gain of group A was $11.21 \pm 2.34$ kg, whereas that of group B was $19.01 \pm 4.04$ kg. As shown in Table 1, types I and II pelvic floor muscle fiber strength of group B was significantly lower than that of group A ($p < 0.05$). This finding shows that a more gestational weight gain indicates more serious muscle damage to the pelvic floor.

Low-frequency electrical stimulation combined with biofeedback training can achieve a better recovery effect on pelvic floor muscles compared with other treatment procedures [21-24]. Therefore, this technique is feasible for postnatal immediate maternal pelvic floor rehabilitation. As shown in Table 2, after training, types I and II pelvic floor muscle fiber strength in all the participants significantly increased. In addition, Table 3 shows that the pelvic floor muscle fiber strength values of group B were significantly lower than those of group A even after training, which suggests that a less gestational weight gain indicates faster pelvic floor muscle strength recovery and a better training effect.

In summary, a more gestational weight gain results in a greater damage to pelvic floor muscles. This type of damage can be cured by effective low frequency electrical stimulation combined with biofeedback training. A less gestational weight gain suggests a more rapid pelvic floor muscle strength recovery, as well as a more effective training outcome.

---

Table 1. — Comparison of the two groups’ maternal pelvic floor muscle strength before rehabilitation.

<table>
<thead>
<tr>
<th>Group</th>
<th>Number</th>
<th>PFMFS I (Mean ± SD)</th>
<th>PFMFS II (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>56</td>
<td>2.75 ± 1.68</td>
<td>2.18 ± 1.45</td>
</tr>
<tr>
<td>B</td>
<td>70</td>
<td>1.57 ± 1.67</td>
<td>1.00 ± 1.32</td>
</tr>
<tr>
<td>t</td>
<td></td>
<td>3.926</td>
<td>4.763</td>
</tr>
<tr>
<td>p</td>
<td></td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

PFMFS: pelvic floor muscle fibers strength.

Table 2. — Comparison of maternal pelvic floor muscle strength before and after rehabilitation.

<table>
<thead>
<tr>
<th>Period</th>
<th>Number</th>
<th>PFMFS I (Mean ± SD)</th>
<th>PFMFS II (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before training</td>
<td>126</td>
<td>2.10 ± 1.77</td>
<td>1.52 ± 1.50</td>
</tr>
<tr>
<td>After training</td>
<td>126</td>
<td>4.35 ± 1.08</td>
<td>3.70 ± 1.40</td>
</tr>
<tr>
<td>t</td>
<td></td>
<td>12.602</td>
<td>12.979</td>
</tr>
<tr>
<td>p</td>
<td></td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
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</table>

PFMFS: Pelvic floor muscle fibers strength.

Table 3. — Comparison of the two groups’ maternal pelvic floor muscle strength after rehabilitation.

<table>
<thead>
<tr>
<th>Group (kg)</th>
<th>Number</th>
<th>PFMFS I (Mean ± SD)</th>
<th>PFMFS II (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>56</td>
<td>4.68 ± 0.60</td>
<td>4.07 ± 0.97</td>
</tr>
<tr>
<td>B</td>
<td>70</td>
<td>4.09 ± 1.28</td>
<td>3.40 ± 1.62</td>
</tr>
<tr>
<td>t</td>
<td></td>
<td>3.419</td>
<td>2.883</td>
</tr>
<tr>
<td>p</td>
<td></td>
<td>0.001</td>
<td>0.005</td>
</tr>
</tbody>
</table>

PFMFS: pelvic floor muscle fibers strength.
References


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Sublingual misoprostol is better for cervical ripening prior to hysteroscopy in post-menopausal women

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Summary

Background: The aim of the present study was to evaluate the efficacy of misoprostol administered sublingually, vaginally or rectally on cervical ripening before hysteroscopic surgery in post-menopausal women. Materials and Methods: Post-menopausal women were randomised to receive either 400 ug of misoprostol, administered sublingually, vaginally or rectally six hours and 12 hours prior to operative hysteroscopy. Results: Patients were randomized to receive receive sublingual (n = 30), rectal (n = 30) or vaginal (n = 30) misoprostol. The control group did not receive misoprostol (n = 30). The four groups were comparable in terms of preoperative cervical width after misoprostol administration. The mean cervical widths for control group was 9.0 ± 1.1 mm and the mean post-treatment cervical widths for the sublingual, vaginal, and rectal groups were 7.1 ± 1.1 mm, 8.9 ± 1.3mm, and 8.6 ± 1.5 mm, respectively. The cervical widths of sublingual group were significantly different from control, vaginal, and rectal groups (p < 0.001). Conclusion: Four hundred micrograms of sublingual misoprostol, 12 and six hours prior to operative hysteroscopy has a significant cervical ripening effect compared with vaginal, rectal, and control groups in post-menopausal women.

Key words: Cervical ripening; Hysteroscopy; Misoprostol.

Introduction

Hysteroscopy is a valuable procedure to the direct study of the uterine cavity. It permits a panoramic view of the uterine cavity and direct biopsy of lesions, but has some limitations, including the occasional need for cervical dilatation. Cervical ripening and dilatation is a critical step in operative hysteroscopy. Complications such as bleeding, cervical tear, and uterine rupture might be related to the difficulties with cervical dilatation. Nulliparous and post-menopausal women are particularly at risk of these complications [1, 2].

Different methods are effective for ripening the cervix: mechanically with osmotic dilators, or balloon catheters, and biochemically with misoprostol or antiprogestins, although prostaglandins are the most commonly used agent for cervical ripening [3].

Cervical ripening with misoprostol before hysteroscopy may facilitate passage of the hysteroscope through the cervix and complications may be avoided or reduced. However the route of administration, optimal dosage is still unclear for misoprostol usage in post-menopausal women [1-3].

To date there have been a few reports that have evaluated the effects of preoperative misoprostol on cervical ripening before hysteroscopic surgery in post-menopausal women [4, 5].

One study found that vaginal misoprostol and estradiol were more effective than placebo for preoperative cervical ripening in post-menopausal women [4]. While the other found no difference between oral misoprostol and placebo [5]. However, there have been no studies comparing different route of administration of misoprostol in post-menopausal women before hysteroscopic surgery.

The aim of our prospective study was to evaluate the effect of different route of administration of misoprostol for cervical ripening before hysteroscopy in post-menopausal women.

Materials and Methods

This prospective study was conducted between October 2011 and September 2012 at the department of Obstetrics and Gynecology at the Derince Education and Research Hospital. The primary outcome measure in this study was the preoperative cervical width after misoprostol administration. Patients who had post-menopausal bleeding were suspected as having intrauterine pathology, such as atrophic endometrium, endometrial polyps, endometrial cancer, endometrial hyperplasia or other endometrial pathologies based on the transvaginal ultrasound were enrolled. All patients who had post-menopausal bleeding were scheduled for hysteroscopic surgery and were admitted to the hospital at the day of surgery. The institutional ethics review committee approved the study, and informed consent was obtained prior to participation of study.

All participants underwent a physical examination, and detailed medical, obstetric, and gynecological histories were obtained. The study included post-menopausal women whose bleeding began at least one year after cessation of their menses. Exclusion criteria included any evidence of a contraindication or allergy to misoprostol, any sign of genital infection, women taking hormonal replacement therapy, bleeding dyscrasias, anticoagulant therapy, transvaginal ultrasound showing adnexal pathology or patients that were not candidates for surgery. Patients were randomly allocated into four groups at the gynecology department to the following treatment regimens. The vaginal, rectal, and sublingual groups received a total 400 ug of misoprostol.
misoprostol (two tablets of 200 ug), and the patients were adminis-
tered the medications vaginally, rectally or sublingually 12 hours
and six hours before surgery. Same doctor performed all of the
hysteroscopic procedures to decrease interobserver variability. Be-
fore the operative hysteroscopy, the operator measured the pre-
operative degree of cervical dilatation by passing Hegar dilators
through the cervix in ascending order starting with a size of two
mm. The size of the largest dilator passed into the inner cervical
ostium without subjective resistance felt by the operator recorded
as the preoperative degree of dilatation. If there was initial resist-
ance with Hegar dilator size of two mm, the result recorded as
zero mm. After the cervical canal was dilated to a Hegar dilator of
size 11 mm, operative hysteroscopy with bipolar electrode was
passed into the uterine cavity with using a ten-mm, 15-degree op-
tical system under anesthesia. A sodium chloride 0.9 % isotonic
solution was used as uterine distension, with an insufflator that
maintains 100–150 mmHg pressure in the uterine cavity. A bipo-
lar resectoscope unit was routinely used for resection of endome-
trial polyps and targeted endometrial biopsies. For haemostasis, a
current of 50 watts was applied. After the operation, the patients
were monitored at the post-anesthesia care unit for a minimum of
one hour and transferred to gynecology unit. After hysteroscopy, the
women were observed for six hours before being sent home. The
primary outcome measure in this study was the preoperative cer-
vical width after misoprostol administration. Statistical analyses
were performed with SPSS software for Windows. Results are ex-
pressed as means ± SD (standard deviation). Study groups were
analysed with one-way ANOVA and post hoc Tukey tests. Ho-
mogeneity of variances were evaluated with Levene test and, p
values < 0.05 were considered statistically significant.

Results

From October 2011 and September 2012, 120 eligible pa-
tients were included in the study. There were 90 women in the study group and 30 women in the control group. The study group were randomized to receive sublingual (n = 30), rectal (n = 30) or vaginal (n = 30) misoprostol. The control group did not receive misoprostol (n = 30). The four groups were comparable in terms of age, body mass index (BMI) and pathology (Table 1).

The mean cervical widths for control group was 9.0 ± 1.1 mm and the mean post-treatment cervical widths for the sublingual, vaginal, and rectal groups were 7.1 ± 1.1 mm, 8.9 ± 1.3 mm, and 8.6 ± 1.5 mm, respectively (Figure 1). These cervical widths were similar between the control, vaginal and rectal groups (p > 0.05), but the cervical widths

| Table 1. — Demographic characteristics of patients in the oral, vaginal, and rectal and control groups. |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Characteristics | Misoprostol, 400-ug doses | | | |
| | Sublingual (30) | Vaginal (30) | Rectal (30) | Control (30) |
| Age, years | 55.7±3.9 | 56.1±3.1 | 56.4±2.9 | 55.5±3.4 | 0.532 |
| BMI (kg/m2) | 23.2±3 | 22.9±2.7 | 23.5±2.5 | 22.7±2.9 | 0.366 |
| Pathologic findings | | | | |
| Atrophic endometritis | 16 (53.3%) | 18 (60 %) | 19 (63.3%) | 17 (56.6%) |
| Endometrial polyp | 6 (20%) | 5 (16.6%) | 3 (10%) | 4 (13.3%) |
| Simple hyperplasia without atypia | 4 (13.3%) | 5 (16.6%) | 5 (16.6%) | 6 (20%) |
| Simple hyperplasia with atypia | 2 (6.6%) | 1(3.3%) | 3 (10%) | 1(3.3%) |
| Complex hyperplasia without atypia | 1(3.3%) | 0 | 0 | 1(3.3%) |
| Complex hyperplasia with atypia | 1(3.3%) | 0 | 0 | 1(3.3%) |

Data are expressed as mean±SD.
of sublingual group were significantly different from control, vaginal, and rectal groups ($p < 0.001$).

Complications during cervical dilatation occurred in three patients. Cervical tearing occurred at the tenaculum site in two patients in the rectal group and one patient in the vaginal group. Cervical lacerations were treated conservatively with close observation without suturing. One patient in the rectal group and one patient in the sublingual group had nausea due to misoprostol side-effects, whereas vomiting or diarrhea was not seen in any of the patients. All patients were discharged after six hours of observation without any complications.

Discussion

This trial shows that 400-ug doses of sublingual misoprostol 12 hours and six hours before outpatient hysteroscopy is effective for cervical ripening compared with vaginal and rectal groups in post-menopausal women. The need for cervical dilatation before hysteroscopy was considerably higher in the control or no treatment group. Cervical ripening is needed to prevent or reduce complications before transcervical procedures [1-4]. In the literature, there are studies that have compared vaginal and oral routes of misoprostol administration, with different results. Waddell et al. found the use of vaginal misoprostol hysteroscopy reduced the pain and the force needed to dilate the cervix [5]. Oppegard et al. studied self-administered vaginal misoprostol and vaginal estradiol prior to operative hysteroscopy, and found a significant cervical ripening effect compared with placebo in post-menopausal women [6]. Ngai et al. failed to demonstrate any beneficial effect for oral misoprostol on cervical ripening in post-menopausal women before hysteroscopy [7].

The different results of the studies can be attributed to some possible factors. The first possible factor is the difference in dosage of misoprostol and the second factor is timing of misoprostol insertion prior to hysteroscopy. The optimal dose and time interval from medication to hysteroscopy vary in literatures. Based on recent studies, 400-ug has been most widely used dose [4, 7]. The time interval before hysteroscopy varied from two to 12 hours for the oral and vaginal routes [6, 7]. The present authors compared the effectiveness of 400 micrograms of sublingual, rectal, and vaginal misoprostols given 12 hours, and six hours before hysteroscopy and found increased ease of cervical dilatation after administration of sublingual misoprostol in post-menopausal women.

The side-effects of misoprostol in this study were lower than in literature [8]. This might be a short time period between misoprostol administration and operation and side-effects were tolerable without need for further treatment.

In conclusion, no study has compared sublingual, rectal, and vaginal routes of misoprostol administration before hysteroscopy in post-menopausal women. The sublingual misoprostol is better than oral and vaginal misoprostol for cervical ripening prior to hysteroscopy in post-menopausal women. This regimen is highly acceptable and easy to use and adverse effects were few. Cervical ripening before hysteroscopy in post-menopausal women should be investigated in large series, and comparisons should be done with different routes of administration in further studies.

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Thermal balloon ablation versus transcervical endometrial resection: evaluation of postoperative pelvic pain in women treated for dysfunctional uterine bleeding

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Summary

Purpose of the study: To evaluate postoperative pain after mini-invasive surgical treatment for dysfunctional uterine bleeding (DUB) with transcervical endometrial resection or thermal ablation balloon. Materials and Methods: A longitudinal observational study, analyzing 47 women affected by DUB who underwent endometrial ablation was conducted. The authors collected evaluation of pelvic pain at one and four hours after intervention and the individual necessity of analgesics. Results: Pelvic pain was higher one and four hours after procedure in thermal balloon ablation group, and patients in the same group required more analgesic rescue dose. There were no complications such as uterine perforation, heavy blood loss or thermal injuries with both the procedures. Conclusion: Thermal balloon ablation appears a more painful procedure than endometrial resection, both in the immediate postsurgical time and 30 days after surgery. Ad hoc anaesthesiologic and analgesic protocol should be adopted to ensure quick recovery and good acceptance of the procedure.

Key words: Transcervical endometrial resection; Thermal balloon ablation; Pelvic pain; Complications; Dysfunctional uterine bleeding.

Introduction

Dysfunctional uterine bleeding (DUB) refers to uncategorized bleeding from the uterus that occurs in the absence of recognizable pelvic pathology, general medical disease, or pregnancy. It reflects a deregulation of the hormonal cyclic stimulation with a chronic unopposed estrogen to the endometrial lining. Most of time bleeding appears suddenly and it is unpredictable. It could be excessively heavy or light and it may be prolonged, frequent, or random. DUB is one of the most common presenting complaints encountered in a Gynecologist’s office and accounts for almost 30% consultations in any busy out-patient clinic. It affects about 20% of women subjected to hysteroscopy and represents a major clinical problem for health economies [1]. The evaluation of women with DUB includes a thorough medical history and physical examination, appropriate laboratory and imaging tests, and consideration of age-related factors [2]. The diagnosis is made only after having excluded organic lesions as polyp, myoma, and endometrial cancer [3-6]. DUB can be managed with medical or surgical treatment because it can result in anemia, impaired quality of life, and psychological distress. Surgery should be considered in these cases in which medical treatment has failed, or when it cannot be tolerated or it is contraindicated. Surgical options could be both radical and conservative. The limit of surgical solution is that it often leads to perform a hysterectomy most of time when it is not needed [7-9]. DUB are estimated to be responsible of over one-third of the hysterectomies annually performed in Europe and North America. Hysterectomy is associated with 100% success in treating heavy menstrual bleeding and a high patient satisfaction up to 95% [10, 11], but it can have complications and rarely operative mortality. For this reason, hysterectomy should be only considered when other treatment options have failed. Conservative treatments consist in eliminating the full thickness of endometrium without removing uterus, which signifies lower procedure-costs and less invasiveness. Nowadays two of the most conservative techniques used are Transcervical endometrial resection (TCER) and thermal balloon ablation (TBA); they both have demonstrated to be cost effective and well-accepted surgical alternatives to hysterectomy in women with DUB [12,13]. TCER was introduced by Neuwirth in 1976 as a conservative surgical technique and it is still effective in the treatment of recurrent menorrhagia, with a success rate of 75-80% at five years. Only 10-12% of women who experienced this treatment required a hysterectomy [14, 15].

The limit of this technique is that it is surgeon-dependent, namely it is a valid technique in a skilled surgeon’s hand; therefore a long training curve is necessary to avoid the incidence of severe complications, such haemorrhage or metabolic effects. Nevertheless, this procedure could be currently used to treat atypical endometrial hyperplasia in young women with high success rate [16]. TBA belongs to the second generation techniques of endometrial ablation, introduced in the late nineties, with the aim of reduc-
ing both difficulties and complications of the first generation procedures. TBA was first described in 1993 and it is reported an overall success rate of 92%–98%, with an amenorrhea state of 22%–68% and a patient’s satisfaction ranging from 57% up to 94% [17-19].

Materials and Methods

The authors conducted a longitudinal observational study and they analyzed the clinical history of 47 women affected by DUB who underwent endometrial ablation between 2010 and 2012 in the Unit of Minimally Invasive Pelvic Surgery and Operative Obstetrics, Department of Women and Children Health, University of Padua (Italy). The inclusion criteria were: recurrent menorrhagia, uterus length less than 12 cm, absence of any organic lesions and/or uterine malformations, and no previous hormonal therapy during the last six months. Women who desired future pregnancy were excluded. The preoperative check-up consisted in Pap smear, transvaginal ultrasound, and hysteroscopy with endometrial biopsy to exclude endometrial malignancies. All patients were free from any clinical or laboratory evidence of hepatic, renal, pulmonary, neurologic, metabolic or cardiovascular diseases. Blood tests such as hemoglobin concentration, serum urea and creatinine, fasting blood sugar, and electrocardiogram were within normal limits. Age, parity, and body mass index (BMI) were recorded. Surgical procedures were performed in the endometrial proliferative phase (7th-10th day of cycle), under mild unconscious sedation with spontaneous breathing. They were all administered fentanyl 0.1 mcg iv and propofol in appropriate doses respectively for induction and maintenance of sedation. The authors collected evaluation of pelvic pain in each patient one and four hours after intervention, using Visual Analogue Scale (VAS), and eventually analgesic therapy requested was recorded. Pelvic pain was considered mild if VAS was between 0 and 3; moderate from 4 to 7, and severe from 8 to 10. Analgesics after the procedure were administered only if requested by the patient. The first-line therapy was paracetamol one gr iv and in patients in whom paracetamol had not been resolutive, the second-line therapy was tramadol 100 mg iv. After 30 days, all patients underwent a gynecological visit during which they were investigated for health, temperature, surgical time, serum urea and creatinine, fasting blood sugar, and electrocardiogram. The patients were then asked about their satisfaction with the procedure and any complications or side effects they had experienced. The data were collected and analyzed using SPSS for Windows, version 19.0.

Results

Among the 47 patients enrolled, 39 (83%) were multiparous and eight (17%) nulliparous. The mean age was 46.5 ± 4.7 years and the mean BMI was 21.5 ± 2.2. The procedure was completed in all 47 patients: 25 (53.2%) were submitted to TCER and 22 (46.8%) to the TBA. Surgical time, as measured from the initial introduction of the resectoscope to its final removal in case of TCER, was 19 ± 3.03 minutes, whereas surgical time with TBA ten minutes according to standard procedure. There were no complications such as uterine perforation, heavy blood loss or thermal injuries in both the procedures. In the group of patient submitted to TCER, VAS score one hour after treatment (VAS-1H) was mild in 14/25 (56%), moderate in 10/25 (40%) and severe in 1/25 (4%). In patient submitted to TBA, the VAS-1H was mild in 4/22 (18.2%), moderate in 12/22 (54.5%) and severe in 6/22 (27.3%). The VAS-1H was statistically different (p<0.05) between the two groups (Table 1).

In the group of patient submitted to TBA, the VAS score four hours after treatment (VAS-4H) was mild in 18/25 (72%), moderate in 7/25 (28%), and severe in 0/25. In patient submitted to TBA, the VAS-4H was mild in 7/22 (31.8%), moderate in 13/22 (59.1%) and severe in 2/22 (9.1%). The VAS-4H was statistically different (p<0.05) between the two groups (Table 1).

Six patients (24%) of the group submitted to TCER and 11 (50%) of the group submitted to TAB requested paracetamol after procedure, with no statistically significant difference. No patients of the group submitted to TCER and 22 (46.8%) to the TBA. Surgical time, as measured from the initial introduction of the resectoscope to its final removal in case of TCER, was 19 ± 3.03 minutes, whereas surgical time with TBA ten minutes according to standard procedure. There were no complications such as uterine perforation, heavy blood loss or thermal injuries in both the procedures. In the group of patient submitted to TCER, VAS score one hour after treatment (VAS-1H) was mild in 14/25 (56%), moderate in 10/25 (40%) and severe in 1/25 (4%). In patient submitted to TBA, the VAS-1H was mild in 4/22 (18.2%), moderate in 12/22 (54.5%) and severe in 6/22 (27.3%). The VAS-1H was statistically different (p<0.05) between the two groups (Table 1).

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Five (22.7%) of the group submitted to TAB requested tramadol in addition to paracetamol after procedure, and this difference was statistically significant ($p < 0.05$) (Table 2).

All patients submitted to TCER and 20 (90.1%) submitted to TAB were discharged within six hours after surgery, while two patients submitted to TAB were dismissed after 24 hours of observation because of abdominal pain.

At gynaecologic control 30 days after procedure, five (20%) patients of TCER group still reported mild pelvic pain associated with heavy menstrual bleeding, while in the TBA group, ten (45.4%) patients reported mild pelvic pain. In TBA group five (22.7%) patients complained for vaginal discharges and six (27.3%) referred symptoms of cystitis, not confirmed at urine culture test. No patient reported fever.

**Discussion**

The main option proposed to women with recurrent menorrhagia in the 1970s and 1980s, was total hysterectomy [7, 8]. In the last three decades the development of new endoscopic technology have led to the introduction of first and second generation endometrial ablation techniques.

Among first generation techniques, the endometrial resection is the gold standard technique [18]. The aim of this procedure is the excision or destruction of endometrium and basal layer in order to prevent tissutal proliferation and menstrual bleeding. Particularly the menses bleeding during the first six months after the treatment develops a progressive reduction, showing that it is an efficacious treatment. Some authors demonstrated the long-term efficacy of endometrial resection up to eight years of follow up, particularly the efficacy become progressively higher with increasing age [20, 21]. The endometrial transcervical resection requires a specific skill, it requires a long learning curve and it shows a moderate rate of intraoperative complications such fluid overload syndrome with hypotoniaemia, water intoxication, cerebral edema and cardiac overload, bowel or bladder thermal damage, and uterine perforation [22]. There are several new devices designed to perform global endometrial ablation without the use of resectoscope. These devices have been developed to reduce operative time, decrease risk of fluid overload syndrome, and to provide a means of performing endometrial ablation without the technical skill required for the use of a resectoscope [23, 24]. The new techniques developed are: the Hydro ThermAblator, a hysteroscopic system of circulating intrauterine heated normal saline [25-29]; NovaSure, which uses radiofrequency electrosurgical energy and thermal balloon ablation (TBA) which uses a heated intrauterine balloon. These new ablation techniques need simple instrumentation, their application is easier and the procedures are rapid; all of these aspects allowed the rapid diffusion of these techniques [30]. Moreover these procedures, thanks to the possibility of using spinal anesthesia, find indication in case of recurrent menorrhagia in women with high anaesthetic risk as cardiovascular and/or autoimmune disease [31]. The thermal balloon endometrial ablation is performed by heating a fluid – filled balloon inside the uterine cavity and using both heat and pressure to disrupt the endometrium [32]. The balloon is filled with normal saline heated at 78-80°C for ten minutes with an internal pressure of 230 mmHg and it produces an endometrial necrosis coagulation thanks to indirect heat transfer from balloon to endometrium.

Many studies in vitro analysed hyperthermic effect on uterine myomas and close myometrium: the myometrial cell necrosis arise until 88% when they are exposed to the temperature of 80°C for ten minutes. Furthermore the intravertine pressure is transmitted to myoma’s vessels with subsequent hypoxia and necrosis [33]. Clearly the high temperature achieved with thermal balloon ablation causes an important pelvic discomfort in patients, therefore clinicians should assure a good analgesic cover both during and after the intervention. Most women treated with TCER, reported a low-moderate pelvic pain often solved within the first hours after surgery while TBA is associated with pelvic pain, vaginal discharge, and urinary symptoms up to one month after the procedure. From the analysis of our data, TBA resulted a more painful technique with a higher VAS score both after one and four hours from the procedure, and patients required more often analgesic rescue dose. Even if TBA could result an easier technique to be performed in contrast with TCER, TBA probably needs a specific anaesthesiologic protocol and more analgesic rescue doses in order to assure good control of postsurgical pain. An advantage of endometrial resection is the possibility, using a resectoscope, of removing some intracavity lesions as polyp or submucous myoma [5], which is impossible with TBA that should be used only when uterine cavity is normal, or when uterine lesions such as polyps or submucosal myomas have already been removed. On the other hand also TCER can be associated with some complications as: hemorrhage, pelvic inflammatory disease, endometritis, first-degree skin burns, hematometra, vaginitis, and cystitis [23]. Otherwise women with abnormal uterine bleeding and high-risk factors for endometrial carcinoma who did not respond to medical treatment may safely undergo endometrial ablation but they must have a preablation biopsy indicating normal endometrium, because persistent hyperplasia unresponsive to hormonal therapy should influence the selection of a hysterectomy [34, 35].

**Conclusion**

Surgical mini-invasive treatment for DUB are proved to be safe and effective. While TBA results easier to perform, it appears a more painful procedure than TCER, both in the immediate postsurgical time and 30 days after surgery. Ad hoc anaesthesiologic and analgesic protocol should be adopted to ensure rapid recovery and good acceptance of the procedure.
Is there any association between mild hypertension and hot flash experience among women?

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Summary

Objective: To determine the association between ambulatory blood pressure (ABP), heart rate, and hot flash (HF) experience among women. Materials and Methods: The authors recruited 110 women aged 22 to 65 years with mild essential hypertension or normotension confirmed by 24-hour ABP monitoring. None of the women had organ damage, inflammatory diseases, on estrogen replacement therapy or any other risk factors. Participants wore an ABP monitor that both records heart rate during 24 hours and noted their awake and sleep times. HF were assessed using an everyday complaint questionnaire that included symptoms associated with menopause. Each participant was asked whether or not she had experienced each symptom during the two weeks before the interview. Results: Fifty-five of the participants (45%) reported having had HF during the two weeks before they completed the questionnaire. The results show that the prevalence of essential hypertension (EH) in the group of women who had HF was significantly higher than the group of women that did not have HF (p = 0.035). The authors also found that hypertensive women had HF more often than normotensive women (p = 0.035), but other parameters including mean awake and sleep systolic BP values, mean awake and sleep diastolic BP values, heart rates, and nocturnal dipping of BP did not differ statistically among the group of women who had HF and the group of women who did not have HF (p > 0.05). Conclusions: These data suggest that the prevalence of EH in the group of women who have HF is significantly higher than the group of women that does not have HF.

Key words: Hot flashes; Hypertension; Ambulatory blood pressure; Heart rate variability; Menopause.

Introduction

During menopausal years, approximately 70% to 80% of women have symptoms and clinical findings due to an estrogen deficiency and symptoms appear after the beginning of the changes in ovarian function. However, cardiovascular diseases, which are associated with a high morbidity and mortality, manifest in the later period of women’s life. [1, 2]. Increased blood pressure is a risk factor for cardiovascular diseases. [3, 4] Furthermore, several studies showed that menopause was associated with increased blood pressure (BP). [5,6] Changes in the sex steroids, endothelin, renin-angiotensin system (RAS), gaining weight, and activation of the sympathetic system have all found to be responsible for this blood pressure changes [7].

Most postmenopausal women experience vasomotor symptoms up to a some degree [8]. Currently, the mechanism of hot flashes (HF) thought to be the result of activation of the sympathetic nervous system, may also be responsible for postmenopausal hypertension (HT) [7, 9].

If there was any association between HF and HT, HF would probably trigger or disclose this association. The authors aimed to investigate whether there is any relationship between HF and HT.

Materials and Methods

A total of 110 women were invited for this study from Zekai Tahir Burak Education and Research Hospital, Gynecology Clinic and Yüksek İhtisas Heart-Education and Research Hospital, Cardiology Clinic between 2008 and 2009. Patient’s mean age was 49.06 ± 9.5 (range 22-65). Exclusion criteria were defined as any systemic disease or cardiovascular disease except mild essential HT which was defined as BP less than 160/100 mmHg and patients who were prescribed hormone replacement or oral contraceptive therapy in the last six months. This project was approved by Local Ethical Review Board and informed consent was taken from all participants.

All personal and medical information including age, education level, illicit drug and alcohol use, cigarette smoking, average coffee and tea consumption per day, past medical history, oral contraceptive use in the last six months, and family history of HT were obtained by a questionnaire. During the same visit, anthropomorphic measurements (weight, height) were recorded. Body mass index (BMI) was calculated as follows: weight (kilograms)/height (meters) [2]. Menopause was defined as the absence of menstrual periods in the last twelve months. Patients who did not have any periods less than twelve months were considered as premenopausal or peri-menopausal. Greene climacteric scale [10] was used for the assessment of vasomotor symptoms occurring in the prior two weeks. Patients’ HF’s or night sweats were scored between 0 - 3 according to severity of their symptoms. (absent, mild, moderate, and severe).

All women’s BP were assessed by measuring 24-hour ambulatory BP (ABP). Left arm was used for BP measuring if they were not left-handed and recording machine was wrapped around the patient’s waist. Patients were instructed not to use left arms during BP measurement and all BP data were delivered to computer after 24-
hour period. During the day, BP recordings were performed every 15 minutes and during night, BP measurements were performed every 30 minutes and mean BP were calculated as all BP measurements divided by total number of recordings. Sleeping and non-sleeping periods were assigned by patients. At least five BP measurements during night and daytime were required in order to be included in the study. Mean BP measurement count was 68.7 ± 11.66. Hypertension was defined as any patient who have been under treatment of HT or whose 24-hour ambulatory mean systolic and diastolic BP were above 130 mmHg and/or 80 mmHg, respectively, or women who had daytime mean BP above 135/85 mmHg or overnight mean BP above 120/70 mmHg (European Society of Hypertension - European Society of Cardiology: ESH-ESC 2007).[11] Patients who were under HT drug therapy stopped treatment before two weeks of this study. Patients who had BP above 160/100 mmHg before or after treatment were also excluded from the study. Absolute dipping was calculated as subtraction of mean overnight systolic BP from mean daytime systolic blood pressure. Relative dipping was calculated as 1 was subtracted from the ratio between the mean overnight systolic BP and mean daytime BP. Patients who had less than 15% decrease of overnight mean BP from mean daytime BP were considered as non-dipper which is also found to be associated with cardiovascular diseases.[12]

Statistical analysis of the study was performed using the SPSS version 11.5. Shapiro Wilk test was used whether continuous variables distributed normally. Descriptive statistics for the continuous variables were expressed as mean ± standard deviation or median (minimum-maximum), for the categorical variables, they were expressed as case count or percentage (%). To determine whether or not differences existed between the groups in age and BMI, student’s t test was employed. For the other parameters including gravity, parity, tea and coffee consumption, and 24-hour BP, Mann-Whitney U test was employed. All p values below 0.05 were considered statistically significant. Pearson’s chi-square test was used for categorical variables.

Results

The socio-demographic data of women are shown on Table 1. Study patients’ age range were between 22 and 65 with a mean of 49 years. Fifty-five of the patients were hypertensive and remaining 55 patients were normotensive. Fifty-four of the patients (49%) were post-menopausal and remaining 56 patients (51%) were pre- or peri-menopausal (55%).

HF were seen in 55.4% of the patients and there was no difference in the mean age who had HF and who did not them (p = 0.092). However, distribution of the age were different between the groups since women who did not have HF were mostly under 45 years and women who had HF were mostly between 45-54 years (p = 0.019).

When severity of the HF were assessed, 45.9% of the women had mild, 34.4% women had moderate, 19.7% of the women had severe HF, and 35.5% of the study participants had night sweats.

There was not any statistical difference between the HF and non-HF group in terms of menopausal state, BMI, education level, occupational state, tea and coffee consumption (p > 0.05).
Is there any association between mild hypertension and hot flash experience among women?

The prevalence of the HT and night sweats were significantly higher in HF group compared to the non-hot-HF (p = 0.035 vs p < 0.001).

Twenty-four hour BP, pulse, and pulse pressure measurements were compared between the HF and non-HF group and none of the parameters compared were statistically different (p > 0.05, Table 2).

Table 3 shows the demographic features of the patients who were grouped according to their HT status. Mean age of the hypertensive patients were significantly higher than the normotensive women (p < 0.001). Post-menopausal state prevalence and BMI of the hypertensive group were significantly higher than normotensive group (p = 0.008 and p = 0.002, respectively).

Table 2. — Comparison of the hot flashes with some of the 24-hour BP, pulse, and pulse pressure measurements

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hot flash (-) (n=49)</th>
<th>Hot flash (+) (n=61)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean systolic BP mmHg</td>
<td>122.3 ± 16.4</td>
<td>126.8 ± 16.5</td>
<td>0.097</td>
</tr>
<tr>
<td>Mean diastolic BP mmHg</td>
<td>77.5 ± 10.6</td>
<td>78.8 ± 11.8</td>
<td>0.630</td>
</tr>
<tr>
<td>Daytime systolic BP mmHg</td>
<td>124.7 ± 15.7</td>
<td>129.9 ± 16.3</td>
<td>0.067</td>
</tr>
<tr>
<td>Daytime diastolic BP mmHg</td>
<td>79.7 ± 10.8</td>
<td>81.8 ± 11.6</td>
<td>0.529</td>
</tr>
<tr>
<td>Overnight systolic BP mmHg</td>
<td>116.2 ± 19.2</td>
<td>118.6 ± 18.6</td>
<td>0.400</td>
</tr>
<tr>
<td>Overnight diastolic BP mmHg</td>
<td>71.4 ± 12.5</td>
<td>71.2 ± 12.2</td>
<td>0.945</td>
</tr>
<tr>
<td>Mean measurement count</td>
<td>70.3 ± 11.8</td>
<td>67.4 ± 11.5</td>
<td>0.108</td>
</tr>
<tr>
<td>Daytime measurement count</td>
<td>53.2 ± 12.7</td>
<td>51.2 ± 11.2</td>
<td>0.164</td>
</tr>
<tr>
<td>Overnight measurement count</td>
<td>16.7 ± 4.7</td>
<td>16.2 ± 4.0</td>
<td>0.779</td>
</tr>
<tr>
<td>Dipping absolute mmHg</td>
<td>9.2 ± 9.4</td>
<td>11.2 ± 10.1</td>
<td>0.204</td>
</tr>
<tr>
<td>Dipping relative %</td>
<td>7.6 ± 7.8</td>
<td>8.9 ± 7.7</td>
<td>0.295</td>
</tr>
<tr>
<td>Mean pulse/min</td>
<td>74.6 ± 9.2</td>
<td>74.7 ± 8.0</td>
<td>0.789</td>
</tr>
<tr>
<td>Daytime pulse/min</td>
<td>77.7 ± 9.9</td>
<td>77.8 ± 8.1</td>
<td>0.754</td>
</tr>
<tr>
<td>Overnight pulse/min</td>
<td>65.4 ± 8.7</td>
<td>66.3 ± 7.8</td>
<td>0.411</td>
</tr>
<tr>
<td>Mean pulse pressure mmHg</td>
<td>44.9 ± 9.5</td>
<td>47.9 ± 11.0</td>
<td>0.127</td>
</tr>
<tr>
<td>Daytime pulse pressure mmHg</td>
<td>45.0 ± 9.6</td>
<td>48.3 ± 11.5</td>
<td>0.133</td>
</tr>
<tr>
<td>Overnight pulse pressure mmHg</td>
<td>44.8 ± 9.8</td>
<td>47.2 ± 11.5</td>
<td>0.254</td>
</tr>
<tr>
<td>Dipper</td>
<td>9 (18.4%)</td>
<td>11 (18.0%)</td>
<td>0.964</td>
</tr>
</tbody>
</table>

Table 3. — Demographic features according to blood pressure status.

<table>
<thead>
<tr>
<th>Variables</th>
<th>HT (-) (n=55)</th>
<th>HT (+) (n=55)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>45.4 ± 9.8</td>
<td>52.7 ± 7.9</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Age groups</td>
<td></td>
<td></td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>&lt; 45 years</td>
<td>22 (40.0%)</td>
<td>9 (16.4%)</td>
<td></td>
</tr>
<tr>
<td>45-54 years</td>
<td>22 (40.0%)</td>
<td>17 (30.9%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 54 years</td>
<td>11 (20.0%)</td>
<td>29 (52.7%)</td>
<td></td>
</tr>
<tr>
<td>Menopausal state</td>
<td></td>
<td></td>
<td>0.008*</td>
</tr>
<tr>
<td>Pre- or peri-menopausal</td>
<td>35 (63.6%)</td>
<td>21 (38.2%)</td>
<td></td>
</tr>
<tr>
<td>Post-menopausal</td>
<td>20 (36.4%)</td>
<td>34 (61.8%)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>27.3 ± 4.4</td>
<td>30.3 ± 5.2</td>
<td>0.002*</td>
</tr>
<tr>
<td>Occupational state</td>
<td></td>
<td></td>
<td>0.119</td>
</tr>
<tr>
<td>Works</td>
<td>29 (52.7%)</td>
<td>37 (67.3%)</td>
<td></td>
</tr>
<tr>
<td>Does not work</td>
<td>26 (47.3%)</td>
<td>18 (32.7%)</td>
<td></td>
</tr>
<tr>
<td>Education level</td>
<td></td>
<td></td>
<td>0.622</td>
</tr>
<tr>
<td>Uneducated</td>
<td>5 (9.1%)</td>
<td>5 (9.1%)</td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>17 (30.9%)</td>
<td>23 (%41.8%)</td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>5 (9.1%)</td>
<td>7 (%12.7%)</td>
<td></td>
</tr>
<tr>
<td>High school</td>
<td>13 (23.6%)</td>
<td>10 (%18.2%)</td>
<td></td>
</tr>
<tr>
<td>University</td>
<td>15 (27.3%)</td>
<td>10 (%18.2%)</td>
<td></td>
</tr>
<tr>
<td>Gravity</td>
<td>3 (0 - 10)</td>
<td>3 (0 - 12)</td>
<td>0.010*</td>
</tr>
<tr>
<td>Parity</td>
<td>2 (0 - 8)</td>
<td>3 (0 - 7)</td>
<td>0.077</td>
</tr>
<tr>
<td>Smoking</td>
<td>16 (29.1%)</td>
<td>11 (20.0%)</td>
<td>0.268</td>
</tr>
<tr>
<td>HF 25 (45.5%)</td>
<td>36 (65.5%)</td>
<td>0.035*</td>
<td></td>
</tr>
<tr>
<td>Night Sweat</td>
<td>13 (23.6%)</td>
<td>26 (47.3%)</td>
<td>0.010*</td>
</tr>
<tr>
<td>Family history of HT</td>
<td>35 (63.6%)</td>
<td>45 (81.8%)</td>
<td>0.032*</td>
</tr>
<tr>
<td>Tea consumption</td>
<td>4 (0 - 12)</td>
<td>3 (0 - 2)</td>
<td>0.452</td>
</tr>
<tr>
<td>Coffee consumption</td>
<td>0 (0 - 3)</td>
<td>0 (0 - 2)</td>
<td>0.444</td>
</tr>
</tbody>
</table>
In the hypertensive group, 24-hour mean BP was 136/85 mmHg, mean, daytime mean BP was 138/88 mmHg, and overnight BP was 130/79 mmHg. In the normotensive group, 24-hour mean BP was 113/70 mmHg, daytime mean BP was 117/73 mmHg, and overnight BP was 104/63 mmHg. Absolute and relative dipping values were significantly lower in the hypertensive group (p = 0.003 and p < 0.001, respectively). Mean daytime and overnight pulse did not differ (p > 0.05). Mean daytime and overnight pulse pressures were significantly higher in the hypertensive group (p < 0.01). In the mean time, dipper frequency was significantly higher in the normotensive group (p = 0.048, Table 4).

The women in the hypertensive group were found to be suffering from HF and night sweats were 65.5 and 47.3, respectively. In the normotensive group, 45.5% of the women were determined to have HF and 23.6% of them were determined to have night sweats.

Night sweats and HF frequency were significantly higher in the hypertensive group than normotensive group (p < 0.05).

### Discussion

The present data suggest that the prevalence of essential HT in the group of women who have HF is significantly higher than the group of women that does not have them.

HF prevalence was found to be 55.45% in the present study participants. This ratio was higher from many studies [13-16].

Gerber et al. showed that women who had HF were postmenopausal and older which is consistent with previous studies [13, 15-17]. In the present study, there was no statistical difference in the menopauseal state between HF and non-HF group.

There has been some controversy with the association between HF and BMI. Some investigators found that more HF were seen when BMI increased and this was linked to the isolation effect in the thermo-neutral zone by the adipose tissue [18-20]. Conversely, some studies showed that decreased BMI was associated with HF which was thought to be caused by less conversion of androgens to estrogen [21]. The present authors did not show any difference in the BMI of the HF and non-HF groups and their result was in agreement with the study done by Gerber et al. [13] and Zhang et al. [22].

There were some studies performed in order to explain the mechanism of the HF. Activation of the sympathetic nervous system might have a role in this mechanism [23].

Several studies showed increased level of 3-methoxy-4-hydroxyphenylglycole, which is a central metabolite of the norepinephrine in women who had HF compared to the women who did not have them [9, 23, 24]. In other studies trying to elucidate the association between HF and HT, Gerber et al. did not show any difference in hypertensive and normotensive women considering the HF. [13] In the present study, hypertensive women had significantly higher rate of HF.

James et al. [25] showed that symptomatic HF group (HF during study) had higher BP at work than the asymptomatic (HF in the past) and non-HF group (no history of HF). Gerber et al. [13] found increased daytime and overnight systolic BP in HF group. Gast et al. [26] showed that women with complaints of flushing or night sweats have an unfavorable cardiovascular risk profile with increased cholesterol levels, systolic and diastolic BPs, and BMI compared with women without vasomotor complaints. The present authors did not find any statis-
ual difference between HF and non-HF group regarding the 24-hour, daytime and overnight mean systolic and dia-stolic BP measurements.

Many studies showed that essential hypertensive and nondipper patients were at risk of target organ damage. Verdeccia et al. found that left ventricular (LV) mass was greater in hypertensive subjects with nondipping [27]. Increased activation of the sympathetic nervous system and decreased activation of the parasympathetic system might have a role in nondipping BP mechanism [28, 29]. They found that the night time fall in both norepinephrine (NE) and epinephrine (EPI) excretion rates was reduced in nondippers compared with dippers [28]. This result might make us think that women have HF experience can have nondipper pattern and as a result HF women can have more cardiovascular morbidity.

However in the study of Gerber et al., decreasing HF overnight (dipping) was no different between hypertensive group and normotensive group, HF, and non-HF group [13]. Conversely, the present authors found that hypertensive group had decreased absolute dipping and relative dipping values, but they did not show any difference in the dipping pattern of HF and non-HF groups and this result was in agreement with the study of Gerber et al. [13].

Conclusion

The prevalence of essential HT in the group of women who have HF is significantly higher than the group of women that does not have them. Vasomotor symptoms may be the preliminary manifestations of HT that is one of the major risk factor for cardiovascular diseases. So until further studies will be performed and the association between HF and HT clearly explained, women who complain of HF should be evaluated for HT in the office and appropriate treatment should be commenced promptly.

Acknowledgments

The authors thank the women who agreed to participate in this study.

References


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e-mail: drnboz@yahoo.com
High rates of abnormalities in hysterosalpingography in couples with male factor infertility

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1Department of Obstetrics and Gynecology Barzilai Medical Center, Ashkelon
2Department of Obstetrics and Gynecology, Shaare Zedek Medical Center, Jerusalem (Israel)

Summary

The rate of anatomical abnormalities in infertile couples with obvious male factor is unknown. For this purpose the authors retrospectively analyzed 376 hysterosalpingographies (HSG) of couples with severe male factor. Patients were subdivided into four groups according to the woman’s age, and primary or secondary infertility: A - less than 35-years-old, primary infertility, B - less than 35-years-old, secondary infertility, C - 35-years-old or more, primary infertility, and D - 35-years-old or more, secondary infertility. Overall, abnormalities in HSG were demonstrated in 25.5% of the patients, and in 18, 21, 52, and 40 percent of patients in groups A, B, C and D, respectively. Age was found to be a significant independent risk factor (p < 0.05) while primary or secondary infertility was not. The adjusted odds ratio for woman who were 35-years-old or more to have any abnormalities in HSG were 3.7-fold greater (95% CI 2.2- 6.23), than women who were less than 35-years-old. In conclusion, relatively high rates of female mechanical abnormalities may be found even in infertile couples with obvious male factor and are significantly more prevalent in older women.

Key words: Hysterosalpingography; Male factor; Infertility; Mechanical factor; Age; Anatomical abnormalities.

Introduction

Evaluation of the reproductive tract in women is an integral part of the investigation of infertile couples. The rates of mechanical abnormalities among infertile women are variable in the different studies and range between 3% to 17% in the uterus, 18% to 37% in the tubes, and 4% to 25% in the pelvis [1-8]. Most of the studies did not report the relationship between the couple’s background parameters and the pathologic findings. Kasby et al. found correlation between mechanical problems to history of pregnancy. He found tubal pathology in 18% of woman with primary infertility and as much as 30% in those with secondary infertility [3]. In addition, age may be possible factor for mechanical problems. It is well known that the existence of uterine fibroids and endometrial polyps are age-related, and that the cumulative potential exposures to pelvic insult events such as pelvic infection are higher as the woman becomes older [9, 10].

The basic evaluation of couples with infertility includes investigation of male factors, ovulation function, and mechanical problems. Hysterosalpingography (HSG) examination is common tool for the evaluation of the female reproductive tract. Its main advantage is the ability to demonstrate in one examination the uterine cavity, the tubes, and the female pelvis. Although the specificity and sensitivity are limited, it is an integral part of the evaluation of couples who suffer from infertility [7, 8]. However, it may be questionable whether it is justified sending women for mechanical evaluation in cases with clear male factor. The goal of the present study was to evaluate the female mechanical status in cases where there was an obvious male cause for infertility. For this purpose the authors investigated retrospectively the HSG results of infertile couples with severe male factor. In addition they evaluated the relation between the women background parameters to the rate of mechanical abnormalities in the uterus, tubes, and pelvis. If there are considerable mechanical pathologies, it signifies that women mechanical evaluation should be done even in cases of male subfertility.

Materials and Methods

Over six consecutive years, 1,271 new couples were enrolled to the in vitro fertilization (IVF) clinic in Shaare Zedek Medical Center. The women underwent HSG for mechanical evaluation and the male partners underwent sperm analysis as a prerequisite for treatment. Only the couples with severe male factor were included in the current study population. Three hundred and seventy six males (30% of the total) were diagnosed as having severe male factor. The diagnosis was established following two sperm examinations taken at least six weeks apart. Severe male factor was diagnosed when the sperm concentration was less than five million/ml or if the total motile count was less than one million. HSG analysis was performed by an expert radiologist. Follicle stimulating hormone (FSH) higher than ten IU was diagnosed as “high”. Any case of irregular vaginal bleeding, oligomenorrhea or polycystic ovarian syndrome (PCOS) was diagnosed as “dysovulation”.

The authors retrospectively analyzed the HSG results of the women into four main groups:

• A (n = 196) – Women less than 35 years old with primary infertility,
• B (n = 86) – Women less than 35 years old with secondary infertility,
C (n = 42) – Women 35 years old or more with primary infertility,
D (n = 52) – Women 35 years old or more with secondary infertility.

The analysis of reproductive tract abnormalities was classified according to three anatomical sites examined in HSG - the uterus, the fallopian tubes, and the pelvis:

• In the uterus: congenital uterine malformations, acquired abnormalities (polyps and/or adhesions and/or subserous fibroid) and ‘any uterine abnormalities’ (congenital or acquired).

• In the fallopian tubes: unilateral proximal occlusion, bilateral proximal occlusions, and ‘any proximal occlusions’.

• In the pelvis: pelvic adhesions and ‘any pelvic abnormalities’. Distal tubal occlusions/hydrosalpinx which express pelvic abnormality – were also included in this category.

Institutional Review Board of Shaare Zedek Medical Centre approved this study.

Statistical analysis

Statistical analysis included application of the t-test as well as the Mann-Whitney non-parametric test in order to compare quantitative variables between two independent groups. ANOVA was performed when quantitative variables were compared between more than two groups. The Pearson Chi-Square test and the Fisher’s exact test were used for testing the association between two categorical variables. The Logistic Regression model was applied in order to assess simultaneously the significance of the effect of age group (age above or below 35 years old) and infertility group (primary or secondary) on five dichotomous outcome variables as follows: ‘any uterine abnormalities’, ‘any proximal tubal occlusion’, ‘any pelvic abnormalities’, ‘any tubal and/or pelvic abnormalities’, and ‘any abnormalities in HSG’. Using this model, the adjusted odds ratio and its 95% confidence interval (CI) was calculated. All tests applied were two-tailed, and a significance level of 5% or less was considered statistically significant.

Table 1. — Basal parameters in the different study groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>No (%)</th>
<th>Age (Y) ± SD</th>
<th>Infertility years</th>
<th>Children</th>
<th>High FSH (%)*</th>
<th>Dysovulation (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prim&lt;35 A</td>
<td>196 (52)</td>
<td>26.4 ± 3.3</td>
<td>3.3 ± 2.3</td>
<td>0</td>
<td>1</td>
<td>16.8</td>
</tr>
<tr>
<td>Sec&lt;35 B</td>
<td>86 (23)</td>
<td>29.7 ± 3.2</td>
<td>3.2 ± 1.8</td>
<td>1 ± 1.0</td>
<td>2.3</td>
<td>14</td>
</tr>
<tr>
<td>Prim&gt;35 C</td>
<td>42 (11)</td>
<td>40.2 ± 5.2</td>
<td>5.2 ± 5.6</td>
<td>0</td>
<td>19</td>
<td>7.1</td>
</tr>
<tr>
<td>Sec&gt;35 D</td>
<td>52 (14)</td>
<td>40.1 ± 4.7</td>
<td>4.7 ± 3.4</td>
<td>1.3 ± 1.6</td>
<td>7.7</td>
<td>5.8</td>
</tr>
<tr>
<td>Total</td>
<td>376 (100)</td>
<td>30.6 ± 3.7</td>
<td>3.7 ± 3.0</td>
<td>0.4 ± 0.9</td>
<td>4.3</td>
<td>13.6</td>
</tr>
</tbody>
</table>

*p < 0.001

Table 2. — The rate of abnormalities according to anatomical site, age, and infertility status.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Severe less than 35 years old</td>
<td>PRIM. A (196)</td>
<td>3.1</td>
<td>2.0</td>
<td>5.1</td>
<td>7.1</td>
<td>3.1</td>
<td>10.2</td>
<td>2.3</td>
<td>1.7</td>
<td>4.0</td>
</tr>
<tr>
<td></td>
<td>Male 35 years old or more</td>
<td>SEC. B (86)</td>
<td>5.8</td>
<td>2.3</td>
<td>8.1</td>
<td>7.0</td>
<td>2.3</td>
<td>9.3</td>
<td>2.5</td>
<td>2.5</td>
<td>5.1</td>
</tr>
<tr>
<td></td>
<td>PRIM. C (42)</td>
<td>2.4</td>
<td>11.9</td>
<td>14.3</td>
<td>23.8</td>
<td>4.8</td>
<td>28.6</td>
<td>9.7</td>
<td>12.9</td>
<td>22.6</td>
<td>52.4</td>
</tr>
<tr>
<td>Factor</td>
<td>SEC. D (52)</td>
<td>7.7</td>
<td>5.8</td>
<td>13.5</td>
<td>13.5</td>
<td>0</td>
<td>13.5</td>
<td>6.5</td>
<td>13.0</td>
<td>19.6</td>
<td>40.4</td>
</tr>
<tr>
<td>TOTAL</td>
<td>4.3</td>
<td>3.7</td>
<td>8.0</td>
<td>9.8</td>
<td>2.7</td>
<td>12.5</td>
<td>3.6</td>
<td>4.0</td>
<td>8.1</td>
<td>25.5</td>
<td></td>
</tr>
</tbody>
</table>

*p = 0.04; **p = 0.026; ***p < 0.001; ‡p < 0.001

Table 1. — Basal parameters in the different study groups.

<table>
<thead>
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<th>Group</th>
<th>No (%)</th>
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<tr>
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<td>16.8</td>
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<td>Sec&lt;35 B</td>
<td>86 (23)</td>
<td>29.7 ± 3.2</td>
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<td>1 ± 1.0</td>
<td>2.3</td>
<td>14</td>
</tr>
<tr>
<td>Prim&gt;35 C</td>
<td>42 (11)</td>
<td>40.2 ± 5.2</td>
<td>5.2 ± 5.6</td>
<td>0</td>
<td>19</td>
<td>7.1</td>
</tr>
<tr>
<td>Sec&gt;35 D</td>
<td>52 (14)</td>
<td>40.1 ± 4.7</td>
<td>4.7 ± 3.4</td>
<td>1.3 ± 1.6</td>
<td>7.7</td>
<td>5.8</td>
</tr>
<tr>
<td>Total</td>
<td>376 (100)</td>
<td>30.6 ± 3.7</td>
<td>3.7 ± 3.0</td>
<td>0.4 ± 0.9</td>
<td>4.3</td>
<td>13.6</td>
</tr>
</tbody>
</table>

*p < 0.001

Table 2. — The rate of abnormalities according to anatomical site, age, and infertility status.

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Severe less than 35 years old</td>
<td>PRIM. A (196)</td>
<td>3.1</td>
<td>2.0</td>
<td>5.1</td>
<td>7.1</td>
<td>3.1</td>
<td>10.2</td>
<td>2.3</td>
<td>1.7</td>
<td>4.0</td>
</tr>
<tr>
<td></td>
<td>Male 35 years old or more</td>
<td>SEC. B (86)</td>
<td>5.8</td>
<td>2.3</td>
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*p = 0.04; **p = 0.026; ***p < 0.001; ‡p < 0.001

Results

The basal parameters of the study groups are summarized in Table 1. Seventy-five percent of the women were aged less than 35 years and 25% were older. The mean age in the younger groups was 26 ± 3 to 30 ± 3 years and in the older group 40 ± 5 years. Overall 63% of the women in the study population had primary infertility and 37% had secondary infertility. Dysovulation was apparent in more women younger than 35 years as compared with the older group (14-17% vs 6-7%) (p < 0.001), while the older group had a higher prevalence of high FSH levels (1% - 2% vs 8% - 19%) (p < 0.001, Table 1).

Overall some abnormality was found in 25.5% of the patients who underwent HSG. ‘Any uterine abnormalities’, ‘any proximal tubal occlusion’, and ‘any pelvic abnormalities’ were found in 8.0, 12.5, and 8.1 percent of the patients, respectively. Table (2). Even in the younger women with primary infertility (group A) which was the specific subgroup with a lower expected rate of mechanical abnormalities, the authors found ‘any abnormality in HSG’ in 18% of patients (Table 2).

The authors did five different logistic regression models for ‘any uterine abnormalities’, ‘any proximal tubal occlusion’, ‘any pelvic abnormalities’, ‘any tubal and/or pelvic abnormalities’, and ‘any abnormalities in HSG’. In all of them the authors found that age was an independent factor for the HSG abnormalities while infertility type (primary or secondary) was not (p = 0.034, p = 0.005, p = 0.001, and p < 0.001, respectively).

Furthermore, the adjusted odds ratios for woman who were 35 years old or more to have ‘any uterine abnormali-
High rates of abnormalities in hysterosalpingography in couples with male factor infertility

Discussion

In the present study the authors found a high rate of reproductive tract abnormalities, in spite of obvious male factor infertility. The discussion about the significance of each pathological finding in HSG on the female fertility status is beyond the scope of this study. However, all of the abnormalities that were assessed in this study may potentially have some impact on the management of infertile couples or at least in consideration for further mechanical evaluation [11-13]. This study focused on couples with an obvious ‘non-female’ cause of infertility. It does not mean that in this particular group, which probably requires IVF/intracytoplasmic sperm injection (IVF-ICSI), all the pathological findings in HSG are relevant. However it may be extrapolated to emphasize the importance of female reproductive tract evaluation in couples with less severe male factor, or couples without male factor infertility at all.

Surprisingly, even in the younger women (groups A and B) the authors found a relatively high rate (18% - 21%) of anatomical pathologies. However, female age was found to be an independent risk factor for mechanical problems. Women aged 35 years and older (groups C and D) had absolutely very high rates of mechanical abnormalities (40% - 50%). This finding together with the age relates lower ovarian reserve, may emphasize the importance of early anatomical evaluation in fertility assessment of older patients.

The overall prevalence of the HSG findings in the present study concurred with the range described in previous studies [1-6]. Krysiewicz et al. summarized a number of studies on female mechanical abnormalities in couples that underwent infertility evaluation [4]. There were similar rates of uterine/endometrial abnormalities in comparison to this study (2% - 5% vs 8%, respectively), but higher rates of tubal abnormalities (25% - 40% vs 17%, respectively) and peritoneal abnormalities (20% - 25% vs 7%, respectively).

In the present study the authors found that primary or secondary infertility has no correlation with abnormal findings in the female reproductive tract. Similar to their study results, Dhaliwal et al. found no significant correlation between the type of infertility and the HSG findings [2]. In contrast, Shokeir et al. prospectively evaluated 612 consecutive infertile women who underwent a complete fertility workup [14]. The abnormal hysteroscopic findings were higher in those with secondary than those with primary infertility. Behjatinia et al. compared hysteroscopic findings in 248 patients with primary infertility with those of 150 women with secondary infertility [15]. In his study, the prevalence of intrauterine synechiae was significantly higher in the latter group.

The acquired intrauterine abnormalities consist of subserosal fibroids, endometrial polyps and intrauterine adhesions. In the present study the authors found a higher rate of intrauterine abnormalities in the older women. The results confirm that the prevalence of uterine fibroids and endometrial polyps are age-related [9-10]. The authors also revealed a higher rate of pelvic adhesions and tubal occlusions in older women, which are usually caused by pelvic inflammatory disease (PID). The potential life exposure for PID is higher as the women is older [5]. The authors may have expected a higher rate of acquired intrauterine abnormalities in women with secondary infertility, given that Asherman’s syndrome is frequently caused by infected abortion, curettage, and chorioamnionitis [4]. In the present study however, past pregnancy was not correlated with a higher rate of intrauterine abnormalities. The rate of congenital uterine malformations and the high rate of septate/bicornuate uterus in this group are similar to the findings in other studies [16-17].

In summary, in the present study it was demonstrated that female mechanical abnormalities are prevalent even where there is a clear ‘non-female’ infertility cause. Age is an independent risk factor for structural abnormalities while primary and secondary infertility are not. Mechanical evaluation seems to be prudent and should not be postponed, at least in infertile patients 35 years and older.

References


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Frozen section of uterine curetting in excluding the possibility of ectopic pregnancy - a clinicopathologic study of 715 cases

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Summary

Introduction: To investigate the utility of frozen section of uterine curetting in excluding the possibility of ectopic pregnancy (EP).

Materials and Methods: A retrospective analysis of 715 curetting records in the present hospital from July 1999 to May 2009 was obtained. All specimens were processed routinely with frozen section and paraffin section. Results: Of 715 cases, frozen section analyses were discordant in 33 cases (4.6%), including 32 cases under-diagnosed, and one case over-diagnosed, compared with the final diagnoses. Frozen section had a sensitivity of 92.6%, specificity of 99.6%, and frozen section accuracy rate of 95.4%. Conclusions: Frozen section is a useful and rapid method to differentiate EP from intrauterine pregnancy.

Key words: Uterin curetting; Ectopic pregnancy; Frozen section.

Introduction

Ectopic pregnancy (EP) is a potentially serious threat to women’s health, which may lead to catastrophic presentation or death in case of ruptured EP. Commonly, a diagnosis of “suspicion of EP” is suggested by pelvic examination, β-ultrasonography, and serial serum β-subunit human chorionic gonadotropin (β-HCG) titers, but sometimes when patients presented with mild abdominal pain and minimal vaginal bleeding, β-HCG and β-ultrasonography cannot assist in differentiating threatened abortion from EP, then curettage may serve to exclude the possibility of EP. For this reason, if villi are not identified by immersing curettings in water, the curettings would be submitted to histopathology diagnosis and the patient would be admitted until the site of pregnancy is determined. Thus the pathology diagnosis is essential for further management. However, it may take two to three days to make the final pathology diagnosis. The waiting period is not only a burden to the patient and her relatives, but a waste of medical resources. Frozen section takes 20 minutes after curettage, which is much quicker than paraffin section. If the frozen section analysis of uterine curetting is as reliable as that of paraffin section, the problem can be solved. Previous studies [1-4] have demonstrated the accuracy of uterine curetting, but they have been studied only in small series and the authors paid more attention on clinical issues. In order to investigate the utility of frozen section of uterine curetting in ruling out the possibility of EP, 715 cases of uterine curetting from July 1999 to May 2009 were reviewed and compared histopathologically, especially those cases between frozen sections and paraffin sections.

Materials and Methods

The study included 715 cases of uterine curetting from July 1999 to May 2009 that were selected retrospectively. All the patients were administrated by a complete endometrial curettage. The selection criteria included cases in which the frozen and paraffin sections were simultaneously performed due to the clinical diagnosis ruling out EP. Two cases were excluded because no paraffin sections were performed.

Procedures of sampling, preparing and interpreting the curettings:
1) For the diagnosis of frozen section: usually only one block of section was frozen for diagnosis. If intrauterine pregnancy was suspected in the frozen section, one more block was sampled for the diagnosis of frozen section.
2) For the diagnosis of paraffin section: the frozen tissues were also fixed, embedded, and routinely prepared for diagnosis. One block was selected for paraffin section if the evidence of intrauterine pregnancy had appeared in the frozen sections. The remaining fragments were sectioned to avoid overlooking the tissues of intrauterine pregnancy if no evidence of intrauterine pregnancy had appeared in the frozen sections. The diagnosis of paraffin section was based on a thorough microscopic examination of the fixed frozen tissues, the original frozen section, and the paraffin sections. (Occasionally, the diagnosis of re-embedded frozen tissues is not the same as that of the original frozen section because tissues in the original ones may be cut away and lost forever).

The diagnoses of paraffin section and frozen section were concordant if either of the following interpretations were made:
1) The diagnosis of the paraffin section and that of frozen section were the same.
2) Frozen section diagnosis was trophoblast cells or basal decidual; paraffin section diagnosis was villi.
3) Frozen section diagnosis was villi; paraffin section diagnosis was trophoblast cells or basal decidua.

The diagnoses of paraffin section and frozen section were discordant or inconsistent if either of the following reports were made:
1) Under-diagnosed cases: frozen section diagnosis was decidua or secretory endometrium; Paraffin section diagnosis was trophoblast cells or decidua or villi.

2) Over-diagnosed cases: frozen section diagnosis was villi, basal decidua or trophoblast cells; not any of these two tissues had appeared in the paraffin section. Review of those frozen sections and paraffin sections denied any of these three issues by experienced hands.

Inconsistent sections were reviewed by two pathologists to analyze the reasons for its inconsistency and follow-up data was obtained if necessary. For three cases of frozen sections, the pregnancy tissues could be seen, but the paraffin sections did not show the evidence. The original diagnoses were proved correctly after review and the follow-up data suggested the intrauterine pregnancy. Therefore, the diagnoses between frozen section and paraffin section were believed to be concordant.

Results

1. Clinical data

Patient age ranged from 19 to 48 years (mean 30.6), with amenorrhea period from 30 to 70 days (mean 50.2). Of all 402 cases of intrauterine pregnancy made based on frozen section, 401 cases were concordant with the diagnosis on paraffin section and one case was over-diagnosed in frozen section. Of all 313 cases with evidence of pregnancy, 281 cases were concordant and 32 cases under-diagnosed.

For the patients whose diagnoses were discordant between frozen section and paraffin section, their age ranged from 19-44 years (mean 31.0) and amenorrhea period was 39-62 days (mean 48.9). A total of 32 cases of frozen sections were under-diagnosed, of which 22 cases of frozen sections were interpreted as decidua only, ten cases of frozen sections were interpreted as secretory endometrium. Of 22 decidua-only cases, six cases had decidua basalis in paraffin sections. Of ten secretory endometrium cases, eight cases of paraffin sections had villi and two cases of paraffin sections had decidua basalis. For one case with over-diagnosed of frozen section, the interpretation was decidua basalis in frozen section and only decidua was seen in paraffin sections. Reviewing this frozen section, the authors believe there was no pregnancy evidence appearing on the slide.

2. Ending of patients without intrauterine pregnancy in frozen section diagnosis.

There were 313 patients without intrauterine pregnancy in frozen section diagnosis, such as trophoblast cells, basal decidua or villi, of which 32 cases had intrauterine pregnancy evidence in paraffin sections and 281 cases had no intrauterine pregnancy evidence in paraffin sections. In 281 cases, 259 cases were proved with extrauterine pregnancy after abdominal laparotomy. For 22 cases, their serial serum β-HCG titer quickly reduced to normal after curettage and the B-ultrasonic results showed that “there was no intra or extrauterine gestational sac”.

3. Ending of patients with intrauterine pregnancy evidence in frozen section diagnosis.

1) There was a total of 402 patients with intrauterine pregnancy evidence in frozen sections. For one case, villi were seen in both frozen section and paraffin section, β-HCG titer continued to rise, and the B-ultrasonic results showed that “there was a hemorrhagic ovarian mass beside left adnexa”. Therefore the patient was diagnosed with a “heterotopic pregnancy”. The patient was administrated with methotrexate, and discharged with normal serum β-HCG level.

2) There were 72 cases with decidua basalis or trophoblast cells in frozen section, of which 47 cases of paraffin sections had villi, 21 cases of paraffin sections had basal decidua, and three cases of paraffin sections had decidua tissue or secretory endometrium. After review of the latter three cases, decidua basalis was exactly seen in frozen sections; one case of frozen section was decidua basalis and only decidual tissue was seen in paraffin sections.

4. Analysis of the reasons for under-diagnosing the frozen sections

Thirty-two cases (4.5%, 32/715) were under-diagnosed after reviewing the frozen sections, of which 18 cases (56.3%, 18/32) had no villi sampled in the frozen sections and there were intrauterine pregnancy tissues in the re-sampled paraffin sections, in which three cases (9.4%, 3/32) it could not be seen whether the intrauterine pregnancy tissues were present or not in the re-sampled paraffin sections due to poor preparation of frozen sections. Of these 32 cases, 14 cases (43.8%) of frozen sections were reviewed with intrauterine pregnancy tissues (a large number of fibrinoid deposits mixed with trophoblast cells were seen in five cases of frozen sections; small amount of decidua basalis were seen in three cases of frozen sections; Villi were seen in six cases of frozen sections, in which a two-layer trophoblast was seen in one case with significant edema and expansion, but the double layer structure was thin and interstitial structure was not clear, and re-cutting (section the block at deeper levels) or re-sample (select tissues at the remaining fragments) was required at that time. In one case of frozen sections, the villi were mixed with many secretory glands and difficult to distinguish).

5. Analysis of the reasons for over-diagnosing the frozen sections

In one case with over-diagnosed frozen section, the frozen section suggested decidua basalis and no pregnancy evidence was seen both in frozen section and paraffin section after review. The authors contacted the patient, and the urine pregnancy test was negative one week after uterine curettage, β-ultrasound showed “there was no intra and extra uterine gestational sac” with clinical diagnosis of intrauterine pregnancy. However in our study, it was considered as over-diagnosed.
6. Comparison of frozen section results and pathological results

Of 715 cases, the diagnosis of frozen sections in 682 cases (95.4%) was concordant with paraffin sections and there were 32 cases with no intrauterine pregnancy evidence seen in frozen sections but with pregnancy evidence in paraffin sections, and one case of paraffin section with decidua basalis, and no intrauterine pregnancy evidence in paraffin section.

Conclusions

Problems existed in the diagnosis of frozen sections

1) Most discordant cases (32/33, 96.7%) were patients with under-diagnosed frozen sections in this group of experiments, and the problems that were diagnosed with frozen sections were analyzed as follows:

A. Inadequate selecting of the specimen at the time of frozen section. In this study, no intrauterine pregnancy tissue was sampled in the frozen sections in 18 cases (56.3%, 18/32), and in the final diagnosis, intrauterine pregnancy tissue was seen in re-sampled sections, which suggested that the biopsy technique needed to be improved. In general, when there were no obvious villi macroscopically, the hemorrhagic areas of the curettage specimen increased the detection rate of intrauterine pregnancy tissues.

B. Poor quality of sections. Of 18 cases of frozen sections with no intrauterine pregnancy tissue drawn, three discordant cases were caused by poor quality of section preparation, and a clear section could have facilitated the reading.

C. Inexperienced of the pathologist. In 32 cases of under-diagnosed frozen sections, there were 14 cases with intrauterine pregnancy tissues after review, so improving the experience of interpretation is necessary.

a) Nitabuch’s fibrinoid (Figure 1). One layer of fibrinoid deposits on the surface of decidua is known as Nitabuch’s layer. There are trophoblast cells in the vicinity of this layer, which is the evidence of intrauterine pregnancy [5].

b) Decidua basalis. Decidua basalis is the decidua at the site of implantation. Intermediate trophoblast cells are characteristic of dark stained cells scattered within the decidua, the existence of decidua basalis can be regarded as intrauterine pregnancy. In this study, of under-diagnosed 32 cases, decidua basalis was seen in three cases after reviewing the frozen sections, and theses three cases could be diagnosed as intrauterine pregnancy.

c) Syncytiotrophoblast cells (ST). Isolated STs, with hyperchromatic multi-nuclei, often fall from the villus. The emergence of free STs can be regarded as intrauterine pregnancy. If small amounts of free STs and villi occurred in the curetting, re-cutting or re-sampling was required to find the decidua basalis. Because, in rare cases, a small amount of free trophoblast cells and villi can backflow into the uterine cavity through isthmus portion of the fallopian tube. In this study, after reviewing the under-diagnosed frozen sections, free trophoblast cells were seen in five cases, and the follow-up results showed intrauterine pregnancy.

d) When the following images occurred in the sections, re-cutting or resample were performed to improve the detection rate of intrauterine pregnancy:

- many open blood sinusoid and extensive areas of hemorrhage in slides;
- much fibrinoid deposits.

2) Problems existed in the over-diagnosis of frozen sections

A. In this group, one case was over-diagnosed, and the decidual tissues were misdiagnosed as decidua basalis, and after review, there was no decidua basalis, which was related to the diagnosis experiences.

B. Improving the experience of interpretation on microscopic slides.

a) Identification of villi and decidua. Sometimes in frozen section, small amount of decidua may be encapsulated by endometrium glands, which can be confused with the villi. The outline of glandular cells is of single layer structure, and the villa is surrounded by two-layer trophoblast cells with cytotrophoblasts at the inner layer and STs at the outer layer.

b) Identification of blood vessels and highly degenerative villi in the fibrinoid deposits. Both of them have tubular structures, degenerative, and obscure figures. However the blood vessel contains erythrocytes or plasma-like amorphous materials and the villa has two-layer trophoblast cells.

c) Identification of glands with Arias-Stella (A-S) change and trophoblast cells fall from the villus. Both of them have larger dark-stained nuclear. The hyperchromatism cells with A-S change are glandular and emerge on the spongiosa...
layer of endometrium. The trophoblast cells fall from the villi and are scattered in the fibrinoid deposits or on the surface of the decidua.

3) In case of rare heterotopic pregnancy (it is reported that its incidence is about 1:30,000 and the incidence has increased with the development of assisted reproductive technology), we need to rely on other clinical and ancillary laboratory, and the frozen section and only pathology can diagnose the tested scrapings and cannot predict whether or not the extrauterine pregnancy is incorporated at the same time.

7. Significance of the scrapings in the diagnosis of frozen sections on excluding the extrauterine pregnancy.

There were a total of 715 cases in this study, of which frozen section diagnosis were discordant with paraffin section diagnosis in 33 cases and most of them were under-diagnosed, and one case was over-diagnosed, which was related to the diagnosis experiences. Previously reported data have shown that using frozen section to diagnose intrauterine pregnancy has a certain false negative and small amount false positive. Spandorfer et al. reported a sensitivity of 78.3%, specificity of 98.4% for the diagnosis of frozen section [1]; Barnhart et al. reported sensitivity of 87.5%, specificity 100% [2]; Barak et al. 76%, 97.8%, respectively [3]. In the present study, there were a total of 715 cases in a decade with sensitivity of 92.6%, specificity of 99.6%, positive predictive value of 99.7%, negative predictive value of 89.8%, and frozen section accuracy rate of 95.4%, so the authors believe that the diagnosis of frozen sections are valuable for excluding the extrauterine pregnancy. The diagnosis of frozen sections can determine whether the curetting contain the evidence of intrauterine pregnancy in a short time (20-30 min), thereby the patients with exact intrauterine pregnancy can avoid being hospitalized for observation and go home without misgivings; the patients with highly suspected extrauterine pregnancy can be immediately confirmed with further treatment, the waiting time is reduced, the waste of medical resources is also reduced, and the diseases of the patient also can be effectively and quickly treated.

References


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Increased platelet count in severe peritoneal endometriosis

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Dicle University, School of Medicine, Diyarbakir (Turkey)

Summary

Objective: Platelet count (PC) is higher in chronic inflammatory diseases. The aim of this study was to evaluate the PC in patients with severe pelvic endometriosis. Materials and Methods: Patients with advanced stage pelvic endometriosis were retrospectively evaluated in a tertiary center between January 2009 and December 2011. Patients with pelvic endometriosis were divided into two groups; advanced stage peritoneal endometriosis were classified as Group 1 (n = 28). Group 2 consisted of 29 patients which had ovarian endometrioma without clinically apparent peritoneal endometriosis foci. Group 3 included 51 women as control subjects. PC between the groups was tested by Student’s t test. The mean values of three groups were analyzed by using one way ANOVA test followed post-hoc test Bonferroni. Results: PC in patients with pelvic endometriosis were found to be higher from the control group (290 ± 67 10⁹/l; 264 ± 63 10⁹/l, respectively; p = 0.038). Patients with peritoneal endometriosis (Group 1) had significantly higher PCs compared with the healthy controls (309 ± 65 10⁹/l; 264 ± 63 10⁹/l; respectively; p = 0.011). Conclusion: Increased PC in advanced stage pelvic endometriosis may be a sign of increased systemic inflammation. The systemic inflammation may be more apparent in advanced stage peritoneal endometriosis.

Key words: Endometriosis; Inflammation; Platelet count.

Introduction

Endometriosis is defined as presence of endometrial glands and stroma outside the uterine cavity and generally develops within the pelvis. It is a chronic estrogen-dependent disorder. The etiology of this disorder is still unknown. The implantation theory of Sampson, the coelomic metaplasia theory of Mayer, and the induction theory are the classical theories attempting to explain origin of the disease. Combination theory also explains the difference between ovarian and peritoneal endometriosis. Endometriosis lesion has distinctive morphologic appearance; active lesions include vesicles, flat plaques and black coloration[1, 2]. Secretion of various cytokines by endometriotic implants results to activation of inflammatory cells into the peritoneal cavity and leads to a sterile local inflammation of peritoneum[3]. Active endometriotic lesion has metabolic activity, as is suggested by their high concentrations of prostaglandin metabolites. Pain as secondary dysmenorrhea or chronic pelvic pain, is associated with inflammation and anti-inflammatory drugs are used for treatment of pain. Progressive fibrosis occurs and lesion being inactive in the long term [1]. Some researchers suggests that active phase of the disease is associated with systemic subclinical inflammation[4].

Platelets play an important role in thrombosis and hemothasis however they have relevant functions in inflammation. Inflammation is an important stimulant for platelets [5]. The role of platelets in chronic inflammatory diseases has now been convincingly demonstrated. Platelet count (PC) has been reported to be increased in rheumatoid arthritis, ankylosing spondylitis, familial mediterranean fever, and in patients with atherosclerosis which are accompanied with chronic inflammation[6-9].

Like benign chronic disorders, PC has been reported to be increased in solid tumors including gynecologic cancers. Malignant cells produce certain cytokines and growth factors, which are capable of inducing platelet production. Previous studies suggest that elevated platelet count is associated with factors reflecting more aggressive tumor biology, and predicting poor survival in women with such tumors[10, 11].

The aim of present study was to investigate PC in severe pelvic endometriosis especially in patients with severe peritoneal group. To the authors’ knowledge, the present study is the first study investigating PC in patients with severe endometriosis.

Materials and Methods

Women with endometriosis which managed and operated at Dicle University School of Medicine, Department of Obstetrics and Gynecology between January 2009 and December 2011 were retrospectively evaluated. Endometriosis was diagnosed by laparoscopy/laparotomy with histological confirmation of the disease. Operative findings and stage of disease consisted of a written report with the use of the revised American Fertility Society classification for Endometriosis[12]. All operations were performed by the four authors (MSE, HES, MES, and AO). Study population consisted of 57 patients with severe pelvic endometriosis that were Stage 3 and/or Stage 4. Patients with minimal or mild stage of endometriosis were not included in the study. Patients with histories of myeloproliferative disorders, presence of acute or chronic inflammatory diseases or history of receiving hormonal therapies...
for the last three months were also not included. After excluding improper subjects from the study, patients with severe pelvic endometriosis were divided into two groups according to the presence of severe peritoneal endometriosis. Patients with peritoneal endometriosis were classified as Group 1 (n = 28) and, patients with ovarian endometrioma without clinically apparent peritoneal endometriosis foci as Group 2 (n = 29).

Control group (Group 3) included 51 women recruited from the patients admitted to outpatient clinic without any gynecological diseases. All the subjects were aged between 18-35 years. A preoperative automated complete blood count was available for all patients. The following relevant data were retrospectively determined from medical records: age of subjects, hemoglobin, white blood cell counts, PC, presence of Stage 3-4 peritoneal endometriosis or Stage 3-4 ovarian endometrioma. The study protocol was approved by the Medical Ethics Committee of Dicle University.

Statistical analysis
Statistical analysis was performed by SPSS statistical software (SPSS for windows 15.0, Inc., Chicago, IL, USA). Data were presented as mean ± standard deviation. Differences between the two groups were tested by Student’s t test. The mean values of three groups were compared by using one way ANOVA test followed post-hoc test Bonferroni. A p value less than 0.05 was accepted as statistically significant.

Results
Patients with pelvic endometriosis (290 ± 67 10^9/l m^3) had significantly higher PC compared with the control group (264 ± 63 10^9/l) (p = 0.038). Mean diameter of endometrioma cyst were 6.18 ± 1.96 cm (min-max, 3-11) in Group 2. Hematological parameters are shown in Table 1.

PCs also were compared according to coexistence of peritoneal endometriosis. The mean PC was significantly higher in Group 1 (severe peritoneal endometriosis) when compared with Group 3 (control subjects) (309 ± 65 10^9/l and 264 ±63 10^9/l; respectively; p = 0.011). No significant difference was found in PC between peritoneal endometriosis group and the ovarian endometrioma subjects (Table 2).

Discussion
Endometriosis is associated with increased inflammatory activity. Patients with endometriosis had higher rates of autoimmune inflammatory diseases, allergies, and asthma, when compared with the general female population [13]. Elevated peritoneal fluid inflammatory markers have been observed in the literature. Pelvic pain related to endometriosis, is relieved by anti-inflammatory drugs, supporting thus the contribution of chronic inflammation in the pathogenesis of this disease [1, 4]. Agic et al. [4] reviewed the literature and found a number of studies related to increased number of activated macrophages in peritoneal fluid of women with endometriosis and that secrete various local products, such as growth factors and cytokines. Levels of many cytokines in the peritoneal fluid of women with endometriosis have been found to be increased, thus implicating that these cytokines might be important for the progression of endometriosis. Furthermore, it has been reported that the levels of various cytokines also increased in the serum of patients with endometriosis and this suggested that there was an association of subclinical inflammation in patients with endometriosis. Although many studies showed increased inflammatory cytokine levels, there were also some researchers that found no difference in levels of inflammatory markers in endometriosis [4]. The differences in various studies may be due to that endometriosis lesions are sometimes inactive; estrogen status of the patients may differ at the time of the study, difference etiopathogenesis of ovarian or pelvic endometriosis and the severity of the disease. In this study, PC was significantly higher in severe pelvic endometriosis and in severe peritoneal endometriosis group compared to control. The authors suggest that further studies to investigate inflammation in advanced endometriosis must examine peritoneal endometriosis and ovarian endometrioma groups separately. Inflammatory markers (IL-6, TNF-α), especially have been found in higher concentrations in severe endometriosis groups [4, 14]. In this study the authors investigated the PC in severe endometriosis patients and despite different etiopathogenesis of the ovarian and peritoneal endometriosis, they cal-

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<td>** = The differences between Group 1 - Group 3 were found significant by Bonferroni post-hoc test</td>
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<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Table 2. — The comparisons of age and hematological parameters between endometriosis and control groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>GR1+ GR2 (x ± SD)</th>
<th>GR3 (x ± SD)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>29.7±4.2</td>
<td>29.4±4.1</td>
<td>28.2±5.3</td>
</tr>
<tr>
<td>Platelet count (10^9/l)</td>
<td>309±65</td>
<td>272±64</td>
<td>264±63</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>12.8±0.8</td>
<td>12.8±0.9</td>
<td>0.755</td>
</tr>
<tr>
<td>White blood cell (x10^9/l)</td>
<td>8,3±1.6</td>
<td>7,9±1.6</td>
<td>0,151</td>
</tr>
<tr>
<td>PC = Platelet count</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NS = not significant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>* = The mean values of three groups were analyzed by using one way ANOVA test followed by Bonferroni post-hoc test</td>
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<td></td>
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<tr>
<td>** = The differences between Group 1 - Group 3 were found significant by Bonferroni post-hoc test</td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (x ¯ ± SD)</th>
<th>Group 2 (x ¯ ± SD)</th>
<th>Group 3 (x ¯ ± SD)</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>29,7±4,2</td>
<td>29.4±4.1</td>
<td>28.2±5.3</td>
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<tr>
<td>PC (10^9/l)</td>
<td>309±65</td>
<td>272±64</td>
<td>264±63</td>
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</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
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<td>12.8±0.9</td>
<td>0.755</td>
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<tr>
<td>PC = Platelet count</td>
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</tbody>
</table>
culated PC separately in Stage 3-4 ovarian endometrioma group (without clinically apparent peritoneal endometriosis foci) and Stage 3-4 peritoneal endometriosis.

In conclusion, the authors found significantly increased PC in severe peritoneal endometriosis group when compared with the control subjects and this finding may be a sign of increased systemic inflammation. Increased PC in patients with severe peritoneal endometriosis may be related to chronic inflammation that in long term may cause some negative health consequences such as atherosclerosis.

References


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Risk of recurrent menorrhagia after hydrothermoablation: role of GnRH analogues neoadjuvant treatment in long term successful rate

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Summary

Objective: to evaluate the long term effectiveness of presurgical therapy with GnRH analogues in patients who underwent hydrothermal endometrial ablation (HTA) for menorrhagia and assess the relationship between sonographically measured myometrium thickness and pelvic pain. Materials and Methods: A prospective randomized control study comparing 15 women (Group A) with presurgical subcutaneous triptorelin depot injection before HTA with controls (Group B, n=15). Inclusion criteria were: recurrent menorrhagia, uterus length < 12 cm, no previous hormonal therapy for at least six month, and family plan completed. Student’s t test was applied, as appropriate, to compare continuous variables. Proportion were compared with chi-squared. Results: After 12 months of follow-up, Group A showed a significantly lower (0% vs 20%; p = 0.03) failure rate after hydrothermoablation than the Group B and a generally higher successful rate at 24 and 48 months. The discomfort, evaluated with VAS, showed a mean value of 47.6 ± 15.9 (± SD); 96.7% of women reported a mild-moderate postoperative pain. No perioperative and late complications were recorded. Conclusions: Presurgical treatment with GnRH analogues seems to improve long term efficacy of HTA. Perioperative pelvic pain seems to not be affected by myometrium thickness.

Key words: Menorrhagia; Hydrothermoablation; GnRH analogues.

Introduction

The prevalence of heavy menstrual bleeding interests about 65% of women during perimenopausal period [1]. The first thing that has to be excluded in the management of vaginal bleeding is endometrial cancer, that could be ruled out by hysteroscopy and endometrial biopsy [2, 3]. The hysteroscopic evaluation also allows to diagnose organic lesions such as polyps or submucosal myomas that can be removed with excellent results [3, 4]. Dysfunctional uterine bleeding (DUB) refers to unspecified bleeding from the uterus that occurs in the absence of any recognizable pelvic pathology. It affects about 30% [5] of women and can be treated with medical therapy or with surgery; however, some women do not accept hormonal treatment for contraindications or for intolerance. Moreover, in case of failure of medical therapy many, women are referred towards hysterectomy, which, although it can be performed in a minimally invasive way, remains a major surgical intervention [6]. Transcervical endometrial resection was introduced by Neuwirth in 1976 as a conservative surgical treatment and it is still now effective for the control of recurrent menorrhagia, with a success rate of 75-80% at five years and only 10-12% of failure managed with subsequent hysterectomy [7-11]. Hysteroscopic endometrial resection is a valid technique in a skilled surgeon’s hand, but it requires a long learning curve and it could have some side effects and even serious complications such haemorrhage or metabolic effects [12]. The second generation ablation techniques were introduced at the end of the 1990s; they were implemented with the aim to reduce the difficulties of the resectoscopic technique, hence to increase the diffusion of these less invasive procedures. The main purpose of these procedures is to reduce hysterectomies for abnormal uterine bleeding in an anatomically normal uterus [13, 14]. Hydrothermoblator is a simple procedure which uses a hysteroscope in a specific sheath introduced in the cervix; the uterine cavity is filled with saline solution at 90°C [15].

The aim of the present study was to evaluate the long term efficacy of presurgical treatment with GnRH analogues on the success rate of hydrothermal endometrial ablation (HTA) in the treatment for menorrhagia, and the relationship between myometrial thickness and pelvic pain.

Materials and Methods

Thirty premenopausal women with menorrhagia (abnormal uterine bleeding refractory to medical management) were enrolled in a longitudinal prospective clinical trial in the Department of Women’s and Children’s Health, Obstetrics and Gynecology Clinic, University of Padua (Italy).

An informed consent was obtained from all patients, which explained the involved side effects, risks, and benefits of medications and the procedures.

The patients were divided in 2 groups (A and B) on the basis of their arrival to the present Day Hospital ambulatory, in a ratio 1:1.
Group A included 15 women which received subcutaneous triptorelin depot injection, (3.75 mg every 28 days for two times) [12]; the subsequent HTA was performed after 15-20 days from the last injection. Group B (control group) included 15 women and the HTA was performed in the proliferate phase, at days 7 - 10 of the menstrual cycle.

Inclusion criteria were: recurrent menorrhagia, uterus length < 12 cm, no previous hormonal therapy for at least six months, and completed family plan. All women underwent presurgical evaluation with physical examination, office hysteroscopy and endometrial biopsy, Pap smear, and transvaginal ultrasound for excluding endometrial and cervical cancer.

Other exclusion criteria were for preservation of fertility, suspected genital tract infection or malignancy and previous endometrial ablation, submucous myoma larger than three cm or intramural myoma ≥ five cm in the largest diameters, structural uterine anomalies, and adnexal pathologies.

At the presurgical transvaginal ultrasound, the authors also measured the anterior and the posterior uterine wall thickness, taking the size at the middle of the longitudinal scan in absence of myoma, and distinguished the measurement in ≤ 25 mm, 26-30 mm, and ≥31 mm.

Surgical procedure
Hta procedure consisted of cervical dilatation with Hegar dilator up to 7.5 mm; then a 2.9 mm fibroscope (0°) was introduced in an insulated hysteroscopic sheath. Its control mechanism was housed in a compact console mounted on a mobile cart. Circulation of fluid (0.9 % saline solution) was controlled by gravity, based on the height of the fluid container above the patient uterus, with actual intrauterine pressure reduced from hydrostatic pressure by the effect of the evacuation pump that recirculates fluid to the elevated reservoir. Only then the heating of circulating saline began, with a therapy cycle of ten minutes.

On completion of the therapy cycle, the operator was prompted to wait for one minute refreshing cycle to finish. As a safety feature, the HTA system was calibrated to detect loss of as little as ten ml of saline from closed loop circulation. The intrauterine pressure was determined by a microprocessor within 50-55 mmHg; over this value the passage of the saline solution through the salpinx may happen [15]. Four hours after the procedure, the authors evaluated the subjective symptoms as pelvic pain, cystitis, objective symptoms as vaginal and vulvoperineal burns, and the necessity of painkiller medicine.

The discomfort was assessed with visual analog scale (VAS) using this score: 0 as no pain and 100 the most painful. The pelvic pain was considered as mild from 0 to 40; moderate from 41 to 70, and severe from 71 to 100. These results were related to the measurement of the anterior and the posterior uterine wall thickness assessed at the presurgical transvaginal ultrasound.

All the women have been evaluated seven days after the procedure with a questionnaire by a telephonic interview asking the presence of foul smelling vaginal discharges, pelvic pain, fever, and urinary tract infections. An improvement of the menorrhagia as eumenorrhrea, hypomenorrhea, and amenorrhrea where considered a success of the procedure. The persistence of menorrhagia was considered a failure.

The follow up was conducted at 12, 24, and 48 months with a telephone interview after seven days confirmed no late complications.

In the Group A, at 12 months, the successful rate was 100% (ten eumenorrhrea, one hypomenorrhea, four amenorrhrea), at 24 months was 93.3% with nine eumenorrhrea and five amenorrhrea in Group A; in one patient there was a recurrent menorrhagia, but the patient did not need any further conservative or demolition surgical treatment. At 48 months the successful rate persisted at 93.3% with seven eumenorrhrea, three hypomenorrhea, four amenorrhrea; the same woman persisted in recurrent menorrhagia (Table 1) and underwent laparoscopic hysterectomy 39 months after endometrial ablation. No long term complications were referred and the satisfaction rate for the procedure was high in 80% of cases.

In Group B, at 12 months the success rate was 80% with seven eumenorrhrea, two hypomenorrhea, three amenorrhaea; in the remaining three cases there were recurrent menorrhagia after four, six, and eight months, respectively. At 24 months the success rate persisted in 80% with seven eumenorrhrea, two hypomenorrhea, three amenorrhrea; the failure persisted in three cases and one of these underwent a laparoscopic supracervical hysterectomy 14 months after the treatment. At 48 months the success rate decreased to 73.3 % with five eumenorrhrea, six amenorrhrea, two persistent menorrhagia, and another one recurred with menorrhagia after 36 months. None of these three patients recurred to other conservatives or demolition procedures (Table 1). No long term complications were referred; the satisfaction rate for the procedure was 67%.
Through statistical analysis, Group A with GnRH analogues neoadjuvant treatment showed a significant lower failure rate after hydrothermoablation than in Group B ($p = 0.03$; Table 1).

The discomfort, evaluated with VAS, showed a mean value of 47.6 ± 15.9; 13 patients had mild pain; 16 had moderate, and one had severe pain. In Group A there were six patients with mild pain, eight with moderate pain, and one with severe pain. In Group B there were seven women with mild pain and eight women with moderate pain. Only seven patients (one mild, five moderate, and one severe) needed painkiller therapy in postoperative time (ketorolac tromethamine ten mg i.v.). All the patients were discharged within eight hours after surgery.

There was no relationship between perioperative pelvic pain score and myometrial thickness (Table 2); no differences were observed between anterior or posterior wall myometrial thickness and pain score. Only one patient in Group A had severe pain, and an anterior and posterior wall uterine thickness of more than three cm was observed.

### Discussion

Recurrent menorrhagia is the most common finding, frequently associated with a bad quality of life. Until 20 years ago, total hysterectomy was the option proposed for solving recurrent menorrhagia. In the last three decades recent developments in endoscopic technology have led to increase conservative and mini-invasive treatment of intrauterine lesions, including pre-neoplastic lesions, in women who require the preservation of the uterus [16, 17]. Also the conservative surgical treatment of DUB has made progress in recent years in the production of significantly modified endometrial ablation technology, with the introduction of the first and second generation ablation techniques.

Among first generation techniques the endometrial resection was the gold standard technique. The aim of this procedure is the excision or the destruction of endometrium and basal endometrial layer, thus preventing its future growth with progressive decrease in the menses at least over the first six months after the treatment [9]. Some authors demonstrated the long term efficacy of endometrial resec-

| Table 1. — Triptorelin depot injection, 3.75 mg treatment (Group A) vs no treatment (Group B). |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Menstrual Status**            | **12 months**   | **24 months**   | **48 months**   |
| **A (15)**                      | **B (15)**      | **A (15)**      | **B* (14)**     | **A (15)**      | **B* (14)**     |
| Eumenorrhea (%)                | 10 (66.7)       | 7 (46.7)        | 9 (60)          | 7 (46.7)        | 5 (33.3)        |
| Hypomenorrhea (%)              | 1 (6.7)         | 2 (13.3)        | 0               | 2 (13.3)        | 3 (20)          |
| Amenorrhea (%)                 | 4 (26.6)        | 3 (20)          | 5 (33.3)        | 3 (20)          | 4 (26.7)        |
| Success (%)                    | 15 (100)        | 12 (80)         | 14 (93.3)       | 12 (85.7)       | 14 (93.3)       |
| Failure (%)                    | 0               | 3 (20)          | 1 (6.7)         | 2 (14.3)        | 1 (6.7)         |

(*) One patient underwent laparoscopic supracervical hysterectomy at 14° month from HTA.

| Table 2. — Comparison between uterine wall thickness and postoperative pain. |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Group A: anterior uterine wall** |
| Thickness                       | Mild pain       | Moderate pain   | Severe pain     |
| (mm)                            | (0-40)          | (41-70)         | (71-100)        |
| ≤ 25                            | 6               | 6               | -               |
| ≥ 25                            | -               | -               | 1               |

| **Group B: anterior uterine wall** |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Thickness                       | Mild pain       | Moderate pain   | Severe pain     |
| (mm)                            | (0-40)          | (41-70)         | (71-100)        |
| ≤ 25                            | 5               | 6               | -               |
| ≥ 25                            | 2               | 2               | -               |

| **Group A: posterior uterine wall** |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Thickness                       | Mild pain       | Moderate pain   | Severe pain     |
| (mm)                            | (0-40)          | (41-70)         | (71-100)        |
| ≤ 25                            | 6               | 6               | -               |
| ≥ 25                            | -               | 1               | 1               |

| **Group B: posterior uterine wall** |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Thickness                       | Mild pain       | Moderate pain   | Severe pain     |
| (mm)                            | (0-40)          | (41-70)         | (71-100)        |
| ≤ 25                            | 4               | 6               | -               |
| ≥ 25                            | 2               | 2               | -               |

| **Group A: posterior uterine wall** |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Thickness                       | Mild pain       | Moderate pain   | Severe pain     |
| (mm)                            | (0-40)          | (41-70)         | (71-100)        |
| ≤ 25                            | 1               | -               | -               |
| ≥ 25                            | -               | 1               | 1               |

| **Group B: posterior uterine wall** |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Thickness                       | Mild pain       | Moderate pain   | Severe pain     |
| (mm)                            | (0-40)          | (41-70)         | (71-100)        |
| ≤ 25                            | 1               | -               | -               |
| ≥ 25                            | -               | 1               | 1               |
To reduce the technical skill required to perform the endometrial resection, other new techniques, that include direct circulation of heated saline solution (hydrothermal ablation), microwave ablation, radiofrequency hyperthermia, and thermal balloon were created. These new ablation techniques require a simple instrumentation and their application is simple. These aspects are very important to reduce the rate of complications of the transcervical endometrial resection and to permit the diffusion of these techniques [12, 19]. These techniques are a good solution in the management of recurrent menorrhagia in high anaesthesiologic – surgical risk patients because they do not use hypotonic solution.

The thermal balloon endometrial ablation is performed by heating a fluid – filled balloon inside the uterine cavity and using both heat and pressure to destroy the endometrium [20]. The balloon is filled with saline solution heated at 82°C for eight minutes with an internal pressure of 170 mmHg. It produces a necrotic coagulation of the endometrium for indirect heat transfer from the balloon to the endometrium.

HTA is the only procedure which is performed under direct hysteroscopic vision [21-24]. The innovation of this technique consists in free circulation of saline solution at 90°C; this aspect permits the heat to spread within the entire uterine internal area, even the tubal ostia, with a myometrial deep thickness of one to three mm [23]. This procedure could be performed in presence of submucous myomas because the heated saline solution takes a coagulative effect also on irregular surface [25]. This is an important advantage, over many other endometrial ablation devices, which need a regular uterine cavity. During HTA procedure myoma’s vessels are completely obliterated and sometimes the myoma could be reduced for necrosis.

Many studies carried out in vitro had analysed the cryothermic and hypertermic effect on human myomas and the nearest myometrium. The myocell necrosis increases from 17% to 88% when these cells underwent an increase of the temperature from 45°C to 80°C for ten minutes. Instead the myocell necrosis increases from 12% to 27% when the temperature decreases from –20°C to –80°C. Moreover, the intrauterine pressure produces a compression on myoma’s vessel with hypoxia and necrosis of the myoma [24].

The choice of these procedures is due to the necessity of the treatment of “difficult” patients for dyscoagulopathies, hearth disease, autoimmune disease, and transplants; they are at high anaesthesiologic and surgical risk and cannot undergo dangerous surgical procedures (i.e. endometrial resection, hysterectomy).

Brun et al. have demonstrated an amenorrhea rate after six months of approximately 20% and 36% after 12 months from treatment with Cavaterm and an amenorrhea rate of 21% and 29% after six and 12 months with endometrial resection [26], whereas Hawe and Mettler in pilot studies have obtained an amenorrhea rate of more than 50% but these results have not been confirmed in comparative trials [27-30].

The large reduction in menstrual blood loss after endometrial ablation results in a high satisfaction rate: 93% to 89% after Cavaterm and 80% to 79% after resection at six and 12 months of follow up, respectively [26].

The use of high temperature for ablation (80°C for the balloon and 90°C for HTA) forced many doctors to assess the cardiac effects, pelvic pain after endometrial ablation, the depth of the thermal damage on the uterus, and surrounding organs. In the procedure with balloon, they observed that the thermal damage was limited to the endometrium and the inner part of the myometrium [26].

After the treatment with balloon, some uteri were histopathologically examined after hysterectomy; the larger depth of myometrial damage (5.8 mm) was reached at the anterior wall at the hystmic portion. Instead in the nearest areas, excluding the uterine cornua where the wall thickness is very thin, the myometrial destruction occurred till 3.3 mm. The mean maximum depth of the myometrial damage in all the uterus was 3.4 ± 1.8 mm; in uterus treated for three times of 24 minutes at 81°C, the maximum depth of damage was 5.0 mm. This study showed that the depth of endomyometrial damage and the temperatures reached at uterine serosa permitted to perform the procedure safety and with low complication risks [23].

Among the second generation procedures, HTA is more versatile and it uses the coagulative effect of the hot saline solution on the endometrium and first layer of the myometrium. It has a good success rate with respect to the menorrhagia resolution and avoiding a hysterectomy. Moreover, it has the advantage of reducing the risks of fluid overload syndrome.

The present prospective randomised study on 30 patients let the authors to monitor the menstrual blood loss characteristics after the HTA treatment with a follow up of 12, 24, and 48 months. Among these patients, 15 were treated with GnRH analogues before surgery. The GnRH analogue neoadjuvant treatment aimed to reduce the endometrial vascularization and make an endometrial mucosa atrophy with better thermal destroying effect [26]. These effects induce a better visibility during the procedure and a less quantity of re-absorbed distension solution. The follow up at 12, 24, and 48 months highlighted how the patients pre treated with Triptorelin showed a better efficacy of the procedure rather than not treated patients, with a successful rate at 12 months of 100% vs 80%, and at 24 months of 93.3% vs 80%. At 48 months the global successful rate was 93.3% for Group A versus 73.3% of Group B. No difference with respect to intraoperative and long term complications of procedure were observed between the two groups. This is probably due to the action of Triptorelin on the endometrium and the first layers of the myometrium with a reduction of vessel number, and a decrease of the endometrial thickness and surface.
The analysis of the relationship between the thickness of the uterine wall and the postoperative pain highlighted the concept that there was no correlation between these two factors. A thick uterine wall seems not to protect during HTA, as well as a thinner wall does not expose to a risk of intensive pain. Likewise the thickness of the wall has no influence on the intensity and the length of perioperative pain.

The present results confirmed that endometrial ablation is an interesting alternative procedure to hysterectomy for menorrhagia, with a success rate of around 80-90%, and low patient’s discomfort and hospital stay [31, 32].

Although it is well known that this technique could fail in 10-15% of cases just within 12 months, pre-surgical treatment with GnRH analogue seems to improve long term efficacy of HTA with a successful rate more than 90% at 48 months follow up. HTA is a simple surgical procedure with low complication rate and high acceptability of patients who preserve their psychophysical well being [33-35].

It is important to underline that the patient must have correct information and she has to decide the better treatment for herself. The most important thing is the high satisfaction rate of the women who maintain the integrity of their genital tract. The exclusion of patients who should be subject to other procedures [6, 36] and the correct selection of patients who undergo these procedures permit to obtain a high success rate at long term with an amenorrhoea rate of 40%.

References


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Serum levels of androgens and prostate-specific antigen in endometriosis

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Summary

Objective: The aim of the present study was to evaluate the levels of serum androgens and prostate-specific antigen (PSA) levels in patients with endometriosis. Materials and Methods: Patients with Stage III/IV (advanced stage) endometriosis were compared to controls with respect to basal serum levels of total testosterone (T), free testosterone (fT), androstenedione (A), dehydroepiandrosterone (DHEA), dehydroepiandrosterone-sulphate (DHEA-S), and PSA in the early follicular phase of menstrual cycle for this prospective case control study. Results: Level of T, fT, A, DHEA, and DHEA-S were higher in patients with endometriosis when compared to control subjects, but the difference was not statistically significant. The mean PSA level was 0.0074 ± 0.0120 ng/ml in patients with endometriosis and 0.0059 ± 0.0056 ng/ml in control group and there was no statistically significant difference between groups (p = 0.58). Conclusion: Serum basal androgens and PSA levels are higher in endometriosis group with respect to control but the differences are not statistically significant.

Key words: Endometriosis; Androgens; Prostate-specific antigen.

Introduction

Endometriosis is a gynecological condition where endometrial gland and stromal structures are situated outside of the uterine cavity. This hormone-dependent disease in which estrogen plays the most prominent role affects five to ten percent of the women in their reproductive age. The patients frequently complain of chronic pelvic pain, dyspareunia, and infertility [1-3]. Danazole is a testosterone derivative which is used in the clinical treatment of endometriosis and induces regression of endometrial foci [4].

In women, sources of hormones are ovaries, adrenal glands, and peripherally transformed forms of precursor hormones released from these organs. With their systemic effects androgens play a role in physiological events such as sexual hair growth, calcium storage in bones, and libido [5,6]. In the ovary; androgens, primarily testosterone (T) and androstenedione (A), in addition to their roles in acting as metabolic precursors for steroid production, have paracrine effects so as to enhance follicular recruitment and maturation [7,8]. In physiological and pathological conditions of endometrium; androgens have been reported to counteract against estrogen effects during cellular proliferation [9].

Prostate-specific antigen (PSA) is a molecule produced in the prostatic tissue and secreted in seminal fluid. It is quite specific for the diagnosis and monitoring of prostatic adenocarcinoma [10]. Production of this marker which represents androgenic load, was recently revealed in women and its presence has been demonstrated in ovary, breast tissue, amniotic fluid, and breast milk. Increase in PSA levels in female patients with PCOS, hyperandrogenemia, and hirsutism relative to the control group has been demonstrated and decrease in PSA levels with anti-androgen treatment has been reported [11-15].

Keeping in mind the fact that endometriosis is an estrogen-dependent disease and androgen derivatives cause clinical symptomatic relief in endometriosis [3,4]. Theoretically intrinsic androgen insufficiency can be implicated in endometriosis. Adequate numbers of studies investigating androgens levels have not been conducted so far, and PSA levels which represent androgenic load in endometriosis patients have not been investigated previously. To the best of the authors’ knowledge, this is the first study to investigate the effect of PSA in the pathophysiology of endometriosis. In this study, evaluation of androgens and PSA levels in patients with endometriosis was intended.

Materials and Methods

The present prospective case control study was performed between January to June 2012 in the Obstetrics and Gynecology Clinic at the Dicle University Medical Faculty. Sixty-seven patients who had undergone laparoscopy and/or laparotomy for infertility evaluation and/or for benign gynecologic disorders, such as dermoid cyst (23 women), tubal ligation (11 women), and endometriosis (33 patients) were recruited in the study. Endometriosis was diagnosed by laparoscopy and/or laparotomy with histological...
confirmation of the disease. Stage I/II endometriosis (three patients) were not included in the study because of small sample size. Women with endometriosis which were Stage III/IV (advanced stage) according to the revised American Fertility Society classification for Endometriosis [16] were enrolled as the study group.

Patient and control groups were in reproductive age period and their ages ranged from 19-38 years. All women had regular menstrual cycle (intervals of 21 and 35 days) and had no acute or chronic inflammatory diseases or history of hormonal treatment for the last three months.

Women who had history of a diagnosis of polycystic ovary syndrome, endocrinopathy, and complaint/sign of hirsutism were not included in the study. Also exclusion criteria for control group included: complaint of secondary dysmenorrhea, chronic pelvic pain, and dyspareunia.

Six patients in endometriosis group and nine patients in control group were not included in the study because their PSA level was not available. Following application of inclusion and exclusion criteria, women in study group consisted of 24 patients whereas controls were 25 patients.

Groups were compared with respect to demographic, hematologic parameters, CA-125, and basal hormones including androgens total T, free testosterone (fT), A, dehydroepiandrosterone (DHEA), dehydroepiandrosterone-sulphate (DHEA-S), and PSA levels. The study protocol was approved by the Medical Ethics Committee of Dicle University and the informed consent was obtained from all subjects involved in the study.

### Serum sampling

Blood samples were drawn from women (day 2-4) in the follicular phase during menses between 8.00-10.00 a.m. on the day after an overnight fasting period before the surgery. The phases of menstrual cycle were determined by the last menstrual period. Each collected blood sample was immediately centrifuged at 4,000 rpm/s + four C for ten min and then transferred into an Eppendorf tube. Samples were transferred on ice and kept in -70°C deep freeze until the end of the study. Only the serum samples of the patients in both groups were studied after the histological confirmation of endometriosis and after exclusion of the noneligible patients for the study.

### Hormone assays

Serum PSA, FSH, E2, LH, and DHEA-S levels were measured by the method of electrochemiluminescence immunoassay (ECLIA) assay. The intra-assay and inter-assay coefficients of variation for all of these assays were < 4.3% and < 6.1%, respectively.

Radioimmunoassay was used for the determination of Serum T, fT, A, and DHEA levels. The intra-assay and inter-assay coefficients of variation for these assays were < 6.2% and < 9.7%, respectively.

### Statistical analysis

Statistical analysis of the obtained data was conducted by using Statistical Package for Social Sciences (SPSS) version 15.0. Data were presented as mean ± standard deviation. Normality of variance was tested with Kolmogorov-Smirnov test. Comparisons of continuous variables between two groups were applied using Student’s t test. Variables showing non-parametric distribution were compared between groups by using Mann-Whitney U test. A p value less than 0.05 was accepted as statistically significant.

### Results

The mean age and body mass index (BMI) were: 31.4 ± 3.8 years, 23.3 ± 2.67 kg/m², respectively, for endometriosis subjects and 31.5 ± 3.6 years, 23.7 ± 2.25 kg/m², respectively, for endometriosis patients without reaching the statistical significant value.

The mean PSA level was 0.0074 ± 0.0120 ng/ml in patients with endometriosis and 0.0059 ± 0.0056 ng/ml in control group, whereas controls were 25 patients. Following application of inclusion and exclusion criteria, women in study group consisted of 24 patients whereas controls were 25 patients.

Groups were compared with respect to demographic, hematologic parameters, CA-125, and basal hormones including androgens total T, free testosterone (fT), A, dehydroepiandrosterone (DHEA), dehydroepiandrosterone-sulphate (DHEA-S), and PSA levels. The study protocol was approved by the Medical Ethics Committee of Dicle University and the informed consent was obtained from all subjects involved in the study.

### Serum androgens and prostate-specific antigen levels between groups.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Endometriosis (n = 24, mean ± SD)</th>
<th>Control (n = 25, mean ± SD)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>T, ng/mL</td>
<td>0.240 ± 0.124</td>
<td>0.215 ± 0.057</td>
<td>0.38</td>
</tr>
<tr>
<td>fT, ng/mL</td>
<td>1.674 ± 1.0139</td>
<td>1.237 ± 0.432</td>
<td>0.06</td>
</tr>
<tr>
<td>A, ng/mL</td>
<td>1.599 ± 1.279</td>
<td>1.068 ± 0.946</td>
<td>0.12</td>
</tr>
<tr>
<td>DHEA, ng/ml</td>
<td>9.439 ± 6.441</td>
<td>7.348 ± 2.119</td>
<td>0.38</td>
</tr>
<tr>
<td>DHEA-S, µmol/mL</td>
<td>173.9 ± 74.01</td>
<td>169.5 ± 59.9</td>
<td>0.93</td>
</tr>
<tr>
<td>PSA, ng/ml</td>
<td>0.0074 ± 0.0120</td>
<td>0.0059 ± 0.0056</td>
<td>0.58</td>
</tr>
</tbody>
</table>

### Discussion

In this prospective well-designed controlled study, the authors investigated the role of androgens and PSA in the pathophysiology of endometriosis by measuring serum levels of androgens and PSA which has been known as a good marker of androgen load in human body. They found that androgens and PSA has a tendency to increase in endometriosis patients without reaching the statistical significant value.

**Table 2.** — Serum androgens and prostate-specific antigen levels between groups.

**Table 1.** — Comparison of demographics, hematological, and hormonal parameters between groups.
The role of androgens in the pathogenesis of endometriosis is involved in intricate interactions because of the intermingling factors as hormone levels, variations in the hormone receptor levels, and conversion of androgens via aromatization to estrogens.

In the literature, limited number of studies have compared androgen levels between endometriosis and control group. Studies performed in various compartments in the body as serum, peritoneal, and follicular fluids are not sufficient for precise evaluation [17]. Furthermore, androgen levels in these cavities may not correlate with each other. Studies performed during various stages of the menstrual cycle have confronted with difficulties in comparisons between androgenic hormone levels which potentially show variations in different phases of the cycle.

Mahmood et al. [18] compared sex steroids between patients with mild endometriosis and controls at preovulatory period and reported similar A levels in the peritoneal fluid. Pellicer et al. [19] assessed steroid levels in follicular milieu in patient with endometriosis with in vitro fertilization (IVF) cycle and reported decreased T accumulation with the severity of the disease. The role of androgens in the pathophysiology of endometriosis is highly suspected by means of danazol study results. The most recent study reported the effect of danazol in patients having endometriosis associated pelvic pain. Based on Cochrane analysis report, the authors concluded that danazol was an effective therapy in relieving endometriosis associated pelvic pain symptoms [20]. This study may support the hypothesis that androgenic therapy may decrease the estrogenic micro environment volume in patients with endometriosis. However in this study, the authors could not find significant changes in serum levels of androgens in women with endometriosis, compared with controls.

Higher basal testosterone levels have been associated with improved IVF outcomes in diminished ovarian reserve, and higher serum testosterone has been correlated with higher oocyte numbers retrieved at IVF in this group [21]. DHEA is a precursor hormone for estradiol and testosterone and adrenal secretion of it, is potentiated by ovarian hyperstimulation with gonadotropins. Recent clinical reports with encouraging results have demonstrated that co-treatment with androgens, such as DHEA and transdermal testosterone, could increase both quantity and quality of oocytes and embryos, and improve pregnancy outcomes in women with diminished ovarian function [22]. In this study, DHEA levels in patients with endometriosis were higher than those of controls but the difference could not reach statistical significance.

Higher levels of T, fT, A, DHEA, DHEA-S, and PSA were observed in the endometriosis group when compared with the control group without any statistically significant difference. This study has some limitations. Small sample size of the study prohibits generalizability of the results. Serum levels of hormones may not correlate to follicular micro environment. Further studies are welcomed to clarify this issue.

Conclusion

Serum basal androgens and PSA levels are higher in endometriosis group with respect to control but the differences are not statistically significant. Increased production of androgens may have protective effect such as increasing quality of oocytes.

References


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Rising cesarean section rates, a patient’s perspective: experience from a high birth rate country

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2Department of Statistics, Faculty of Economics and Political Sciences and The Social Research Center, The American University in Cairo, Cairo
3Department of Pediatrics, Suez Canal University, Ismailia (Egypt)

Introduction

Cesarean section (CS) is one of the most commonly performed surgical procedures, ranked first in industrialized world [1]. The rates continue to rise despite lack of evidence that mortality or morbidity figures are improved, on the contrary CS is associated with increased complications as maternal mortality, deep venous thrombosis, visceral injury, and hysterectomy [2]. These complications increase with repeated CS [3].

In Egypt, the CS rate has experienced a fivefold increase over the past 20 years [4]. The most recent Egyptian Demographic and Health Survey (EDHS) [4] has shown that overall CS rate in Egypt was 27.6% compared to a rate of 5% in 1992. This drastic increase has urged the authors to investigate its underlying causes. In a previous study [5], the authors investigated the obstetricians' perspectives and attitudes towards CS. They found that a majority of obstetricians in Egypt ignore many obstetric procedures and maneuvers that could reduce cesarean section rates such as external cephalic version for breech presentation, selected vaginal breech delivery, scalp pH measurement, and tubal sterilization during CS.

Other studies have focused on women’s attitudes towards CS. Several studies have focused on maternal request as the sole indication for cesarean section [6, 7]. Maternal request for CS as a preferred mode of delivery range between 7-17% of pregnant women studied at their second or third trimesters [8]. Several factors can contribute to maternal decision-making. Fear of pain, genital trauma or altered sexual function can lead women to prefer abdominal route of delivery [9]. Several studies have addressed the relationship between socioeconomic and educational levels and CS rate. Fairly et al. in 2010 [10] have shown that CS rates significantly differ according to both individual social class and area deprivation.

Knowledge can undoubtedly be considered as a milestone in constructing individual’s decision-making. An important source of knowledge to a pregnant woman is medical health professional during antenatal care sessions. Antenatal care is considered adequate if it entails appropriate number of visits based on risk level. Overall, low risk patients need to be seen less frequently during pregnancy. Adequate antenatal care (ANC) sessions should be able to detect and manage high risk patients and to provide adequate information and guidance to pregnant women in different aspects including the route of delivery [11].

The current study aims at shedding light on the women’s aspect of CS decision-making, by identifying the effect of social class, education, and antenatal care on women preference and CS rate.

Materials and Methods

This is a descriptive study of information gathered from 509 women attending postnatal clinics in three primary care units in Ismailia governorate which is located in northeastern part of Egypt in October 2010. The information was collected via a structured questionnaire. The questionnaire included three sections. The first
Table 1. — Background characteristics of the respondents.  

<table>
<thead>
<tr>
<th>Sample characteristics (N=509)</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age group</strong></td>
<td></td>
</tr>
<tr>
<td>16-20</td>
<td>4.5</td>
</tr>
<tr>
<td>21-30</td>
<td>62.5</td>
</tr>
<tr>
<td>31-40</td>
<td>29.4</td>
</tr>
<tr>
<td>41-45</td>
<td>3.6</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
</tr>
<tr>
<td>Illiterate</td>
<td>28.5</td>
</tr>
<tr>
<td>Primary</td>
<td>54.4</td>
</tr>
<tr>
<td>Secondary</td>
<td>16.1</td>
</tr>
<tr>
<td>High Education</td>
<td>1</td>
</tr>
<tr>
<td><strong>Employment</strong></td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>20.4</td>
</tr>
<tr>
<td>Not employed</td>
<td>79.6</td>
</tr>
<tr>
<td><strong>Parity</strong></td>
<td></td>
</tr>
<tr>
<td>Para 1</td>
<td>17.1</td>
</tr>
<tr>
<td>Multipara</td>
<td>82.9</td>
</tr>
<tr>
<td><strong>ANC</strong></td>
<td></td>
</tr>
<tr>
<td>Inadequate</td>
<td>41.7</td>
</tr>
<tr>
<td>Adequate</td>
<td>58.3</td>
</tr>
</tbody>
</table>

Table 2. — CS rates based on educational levels, employment status, ANC, and wealth quintiles.  

<table>
<thead>
<tr>
<th>Normal Delivery N (%)</th>
<th>CS N (%)</th>
<th>Total N (%)</th>
<th>Total N</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illiterate</td>
<td>50 (80.6)</td>
<td>12 (19.4)</td>
<td>62 (16.4)</td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>52 (64.2)</td>
<td>29 (35.8)</td>
<td>81 (21.5)</td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>92 (48.9)</td>
<td>96 (51.1)</td>
<td>188 (49.9)</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>High</td>
<td>20 (43.5)</td>
<td>27 (56.5)</td>
<td>46 (12.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Employment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>39 (50.6)</td>
<td>38 (49.4)</td>
<td>77 (20.4)</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>174 (58)</td>
<td>126 (42)</td>
<td>300 (79.6)</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>ANC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>41 (66.1)</td>
<td>21 (33.9)</td>
<td>62 (16.4)</td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>49 (55.7)</td>
<td>39 (44.3)</td>
<td>88 (23.3)</td>
<td>0.24</td>
</tr>
<tr>
<td>Good</td>
<td>123 (54.2)</td>
<td>104 (45.8)</td>
<td>227 (60.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Wealth</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>48 (70.6)</td>
<td>20 (29.4)</td>
<td>68 (18.2)</td>
<td></td>
</tr>
<tr>
<td>Level 2</td>
<td>41 (62.1)</td>
<td>25 (37.9)</td>
<td>66 (17.7)</td>
<td></td>
</tr>
<tr>
<td>Level 3</td>
<td>46 (60.5)</td>
<td>30 (39.5)</td>
<td>76 (20.5)</td>
<td>0.372 &lt;0.05*</td>
</tr>
<tr>
<td>Level 4</td>
<td>47 (54.7)</td>
<td>39 (45.3)</td>
<td>86 (23.1)</td>
<td></td>
</tr>
<tr>
<td>Level 5</td>
<td>31 (40.8)</td>
<td>45 (59.2)</td>
<td>76 (20.5)</td>
<td></td>
</tr>
</tbody>
</table>

*psignificant at 0.05

section included background socio-demographic data (age, marital status, work status, and educational level). The second section included obstetrical history for the last pregnancy and delivery. Items included questions related to place and standard of antenatal care. Adequacy of ANC was determined via number of visits, blood tests and ultrasonography performed, and nutritional supplementation. Other questions related to complicated pregnancy, place, timing, and mode of last delivery were asked. The third section included questions related to economic standard including household characters and electric devices and motor vehicle possession.

As a large number of women in study were illiterate, direct questioning, explanation, and filling of the questionnaire was done by the authors or health attendants. The rest of the study group filled the questionnaire themselves with access for help if needed.

ANC was classified as good if it included more than four visits, blood tests, ultrasonography performed, and supplementation given, average if two or more items were present, and poor if two or more items were absent. Economic level was divided into standard five wealth quintiles. Main outcome measures were type of delivery and patient preference. Those who had complications of pregnancy or previous CS were excluded from analysis. Complications included medical or surgical conditions during pregnancy, malpresentations, or fetal macrosomia ≤ four kg.

Data were collected and analyzed by Statistical Package for the Social Sciences (SPSS) for windows version 19.0. Chi-square test was used relating different variables to the outcome measures. A stepwise logistic regression model was used to detect the most significant variables affecting CS rate. Statistical significance was defined at $p < 0.05$.

Results

Table 1 shows the basic characteristics of the whole group (n = 509). It shows that the majority of participants (62.5%) were in the age group of 21-30 years. Most of participants did not receive secondary or higher education. Primary education/illiteracy accounted for 82.9% of the study group. Most of the participants (79.6%) were unemployed at time of interrogation. The majority of participants (82.9%) were multiparae, and the majority (58.3%) received good ANC in their last pregnancy.

The participants that delivered via CS were 266 (52.3%) in their last delivery, 84 participants (16.5%) had a complicated last pregnancy, while 76 (14.9%) had a previous one or more CS. Those who had complicated pregnancies or previous CS were excluded from analyses. The remaining participants were 377 (74%), 164 (43.5%) of them had undergone CS for their last delivery. Of this number, 67 women (40.9%) had their CS planned.

Table 2 relates the CS rate to educational level, employment status, ANC standard, and wealth status. CS rate was significantly higher in highly educated women (56.5%) compared to illiterates (19.4%), and those with high standard of living; wealth level 5 (59.2%) compared to low economic standard; wealth level 1 (29.4%). Employment status and level of ANC received during pregnancy failed to show significant differences.

Out of 377 participants, only 29 (7.7%) reported that they had preferred CS as a method of delivery. In most of this group, 25 (86.2%) had CS in their last delivery ($p < 0.05$).

Table 3 shows the relationship between educational level, employment status, ANC standard and wealth status, and the number of participants preferring CS as a mode of delivery. Significant differences were shown in educational level ($p = 0.02$) and wealth level ($p = 0.01$).

The following factors namely, educational level, employment status, ANC level, wealth level, and method of
women delivering in a government facility to have a cesarean delivery. Cesarean deliveries were more common in urban rather than rural areas, in lower rather than upper Egypt. The rate of cesarean deliveries peaked among women in the highest wealth quintile and the most highly educated sector. Other studies have shown that cesarean delivery increase in the higher socioeconomic class and less deprived areas. The present study conforms to these results. CS rate was significantly higher in highly educated women (56.5%) compared to illiterates (19.4%), and those with high standard of living; 5th wealth quintile (59.2%) compared to low economic standard; 1st wealth quintile (29.4%).

The increased CS rate in women with high standard of living can be attributed to the perception that CS comes with less pain and suffering compared to normal delivery. At the same time, these women can afford the higher cost of the operation. Of note, CS rate was not affected by the ANC; which means that lack of proper counseling and education during that period added to that belief. Also, the physician’s attitude which plays a major role in decision-making had further influence on the outcome of delivery.

**Information given to the patient**

Accurate communication of the chances of clinical outcome is an essential tool for proper decision making by the patient [2]. It is assumed that ANC visits provide an excellent opportunity to detect and treat high risk patients and to provide adequate information guided by best evidence on the best method of delivery [11] The quality of healthcare program differ according to level of development of healthcare provider area [16,17]. The quality of program depend on several factors including number of visits, availability of equipment as ultrasonography, provision of blood tests, and above all, adequate care and time given by the healthcare provider. Assuming proper antenatal care is provided, it would be expected that the CS rate drop to a minimum in a non-complicated pregnancy. The present authors arbitrarily classified ANC service provided to their patients into adequate, average, and poor according to the number of visits (< 4; 4 or

---

**Table 3. — Mode of delivery preference rates based on educational levels, employment status, ANC, and wealth quintiles.**

<table>
<thead>
<tr>
<th>Education</th>
<th>Prefer Normal Delivery N (%)</th>
<th>Prefer CS N (%)</th>
<th>Total N (%)</th>
<th>Total N</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Illiterate</td>
<td>61 (98.4)</td>
<td>1 (1.6)</td>
<td>62 (16.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>75 (92.4)</td>
<td>6 (7.4)</td>
<td>81 (21.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>173 (92.4)</td>
<td>14 (7.5)</td>
<td>188 (49.9)</td>
<td>377</td>
<td>0.02*</td>
</tr>
<tr>
<td>High</td>
<td>38 (82.6)</td>
<td>8 (17.4)</td>
<td>46 (12.2)</td>
<td>377</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Employment</th>
<th>Prefer Normal Delivery N (%)</th>
<th>Prefer CS N (%)</th>
<th>Total N (%)</th>
<th>Total N</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Employed</td>
<td>68 (88.3)</td>
<td>9 (11.7)</td>
<td>77 (20.4)</td>
<td>377</td>
<td>0.11</td>
</tr>
<tr>
<td>Unemployed</td>
<td>279 (93.3)</td>
<td>20 (6.7)</td>
<td>300 (79.6)</td>
<td>377</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Education</th>
<th>Prefer Normal Delivery N (%)</th>
<th>Prefer CS N (%)</th>
<th>Total N (%)</th>
<th>Total N</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor</td>
<td>60 (96.8)</td>
<td>2 (3.2)</td>
<td>62 (16.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>81 (91.4)</td>
<td>7 (8.6)</td>
<td>88 (23.3)</td>
<td>377</td>
<td>0.38</td>
</tr>
<tr>
<td>Good</td>
<td>206 (90.7)</td>
<td>21 (9.3)</td>
<td>227 (60.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Wealth</th>
<th>Prefer Normal Delivery N (%)</th>
<th>Prefer CS N (%)</th>
<th>Total N (%)</th>
<th>Total N</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>64 (94.1)</td>
<td>4 (5.9)</td>
<td>68 (18.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 2</td>
<td>62 (93.3)</td>
<td>4 (6.1)</td>
<td>66 (17.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 3</td>
<td>75 (98.7)</td>
<td>1 (1.3)</td>
<td>76 (20.5)</td>
<td>372</td>
<td>0.01*</td>
</tr>
<tr>
<td>Level 4</td>
<td>78 (90.7)</td>
<td>8 (9.3)</td>
<td>86 (23.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 5</td>
<td>63 (82.8)</td>
<td>13 (17.2)</td>
<td>76 (20.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**Table 4. — Stepwise logistic regression analysis between mode of delivery and expected influencing factors.**

| Coefficient SE Wald test DF p |
|-------------------------------|-----------------|--------|-----|---|
| Mode of delivery | 2.14 | 0.5 | 15.04 | 1 | 0.00** |
| ANC | 0.33 | 0.33 | 0.96 | 1 | 0.32 |
| Education | 1.04 | 0.36 | 8.26 | 1 | 0.004** |
| Wealth status | 0.31 | 0.32 | 0.91 | 1 | 0.34 |
| Constant | -1.88 | 0.43 | 19.05 | 1 | 0.00** |

**Discussion**

The concept of shared decision-making has been gaining popularity over the last two decades among patients, providers and policy makers [12]. Shared decision-making entails a combined decision making by doctors and patients guided by best evidence available and adjusted according to the specific characteristics and values of the patient [13]. Although this concept has been endorsed at several clinical situations in obstetrics and gynecology [14, 15], mode of delivery decisions have not, so far, adopted this model of shared decision making [8]. This papers attempts to discuss how this model can fit the process of CS decision-making in our patients:

**The specific characteristics of the patient**

The 2008 EDHS [4] has shown that more than one-quarter of deliveries in the five-year period before the 2008 EDHS survey were by CS. Women delivering in a private health facility were slightly more likely than
more), provision of ultrasonography examination (yes, no), provision of blood testing (yes, no), and provision of supplements (yes, no) [4, 11]. They failed to find significant differences between the three groups regarding CS rate or prior patient’s preference to perform CS.

The result of this study is in line with other studies that devaluated the input of maternal CS preference rate that ranged between (0.3-14%) in overall CS rate [18, 19]. The authors found maternal CS preference rate to be 7.7% of the whole group who had uncomplicated pregnancies. However this percentage was significantly more represented in the group who had cesarean delivery. This association was the most significant in logistic regression.

This study presents a very high CS rate (52.3%) representing one of the highest CS rates in Egypt. This can be explained in part by the area of the study. Ismailia governorate is one of the Urban Lower Egypt governorates with an average socio-economic standards and an approaching value of CS and normal delivery costs. However, a rising and alarming CS trends can be depicted.

CS decision is a multi-disciplinary procedures with the client (patient) and provider (obstetrician) at the core. Several studies have highlighted the role of obstetricians’ views and attitudes in determining CS rates. This study shows that socio-economic and educational levels together with patient’s preference significantly affect CS rates, although patient preference appear to be in a lower position as compared to other factors including obstetricians’ preference. A clue towards this conclusion is a lack of significant effect of ANC on CS rate.

Acknowledgments

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Effectiveness of pericervical tourniquet by Foley catheter reducing blood loss at abdominal myomectomy

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Summary
Objective: To evaluate effectiveness of pericervical tourniquet by Foley catheter reducing blood loss at abdominal myomectomy. Materials and Methods: Retrospective chart review of 67 cases, with symptomatic myoma uteri and undertaken abdominal myomectomy, was performed. Myomectomy was performed in Group 1 (n = 34) by Foley catheter tourniquet around both uterin vessels and in Group 2 (n = 33) the tourniquet was not performed. Results: The average blood loss during myomectomy was 286.4 ± 137.5 ml for the tourniquet group and 673.8 ± 172.3 ml for the control group. Postoperative blood transfusion was necessary in two patients from the control group. Technique significantly reduced the intraoperative blood loss and postoperative hemoglobin fall in patients. No serious complications occurred on account of the tourniquet technique. Conclusions: The pericervical tourniquet by Foley catheter is a safe and effective method for reducing blood loss during abdominal myomectomy, although it should be evaluated in a randomized controlled trial.

Key words: Abdominal myomectomy; Leiomyoma; Hemorrhage; Pericervical tourniquet.

Introduction
Leiomyomas, also known as fibroids or fibromas are seen as the most common benign uterine neoplasm of the female genital system. This is seen between the ratio of 20–30% in women at reproductive age. Leiomyomas are the most common indications for hysterectomy [1].

Fibroids may be asymptomatic, or may present with menorrhagia, pain, abdominal mass, pressure effects, infertility, or recurrent pregnancy loss. Approximately 25% of women with fibroids experience symptoms, such as heavy bleeding, pelvic pain, and pregnancy complications [2].

Although medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) and hormonal therapy may be used to manage fibroid symptoms, some women require more aggressive forms of treatment [3].

Myomectomy, the surgical removal of myomas, is an important treatment option especially for women who desire to maintain or improve their reproductive potential [4]. Myomectomy has been associated with considerable blood loss intraoperatively and prolonged morbidity postoperatively [5, 6]. This is due to increased vascularity of the fibroid uterus. Uncontrolled hemorrhage may necessitate hysterectomy [7] and blood transfusion can be required in up to 20% of women after abdominal myomectomy [6]. Thus, several methods are employed to reduce blood loss during the operation. These methods include pericervical tourniquet [2], vaginal misoprostol [8], injection of diluted vasopressin and analogues into the myometrium [9], intravenous oxytocin [10], preoperative use of gonadotropin releasing hormone agonist (GnRHa) [11], chemical dissection with sodium 2-mercaptoethane sulfonate (mesna) [12], tranexamic acid, myoma enucleation by morcellation, uterine artery embolization [10], and bilateral uterine artery ligation [13, 14].

In 1953, Rubin replaced Bonney’s metal clamps with a single tourniquet around the cervix to achieve haemostasis during myomectomy [15]. The aim of this study is to investigate the effectiveness of the pericervical tourniquet technique.

Materials and Methods
The study was approved by the local ethical research committee (Application No.B.30.2.SEL.0.28.00.00/130-66). Informed consent form was obtained from each patient. This retrospective non-randomized controlled clinical study was carried out at the Department of Obstetrics and Gynecology at Mevlana University in Turkey, from August 2008 to January 2013.

A total of 67 patients recruited to the study were classified into two groups. The 34 patients assigned to group 1 (study group) underwent pericervical tourniquet by Foley’s catheter (size 14-16), and 33 patients in group 2 (control group) received no intervention. At least one large symptomatic subserosal, intramural or submucous uterine myoma ≥ six cm and who underwent an abdominal myomectomy, was recruited to the study. The indications for surgery included pelvic pain, lower abdominal discomfort, abnormal uterine bleeding, menometrorrhagia, infertility, and pressure symptoms from a pelvic mass. Some women exhibited more than one indication. History taking, clinical examination, basic investigations (urine analysis, complete blood count, fasting plasma glucose levels, liver, and kidney functions) and vaginal examination, as well as abdominal and transvaginal sonography, were performed. Women complaining about abnormal uterine bleeding underwent endometrial biopsy. The patients with concurrent anticoagulant therapy, hypertension, and premalignant endometrial pathology were excluded from the study. Preoperative treatment with GnRHa were not prescribed.
Figure 1. — Pericervical tourniquet was applied prior to myomectomy. Initially, a small hole was made in an avascular space in the broad ligament on either side of the uterine isthmus just lateral to the uterine vessels. Through a small hole in the broad ligament on each side of the uterus, a Foley’s catheter was placed around the lower uterus.

Figure 2. — By tightening the tourniquet sufficiently (over the arterial blood pressure), the blood flow to the uterus is arrested.

Figure 3. — Myomectomy can be performed in a bloodless field.

Pfannenstiel incision was performed in all patients. The surgical technique was always the same. Pericervical tourniquet were applied prior to myomectomy. Initially, a small hole was made in an avascular space in the broad ligament on either side of the uterine isthmus just lateral to the uterine vessels. Through a small hole in the broad ligament on each side of the uterus, a Foley’s catheter was placed around the lower uterus (Figure 1). By tightening the tourniquet sufficiently (over the arterial blood pressure), the blood flow to uterus was arrested (Figure 2). Providing that the venous blood flow is blocked while the arterial blood flow is maintained, it can actually cause blood loss to increase by using the tourniquet. Myomectomy can then be performed in a bloodless field (Figure 3). After reconstruction of the uterus and the determination of adequate hemostasis in the uterus, the tourniquet was removed.

The tourniquet was not applied to the patients in the control group. Transfusions of blood were performed in every patient if the hemoglobin level was less than seven g/dl, or if vital signs were unstable according to hypovolemia.

Clinical data were collected from medical records. The primary outcome measures were estimated blood loss (the difference between soaked and dry towels and blood collected in a drainage system) and the need for blood transfusion. Secondary outcomes included duration of operation, need for intraoperative hysterectomy, postoperative hemoglobin, and hematocrit levels. These results were compared statistically in the study and control groups.

SPSS version 20 program was used for the statistical analysis of data. The Student’s t-test, chi-square test ($\chi^2$), and Fischer exact test were used to compare the two groups. A $p$ value <0.05 was deemed statistically significant.

Results

From August 2008 through January 2013, 67 patients who gave abdominal myomectomy were diagnosed with myoma uteri. The two groups were similar in age, marital status, main complaints, parity, largest myoma diameter, and myoma localization ($p > 0.05$) (Table 1). The most common indication for myomectomies was menorrhagia (47.1% vs 57.6%), followed by pelvic pain/mass (32.3% vs 30.3%), and abortion/infertility (20.5% vs 12.1%). Abdominal myomectomy was performed successfully in all patients. There was no need for hysterectomy or relaparotomy in the pericervical tourniquet group. None of the patients was given a blood transfusion in the intraoperative period. However, postoperative hemorrhage occurred in one patient in control group. The relaparotomy and five unit blood transfusion were performed in this patient but no transfusions were required in study group. None of the patients did not have damage to uterine artery and its branches related to tourniquet.

A giant myoma sized 25 x 20 cm was successfully removed from an unmarried patient aged 36 years in the study group by using pericervical tourniquet technique. The patient did not require blood transfusion in the postoperative period. Intraoperative photos of the case are included in Figures 4 and 5.

The number of myomas removed from the study group (average, 2.6 ± 1.3) was greater than that of the control group (average, 1.4 ± 0.7). ($p<0.005$) (Table 1). Multiple
Effectiveness of pericervical tourniquet by Foley catheter reducing blood loss at abdominal myomectomy

myomectomies was performed in 36 (53.7%) of the 67 patients in total. The average operating time was significantly less in the study group when compared with the control group (61.1 ± 10.2 vs 78.7 ± 14.6 minutes, p < 0.001) (Table 1).

Intraoperative blood loss was found to be lower in study group (286.4 ± 137.5 vs 673.8 ± 172.3 ml, p < 0.001). There was no statistically significant difference between the two groups in preoperative hemoglobin (Hb) concentrations and hematocrit (Htc) values. However, the average postoperative Hb concentrations were significantly higher in the study group compared with the control group (11.5 ± 1.4 vs 9.9 ± 1.7 g/dl, p < 0.001). Similarly, the average postoperative Htc levels were also significantly higher in the study group (34.8 ± 3.4 vs 30.4 ± 3.6) (Table 2). A significant difference was identified in the comparison of postoperative Hb/Htc decreases (p < 0.03) of both groups. The average postoperative hospital stay duration was significantly shorter in the study group when compared with the control group (2.9 ± 0.2 vs 4.6 ± 0.3 days, p < 0.001) (Table 2).

No intraoperative complication occurred in all patients. Febrile morbidity was found in three patients (8.8%) in the study group and in four patients (12.1%) in the control group. There was no statistical difference between the two groups in this respect.

Discussion
The management of leiomyoma’s in the young population should be conservative for the preservation of fertility. In this case, myomectomy is an important alternative for treatment. However, the most important factor that limits the operations of myomectomy is bleeding in intraoperative uterine incision line [1, 6, 16]. Unless the hemorrhage is taken under control, hysterectomy and blood transfusion is required. Pericervical tourniquet method may be utilized in order to hinder this situation.
The blood flow of uterine is mainly provided from arteries, which branches out from arteries, and these two end branches of arteries do anastomose in ligamentum propria ovarica [17,18]. In the present study, the authors managed to reduce bleeding during myomectomy by reversibly arresting blood flow at uterine artery with pericervical tourniquet. Also ovarian blood flow was not blocked, so the ovarian functions were not affected. Due to collateral circulation during the operation, the authors did not have to open the tourniquet intermittently. Because a permanent suture was not used in the uterine artery, the authors consider that pericervical tourniquet did not affect the reproduction function.

Diluted vasopressin intramyometrial injection can be applied to reduce bleeding during hormonal tourniquet myomectomy operations [9, 19], but limited total dose (20 units diluted in 20 ml normal saline) and the need for intraoperative arterial or central monitoring are the disadvantages of the vasopressin application. Also bradycardia, cardiac arrest, and severe hypotension are the complications reported after the injection of intramyometrial vasopressin [20]. Local intramyometrial infiltration of low-dose vasopressin may cause lethal cardiopulmonary complications [21].

GnRHa can be effective in reducing blood loss in open myomectomy [11, 22]. The drugs must be used for three months before the operation. GnRHa are expensive and associated with estrogen deficient side-effects (such as hot flushes, change in breast size, vaginal symptoms). In addition, GnRHa therapy may alter the myoma-myometrium interface and induce the disappearance of small fibroids; therefore, it may increase the difficulty of fibroid enucleation and the incidence of recurrent fibroids [23].

Uterine artery embolization (UAE) may be an alternative surgery but the reintervention rate is higher at the medium and long terms. UAE cause shrinkage rather than removal of the myomas, and has limited efficacy when used with very large, multiple myomas [16]. Transient ovarian failure has also been reported as a complication of UAE [24]. This procedure should be reserved for women who have completed their child-bearing [25]. It is; therefore, evident that abdominal myomectomy still has a major role to play. There are no limitations on size and number of myomas, and there are good data showing improvement in outcomes of pregnancy following myomectomy [26].

During myomectomy operations, obstructing blood flow of the uterus and ovarian vessels completely [22, 27] should not be the primary goal. Otherwise, ovarian functions, fertility, and wound healing in the uterus may be adversely affected. Utero-ovarian ischemia may be lead to disseminated intravascular coagulation or hemolytic uremic syndrome [28].

The pericervical tourniquet method can be used safely in multiple leiomyomas as well as very large uterine leiomyomas (≥ 20 weeks) [29]. In the present study, myomectomy with a 25 x 20 cm giant leiomyoma could be performed while preserving the patient’s uterus and this caused no excessive intraoperative hemorrhage. None of the patients had excessive intraoperative and postoperative hemorrhage in pericervical tourniquet group.

In conclusion; pericervical tourniquet method should be used to reduce bleeding during operations of abdominal myomectomy. The authors confirmed that the pericervical tourniquet technique was effective, safe, and easily applicable but large randomized controlled trials should be carried out.

Figure 4. — Intraoperative appearance of the giant myoma.

Figure 5. — Giant myomectomy was performed with this technique.
References


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TVT-ABBREVO: efficacy and two years follow-up for the treatment of stress urinary incontinence

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Summary

Purpose: to assess the effectiveness of inside-out TVT-ABBREVO in the surgical treatment of female stress urinary incontinence (SUI) with mean two-year follow-up. Materials and methods: Fifty-six women underwent surgery for moderate-severe SUI. The technology used was the TVT-ABBREVO inside-out. Each woman at 12 and 24 months underwent postoperative evaluation by means of urodynamics, Q-tip test, CST, transperineal ultrasonography, and administration of “King’s Health Questionnaire” (KHQ). Results: The mean age of the women was 57.03 ± 11.1 years (range 42-75). Postoperative urodynamics (12 months follow-up) resulted to be normal in 43/56 patients (76.79 %), in 10/56 (17.86 %) cases resulted in a considerable improvement of the symptomatology, and only 1/56 (1.78%) case had de novo overactive bladder (OAB), in 2/56 (3.57 %) symptomatology unchanged. After administration of the KHQ 43/56 cases (76.79 %) had resolution of the symptomatology, 10/56 cases (17.86%) improvement of the symptomatology, and no change in 3/56 cases (5.36%). Conclusion: In the authors’ experience, the TVT-ABBREVO resulted technically simple. The TVT-ABBREVO procedure provides high objective and subjective long term efficacy, a clinically meaningful improvement in patient quality of life, and an excellent safety profile.

Key words: Stress urinary incontinence (SUI); TVT-Abbrevo.

Introduction

Stress urinary incontinence (SUI) is an important public health problem and affects up to 20% of women worldwide [1]. Combination therapy with estriol plus pelvic floor rehabilitation was effective for treatment of symptoms of urogenital aging in postmenopausal women, such as urogenital atrophy, frequency of urinary tract infections, as well as the symptoms and signs of SUI [2-3]. Recently, the present authors have demonstrated that triple therapy should be considered the first line-treatment for mild SUI in postmenopausal women [4].

Several surgical procedures, both vaginal and abdominal, have been proposed over the years for treating SUI. Nowadays midurethral slings, such as retropubic tension-free vaginal tape (TVT) [5], and the transvaginal tension-free vaginal tape obturator, or transobturator tape (TVT-O, TOT) have become the gold standard to treat severe SUI [6].

The inside-out TVT-Obturator (TVT-O) system was introduced with the objective to abtain the retropubic space in order to avoid the risk of lower urinary tract injury, while providing minimal vaginal and paravaginal tissue dissection and reproducibility of the tape’s insertion [7]. A meta-analysis of randomized controlled trial has demonstrated equivalent SUI cure rates after retropubic and transobturator tape procedures (approximately 85% to 90% at three years postoperatively); however, the transobturator approach is associated with less voiding dysfunction, blood loss, bladder perforation, and shorter operating time [8].

The aim of this study was to assess the efficacy and follow-up of women undergoing TVT-O procedure for SUI. The authors used the TVT-ABBREVO, a new modified TVT-O procedure [9].

Materials and Methods

The TVT-ABBREVO is different from its original counterpart because in this new technique the tape length is shortened to 12 cm without any change in tape’s characteristics (macroporous, monofilament polypropylene mesh).

Short description of the surgical technique

A urethral catheter was inserted and the bladder emptied. Using Alisi clamps for traction, the vagina was incised with scalpel beginning at one cm proximal to the urethral meatus. Initial dissection was carried out with a cold knife blade and further dissection is done by a gentle “push-spread” technique for approximately three cm with fine-pointed, curved Metzenbaum scissors directed toward the ischiopubic ramus in a 45° angle in relation to the coronal plane. Dissection was performed before perforating the obturator membrane, which usually offers more resistance to perforation than the obturator internus muscle. Then a guide was inserted and the helical passer was the sole instrument to perforate the obturator membrane. The TVT-ABRREVO technique has been previously described in detail [9].

Inclusion criteria

- age > 40 < 85 years;
- SUI clinically and urodynamically demonstrated;
- Positive stress test;
- Maximum cystometric capacity ≥ 300 ml.
Table 1. — Characteristics of patients.

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Mean ± SD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>57.03 ± 11.1</td>
</tr>
<tr>
<td>Parity</td>
<td>2.1 ± 1.1</td>
</tr>
<tr>
<td>BMI</td>
<td>28.2 ± 3.5</td>
</tr>
<tr>
<td>Previous hysterectomy</td>
<td>7/56 (12.5)</td>
</tr>
</tbody>
</table>

Exclusion criteria:
- postvoid residual (PVR) ≥ 100 ml;
- detrusor overactivity or acontractility;
- contraindication to anesthesia;
- neurogenic bladder;
- active urinary or vaginal infection;
- pelvic organ prolapse (POP) requiring surgical correction (symptomatic or grade ≥ 3);

Follow-up and quality of life were assessed using the validated King’s Health Questionnaire (KHQ) for SUI [10].

Institutional Review Board approved the study
At the Gynecologic and Obstetric Clinic of Sassari University, 56 patients underwent TVT-Abbrevo procedure to treat moderate-severe SUI. Of the 56 patients, seven reported a history of major gynecological surgery (abdominal hysterectomy).

Before surgery adequate written informed consent was provided to the patients, and all women underwent routine preoperative examinations, urodynamics, urogynecologic examination, and transvaginal ultrasound.

Preoperative evaluation included:
- remote and recent medical history;
- clinical evaluation and analysis of the voiding diary completed by the patient at home for three days;
- urinalysis and urine culture;
- complete urodynamic examination;
- Q-tip test;
- cough stress test (CST).

Postoperative follow-up (mean two years, from six months to three years). The patients were visited at 12, 24, and 36 months after surgery.

The following investigations (12 months postoperatively) were performed:
- clinical assessment;
- complete urodynamic examination;
- Q-tip test;
- cough stress test (CST);
- transvaginal ultrasound to assess the correct positioning of the mesh.

Objective cure was defined as the absence of urine leakage during the CST. Subjective cure was established when patients responded “never” in the question: “does urine leak when you are physically active, exert yourself, cough, or sneeze”.

Quality of life improvement was defined by a decrease in KHQ domain scores. The minimal important clinical difference (the smallest change in score that patients perceived as good) was set at – 5 points for each KHQ domain.

Statistical analysis
Data are presented as means ± standard deviation (SD), medians, or percentages for normally and non-normally distributed continuous variables or categorical variables, respectively. Comparison for continuous variables before and after surgery results were done using the t test for paired data or Wilcoxon signed-rank test.

Table 2. — Domains covered by the King’s Health Questionnaire.

<table>
<thead>
<tr>
<th>Domain</th>
<th>Preoperative</th>
<th>Postoperative</th>
<th>Difference</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>General health</td>
<td>32.72 ± 18.21</td>
<td>22.84 ± 16.31</td>
<td>- 9.89</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Incontinence impact</td>
<td>58.72 ± 23.32</td>
<td>24.68 ± 21.27</td>
<td>- 34.04</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Role limitations</td>
<td>38.72 ± 18.41</td>
<td>13.15 ± 10.31</td>
<td>- 25.57</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Physical limitations</td>
<td>35.64 ± 36.18</td>
<td>10.16 ± 09.53</td>
<td>- 24.88</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Social limitations</td>
<td>23.71 ± 16.67</td>
<td>06.13 ± 05.71</td>
<td>- 17.58</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Personal relationship</td>
<td>18.24 ± 09.84</td>
<td>05.23 ± 08.35</td>
<td>- 13.01</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Emotions</td>
<td>38.13 ± 16.21</td>
<td>12.25 ± 11.37</td>
<td>- 25.88</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Sleep and energy</td>
<td>26.15 ± 09.61</td>
<td>11.07 ± 10.39</td>
<td>- 15.08</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Severity measures</td>
<td>33.24 ± 17.21</td>
<td>15.75 ± 11.31</td>
<td>- 17.49</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

Results
Table 1 shows demographic characteristics of the study population. The age of patients ranged from 48 to 71 years (mean age 57.03 ± 11.1 years).

The mean operative time (from induction of anesthesia until the last suture) was 20 minutes, and all patients were subjected to general anesthesia. No major perioperative complications, such as bladder perforations, vesical injuries and obturator hematomas occurred. The Foley catheter was removed on the day following the intervention, inviting patients to urinate spontaneously. The hospital stay ranged from three to five days (mean three days).

Postoperative urodynamics (12 months follow-up) resulted to be normal in 43/56 patients (76.79 %), in 10/56 (17.86 %) cases resulted in a considerable improvement of the symptomatology, only 1/56 (1.78 %) case had de novo overactive bladder (OAB), in 2/56 (3.57 %) unchanged symptomatology. The Q-tip test was normal (< 30°) and the CST was negative in all patients after surgery. Transperineal ultrasonography demonstrated normal positioning of the sling in all patients. After administration of the “King’s Health Questionnaire” 43/56 cases (76.79 %) had resolution of the symptomatology, 10/56 cases (17.86 %) improvement of the symptomatology, and no change in 3/56 cases (5.36 %). KHQ data analysis showed a statistically significant improvement in all domains (Table 2). Indeed, with regards to clinically relevant improvement, the difference between mean postoperative and preoperative values was over the minimal important clinical difference (the smallest change in score that patients perceived as beneficial) (Table 3).
At follow-up visit, no cases of vaginal erosions were reported. No patients reported persistent groin pain at long-term follow-up.

Discussion

The introduction of prosthetic materials “tension-free” at the level of the middle urethra led to a breakthrough in the surgical treatment of SUI. In particular, Ulmsten at the level of the middle urethra led to a breakthrough in very encouraging to date, given the level of satisfaction of episodes of retention.

Afterwards, in order to avoid complications such as bladder and/or vascular injuries by the needle through the vascular tissues in the path between the suprapubic region and the periurethral, Delorme et al. [13] introduced the transobturator approach for the treatment of SUI. It is an exclusively perineal surgery that provides a natural support to the urethra by means of a cable positioning innovative through the obturator foramen and not the space of Retzius that could carry the risk of vascular lesions. The widespread use of this method, in addition to the reduction of complications, is mainly due to safety and the speed of execution [13].

In the present authors’ experience, the positioning of TVT-ABBREVO was technically simple and very easy to position the tape lying flat under the urethra, reducing the risk of urine retention.

The present study included a sample of 56 patients aged between 42 and 75 years (mean 57.03 ± 11.1), undergoing TVT-ABBREVO from 2010 to 2013. In the postoperative period, a questionnaire was administered [10]. The results obtained by the administration of this questionnaire showed that 43/56 (76.79%) were cured; 10/56 (17.86%) cases showed a significant improvement in symptoms with an overall improvement in quality of life. Only 3/56 (5.36%) cases showed no improvement.

The present study showed a success rate of 94.64% (considering the total resolved cases and cases with marked improvement) and only in 5.36% of patients the problem of SUI was unresolved. Besides these encouraging data, the authors reported the absence of vascular complications such as bladder or bowel perforation, and episodes of retention.

In conclusion, the results of the present study proved very encouraging to date, given the level of satisfaction of patients treated with this minimally invasive technique and the great results of the objective, linked to a recovery of a real functional well-being.

References


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Is thrombin-activatable fibrinolysis inhibitor antigen (TAFIag) level significant in recurrent miscarriage?

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Summary

Objective: The aim of this study was to evaluate the plasma thrombin-tat fibrinolysis inhibitor antigen (TAFIag) levels in women with recurrent miscarriage (RM) and age-matched healthy parous women as controls. Materials and Methods: A total of 80 patients were enrolled in this study. As a study group (group 1), the authors evaluated 49 RM patients who had two or more consecutive abortions with unknown etiology before 12 weeks of gestation. The remaining 31 patients (group 2) were age-matched healthy parous women with no history of miscarriage and experienced at least one live baby. Results: Comparisons of blood TAFIag levels revealed no statistically significant difference between women with recurrent miscarriages and control group. Conclusions: The findings of the present study indicated that TAFIag level was not associated with recurrent miscarriages.

Key words: Thrombin-activatable fibrinolysis inhibitor; Recurrent miscarriage; Unknown etiology.

Introduction

Recurrent miscarriage (RM), defined as three consecutive miscarriages, affects approximately one to three percent of couples trying to have a child with the same partner [1]. Recently, RM is defined as two or more consecutive early pregnancy losses by many clinicians [2]. Genetic and uterine abnormalities, thrombophilias, environmental, endocrinologic, and immunologic factors have been proposed to play a role in the etiology of RM, and underlying pathology remains unidentified in approximately 30-50% of the recurrent miscarriages [3].

A successful pregnancy requires cooperation between coagulation and fibrinolysis during placentation of embryo and trophoblastic invasion. The imbalance between coagulation and fibrinolysis creates a tendency to thrombosis. Thrombosis and hypofibrinolysis are considered to be the causes of RM [4].

Plasmin is important for the fibrinolysis and produced in the liver as an inactive plasminogen form and t-PA and urokinase convert plasminogen to plasmin which is the active form. Plasminogen cannot degrade fibrin without tissue plasminogen activator (t-PA) and urokinase. Also, plasmin stimulates its own formation by producing both t-PA and urokinase. The role of the plasmin is to break down the fibrin clots into soluble fibrin degradation products. Plasmin activity is reduced by thrombin activatable fibrinolysis inhibitor (TAFI) [5].

TAFI is a glycoprotein synthesized by the liver and megakaryocytes. Thrombin, thrombin-thrombomodulin complex, and plasmin cleavage TAFI at Arg 92, and provide activated TAFI (TAFIa). It is a well-known attenuator of the fibrinolytic rate and inhibits fibrinolysis by removing carboxyterminal residues from partially degraded fibrin, thus decreasing plasminogen binding on the surface of fibrin [6]. In a previous study, TAFI has been shown to be involved in normal pregnancy. Plasma level of TAFI has been found to be unchanged or reduced during pregnancy [7] or on the contrary, increase during normal pregnancy and then return to baseline levels after delivery [8]. Increased TAFI level has been associated with low level of fibrin degradation and thrombotic conditions which is necessary for normal pregnancy [9]. TAFI may be a contributing factor in the development of thrombotic events and it may act as a link between coagulation and fibrinolysis [10]. The importance of TAFI for RM is undefined. Therefore the aim of this study was to assess TAFI levels in women with RM with unknown etiology.

Materials and Methods

This prospective case-control study was performed in the Zeynep Kamil Training and Research Hospital, Department of Obstetrics and Gynecology, between September 2010 and June 2011. The study protocol was conducted according to the revised Declaration of Helsinki and was approved by the local Research and Ethics Committee of the hospital. Written informed consent form was also obtained from all participants.

A total of 80 patients were included in our study. These patients were grouped as 49 patients with unknown etiology who had two or more consecutive miscarriage before the 12 weeks of gestation as group 1 (study group) and the remaining 31 patients with age-matched healthy parous women who had no history of miscarriage and had experienced at least one live baby as group 2 (control group).

There were no known etiological factors for RM in the study group. In other words; gynecological examination, transvaginal ultrasonography, endocrinologic analysis (ovarian hormones, adre-
nal androgens, thyroid function tests), blood glucose level, chromosomal analysis (maternal and paternal), Lupus anticoagulants, thrombophilia pattern (protein C, protein S, activated protein C resistance, antithrombin III, hyperhomocysteinemia), thrombophilic gene mutations (factor V, prothrombin G20210 A, methylene tetrahydrofolate reductase C677T), coagulation parameters (activated partial thromboplastin time, prothrombin time), hysterosalpingography, and hysteroscopy (if performed because of any suspicious finding) were normal.

The exclusion criteria were history of venous thromboembolism, hepatic diseases and renal diseases, known cancer, pregnancy and women with only terminated pregnancy, ectopic pregnancy or recent child birth, taking anticoagulant, antiplatelet medications, and oral contraceptives for at least six months.

For TAFI analysis, blood samples were obtained from the antecubital vein into citrated tubes, centrifuged at 1,500 rpm for 15 minutes and stored at –80°C until analysis. Plasma TAFIag level were measured with an Imuclone TAFI enzyme linked immunosorbent assay (ELISA) kit. Frozen plasmas were thawed rapidly at 37°C. Thawed plasmas were stored at 2°–8°C and assayed within four hours.

Datas were given as mean ± standard deviation (sd) or percentage (%) as appropriate. The SPSS for Windows 17.0 software was used for the statistical analyses. Student’s t and chi-square tests were performed as appropriate. A \( p < 0.05 \) was accepted as statistically significant.

### Results

A total of 80 women were enrolled in this study as 49 women had recurrent miscarriage with unexplained etiology (group 1), whereas 31 women had at least one uncomplicated pregnancy without any miscarriage (group 2). The demographic characteristics and TAFIag levels of groups are presented in Table 1. There was no statistically significant difference between the study and control group for maternal age, body mass index (BMI), and tobacco use. Comparisons of blood TAFIag levels revealed no statistically significant difference between the groups (group 1; 66.2 ± 25.3, group 2; 62.6 ± 30.7, \( p = 0.240 \), Table 1).

Between the subgroups studied, a statistically significant difference in maternal age, BMI, tobacco use, pregnancy loss week were not observed (Table 2). TAFI was lower in group IC when compared with group IA and IB. However, this difference was not statistically significant (group IA; 68.4 ± 19.9 U/dl, group IB; 68.1 ± 28.4 U/dl, group IC; 59.7 ± 29.4 U/dl, \( p = 0.603 \), Table 2, Figure 1).

Table 1. — Demographic characteristics and TAFIag levels of the study and control group.

<table>
<thead>
<tr>
<th></th>
<th>Study group</th>
<th>Control group</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>(women with RM)</td>
<td>n = 49</td>
<td>n = 31</td>
<td></td>
</tr>
<tr>
<td>Maternal age (years)</td>
<td>29.5±5.6</td>
<td>31.2±6.1</td>
<td>0.208</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>23.1±2.4</td>
<td>23.4±2.6</td>
<td>0.681</td>
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<tr>
<td>Tobacco (%)</td>
<td>18.4</td>
<td>19.4</td>
<td>0.912</td>
</tr>
<tr>
<td>TAFIag level (U/dl)</td>
<td>66.2±25.3</td>
<td>62.6±30.7</td>
<td>0.240</td>
</tr>
</tbody>
</table>

Table 2. — Demographic characteristics and TAFIag levels of the study population subgroups.

|                      | Group 1A (2 losses) | Group 1B (3 losses) | Group 1C (≥ 4 losses) | \( p \) |
|----------------------| n = 20              | n = 17              | n = 12                |        |
| Maternal age (years)| 29.3±5.7            | 28.9±5.2            | 30.7±6.4              | 0.691  |
| Pregnancy loss week | 7.1±1.7             | 6.7±1.5             | 7.3±1.1               | 0.619  |
| BMI (kg/m²)          | 23.2±2.7            | 23.5±1.6            | 22.3±2.3              | 0.428  |
| Tobacco use (%)      | 15                  | 17.6               | 25                    | 0.775  |
| TAFIag level (U/dl)  | 68.4±19.9           | 68.1±28.4           | 59.7±29.4             | 0.603  |

Figures and tables are included for clarification of the results and methodologies.
Discussion

The relationship between thrombosis and recurrent miscarriage has been derived from numerous studies. Several maternal thrombophilic conditions such as protein C, protein S and anti-thrombin III deficiency, hyperhomocysteinemia, and thrombophilic gene mutations have been shown to be involved in RM [11]. Microthrombosis and necrosis were commonly found in placentas of patients with RM [12]. A successful pregnancy requires cooperation between coagulation and fibrinolysis and the fibrinolysis is important in this balance because of shown participation of fibrinolytic system in the regulation of early human trophoblastic invasion [13].

Previous studies have been focused on fibrinolytic defects and RM, but the role of TAFI is unclear in women with RM and there are conflicting results in the literature [14-17]. As a result of increased TAFI, hypofibrinolytic states have been thought to be associated with vascular thrombosis, uteroplacemental thrombosis and finally miscarriage [16]. By contrast with this hypothesis, studies suggested that increasing levels of TAFI during normal pregnancy may protect against early RM and also reported that high TAFI levels were not associated with increased risk of early RM [5,14,15]. Hypofibrinolysis prevent formation of fibrin degradation product. Therefore fibrin degradation products which have negative effects on trophoblasts as trophoblastic apoptosis which leads to RM are not observed [18].

The studies in which TAFI is investigated contain heterogeneous groups in terms of etiology [5, 14-16]. When the researches about the effect of TAFI to the maternal hemostatic system at the patients having recurrent miscarriages, are designed, it is important to consider the false affects of the other factors at the etiology of the recurrent miscarriages. For example, in patients with antiphospholipid syndrome (APS), reduced fibrinolytic activity has been described which may be responsible for thrombotic events [18]. In same way, in thrombophilia patients, increased thrombin generation may enhance TAFI activation leading to a hypofibrinolytic state, which may further contribute to the thrombotic tendency. For these reasons, with the aim of preventing patient selection bias and obtaining more reliable data, the present authors created their study groups comprising of women with RM with unexplained etiology, so there were no proven thrombotic condition. In the present study, the authors did not demonstrate any difference between control group and RM group with unexplained etiology in terms of TAFIag level. This study was strengthened by the homogenous group of RM with unexplained etiology. None of subjects were with proven thrombotic condition. One of the limitations of this study was relatively small sample size, therefore studies which include homogen group of RM with larger sample sizes are needed.

In conclusion, there was no significant difference in terms of TAFIag levels between the women with recurrent miscarriages with unexplained etiology and control group.

References


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Experience of hysteroscopy indications and complications in 5,474 cases

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Summary

Objective: To evaluate the indications, intraoperative diagnoses, and complication rates of both diagnostic and operative hysteroscopic procedures. Materials and Methods: Five thousand four hundred seventy-four (5474) hysteroscopic procedures performed in the department of gynecologic endoscopy unit between May 2005 and December 2012 were retrospectively analyzed from the archives. Indications, intraoperative diagnosis, and complications of all gynecological endoscopic procedures are recorded. Results: Abnormal uterine bleeding in premenopausal and postmenopausal women was the most frequent indication for diagnostic hysteroscopies in 1,887 (40%) cases. The most common preoperative indication for operative hysteroscopy was endometrial polyps in 469 (55.7%) cases and submucous leiomyomas in 151 (17.9%) cases. In this series, the most common complication was uterine perforation which occurred in 15 (0.27%) out of 5,474 cases and the rate for diagnostic hysteroscopy and operative hysteroscopy was 0.06% and 1%, respectively. Conclusion: Hysteroscopy is a safe and effective minimally invasive procedure with very low complication rate.

Key words: Hysteroscopy; Indications; Complications.

Introduction

Hysteroscopy is performed for evaluation and also for treatment of abnormal uterine bleeding, infertility, and recurrent pregnancy loss. It is an easy procedure with less morbidity ratios compared with other, more invasive procedures [1]. The increased clinician training, advances in the equipment, and distention media, and development of small diameter instruments have led to a widespread use of this procedure. The authors aimed to evaluate the indications, intraoperative diagnoses, and complication rates of both diagnostic and operative hysteroscopies.

Materials and Methods

This study was designed to assess all diagnostic and operative hysteroscopic procedures, 5,486 cases in total, from the hospital archives database of the gynecologic endoscopy unit at Zeynep Kamil Women and Children Diseases Training and Research Hospital in Istanbul, between May 2005 to December 2012. The authors could not access reports of 12 (0.21%) patients, therefore a total of 5,474 patients were analyzed.

Indications for diagnostic hysteroscopy depended on: patient complaints, preoperative uterine ultrasound scan, and abnormal hysterosalpingographic findings. Diagnostic hysteroscopy was performed without anesthesia. A 5.5-mm rigid hysteroscope was inserted into uterine cavity and for distention of uterus, low-viscosity liquid electrolytic media (saline) was used. At the diagnostic hysteroscopy procedure the authors defined hysteroscopic findings as the diagnostic impression based on the appearance of the lesion which were not defined by their appearances as polyp or myoma. Accuracy of hysteroscopy to diagnose polyps and submucous myomas were determined in correlation with postoperative histopathological findings. Although several reports have been reported in the literature to discuss the accuracy of hysteroscopy to diagnose uterine pathology as polyp, myoma, hyperplasia and cancer, this comprehensive report of conditions is beyond the scope of this article [3, 4].

Operative hysteroscopy was performed under general anesthesia after dilatation of the cervix to Hegar number 9. A nine-mm rigid resectoscope was inserted into the uterine cavity. Distention of cavity was achieved using 1.5% glycine with an inflow pressure of 110 mmHg. Procedures included polypectomy, myomectomy, septum resection, endometrial ablation, and removal of the intrauterine device which was malpositioned and extended into the myometrium. In some situation an ultrasonography (USG) was used to perform cervical dilatation safely; also USG guidance enabled to safely perform a septum resection, endometrial ablation, and dissection of uterus in Asherman’s syndrome.

These findings were recorded in an Excel program and analyzed using statistical software package, version 7.0.

Results

A total of 5,474 hysteroscopic procedures were performed over the seven-year period and 4,633 of these procedures were diagnostic and 841 of them were operative hysteroscopies. The mean age of patients was 43 years (range 34 - 53).

Diagnosis of hysteroscopy indications and postoperative hysteroscopic diagnosis are shown in Table 1. The most common indication for diagnostic hysteroscopy was ab-
normal uterine bleeding as menorrhagia, metrorrhagia, menometrorrhagia, and polymenorrhea in perimenopausal or postmenopausal period in 1,887 (40%) of the cases. The second most common indication was evaluation of infertile patients with abnormal hysterosalpingography or recurrent IVF failure in 1,463 (31%) of the cases. The most common pathologic finding of the diagnostic hysteroscopy was polyp with the ratio of 31.7% (1,469) and than submucous myoma with the ratio of 8.2% (383).

The main indications for operative hysteroscopy were mostly: removal of endometrial polyps, submucous leiomyomas, and resection of intrauterine septum at the rate of 469 (55.7%), 151 (17.9%), and 122 (14.5%), respectively (Table 2).

In the present study; complications occurred in 15 (0.27%) out of 5,474 patients. The most common complication was uterine perforation. The rate of uterine perforation for diagnostic hysteroscopy was 0.06% (three cases). During operative hysteroscopy, nine cases had perforation at the rate of 1%. The other complications seen during operative hysteroscopy were bleeding in two cases and infection in one case (Table 3). When the complication occurred during the operation, operative hysteroscopy was stopped, four patients required diagnostic laparoscopy, and two patients required laparatomy due to suspicion of thermal bowel injury. The other three perforations which occurred during cervical dilatation were followed with hemodynamic status of patients without operation. Intraoperative bleeding was encountered during the submucous myomectomy. In one patient bleeding was controlled with electrocautery and in other patient bleeding could not be controlled by electrocautery; a foley catheter was inserted into uterine cavity and the bulb inflated with 20 to 30 ml of liquid to tamponade the bleed-
ing and the catheter was removed after 24 hours. Infection as a late complication was reported in only one case of operative hysteroscopy (Table 3). No case of fluid overload, urinary tract or bowel injury was noted. The complication rate was related to experience of the surgeon as 11 out of 15 complications were experienced by staff with a less than one year of experience.

Discussion

Improvement in technology and increased clinician training have led to a widespread use of hysteroscopy and thus has become the method of choice for the treatment of intrauterine pathologies.

In the present study, the most common indication for diagnostic hysteroscopy was abnormal uterine bleeding (40%) as in other studies [5–7]. During diagnostic hysteroscopy, the most common abnormal finding was endometrial polyps (31.7%). Transcervical removal of endometrial polyps at the rate of 55.7% was the most common procedure of operative hysteroscopy. In the Lansmar et al. study, endometrial polyps were reported in 33.9% of the diagnostic hysteroscopies [6]. This data is in accordance with the present study with regards to the identification of endometrial polyps as the most frequent finding in patients with abnormal uterine bleeding.

The acute complication rate associated with both diagnostic and operative hysteroscopy was in total 0.27 % in 5,474 cases. According to Passini et al. exact complication rates are difficult to determine owing to the natural tendency to report successes but not complications [8]. Other published reports cite the overall complication rates ranging widely between at least 0.22% in 21,676 case and maximum to 13.6% in 697 case [8, 9]. In the present study the complication of operative hysteroscopy is higher than diagnostic hysteroscopy; the rates were 1% and 0.06%, respectively. Also in other studies the complication rate has been reported to be higher with operative hysteroscopy [7, 10]. During operative hysteroscopy, uterine perforation, bleeding, and air emboli because of used distention medium and hyponatremia which resulted from infusion of large amounts of distention medium into circulation and allergic reactions can occur [11]. The main complications in the present study were found to be uterine perforation with a rate of 0.06% for diagnostic hysteroscopy and 1% for operative hysteroscopy, which is similar to that reported by other authors [9, 10].

Hysteroscopic complications vary depending on the type of intervention. Among hysteroscopic procedures, myomectomy, resections of uterine septa, dissection of uterus in Asherman’s syndrome or endometrial ablation have significantly higher rates of complications, especially uterine perforation and bleeding. Propst et al. evaluated complications in 925 women and found that those who had operative hysteroscopic myomectomy and septum resection had greater odds for complications than those who had polypectomy or ablation procedures; 7.4 and 4.0 versus 0.1 and 0.4, respectively [12].

The knowledge of risks are important to avoid any complications of hysteroscopy during diagnosis or treatment. Dilatory agent or cervical softening can be used if deemed necessary for cervical dilatation. In order to minimize perforation risk, it is important to perform the procedure with the guidance of ultrasonography. Also it is important to keep in mind that the thickness of myometrial layer can be less than one cm when the uterine cavity is distented. Hysteroscopy can also be guided by concomitant laparoscopy. Shokeir et al. reported that previous uterine surgery among young women with reproductive failure whether the uterine cavity is opened or not does not appear to affect adversely the performance and safety of subsequent major surgical hysteroscopy guided by concomitant diagnostic laparoscopy [13].

Training and experience of the surgeon are not the only factors that affect the safety of the procedure. Working with the experienced anesthesiologist who knows good fluid management is also important for the safety. The present authors did not observe fluid overload. Propst et al. reported fluid overload as the most common complication [12]. In Pasini et al. study, excessive intravasation of electrolyte-free fluid occurred in 35 patients [8]. This may be due to the present authors’ principles that they prefer to stop the intervention when deficit reached 1,000-2,000 ml or if serum sodium level reached 130 mmol/l. These precautions might limit the serious complications of these procedures.

In conclusion, as a consequence of increased experience and also technological advancements, an increasing number of gynecological conditions, traditionally treated by laparotomy, can now be treated safely and effectively by operative hysteroscopy. In order to minimize risk, it is important to perform the procedure with the guidance of ultrasonography. Safety is the result of the team work of a experienced surgeon with an anesthesiologist who performs good fluid management. Experience of the surgeon plays an important role for the safety of the procedure in terms of where and when to stop the procedure.

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References


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Effects of natural progesterone on endometriosis in an experimental rat model: is it effective?

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Summary

Purpose: To assess the effects of the natural progesterone on the endometriosis in a rat model. Materials and Methods: Endometriosis was surgically induced in 20 rats by transplanting an autologous fragment of endometrial tissue onto the inner surface of the abdominal wall. Rats in control group had no medication but 2.5mg/kg/weekly natural progesterone was administered to rats in study group for four weeks. After that, all rats were sacrificed and dimensions of endometriosis were measured and they were evaluated morphologically and histologically. Scoring systems were used to evaluate preservation of epithelia. Results: Two rats in the study group and one rat in the control group died of complications related to surgery. At the end of the treatment, there was a reduction in the size of the endometriotic lesions in the study group (p < 0.01). According to histological evaluation, the study group had lower score than control group which was statistically significant (p = 0.014). Conclusions: Natural progesterone is effective against endometriosis in rat model.

Key words: Natural progesterone; Endometriosis.

Introduction

Endometriosis is defined as the presence of endometrial gland and stroma outside the uterus. Despite many studies to elucidate its pathogenesis and treatment, it still remains one of the most serious problems in gynecology because of its frequency, bothersome symptomatology, associated infertility, and potential for invasion of adjacent organs such as the gastrointestinal or urinary tract. It affects up to 10% of women of reproductive age and as many as 30% to 50% of all infertile women [1, 2].

Exact etiology of endometriosis is not well known but several factors are involved in the initiation and spread of endometriosis, including retrograde menstruation, coelomic metaplasia, immunologic changes, and genetic predisposition. Therefore, there are many hypotheses regarding its pathophysiology. Among them, retrograde menstruation theory of Sampson is widely accepted to explain the possible mechanism for endometriosis formation [3]. Endometrial tissue which is normally shed at the time of menstruation, is viable and capable of growth in vivo or in vitro. It was shown that almost 90% of women with patent fallopian tubes have reflux menstruation into the peritoneal cavity [4].

Although it is a histologically benign pathology, endometriosis shares many characteristics of malignancy such as local invasion and widely dissemination [5]. Therefore it may cause bothersome complaints and should be treated. It is known that it is a estrogen-dependent gynecological disease. In patients with endometriosis, estradiol can be synthesized locally in the endometriotic lesions from inactive precursors of adrenal or ovarian origin, via the aromatase pathway. These increased estradiol levels stimulate proliferation of endometriotic tissue. Interestingly, cyclic hormones tend to induce its growth, but continuous hormonal exposure, especially at high doses, generally induces significant regression. The synthetic progestins (e.g medroxyprogesterone acetate, dydrogesterone, and dienogest) have been used in the therapy of endometriosis for more than 40 years but their pharmacological action is still not understood in detail.

In this study, the authors aimed to show the effects of injectable natural progesterone, which has been used in clinical practice recently, on endometriosis foci in rat model.

Materials and Methods

Twenty female nonpregnant healthy Wistar albino rats weighting between 250 and 300 grams were used as a model for experimental induction of endometriosis. The rats were caged individually in a controlled environment with 12-hour light/dark cycles and were fed ad libitum.

Endometriosis was surgically induced in rats by transplanting an autologous fragment of uterine tissue onto the inner surface of the abdominal wall and arterial cascades of the small intestines adjacent to mesenteric blood vessels, as proposed by Vernon and Wilson [6] with modifications by Lebovic et al. [7]. Before the
operation, each rat was anesthetized with an intramuscular injection of ketamine. After that an abdominal skin was shaved and antisepsis was obtained by 10% povidone iodine solution. Using sterile techniques, a five-cm vertical midline incision was made and both uterine horns were exposed. A distal segment, one-cm in length, was resected from the right uterine horn. The segment was placed in phosphate-buffered saline at 37°C and split longitudinally, and a 5.5 mm piece was sectioned. This piece of uterine tissue was transplanted without removing the myometrium on to the inner surface of the right abdominal wall with the serosal surface apposed and secured with single nonabsorbable 5-0 polypropylene suture at the middle to the abdominal wall. Before closure of the abdominal wall, two ml of saline was administered into the abdominal cavity to prevent drying and minimize adhesion formation. The abdominal incision was closed in two layers with the use of a simple interrupted 4-0 polyglactin suture for the peritoneum-fascia and for the skin.

After operation, the rats were randomized into control and study groups and all rats in both group were fed with top water and ad libitum (same protocol). After two months, all of the 20 rats in both groups underwent abdominal incision to see and measure the endometriotic tissue volume which was calculated by ellipsoid formula; volume (mm³) = 0.52 x width x length x height. Development of endometriosis was seen in all rats. After that, the rats in control and study groups were treated with intramuscular two ml saline and 2.5 mg/kg/week natural progesterone, respectively. The treatment of the groups were continued for four weeks. At the end of four weeks treatment, all rats in both control and study groups were sacrificed and the volume of the each ectopic uterine tissue was measured by ellipsoid formula (Figure 1). After excision, all samples were fixed in 10% buffered formalin solution for 24 hours. Then, routine tissue processing procedure was performed and then sampled tissues were embedded in paraffin. Paraffin wax blocks were cut in four µm thickness. Prepared sections were stained with hematoxylin-eosin (HE).

The histologic diagnosis of endometriosis was based on the morphologic identification of endometrial glandular tissue and stroma; glands and stroma of the endometrial type, with epithelial lining and luminal formation. In microscopic examination, the preservation of endometrial tissue was evaluated according to a semiquantitative scoring method as described by Keenan et al. [8]. Accordingly a well-preserved epithelial layer = score 3, a moderately preserved epithelium with leukocyte infiltrate = score 2, a poorly preserved epithelium (occasional epithelial cells only) = score 1, and no epithelium = score 0. All histological evaluations were performed by two different histologists who were blinded to the groups.

In present study, the mean volume of the endometriosis and endometrial tissue scores were compared between control and study groups before and after treatment. Mann-Whitney U test and Wilcoxon Rank tests were applied for statistical analysis by using SPSS program. Any p value less than 0.05 was considered as significant at 95% confidence level.

Results

Two rats in the study group and one rat in the control group died during follow up after randomization due to surgery related complications. Therefore, nine in control and eight rats in study groups were included in this experimental study. The standardized surgical procedures and the administration of the protocols were well tolerated by the remaining animals (n = 17). All laparotomy sites were intact and none of the animals had an incisional hernia. No side effects related to medication were observed in the treatment group.

The mean weight of rats in control and study groups was not statistically different from each other (293 ± 10.1 g vs 301 ± 11.8 g, respectively, p = 0.65). It was seen that all rats in both groups developed endometriosis at the end of the second month. The mean endometriosis volume before treatment was 62.96 ± 4.97 and 63.71± 5.66 mm³ in control and study groups, respectively. The mean endometriosis volume before treatment in both groups didn’t differ significantly (p = 0.792).

At the end of the study, the mean volume of the endometriosis in control group rats became enlarged and was calculated as 78.01 mm³. This increase in control group was statistically different than its prior measurement (62.96 ± 4.97 vs 78.01 ± 7.23, p = 0.01). However, the mean vol-
Effects of natural progesterone on endometriosis in an experimental rat model: is it effective?

The volume of endometriosis in study group was lower than the value measured before treated with natural progesterone. The difference in study group before and after treatment was significant (63.71 ± 5.66 vs 6.24 ± 1.9, respectively, \( p < 0.001 \)). Also, the mean value between control and study groups after treatment differed significantly (78.01 ± 7.23 vs 6.24 ± 1.9, \( p < 0.001 \)) (Figure 1, Table 1).

According to histological examination of specimens, scoring in natural progesterone group was lower than the control group. The difference between mean scores of the groups was statistically significant (1.50 ± 1.30 vs 2.55 ± 0.88 respectively, \( p = 0.014 \)) (Figures 2-3).

Discussion

Endometriosis is a common health problem among women in reproductive age and exact underlying pathophysiology is currently not well understood. It is mostly located at genital system but theoretically can occur anywhere in the body. Although it is sometimes asymptomatic, it may often result in serious symptomatology according to its location and volume. Therefore, gynecologists tend to treat endometriosis and its related symptoms.

Investigations on endometriosis were done in both clinical and experimental studies. In preclinical studies, sur-

![Figure 2](image1.png)

**Figure 2.** — Histology of the ectopic endometrium in control group. (c) Arrows show gland-stroma areas of endometrium (HE x40) (d) Endometrial glandular epithelium (long arrows) and hemosiderin-laden macrophages (short arrows) (HE x100) (Score = 3).

![Figure 3](image2.png)

**Figure 3.** — Flattened glandular epithelium and decreased stromal structure in natural progesterone group. (e) The compressed endometrial glandular epithelium and reduction in the stroma (long arrows), stripped muscle tissue (short arrow) can be seen. (f) Hemosiderin laden macrophages (HE x200) (Score = 1)

<table>
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<th>Volume of endometriosis Before treatment</th>
<th>Volume of endometriosis After treatment</th>
<th>( p ) value</th>
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</thead>
<tbody>
<tr>
<td>Control group (n = 9)</td>
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<td>78.01 ± 7.23</td>
<td>0.04</td>
</tr>
<tr>
<td>Study group (n = 8)</td>
<td>63.71 ± 5.66</td>
<td>6.24 ± 1.9</td>
<td>&lt;0.001</td>
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</table>

Table 1. — Comparison of the pre- and post-treatment volumes (mm³) in the control and study groups.
gically induced endometriosis in rat models is useful in the attempt to understand the effect of possible therapeutic agents on the proliferation of endometrial tissue outside the uterine cavity [6, 9]. In the present study, the authors used the rat model of surgically induced endometriosis to test the efficacy of natural progesterone on endometriosis tissue.

Today, the effect of progesterones on endometriosis is well established. They inhibit endometriotic tissue growth by causing decidualization initially, and then atrophy. Additionally, they also inhibit pituitary gonadotropin secretion and ovarian hormone production. Therefore, the effectiveness of progesterones for treating endometriosis is not just linked to its growth inhibiting actions, but also to its induction of anovulation, inhibition of blood vessel growth, and anti-inflammatory actions.

Progesterones are divided into two groups, one is synthetic, and the other is natural progesterones. Synthetic analogues of progesterone which is more potent than its natural form have been developed to make the hormone available orally and to produce longer lasting effects [10]. They have been widely used and have almost similar bioactivity as progesterone. However, they are synthetically made in the laboratory and have been slightly altered biochemically to mimic natural progesterone [10]. The first synthetic progestin, norethindrone, was invented in 1951 and used in the first oral birth control pills. The most common progestins are medroxyprogesterone acetate and megestrol acetate. Synthetic progesterone-based therapies are well-established in the treatment of endometriosis since they lead to a regression of the disease and reduction of pain [11].

When a hormone is described as natural or bioidentical it signifies that its molecular structure is identical to the form naturally produced in the human body. In 1998, an oral natural (bioidentical) progesterone received FDA approval. Besides the administration through a variety of routes including oral, transdermal, vaginal, rectal, sublingual/buccal, and intrauterine there is also an injectable form of natural progesterone which was used for this study. Plasma levels of progesterone are most reliable and consistent when the hormone is given as an intramuscular injection of progesterone [9]. It is rapidly absorbed, and a 100-mg injection produces plasma concentrations of 40 to 50 ng/ml in two to eight hours [12]. In this study, the authors also preferred intramuscular route to be sure to give the exact dosage of progesterone.

Although they may have side-effects, progesterones are generally safe medications in treatment of endometriosis. In a review literature, Rudel and Kincl noted that no toxicities were reported up to now after long-term oral or parenteral administration [13]. Their only finding was an increase in the body and liver weights of female rats receiving parenteral progesterone. However some authors reported quiet frequently such complaints as drowsiness, headache, dizziness, nausea, etc after oral or parenteral progesterone administration [12, 14]. Also, intravenous administration induces sleep at doses of 250 to 500 mg [12]. On the other hand, synthetic progestins often cause androgenic side-effects such as acne, body and facial hair, depression, and weight gain.

Natural progesterone is a recent subject of gynecology which is chemically identical to human physiologic progesterone. There is an ongoing debate between the superiority of natural progesterone on its synthetic identical in gynecologic disease treatment. Although there is limited number of comprehensive studies, it is logic to expect no clinical difference regarding the effect of them on gynecologic disease such as osteoporosis prevention, endometriosis, premenstrual syndrome, etc. However some authors stated fewer side-effects among women on natural progesterone treatment. Also, secondary benefit as lipid profile enhancement of natural progesterone usage were noted [15]. In the present study, the authors did not compare natural progesterone with synthetic counterpart. They attempted to demonstrate the potential effect of natural progesterone on endometriotic tissue.

According to the authors’ knowledge, there was no study to investigate the effects of natural progesterone on endometriosis in literature. Hence they designed an animal model of endometriosis in 20 rats and divided them into two groups, one was control and the other was study group that were administered natural progesterone weekly via intramuscular route. At the end of the study, lesions size measured and histological staging were performed and compared with control. They demonstrated that the mean endometriotic lesions’ diameter was smaller in the study group than controls. In addition, reducing the size of the endometrial explants is clearly supported by the lower histological score in study group which had statistically significant.

The main limitation of this experimental study is that the authors did not compare the effect of synthetic progesterone with its natural counterparts due to limited number of rats. Secondly small number of rats in the groups was another limitation. However, the present study is the first study to show the efficacy of natural progesterone on ectopic uterine tissue in rat model. The result give an idea regarding the natural progesterone effect on endometriosis.

Conclusion

As a conclusion, use of natural progesterone was effective on rat model endometriosis. It may be logic to use natural progesterone because of its non-toxicity, fewer side-effects, and less is expense than synthetic progestins. However further experimental and clinical studies are required to compare its efficacy with the synthetic counterpart.
Effects of natural progesterone on endometriosis in an experimental rat model: is it effective?

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Marked improvement of the autoimmune syndrome associated with autoimmune hepatitis by treatment with sympathomimetic amines

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Summary

Purpose: To evaluate the effect of sympathomimetic amine therapy for a life threatening autoimmune disorder. Materials and Methods: Dextroamphetamine sulfate was used to treat edema, myalgia, and chronic fatigue associated with autoimmune hepatitis (AIH). Results: Sympathomimetic amine therapy completely abrogated the symptoms associated with AIH. Conclusions: AIH should be added to the long list of chronic treatment-refractory conditions that respond quickly and effectively to treatment with sympathomimetic amines.

Key words: Autoimmune hepatitis; Sympathetic hypofunction; Chronic fatigue.
mochromatosis. A liver biopsy revealed lobular scarring but no portal involvement, and a subsequent diagnosis was made of AIH and possibly lupus erythematosus. The autoimmune hepatitis was thought to potentially have been triggered by a hepatitis B booster vaccine, as the patient had experienced similar symptoms after receiving her first hepatitis B vaccine ten years prior.

She was started on prednisone 60 mg daily upon diagnosis, but after an allergic reaction this was switched to mycophenolate mofetil, which also caused significant side effects. Finally, she was switched to azathioprine 100 mg daily, which has been maintaining AST and ALT within normal range for the past three years.

She sought the authors’ opinion because despite the azathioprine keeping her liver enzymes within normal limits and thus controlling the AIH, she was completely incapacitated by the chronic fatigue and joint pain. She was currently taking azathioprine 100 mg daily, furosemide 80 mg daily, spironolactone 25 mg daily, hydrocodone/ibuprofen TID PRN, promethazine 10 mg TID, hydrocodone 10 mg daily, furosemide 80 mg daily, spironolactone 25 mg daily, cyclonazine 25 mg TID PRN, aspirin 81 mg daily, potassium chloride 20 meq BID, estradiol cypionate 5 mg/ml, one ml IM every two weeks, testosterone cypionate 100 mg/ml, 0.1 ml IM every two weeks, and Vitamin B12 1,000 mcg/ml one ml IM every month.

She was started on dextroamphetamine sulfate 15 mg BID, and almost immediately noticed a decrease in swelling, elimination of pitting edema, and decreased muscle spasms, but no improvement in joint pain. One month later, the dosage was increased to 20 mg BID. This resulted in a decrease in knee and generalized joint pain, as well as increased energy. She was maintained on this dose for 14 months and continued to experience symptom improvement. The dose was recently increased to 25 mg BID and she continues to do so well that, while she had been on complete disability, she has now has resumed working five days a week for ten hours a day as a nurse.

**Discussion**

The use of dextroamphetamine sulfate has much less potentially long-term pathological consequences than continued immunosuppression. Eventually the authors plan to wean the patient off the azathioprine to see if the dextroamphetamine sulfate which completely abrogated all the other autoimmune symptoms and conditions associated with AIH can also keep the hepatitis under control with monotherapy.

The various syndromes of sympathetic nervous system hypofunction, known as the sympathetic neural hyperalgiesia edema syndrome, is most known to gynecologists because sympathetic nervous system hypofunction is the most common and also most remediable cause of chronic pelvic pain including dysmenorrhea, middle/schmerz, dyspareunia, vulvovaginitis, interstitial cystitis, and backaches [7-10]. Even if the woman does not ask the opinion of the gynecologist for treatment or diagnosis since the immediate connection is not clear, the patient should reveal other pathologic states to the gynecologist during their annual gyn examination. The gynecologist in turn could offer this potential therapy to the patient or at least consult with her treating specialist.

It is quite possible that this patient’s previous pelvic pain resulting in hysterectomy may have been related to sympathetic nervous system hypofunction and initiation of dextroamphetamine sulfate may have prevented the need for hysterectomy.

**References**


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Abdominal intrauterine vacuum aspiration

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Summary
Evaluating and “cleaning” of the uterine cavity is probably the most performed operation in women. It is done for several reasons: abortion, evaluation of irregular bleeding in premenopausal period, and postmenopausal bleeding. Abortion is undoubtedly the number one procedure with more than 44 million pregnancies terminated every year. This procedure should not be underestimated and a careful preoperative evaluation is needed. Ideally a sensitive pregnancy test should be done together with an ultrasound in order to confirm a uterine pregnancy, excluding extra-uterine pregnancy, and to detect genital and/or uterine malformations. Three out of four abortions are performed by surgical methods. Surgical methods include a sharp, blunt, and suction curettage. Suction curettage or vacuum aspiration is the preferred method. Despite the fact that it is a relative safe procedure with major complications in less than one percent of cases, it is still responsible for 13% of all maternal deaths. All the figures have not declined in the last decade. Trauma, perforation, and bleeding are a danger triage. When there is a perforation, a laparoscopy should be performed immediately, in order to detect intra-abdominal lacerations and bleeding. The bleeding should be stopped as soon as possible in order to not destabilize the patient. When there is a perforation in the uterus, this “entrance” can be used to perform the curettage. This is particularly useful if there is trauma of the isthmus and uterine wall, and it is difficult to identify the uterine canal. A curettage is a frequent performed procedure, which should not be underestimated. If there is a perforation in the uterus, then this opening can safely be used for vacuum aspiration.

Key-words: Vacuum aspiration; D&C; Dilatation; Suction; Curettage; Abortion; Complication; Bleeding; Hemorrhage; Medical abortion; Failed attempted abortion.

Introduction
Almost 44 million pregnancies ended in an induced abortion in 2008 worldwide [1]. The performance of an abortion is probably one of the most frequent surgical procedures in women. First trimester abortions can be accomplished by medical and surgical methods. Despite the fact that medical abortion with mifepristone is simple and safe, still 75% of the abortions are performed by surgical methods [2]. Surgical methods include a sharp - or blunt curettage or a vacuum aspiration (suction curettage). The latter is the preferred method. Surgical abortion appears to be an extremely save procedure with major complications in one to three percent of cases [3-5]. In “illegal” abortion the figures are, as to be expected, higher. According to the WHO, each year 21.6 million women experience an unsafe abortion worldwide [6]. Each year 47,000 women die from complications of unsafe abortion. Deaths due to unsafe abortion remain close to 13% of all maternal deaths. Worldwide, 49% of abortions were unsafe in 2008, compared to 44% in 1995. About one in five pregnancies ended in abortion in 2008 [1]. Abortion is a major health issue and the figures have not changed much in the last decade. The present report would like to emphasize this by describing the performance of an abdominal suction curettage in case of a patient with perforations and severe haemorrhage. The goal of present article is to point out that a perforation can safely be used for vacuum aspiration.

Case Report
It presents a 24-year-old woman who initially had an abortion at eight weeks of amenorrhea. A vacuum aspiration was performed, however no fetal of placental tissue was seen in during histological examination. Subsequently an extra-uterine pregnancy was suspected. A repeated vaginal ultrasound revealed remnants of an intrauterine pregnancy and no signs of an extra-uterine pregnancy. A second attempt was performed for a vacuum aspiration. During this procedure no clear tissue could be retrieved. In order to clarify this situation, an ultrasound was performed. Under ultrasound guidance a curettage was done and this showed that the aspirator was within the abdominal wall, causing disruption and that there was a perforation at the back wall of the uterus. Furthermore the heart rate of the patient was increasing and there was a drop in blood pressure. An immediate laparoscopy was performed, showing massive blood loss and severe bleeding from the perforation. The uterus had a bicornual aspect. One cornus contained the pregnancy and the perforation and the other cornus had a “normal” non-pregnant size.

Due to the instable situation, laparoscopy was immediately converted to a laparotomy and a request was done for a gynecologic consultant. During laparotomy 1,200 cc blood was removed and applying pressure on the perforation with one finger stopped the bleeding. Suturing the perforation permanently resolved the bleeding. A third attempt was done to perform a vacuum aspiration curettage under abdominal guidance. This confirmed the previous finding of a disrupted myometrial wall of the uterus. The pregnant uterus was typically weak and the false routes were so severe that there was no clear entrance in the cavium uteri. Instead of performing the classical hysterotomy, a suction curettage was done using the previously closed perforation after visual inspection of the uterus. The perforation was closed at the end of the vacuum aspiration. The patient had an unremarkable recovery and was discharged three days later.
Discussion

Despite the fact that vacuum aspiration is a save procedure, severe complications do occur. The rare complications are pelvic infection, excessive bleeding, cervical injury, incomplete evacuation, uterine perforation, uterine wall damage, endometritis, uterine synechia, tubal damage, anaesthesia complications, and ongoing pregnancy [7]. Major complications are less than one percent and the overall death rate for women obtaining legally induced abortions is 0.7 per 100,000 [8]. Hemorrhage and sepsis are each responsible for approximately one-fourth of the abortion related deaths. Embolism, complications of anaesthesia, and other causes account each for approximately 15 % of deaths [8]. Vacuum aspiration has the lowest surgical complication rates. During first and second trimesters the main complications are perforations (0.3% - 0.4%), cervical trauma (0% - 1.0%), bleeding (0% - 2.4 %) and infection (0.6% - 2.5%) [9-11]. The percentages of major complications rise from about two per 1,000 procedures for abortions performed at seven to eight weeks to six per 1,000 at 13–14 weeks and 15 per 1,000 after 20 weeks [12]. A recent randomised trial regarding complications by vacuum aspiration after cervical preparation, with and without misoprostol, showed that preparation of the cervix with 400 µg misoprostol vaginally reduced the incidence of complications [13]. Misoprostol preparation increased the diameter of the cervical canal, thereby reducing the need for mechanical dilatation in 40%. Subsequently this was translated in a reduced risk of cervical laceration, due to the fact that less force was exerted on the cervix. Furthermore the preparation allowed the use of larger suction tubes. Use of a larger suction tube facilitates evacuation of the uterine cavity, and the larger diameter of the cervix after misoprostol treatment also eases emptying of the cavity of any retained tissue by uterine contractions [13]. The main side-effects of misoprostol preparation were increased abdominal pain (55 % vs. 22 % in the placebo group) and vaginal bleeding (37 % vs. 17 %) [13].

In order to perform a safe surgical abortion, it is important to have a preoperative ultrasound, which shows that there is a uterine pregnancy, excludes extra-uterine pregnancy, and detects genital and/or uterine malformations. A sensitive pregnancy test at the beginning is recommended in order to confirm the pregnancy and to have the possibility of hCG monitoring if needed. One could consider performing a hysteroscopy, however this is time-consuming, may cause bleeding, and the additional benefits are low. An immediate gross and meticulous examination of the aspirate should be performed in order to discover failed attempted abortion or incomplete abortion [14]. In case of a questionable specimen, a strict follow-up should be followed in order to detect continuing pregnancy or an ectopic pregnancy. Routine microscopic examination of the tissue aspirates has only minimal diagnostic value. Only in doubt cases, for instance, of repetitive non-medical abortions or if there is the suspicion of a gestational trophoblastic disease, is there an indication for pathological examination.

The complication rates are reduced when the experience of the team is increased. This is particular true for uterine trauma. Nevertheless even in the most experienced hands, uterine perforations do occur. Vacuum aspiration is preferred above sharp or blunt curettage. Not only is it easier to handle, but there is also a reduced blood loss and lesser retained tissue. With sharp or blunt curettage, there is an increased risk of cervical injury and uterine trauma. Despite the fact there is increased endometrial abrasion, there are no data regarding the long-term morbidity, as the risk of developing intracavitary adhesions, cervical stenosis or subfertility [14].

The incidence of uterine perforation and/or trauma is estimated to be 1.2 per 100 vacuum aspirations. The two major dangers are haemorrhage and damage to the abdominal contents. Especially lacerations of the lateral walls of the uterus are dangerous due to the uterine vessels in these locations. Perforation of the fundus is in generally not dangerous. Blood vessels originate from lateral to medial and anastomose which each other. Most perforations therefore do not require any treatment. However a suction tube of the vacuum aspirator or a forceps in the abdominal cavity can cause severe lesions to the bowel, bladder or tubes. Due to the suction or traction, vessels of the organs can be lacerated, leading to severe haemorrhage. In case of a suspicion of perforation, the suction procedure should be stopped and a laparoscopy should be performed in order to access the damage of the uterus and other intra-abdominal organs. Laceration of an organ will not lead to an immediate problem, rupture of vessels on the other hand can lead to an extensive bleeding in a relative short time. Immediate action in these circumstances is required. During laparoscopic exploration, there is often an under-estimation of the bleeding due to the performed suction. It is important to identify the bleeding source as soon as possible and to stop the bleeding immediately by the simplest method. Sometimes several attempts occur arrest the bleeding by coagulation with a small forceps without any success. Due to the continuous suction, the surgeon it often not aware of the amount of blood the patient is loosing. The remark of the anaesthesiologist that the patient is instable is the late wake up call. If the bleeding cannot be directly arrested, pressure should be applied on the bleeding vessels in order to stabilise the patient and to organise you operating theatre. Once every one is in place and the correct surgical armamentarium is acquired, the bleeding problem can be easily solved. Attempting to arrest the bleeding with inadequate material is dangerous, and the patient is placed under unnecessary risks. Keeping focussed on the bleeding and applying pressure, suturing the laceration with only a few stitches resolves this complication in the shortest possible time.

In case of uterine wall trauma and false routes, the perforation can be used to remove the content of the uterine cavity. It should be possible to perform a vacuum aspiration
abdominally by laparoscopy, however, in the current case, this was not performed due to the severe intra-abdominal bleeding and the fact that the laparotomy had already begun. The fact that the patient had a uterus bicornus is probably the cause of the related morbidity in this case. Unfortunately the bicornual uterus was not noted in the preoperative evaluation of the patient. This was the base of the unsuccessful evacuation of the first abortion. Microscopic examination of the aspirated tissue should only “normal” endometrium and no signs of pregnancy. During the second attempt aspiration four weeks later, it was still not known that it was a bicornus uterus, but the vacuum aspirator was accidentally in the right cornus. Unfortunately due to the small cornus, multiple manipulations with force were performed leading to uterine wall trauma and perforation.

Despite the fact that abortion is one of the most frequent procedures performed in pregnant women, it can very dangerous. A meticulous pre-aspiration ultrasound evaluation is essential in reducing morbidity. In case of a perforation, evacuation of the intrauterine content by the abdominal route should be considered. Preferably the latter should be performed by laparoscopy if the patient is stable enough. Otherwise this should be performed by laparotomy, firstly stabilising the patient and secondly, evacuating the pregnancy products via the perforation hole.

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Salmonella ovarian abscess in a patient with rheumatoid arthritis (RA): a case report with literature review

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Summary
Salmonella ovarian abscess in a patient with rheumatoid arthritis (RA) is reported here. A 33-year-old nulliparous woman with a 16-year history of RA who had been treated with corticosteroid and immunosuppressive drugs was diagnosed as having a non-typhoidal Salmonella ovarian abscess which might have been preceded by an occurrence of endometriotic cyst. Multidisciplinary therapy including surgical intervention was required to complete the eradication of infection. Although Salmonella ovarian abscess is rare, it may cause a serious complication in the ovary harboring endometriotic cyst through sustained presence of Salmonella bacteraemia.

Key words: Salmonella infection; Ovarian abscess; Rheumatoid arthritis, Endometriotic cyst.

Introduction
Ovarian abscess most commonly occurs among reproductive aged women and typically results from an upper genital tract infection. Multidisciplinary therapy including antibiotic injection, minimally-invasive drainage treatment, and surgical procedure are required for the treatment of ovarian abscess. Ovarian abscess sometimes causes serious conditions due to the rupture of the abscess that might result in a septic status for the patient, a potentially life-threatening disorder.

In general, gastroenteritis with non-typhoidal Salmonella infection causes a short, febrile, and self-limited illness. However, some Salmonella species can potentially cause bacteraemia that might foster localized infection [1]. Ovarian abscess formation from Salmonella bacteraemia is a rare event. Most of these cases have shown pre-existing ovarian cysts or benign ovarian tumors [2, 3]. It is known that immunocompromised patients who have experienced ailments such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), splenectomy, and immunodeficiencies from hemoglobinopathies are prone to opportunistic infections such as ovarian abscess [4, 5]. The authors report here a case of a RA-associated ovarian abscess, while reviewing pertinent literature.

Case Report
A 33-year-old nulliparous woman with a right ovarian endometriotic cyst was being followed for 18 months. She had a 16-year history of RA with the use of corticosteroids, mizoribine, and methotrexate, and had no high-risk sexual exposure or history of pelvic inflammatory disease. She first showed symptoms of abdominal pain, vomiting, and fever. The patient was diagnosed as suffering from gastroenteritis, and a five-day administration of flomoxef sodium at a local hospital temporarily eased the symptoms.

After having been discharged from the hospital, the patient was readmitted to the same hospital because of recrudescence. Computed tomography (CT) revealed a pelvic abscess, and subsequently a percutaneous drainage procedure was performed. The pus culture from the patient showed Salmonella enteritidis and, therefore, cefpirome sulfate (2,000 mg/day) and clindamycin hydrochloride (1,200 mg/day) were administered. As the patient still had persistent fever and abdominal pain even after the administration of different antibiotics, she was referred to the present hospital.

A physical examination of the patient revealed tenderness in the right lower abdominal quadrant and a pelvic examination suggested that there was a right ovarian mass. The pelvic ultrasound scan showed a complex cystic mass in the pelvic area without any solid component (Figure 1a). A subsequent pelvis CT scan showed an ovarian cystic mass along with an irregular shaped region in thick enhanced walls (Figure 1b). The laboratory study showed a white cell count of 14.3 x 10^3/μl and a C-reactive protein level of 5.59 mg/dl. The patient underwent a CT-guided percutaneous drainage procedure for the pelvic abscess, and the pus culture of the abscess again showed the same bacteria as detected before. The bacterial culture examination for both stool and vaginal discharge were negative at that time point. On the basis of the antibiotics susceptibility test for Salmonella enteritidis, ceftriaxone (1,000 mg every 12 hours intravenous injection) and lincomycin (600 mg every eight hours intravenous injection) were then administered. The follow-up CT after ten days, however, showed a persistent well-defined pelvic abscess. Furthermore, she still suffered from low grade fever and appetite loss. The patient finally underwent a right salpingo-oophorectomy and omentectomy with trans-abdominal drainage. A right ovarian abscess with filmy adhesions to the omentum and the colon was found. A pathologic examination revealed ovarian endometriosis with inflammatory changes and chronic salpingitis. The patient continued to receive the ceftriaxone and lincomycin treatment for another two weeks after the surgery, and she was discharged, without any sequelae, on the 30th day after the treatment.

Discussion
Patients with chronic diseases such as immunodeficiencies are thought to be high risk for having Salmonella infection [6]. In particular, an intensive immunosuppress-
sive therapy for immunodeficiencies might directly compromise host immunity. Table 1 summarizes seven cases of ovarian abscesses due to *Salmonella* infection. All of these were caused by a non-typhoidal *Salmonella* infection. Among these were three cases with SLE, and three other cases with no significant medical history. It should be noted that the occurrence of endometrioma was observed in five of the seven cases, and all cases including our 33-year-old nulliparous patient needed a surgical intervention.

Once a woman is diagnosed as having pelvic inflammatory disease (PID), it is clinically important to decide whether she requires further evaluation for ovarian abscess. In particular, for a woman with PID who has acute illness, significant abdominal tenderness, adnexal masses, and poor response to antibiotic therapy, imaging studies such as pelvic ultrasonography and CT scanning should be considered for the detection of ovarian abscess. Ultrasonographic images typically reveal complex masses that often appear to contain speckled fluid and internal echoes consistent with inflammatory debris [11-13]. Treatment for ovarian abscess includes intensive antibiotic therapy, minimally-invasive drainage procedure, and/or invasive surgery. In general, a prompt surgical intervention should be considered in cases of a suspected intra-abdominal rupture of ovarian abscess with overt signs of sepsis. On the other hand, when patients with abscess under nine cm in diameter are hemodynamically stable, respond adequately to antibiotic therapy, and are premenopausal, they are candidates for a non-invasive medical management. However, if the patients do not respond to an antibiotics treatment within 48 to 72 hours, either a minimally invasive abscess drainage procedure or surgery will be required. It was reported that bacteraemia have been observed among the immunocompromised patients who had a certain non-typhoid *Salmonella* serotype infection [14, 15]. In the present case with RA, the fact that the results of stool and leucorrhea cultures were both negative may support the idea that ovarian abscess due to *Salmonella* infection could be hematogenously disseminated.

### Conclusion

In summary, we report here a rare case of *Salmonella* ovarian abscess associated with RA. It should be considered that endometriotic cysts with the collection of stagnant blood would have been a likely site for the *Salmonellae* local infection.
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Transient sixth cranial nerve palsy following orgasm abrogated by treatment with sympathomimetic amines

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Summary

Purpose: To describe a unique disorder where a transient 6th nerve palsy leading to diplopia following orgasm developed in a 28-year-old woman. This coincided with a weight gain of 100 pounds in a short time without a corresponding change in dietary habits.

Materials and Methods: She was treated with the sympathomimetic amine dextroamphetamine sulfate. Results: Indeed she immediately responded to treatment with dextroamphetamine sulfate sustained release capsules with complete resolution of the episodes of 6th nerve palsy following orgasm. Conclusions: The main importance of this case is that it suggests that orgasm causes a transient generalized decrease in sympathetic nervous system activity and that the achievement of an orgasm may require an increase in the sympathetic nervous system activity.

Key words: Sixth cranial nerve palsy; Diplopia; Orgasm; Sympathetic nervous system hypofunction; Dextroamphetamine sulfate.

Introduction

Clinical issues regarding orgasm can be multifold, e.g., failure to achieve one, the need for excessive orgasm, and severe pelvic pain following orgasm.

The authors report here a unique complication of orgasm in a woman – a sixth nerve palsy associated with diplopia. Even more importantly they report a unique pharmacological therapy that completely corrected the problem.

The fact that the therapy used a sympathomimetic amine which has been used to treat a variety of disorders characterized by diminished sympathetic nervous system activity implies that orgasm may result in a transient hypofunction of the sympathetic nervous system.

Case Report

A 28-year-old woman complained of episodes where her left eye would suddenly turn inward and she would see double. These episodes lasted only a few minutes in duration and were associated with times when she would stand up quickly. Within a few weeks of the onset, the diplopia began occurring with every orgasm even though spontaneous occurrences weaned. Restoration of normal vision would return in about 15 minutes.

At first the patient thought that the problem could be a form of vertigo related to an inner ear problem. However, a specialist in otolaryngology did not know the cause and referred her to a neurologist. As it progressed, the episodes occurred more frequently and appeared to be associated with certain activities such as positional changes when she would go from sitting to standing or bending over. She also noticed they were more frequent premenstrually. However, she said without fail it would always happen with an orgasm and that these lasted longer than the spontaneous episodes.

She was referred to a neuro-ophthalmologist who performed a lumbar puncture which was also negative. The neurologist ordered an electroencephalogram (EEG), magnetic resonance imaging (MRI) of the brain, and a magnetic resonance artery (MRA) study but all were normal. The diagnosis was a sixth nerve palsy diagnosed by clinical observation by a neuro-ophthalmologist following a self-induced orgasm. None of the specialists had any suggestions for etiology or for management. The only suggestion was not to have an orgasm for fear of a possible cerebrovascular accident. Their other suggestion was to seek the opinion of an endocrinologist, particularly a reproductive endocrinologist, which is how the present authors first had their chance to evaluate this woman with this fascinating medical history.

Taking a further history, the patient had a 100 pound weight gain without any subsequent increase in her diet. Furthermore she had developed such severe backache with menstruation that her husband had to help her out of bed during that time.

On physical examination she was six feet tall, her weight was 285.5 pounds, blood pressure 120/70, thyroid normal size and non-tender, heart rate 80 and regular, no murmurs or gallops, no hepatosplenomegaly or abdominal tenderness, and no obvious pitting edema of the extremities.

Laboratory studies showed thyroid studies were normal including free thyroxin level and TSH (the latter at 1.26 mIU/ml). A water load test was abnormal with 1,750 ml urine excretion after four hours while supine but only 500 ml after standing for four hours (abnormal < 55% excretion) [1]. A 1,500 ml water load over 30 minutes was ingested initially each day prior to measuring urine excretion.

Based on the results of the abnormal water load test, the authors concluded that the inappropriate weight gain was most likely related to a defect in the sympathetic nervous system leading to marked fluid retention especially in the upright posture [1-3]. The defect was found to be related to an inappropriately weak response from the sympathetic nervous system to diminish capillary permeability and to prevent the transudation of fluid from intravascular to extravascular spaces that would occur from the increase in hydrostatic pressure that occurs in the orthostatic position [4].
She was advised that she may lose weight following treatment with the sympathomimetic amine, dextroamphetamine sulfate which seems to diminish capillary permeability when standing and thus inhibits edema [5]. She was also advised that though there was no precedent for her specific orgasm condition, based on the wide variety of disorders that were corrected or alleviated by treatment with dextroamphetamine sulfate, it would not be surprising if the strange sixth nerve palsy with and without orgasm may similarly improve [6].

After one month of taking dextroamphetamine sulfate ten mg extended release capsules upon awakening and ten mg at noon the woman reported significant improvement in her lower back pain. The use of sympathomimetic amines has also been demonstrated to provide immediate relief from backache in some cases that were refractory to other therapies [7]. The spontaneous episodes of sixth nerve palsy which previously happened several times per day were reduced to just twice in the month and were also reduced in duration. Interestingly she reported complete resolution of the sixth nerve palsy episodes occurring with orgasm which previously occurred 100% of the time after each orgasm. She lost 9.5 pounds in that first month.

After one year of therapy she reported no episodes of diplopia following orgasm. The one exception was the two times she ran out of her prescription for a few days. She has lost 55 pounds so far.

Discussion

This disorder of diminished sympathetic nervous activity seems to be responsible for a large variety of chronic debilitating disorders not amenable to other therapies including edema, urticaria, chronic lower abdominal pain, interstitial cystitis, pelvic pain, backaches, esophageal motility disorders, gastroparesis, arthritis, and vasomotor symptoms [6, 8]. This has led to the hypothesis that the condition underlying these symptoms is either related to the effects of edema or more likely, to the absorption of toxins into epithelial cells related to increased cellular permeability secondary to diminished sympathetic nervous system activity as evidenced by quick and sustained response to the sympathomimetic amine dextroamphetamine sulfate [6, 8].

Several case reports suggest that the main etiology of the pain and other symptoms may be more associated with the absorption of toxins and chemicals into tissues because of a diminished sympathetic nervous system activity that is not properly suppressing cellular permeability. For example, a cue of pseudointestinal obstruction with dextroamphetamine sulfate therapy was not associated with weight gain and edema but in fact with marked weight loss down to a life threatening level. Soon after starting dextroamphetamine sulfate, her abdominal pain and early satiety markedly improved, as did her bowel movements and she quickly lost weight to the proper level [9].

Other areas of gastrointestinal motility such as the esophagus or stomach seem to be prone to defects in diminished sympathetic activity and respond to therapy with sympathomimetic amines when all other therapies were ineffective [10, 11]. There is also evidence that therapy with sympathomimetic amines can markedly and quickly improve the symptoms of severe long-standing Crohn’s disease and ulcerative colitis that were refractory to standard therapies [12, 13].

Evidence that defects in the sympathetic nervous system can lead to skeletal muscle abnormalities is evidenced by marked improvement in chronic fatigue syndrome with treatment with sympathomimetic amines [14]. Improvement in other cerebral conditions was illustrated by the marked improvement of headaches, including migraines with sympathomimetic amine therapy, which had been refractory to other medications [15, 16].

Based on these observations, one hypothesis to explain this very unusual syndrome reported here of sixth nerve palsy with orgasm is that the palsy was related to the absorption of toxins into the sixth cranial nerve or the ocularomotor muscles that it innervates. The authors hypothesize that there was usually sufficient sympathetic tone to prevent diplopia except under certain circumstances, e.g., sitting up too quickly. However they hypothesize the process of orgasm may be normally followed by a period of decreased sympathetic nervous system activity which would further allow an increase in cellular permeability leading to a critical concentration of toxins and chemicals to cause temporary muscle paresis. Some additional local defect of these muscles must have also been present causing their susceptibility to a temporary decrease in sympathetic tone.

A search of the literature failed to reveal a similar report. The case then also presents another unique presentation for the relatively common problem in women with sympathetic nervous system hypofunction referred to as the sympathetic neural hyperalgesia edema syndrome [8]. Specifically this case presents the report of a strange association of diplopia related to temporary sixth nerve paresis following orgasm amenable to therapy with sympathomimetic amines.

The universal occurrence of the sixth nerve palsy following orgasm and the complete correction of this problem following treatment with a sympathomimetic amines strongly suggests that orgasm is followed by a transient decrease in sympathetic nervous system activity. However, in most people without this defect of sympathetic nervous system hypoactivity, the transient decrease in sympathetic tone does not cause symptoms because there is no presence of a target tissue that has another defect and is thus prone to malfunction following diminished sympathetic activity. Since most cases of the sympathetic neural hyperalgesia edema syndrome are not associated with diplopia following orgasm, this woman presumably also had some rare defect in either the sixth nerve or the extraocular muscles per se allowing the temporary paresis and subsequent diplopia to occur.
References


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Normal evolution of pregnancy complicated by a giant placental chorioangioma

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Summary

Placental chorioangioma is a benign vascular tumour of placental origin. Here the authors report a case of a pregnant patient who presented placental chorioangioma measuring 11 cm in the greatest diameter at 37 weeks at term and in labor.

Key words: Placental; Chorioangioma; Pregnancy.

Introduction

Placental chorioangioma is also called placental hemangioma (angiomatosis of placenta). It is a benign vascular tumour of placental origin arising from primitive chorionic mesenchyme. It is also believed that it is caused by the part of the vascular and stromal active hyperplasia, that lose their normal relation to decidual tissue. Some also believe that it is formed by dysplasia of allantoic vascellum [1]. Most cases of placental chorioangioma tend to be sporadic and usually found incidentally, and the diagnosis needs to be confirmed according to the ultrasound and pathological findings. The authors present a case of a patient with giant placental chorioangioma that delivered spontaneously. Clinical presentation and the pathological findings, differential diagnosis, clinical outcome, and therapeutic approach are discussed in order to improve the understanding of the disease.

Case Report

A 23-year-old patient was admitted to the Obstetrics and Gynecology of the present hospital at 37 weeks because of threatened labor. Ultrasound showed a single live fetus corresponding to 38 weeks of gestation with amniotic fluid index (AFI): 18 cm. Normal AFI ranges from eight to 20 cm. There were no gross structural abnormalities. Placenta was on the anterior wall upper segment, grade II. A well-defined mass measuring 9.8 x 9.2 x 8.5 cm³ different from the rest of the placenta was seen bulging on the fetal side. External fetal monitoring showed a heart rate ranging from 120-140 bpm. Patient went into spontaneous labor and delivered a healthy female baby weighing 3,400 g with Apgar score of 10 at one minute. The placenta weighed 560 g and measured 26 x 24 x 3 cm. The umbilical cord was 40 cm long and 2.5 cm wide with two arteries and one vein. The placenta presented a brownish hemorrhagic mass of firm consistency, measuring 11 cm in the greatest diameter, reaching the margin of the placenta (Figures 1A and 1B). Histological examination of the placental tumor showed the features of chorioangioma.

Discussion

Chorioangioma is a benign vascular tumor of the placenta arising from primitive chorionic mesenchyme. Because of most cases chorioangiomas are asymptomatic, small in size, and buried in the placenta tissues, they are overlooked or easily misdiagnosed. It was formerly thought that its incidence was extremely low. With the increasing ultrasound and postnatal placental pathological examination during pregnancy, the estimated incidence is 0.7%–1.6% [2]. Typically a chorioangioma is located near the insertion of the cord, and protrudes into the amniotic cavity. Three histological types are recognised: angiomatoid, cellular, and degenerative. They tend to occur on the fetal side of the placenta. Large (> five cm) chorioangiomas are much rarer and are often associated with maternal and/or fetal complications. Large chorioangiomas cause several obstetric complications, including premature labor, placental abruption, polyhydramnios, fetal hydrops, fetal growth restriction, fetal hepatosplenomegaly, cardiomegaly, congestive heart failure, and fetal death. The neonatal complications are hydrops fetalis, microangiopathic hemolytic anemia, and thrombocytopenia [3]. In this case the authors present natural childbirth with giant placental chorioangioma and a healthy fetus in their department.

Color Doppler ultrasound is the only effective means of prenatal diagnosis of hemangioma and definitive diagnosis subject to placental pathological diagnosis. Chorioangiomas are usually treated with expectant management, as the majority of tumours are asymptomatic. Small tumours are often monitored with ultrasound ~ every six to eight weeks, whereas large tumours require serial ultrasound examinations more frequently ~ every one to two weeks. Some tumours may even regress spontaneously during pregnancy [4].

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Novel intrauterine treatment options include intravascular transfusion, fetoscopic devascularization, microcoil embolization, and intravascular injection of absolute alcohol.

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Failure to improve a thin endometrium in the late proliferative phase with uterine infusion of granulocyte-colony stimulating factor

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Summary
Purpose: To determine if the treatment with uterine infusion of granulocyte colony-stimulating factor (G-CSF) can improve endometrial thickness in an infertile woman with a double uterus, who consistently showed a thin endometrium in the late proliferative phase either in controlled ovarian hyperstimulation (COH) IVF-ET cycles or with graduated estrogen/sildenafil protocols for frozen embryo transfer (ET).

Materials and Methods: A single uterine infusion of G-CSF was performed in the late proliferative phase in a woman who only attained a five-mm thickness despite a high dose vaginal and oral estradiol regimen plus sildenafil. Results: No increase was found within a couple days. Conclusions: A previous four-case study in another center found 100% improvement in the endometrial thickness in women with consistently thin endometria. Perhaps the uterine anomaly in the present case prevented the response of the endometrium.

Key words: Granulocyte colony-stimulating factor; Thin endometrium; In vitro fertilization-embryo transfer; Intrauterine infusion.

Introduction
Lower pregnancy rates (PRs) per embryo transfer (ET) have been demonstrated in women with thin endometria in the late proliferative phase at the time of human chorionic gonadotropin (hCG) injection [1,2]. One review of the literature concluded that there were no successful pregnancies following in vitro fertilization-embryo transfer (IVF-ET) when the pre-ovulatory endometrium was < six mm [3]. However subsequent to this study, a successful pregnancy following IVF was reported where the maximum endometrial thickness was only four mm [4]. A successful delivery was also reported without IVF-ET in a natural cycle with a maximum endometrial thickness in the late proliferative phase of four mm [5].

A study of 35 women having IVF-ET with a maximal thickness of ≤ five mm found three clinical pregnancies (8.5% per transfer) and two live deliveries (5.7% per transfer) [6]. In that same study there was one live delivered pregnancy out of seven frozen ETs (14.2%) with maximal endometrial thickness ≤ five mm.

Most therapies to improve thin endometria have failed. Though at one time treatment during the follicular phase with vaginal sildenafil seemed promising, other studies failed to confirm any significant beneficial effect on pregnancy rates [7,8].

Another promising treatment for unresponsive thin endometrium has recently been published, i.e., the uterine perfusion of granulocyte colony-stimulating factor (G-CSF) [9]. They reported that four consecutive women with a history of multiple cycles of failing to attain an adequate endometrial thickness despite the use of higher dose graduated estradiol and vasodilators resulting in cancellation of ET cycles [9]. However, with intrauterine infusion of G-CSF, three improved the endometrial thickness to eight to ten mm and one increased to 7.3 mm [9]. Even more important, all four conceived and three delivered live babies [9].

The authors published these cases ahead of two ongoing prospectively randomized studies of G-CSF “because of unexpectedly clear results in clinical circumstances without effective treatment options”. They suggested that this small study could influence other centers to try this therapy and hopefully improve their success rates prior to the publications of the results of the large prospective study.

The present case report is the authors’ first attempt to improve the endometrial thickness of a woman with multiple unresponsive cycles using G-CSF. Unfortunately they present their first case of failure with this technique.

Case Report
This 33-year-old woman had multiple ETs but failed to conceive. The failures were attributed to inadequate endometrial thickness on the day of hCG. She had the remaining frozen embryos transferred to the present IVF center. However despite vaginal and oral estradiol extending to day 10 and vaginal sildenafil 25...
mg 4x/day from day 7, her maximal endometrial thickness was six mm. She failed to conceive. She then had controlled ovarian hyperstimulation (COH) for IVF-ET starting with 225 IU highly purified follicle stimulating hormone (FSH) and 75 IU highly purified menotropins. Despite attaining 23 follicles of adequate size for oocyte retrieval, her endometrial thickness was only a six mm triple line pattern on the day of hCG. She failed to conceive following two ETs. A milder stimulation protocol was used in her next frozen ET cycle and she reached a maximum seven-mm endometrial thickness. She then did another COH IVF-ET cycle and reached a maximum thickness of six mm.

Based on the aforementioned study by Gleicher et al., the present authors elected to add to the estrogen sildenafil protocol uterine perfusion G-CSF which was performed according to the described technique by Gleicher et al. [9]. Unfortunately this therapy failed to increase the five-mm endometrial thickness at all. A blastocyst transfer was performed on day 5 and the pregnancy test was negative.

**Discussion**

Other than the aforementioned cases described of an IVF-ET live pregnancy achieved with a four-mm endometrial thickness, here have been other anecdotal reports of successful pregnancies with very thin endometria [4, 5]. One case was recently reported of a woman with marked diminished oocyte reserve who conceived with her own oocyte following a fresh embryo transfer using a mild ovarian hyperstimulation regimen [10]. Interestingly she had been enrolled in a European IVF center for donor oocytes but after two attempts to improve endometrial thickness with estrogen and then estrogen plus vasodilators, she was advised that they would only transfer the embryos to a gestational carrier. Obviously if she would have used G-CSF (which she did not) the conclusion would have been that the G-CSF must have been responsible for the successful implantation since there had never been one precedent for a pregnancy with IVF or natural with an endometrial thickness < four mm.

There has also been a report of a successful twin pregnancy in a donor oocyte recipient whose maximum endometrial thickness was four mm [11].

The particular woman in the present case report had a double uterus and a vaginal septum. Possibly the uterine anomaly was responsible for the failure to respond to the G-CSF in this case and hopefully G-CSF will prove to be an effective therapy for improving pregnancy rates following ET with thin endometria or prove to be an effective agent to improve implantation rates even if there seems to be adequate endometrial thickness.

The report from Gleicher et al. is not the first to suggest that G-CSF can improve the implantation potential and reduce miscarriage rates [12, 13]. Granulocyte-CSF has even been added to endometrial co-culture cells as early as 1998 [14]. What is unique about the procedure proposed by Gleicher et al. is the use of G-CSF by uterine infusion.

There is no question that although a very thin endometrium is not an absolute factor that prevents successful implantation, there is no question that very thin endometria negatively effects pregnancy outcome following ET. By adding the present case report to the other four, the use of G-CSF is 80% effective. Hopefully the large prospective study that is underway will show an 80% efficacy rate. One just has to be a little careful about conclusions from a study being performed with a patented procedure by a group who benefits from approval. Thus the present authors agree with Gleicher et al. that other centers should independently conduct controlled studies. The problem is that the percentage of women who cannot stimulate a thickness past five mm is low and it may be that these two case reports should encourage more anecdotal reports pro or con to get an early determination of the efficacy of G-CSF for increasing the endometrial thickness.

Of course the use of G-CSF need not be restricted to cycles involving ET. For the aforementioned patient, the authors considered intrauterine infusion of G-CSF even in natural cycles to see if it could improve implantation even if it did not improve endometrial thickness. She elected not to take the G-CSF. Two months later she conceived in a natural cycle. Her only treatment is progesterone which she will continue through her first trimester. Had she decided to continue on monthly G-CSF therapy, who would question that the successful pregnancy was not related to the G-CSF treatment. Instead it is clear that the pregnancy had nothing to do with G-CSF therapy.

Gleicher et al., in their manuscript mentioned that they are in the midst of a prospective randomized study to evaluate G-CSF on thickness and implantation. The authors’ plans are to evaluate G-CSF in a small series in an attempt to corroborate or refute the effect of G-CSF for thin endometria.

**References**


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Introduction

Inversion of the uterus during caesarean section is a rare but life-threatening complication of the procedure that requires immediate treatment, which is reversion and awareness due to the very serious adverse effects that it may have. Materials and Methods: The authors present a case of a 34-year-old para 1 woman of Greek ethnicity who underwent a scheduled caesarean section at 39 weeks of gestation. During the procedure, a uterine inversion occurred as a controlled cord traction was applied in order to achieve placental detachment, after the delivery of the baby. It was managed by immediate manual uterine reversion, which was performed after exteriorization of the uterus. There were no adverse effects. Conclusion: Uterine inversion during caesarean section is a serious complication, but fortunately very rare. However, the obstetrician should be aware that the complication should be quickly identified and act without hesitation because it is critical for the well being of the patient.

Key words: Uterine inversion; Postpartum bleeding; Caesarean section.

Discussion

Uterine inversion is a rare complication of labor. Calder supports the results coming from the analysis of data collected from large studies in India and the Middle East reporting an incidence of one in 20,000 to one in 25,000 deliveries for uterine inversion [14]. This complication may occur after vaginal delivery or during caesarean section. Uterine inversion during caesarean section is con-

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Summary

Introduction: Inversion of the uterus during caesarean section is a rare but life-threatening complication of the procedure that requires immediate treatment, which is reversion and awareness due to the very serious adverse effects that it may have. Materials and Methods: The authors present a case of a 34-year-old para 1 woman of Greek ethnicity who underwent a scheduled caesarean section at 39 weeks of gestation. During the procedure, a uterine inversion occurred as a controlled cord traction was applied in order to achieve placental detachment, after the delivery of the baby. It was managed by immediate manual uterine reversion, which was performed after exteriorization of the uterus. There were no adverse effects. Conclusion: Uterine inversion during caesarean section is a serious complication, but fortunately very rare. However, the obstetrician should be aware that the complication should be quickly identified and act without hesitation because it is critical for the well being of the patient.

Key words: Uterine inversion; Postpartum bleeding; Caesarean section.
sidered to be less likely to happen than the inversion of the uterus after vaginal delivery. Basket et al. reported that the incidence of acute uterine inversion following vaginal birth was one in 3,737, and following caesarean section, one in 1,860 [12]. However, the present authors agree with Vavilis et al. who in their paper consider that this incidence of uterine inversion during caesarean section is an overestimation [1].

It is very difficult to identify the causes of uterine inversion after caesarean section [4]. It is suggested that an inherent weakness of the uterine musculature might be partly responsible for the inversion [1,6,7]. This factor, though, is extremely difficult to prove as Vavilis et al. comment [1]. The fundal insertion of the placenta is also thought to be associated with uterine inversion [7, 14]. Placenta accrete might be a cause of uterine inversion as well [3]. Other factors that could contribute to this adverse event are traction applied on the umbilical cord and the administration of oxytocin [1, 9-11].

The implications of uterine inversion are quite severe, but rare. The most important adverse events of uterine inversion are pain, neurogenic shock, cardiac arrest, and post partum hemorrhage [14]. It is worth mentioning, and somewhat expected, that uterine inversion after vaginal delivery has a higher incidence of massive symptoms than after caesarean section [13]. Cardiac arrest is the most severe complication. There are reports of cardiac arrest following uterine inversion after caesarean section [2, 5], and cases of acute hypotension. Hypotension is associated with delay in re-inversion [8, 9]. These complications are thought to take place due to vaginal stimulation caused by traction on the ligaments supporting the uterus (i.e. infundibulopelvic and broad ligaments) [1, 5]. In the presented case, uterine inversion had absolutely no intraoperative or postoperative consequences. There was no hypotension or any other symptoms of vaginal stimulation and no abnormal postoperative bleeding. However, the uterus was reverted immediately after the identification of the inversion, and thus, it remained inverted for only ten seconds.

The management of uterine inversion after caesarean section is usually simple [6]. The time interval between inversion and reversion of the uterus should be minimized, so the attempt to revert the uterus should be performed with the placenta being attached, meaning no time is lost in attempting to separate the placenta first. Also, it should be noted that no oxytocin should be administered with the uterus being inverted. In case of general anesthesia the uterus could be relaxed after the administration of volatile inhalational agents. If the patient was subjected to spinal or epidural anesthesia, i.e., she is awake, the relaxation of the uterus, which is necessary in order to facilitate the obstetrician’s attempts for reversion, could be achieved by administering ritodrine [1, 9], or nitroglycerin intravenously [15].

Conclusion

As a conclusion, the authors report that uterine inversion during caesarean section is a serious complication, but fortunately very rare. However, the obstetrician should be aware that the uterus might become inverted even after caesarean section because it is critical for the patient that it is reverted quickly, without any delay or hesitation.

Acknowledgements

“KC, PC, and FC performed the operation. KC, NV, MT reviewed the literature, KC and AD analyzed and interpreted the patient data and were the major contributors in writing the manuscript.

References


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Introduction

The gynecologist is most familiar with the use of dextroamphetamine sulfate, a sympathomimetic amine, for the treatment of various types of pelvic pain including chronic pelvic pain, dyspareunia, middleschmertz, vulvodynia, dysmenorrhea, and chronic pelvic pain of bladder origin [1-4].

Most of the data suggest that the mechanism by which the amphetamine relieves pelvic pain is by inhibiting the absorption into various pelvic tissues chemicals and toxins which then evoke an inflammatory reaction [4]. The sympathetic nervous system is responsible for controlling cellular permeability. When there is hypofunction a particular vulnerable tissue will be dependent on increased sympathetic tone to prevent absorption of noxious agents and thus becomes affected. Treating with a sympathomimetic amine empirically dextroamphetamine sulfate corrects the cellular permeability defect and thus markedly improves pain [4].

Thus, endometriosis may be the result of increased permeability but not the cause of the pain and is merely associated with the sympathetic neural hyperalgesia edema syndrome where there is a pelvic tissue permeability defect. This would explain why frequently, despite expert surgical treatments to remove endometriosis, the pain frequently quickly returns whereas it seems to not return following treatment with dextroamphetamine sulfate [4, 5].

The increased cellular permeability defect leads to pain in other areas of the body, e.g., migraine headaches and fibromyalgia [6]. The increased permeability defect leads to the inability to compensate for the increase in hydrostatic pressure when standing which would lead to extravasations of fluid from the intravascular to extravascular spaces thus causing edema because the sympathetic nervous system signal is insufficient to decrease capillary permeability [7,8]. Thus many, but not all, patients with this syndrome have edema or inability to lose weight despite dieting leading to the name sympathetic neural hyperalgesia edema syndrome. Sometimes absorption of noxious factors into muscles leads to abnormal motor function and thus can cause gastrointestinal motility defects, e.g., achalasia, gastroparesis, or pseudointestinal obstruction or chronic fatigue syndrome [9-12].

The gynecologist could get involved with these other pathologic entities in a few ways. For example, by taking a complete history the gynecologist may advise a woman who the gynecologist wants to treat with dextroamphetamine sulfate for pelvic pain, that her chronic migraine headaches that are not responding to her present medication may improve also and she can gradually discontinue the other medications.

Sometimes the gynecologist may be reluctant to treat a gynecologic condition with dextroamphetamine because theoretically another condition may become worse. The present case presents the dilemma of wanting to use dextroamphetamine sulfate for unexplained infertility but with
the patient having complex regional pain syndrome (CRPS) (sometimes called reflex sympathetic dystrophy (RSD)). There could be some concern because of fear the CRPS could get worse since some researchers believe this condition is related to sympathetic hyperactivity.

Case Report

A young woman aged 15 in 1988 tore the triangular fibrocartilage complex (TFCC) in her right wrist while playing tennis. After having arthroscopic surgery to repair the TFCC, she recovered about 85% of her prior strength, endurance, and mobility in the right wrist. It bothered her off and on, and had to remain conscious of being careful with it, but she was able to play racquetball, garden (avoids), play the piano, and live a normal life. She was not able to play tennis or use a small roto-tiller, and if she severely overused the wrist, it would hurt for a few days, which she could just wait it out with the wrist in a brace. In late March of 2006, however, it did not recover after overuse. Instead, it seemed to improve over the course of four to six weeks of being very careful with it, but then normal use would aggravate it to the point where it felt like she had just injured it again.

On May 19, 2006, while trying to push a bulky grocery cart with her left hand, she sprained the left wrist, and now could hardly eat with either hand. A few days later it felt like she sprained the thenar area of her right thumb trying to crack it. In late May of 2006, she consulted the orthopedic surgeon who had performed her first surgery. The magnetic resonance imaging (MRI) of her right wrist showed a peripheral tear of the triangular fibrocartilage complex (TFCC) (on the ulnar side). This was consistent with his diagnosis on examining the wrist. She sprained her left wrist too close to the appointment date to get an MRI on that wrist before seeing the surgeon, but he felt a click on examination that suggested she had also torn something in that wrist. He wanted to wait 3.5 months to see if the wrists would heal on their own without surgery. She asked one of his occupational therapists to fit a molded brace to her hand, wrist, and lower arm.

In June, after a couple of weeks of wearing that brace, she started to get a peculiar shock pain in her right wrist. The symptoms changed from feeling like a sprain to feeling like nerve pain. It constantly felt like she had just hit a ball with a bat in freezing cold weather. She had to stop cooking, cleaning, and driving. She could not even strike a match without her hand going numb. She lost the ability to raise her right pinky or lift her ring finger. Her hands got very weak and slow as well as uncoordinated, and the pain became diffused throughout her hand and wrist and up her forearm. She became very sensitive to even light touch and she could not find a way to rest her right arm. Her right wrist could not take the weight of resting the arm on a chair armrest – the only comfortable position was straight up in the air with a brace on, resting on the elbow. To sleep she had to wrap the wrist and rest it on an extremely soft pillow while laying on her right side. She would lose circulation in the arm if she laid on her back or right side. She saw the surgeon again because of these new symptoms. He said he did not know what it was and instructed her to stop wearing all braces. He suggested a consult with a rheumatologist and a neurologist, and recommended a bone scan, electromyography (EMG), and a functional capacity test with a physical therapist. He told her to use the hand as much as possible. Over the next several months she lost 15 pounds due to difficulty with bringing a fork to her mouth with either hand.

By mid-August she had lost a good deal of strength in her right arm despite trying to use it. She would do well using it for a few days or maybe even weeks, and then she would tweak it doing some normal things, and it would be right back to square one.

On August 21, 2006 (after extensive blood work to rule out autoimmune disorders), she was diagnosed with CRPS by the rheumatologist she consulted. She started occupational therapy (OT) on August 30, 2006. On September 13, 2006, she saw the orthopedic surgeon again, and he agreed with the rheumatologist about CRPS. She did not have the common type of CRPS that causes severe edema and burning pain. She had the type referred to as “cold and stiff”. Her right hand felt like ice and the range of motion in her right wrist and hand was very noticeably reduced. Trophic changes included stiffness, increase in dark hair over the affected region, decrease in sweating, atrophy of nails, osteopenia, muscle atrophy, and abnormal color changes.

In September, 2006 she injured her right elbow turning a shopping cart with her elbows since she could not use the wrists. It took about a year to completely resolve, and it made the CRPS symptoms worse. Now she could not even rest the wrist on her elbow because the elbow was extremely sensitive to pressure and touch. The orthopedic surgeon found nothing mechanically wrong with the elbow. The EMG was negative on both arms. She was started on low (but progressively increasing) doses of gabapentin as prescribed by the rheumatologist.

In October, 2006 she had a bone scan that was positive for possible RSD. In October she injured her right shoulder (likely the rotator cuff – but never saw a doctor about it) doing OT stretches to prevent frozen shoulder syndrome. That injury took about four years to resolve. It was over a year before she could raise her right arm over her head. That immobility further worsened the CRPS.

On October 12, 2006 the orthopedic surgeon saw the bone scans and found them to be consistent with sympathetic over-activity. He also said the scans showed TFCC tears in both wrists, and reiterated that no mechanical correction to the wrists could be done until “the dystrophy component of her problem has subsided”.

She started acupuncture and switched to a physical therapist (PT) that had been recommended by another neurologist. This therapist had great deal of experience treating atypical CRPS cases. He also felt that part of her problem was that she had thoracic outlet syndrome and gave her nerve glides to do that did help with the pain. In December, 2006 she injured her right knee in therapy doing squats and strained her patellar tendon and pulled her quadriceps. In December 2006 she aggravated the right knee further in therapy trying a new way to do a shoulder exercise. The PT wondered if the saphenous nerve was involved, and if this was part of “nerve irritation problem”.

Related to the number of soft tissue injuries she had sustained in less than a year, her neurologist referred her to the genetics department at a University Hospital to rule out connective tissue disorders such as Ehlers-Danlos Syndrome (EDS), Marfan syndrome, and pseudoxanthoma elasticum (PXE). After the exam, interview, and family history the genetics experts decided blood tests were not indicated because they were sure she was negative for a connective tissue disorder.

She consulted another orthopedic surgeon to examine her right knee in January, 2007. He diagnosed her with patella-femoral syndrome and prescribed PT. In the middle of January she hurt her neck. The knee (car accident), neck (car accident, trauma), and shoulder (too many racquet sports) all had had previous problems, but now were in very bad shape. She was extremely weak at this time and was unable to function in simple daily chores. In February, 2007 she consulted another rheumatologist who also diagnosed her with CRPS. He suggested she try pregabalin as well as gabapentin.

Throughout the fall of 2006 and winter of 2007 she experienced gradual improvement in her hands. Acupuncture seemed to be the most helpful. A calcium channel blocker was added to the prega-
bitalgia and gabapentin to help dilate vascular passage in the hope that it would increase nutritional flow to her right hand. Obviously she found PT to be dangerous, but it did improve the strength in her hands and wrists when she was not in too much pain to do the exercises. The addition of the knee injury really complicated things. She could not do stairs more than once a day, get on the floor with her daughter, use her legs to help lift her (back hurt because of that), and it was hard to sit and get out of chairs. She could not stand up out of a chair while holding her daughter. She was stuck upstairs until someone came over and brought her daughter downstairs since she could not navigate the stairs while carrying her. Also she could not do the most helpful shoulder exercise because it involved lying on her stomach on a bed, and she could not get up from that position because she could not roll over, and because of the leg injury, could not get off the bed while on her stomach.

Over the next several years she cycled through times of wrist improvement followed by an “injury” to the right wrist while doing something normal that could set her back to the starting point. Pre-gabalin and gabapentin seemed to dull the pain some, but little things like pushing tissues down in a trash can, trying to play the piano a little, stirring food, turning on a light, cutting meat, opening a doorknob, leaning a little bit on her right hand, etc., were all enough to cause weeks of painstakingly slow PT work.

By the winter of 2009, she was evaluated by the wrist surgeon again. He agreed that “time and testing” had shown that the tear in the right wrist was not going to improve on its own and thought that fixing the tear might lead to a resolution of the CRPS. He revealed after the surgery that it had been an agonizing decision, because the surgery could easily had led to “full-blown RSD”. Up until the surgery, he thought she was about 60% of the way to “full-blown RSD”.

The woman had a previous infertility history of unexplained etiology. She had failed to conceive for 18 years despite trying since age 21. She was treated in our reproductive center and had 18 months of intrauterine insemination with luteal phase progesterone supplementation. Her infertility was unexplained but at her present age it was assumed that she at least now had a luteal phase defect. She had not proceeded to in vitro fertilization-embryo transfer (IVF-ET) for financial reasons.

Finally she attempted an IVF cycle using mild ovarian stimulation. She failed to achieve a pregnancy. She repeated a mild stimulation IVF cycle preceded by lymphocyte immunotherapy [13, 14]. This was successful and she had a full-term delivery of a healthy baby girl.

This problem with CRPS and RSD was not mentioned when she initially sought our infertility help. The reason it was discussed when she returned six years later for help in conceiving a second child was that we discussed an alternative to lymphocyte immunotherapy (which would have forced her to travel to Mexico for therapy since this requires a cost-prohibitive new drug application in the United States). The alternative therapy suggested was the use of dextroamphetamine sulfate which would theoretically inhibit absorption of chemicals and toxins into the endometrium [15].

The woman was concerned that the treatment with sympathomimetic amines could worsen her complex regional pain syndrome Type I (reflex sympathetic dystrophy) since the condition is believed by many clinicians to be related to hyperactive sympathetic outflow to the peripheral regions and that the sympathetic outflow is somehow causally related to the pain [16]. However we explained to her that the role of the sympathetic nervous system as an etiologic factor in RSP is not well understood [17]. Our argument was that since present therapy had not been so effective and since there exists the syndrome known as the sympathetic hyperalgesia edema syndrome which is notorious for causing pain in various parts of the body, yet despite generally being refractory to “standard” therapy, almost always the pain either completely disappears or is markedly impaired shortly after initiating treatment with dextroamphetamine sulfate [18].

We further explained to the woman that we have demonstrated remarkable improvement of frequent bowel movements and pain with Crohn’s disease that had been quite resistant to conventional therapy with demonstration of Stage 4 to Stage 0 within a very short time following treatment with dextroamphetamine sulfate [19]. This could be understood based on the suggestion that Crohn’s disease is associated with para-sympathetic hyperactivity with associated hypovolemic hypoperfusion [20, 21]. In contrast, the data supported the hypothesis that ulcerative is the opposite, i.e., related to sympathetic hyperactivity with parasympathetic dysfunction [20, 21]. Thus theoretically treatment with a sympathomimetic amine, e.g., dextroamphetamine sulfate could worsen ulcerative colitis. However we have found dextroamphetamine sulfate therapy to be highly effective for ulcerative colitis also [22]. Thus we suggested that she try sympathomimetic amine treatment and if the pain worsens, we simply stop the medication.

Despite the concept that sympatholytic drugs which enhance sympathetic tone are the appropriate choice for RSD, the woman decided to try dextroamphetamine sulfate because of its vast benefits in other pain disorders (the syndrome is called the sympathetic neural hyperalgesia edema syndrome). The woman showed considerable improvement on a dosage of just ten mg extended release capsule which is a starting dosage and usually insufficient to help the majority of the various disorders that constitute the sympathetic neural hyperalgesia edema syndrome [18]. She was able to stop expensive physical therapy. She stopped visiting a chiropractor for expensive weekly visits. She even became stronger with the cold weather which usually was her worst time of the year. She withstood cold for 90 minutes with bare hands when typically she would require very insulated mittens in cold weather or her wrist pain would become intense. Her ability to re-bound after muscle soreness and strain was nearly normal and she stated she was feeling almost as good as before the CRPS began. She was even able to play the piano again and do activities that she would not perform while involved with the RSD.

She is now in her second trimester following frozen ET and is taking the dextroamphetamine sulfate throughout the pregnancy.

Discussion

Complex regional pain syndrome has had other earlier names but the one still commonly used is RSD. The CRPS syndrome usually occurs following an injury to a limb although in some instances a traumatic event cannot be recalled. Spontaneous recovery is possible but about 15% will not experience any improvement and 30% remain severe enough that even though they were able to gain employment before CRPS started they can no longer work [23].

Initial presentation can vary with limbs reported to be hot or cold, shiny, swollen or thin, red or blue, scaly skin or clammy skin [24]. Some patients cannot tolerate slight air movement on their skin whereas other complaint of numbness. Joints are reported to be stiff and weak [24].

Goebel describes eight major concepts about the etiology of CRPS [24]. One of them is that CRPS is a sympathetically mediated disorder. There is evidence that the
aspect of CRPS that produce red color and warmth may be related to low rather than high centrally mediated sympathetic outflow to cutaneous vasoconcentration [25].

In 1974 Harrington-Kiff suggested that agents that deplete the limb autonomic nerve endings of noradrenaline, such as regional guanethidine, should, therefore, be effective in treating CRPS [26]. Thus, theoretically based on this assumption the use of sympathomimetic amines should worsen not ameliorate the symptoms of CRPS. Indeed four randomized controlled studies with guanethidine failed to show improvement with CRPS [27]. Thus presently experts in the field have de-emphasized the importance of the concept of sympathetic hyperactivity as the main etiological factor with de-emphasis on sympatholytic therapies.

One therapy involves the concept of central sensitization. It has been observed that after a period of intense or repeated noxious stimulation, innocuous stimuli now become painful and remain painful even if the initial noxious stimulus has been removed [28]. N-methyl-D-aspartate (NMDA) is important in central sensitization [28]. This has led to the treatment of CRPS with the NMDA antagonist ketamine. Indeed two randomized controlled trials (RCTs) found IV ketamine to improve pain from CRPS [29, 30]. However, there is no evidence for high dosage ketamine comas as treatment for CRPS [31].

It should be noted that there is evidence that repeated ketamine treatments may be neurotoxic [32]. Furthermore, ketamine therapy is expensive and either requires a five-day hospital stay or a ten-day out-patient program taking the patient out of normal activities including work.

It is beyond the scope of this manuscript to review the other therapies mentioned in the review by Goebel but those readers interested should refer to Goebel’s review [24]. Another elaborate hypothesis was presented by Codreri and Bennett [16].

There are a multitude of treatment regimes which are all time consuming and expensive and unfortunately have had only limited success. The treatment with oral sympathomimetic amines provides an inexpensive therapy with little or no side effects that does not inconvenience the patient at all. The main concept as to how does treatment with dextroamphetamine sulfate help so many ubiquitous pain syndromes varying from headaches, to fibromyalgia, arthritis, gastrointestinal, pelvic, and bladder is related to the function of the sympathetic nervous system in controlling cellular permeability (the theory contends that hypofunction of the sympathetic nervous system leads to the absorption into tissue of chemicals and toxins that would normally be precluded and this leads to inflammation and pain) [18]. Support for this concept was provided by the initiation of pain with potassium infusion into the urinary bladder in patients with interstitial cystitis which is no longer present when treatment with sympathomimetic amines were given (personal observation).

It is the hope that this case report will stimulate some therapists to attempt RCTs using dextroamphetamine sulfate for CRPS. It is further hoped that the physiologists explaining the etiologic mechanism for CRPS will consider the reported benefit from sympathomimetic amines which could alter their hypothesis to etiology and possibly lead to new novel therapies for a variety of chronic pain syndrome.

For the practicing gynecologist, it is known that the most effective therapy for chronic pelvic pain is dextroamphetamine sulfate treatment [4]. The dramatic ameliorative response to CRPS to dextroamphetamine sulfate in this case report should provide the courage for the practicing gynecologist to prescribe dextroamphetamine sulfate to a woman for pelvic pain even she also has CRPS, i.e., fearing that increasing sympathetic tone could make CRPS worse. The patient should be advised that there is at least a precedent that CRPS would not be hurt by treatment but the pain could even reverse with treatment with sympathomimetic amine therapy.

References


Sympathomimetic amine therapy found effective for treatment of refractory chronic complex regional pain syndrome etc.


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Pallister-Killian syndrome in a preterm newborn who died soon after precipitous delivery: cytogenetic analysis

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Summary
The authors report a preterm neonate with dysmorphic traits and cleft palate who was born preterm because of precipitous delivery and died soon after birth notwithstanding neonatal intensive care unit (NICU) support. The cytogenetic analysis on fibroblasts from post-mortem skin biopsy demonstrated a Pallister-Killian syndrome (PKS). PKS is a cytogenetically syndrome characterized by a tissue limited mosaic distribution of one isochromosome 12p (tetrasomy 12p). Clinical manifestations of PKS are variable, and some symptoms may overlap with other malformative syndromes, thus the correct diagnosis mainly depends on the demonstration of the specific cytogenetic abnormality.

Key words: Pallister-Killian Syndrome; Cytogenetic analysis; FISH.

Introduction
Pallister-Killian syndrome (PKS) is a rare genetic disorder, first described in 1977 by Pallister et al. [1], in two adult patients with severe mental retardation, seizures, hypotonia, “coarse” facies, limbs anomalies, multiple visceral malformations, and anomalies of skin pigmentation. In 1981 Killian and Teschler-Nicola reported a similar clinical phenotype in a three-year-old girl [2].

PKS is cytogenetically syndrome characterized by a tissue limited mosaic distribution of one isochromosome 12p (tetrasomy 12p) [3-5]. The supernumerary chromosome is present in a high percentage of fibroblasts and bone marrow cells, whereas lymphocytes are usually normal. Prenatal diagnosis may be achieved from chorionic villus, amniocytes, whereas lymphocytes are usually normal. Prenatal diagnosis mainly depends on the demonstration of the specific cytogenetic abnormality.

The authors report a preterm neonate with dysmorphic traits and cleft palate, diagnosed as PKS by cytogenetic analysis on fibroblasts from post-mortem skin biopsy.

Case Report
The authors confirm that the patient described in the case report had given her informed consent for the case report to be published.

The patient was a 41-year-old Caucasian woman who came to the present emergency delivery room for preterm labor and immediately delivered a male neonate at a gestational age of 30 weeks who died soon after birth notwithstanding neonatal intensive care unit (NICU) support. The parents were in good health and unrelated. The mother was 41 years and the father 44 years at the time of the delivery. The family history was unremarkable in the maternal family, while a great number of abortions was referred for the grandmother of the patient’s father. The couple had two previous miscarriages in the first trimester, which were not investigated. During the present pregnancy, the sole noted echographic anomaly was polyhydramnios. The woman refused to undergo first trimester ultrasound screening such as combined test with measurement of nuchal translucency.

The newborn, weighing 1,320 grams (25° percentile), showed a coarse face, sparse hair in the frontal area, high forehead, sparse eyebrows, ocular hypertelorism, broad nasal root, short nose, long and smooth philtrum, thin upper lip, cupid bow shape, short neck, diffuse hypertricosis, and sacral dimple (Figure 1). During the autopic examination the external appearance of the brain was normal, with hyperaemic pial membrane. The palate showed a schisis in the posterior side of the arch; the thoracic, abdominal and pelvic organs were normal.

Standard cytogenetics
All the cytogenetic analysis of the patient were performed on cultured skin fibroblasts. The biotic tissue was cut into fine pieces by scissors or sterile scalpel in petri dish containing Hank’s solution supplemented with antibiotics (usually penicillin and streptomycin). The tissue fragments were then transferred into a conical tube containing a collagenase A solution and incubated overnight a 37°C in water bath. The resulting cellular suspension was then centrifuged, the cells were suspended in complete medium, and incubated at 37°C in 5% CO2 atmosphere. A good cell growth was observed two to three days later and a complete monolayer was formed in seven to ten days. For chromosome analysis, the cells were detached from the flask by trypsin treatment, suspended in complete medium, and transferred in suitable aliquots onto 30 mm petri dishes with a coverslip at the bottom. After 24-48 hours the mitotic cells were blocked by colcemid treatment for two hours and harvested by “in situ” method. Briefly, after hypotonic shock with KCl 0,075 M for ten minutes and two passages in fixative methanol: acetic acid 3: 1, the coverslips were removed from dishes and air dried. After 24 hours the slides were stained with Quinacrine mustard for QFQ banding. Routine chromosome analyses of both parents were performed on blood lymphocytes using standard methodologies.
Fluorescence in situ hybridization (FISH) studies

FISH experiments were performed using a whole chromosome painting probe (wcp) and a specific centromeric probe (CEP) of chromosome 12. The slides for FISH were pre-treated with pepsin in order to remove excessive cytoplasmic background, then they were dehydrated through a decreasing alcohol sequence and air dried. Some slides were immediately used for FISH, others were stored in freezer at -20°C until used.

Probes and slides were co-denatured at 72°C for three minutes and then incubated overnight at 37-42°C using a hybridization system. The post-hybridization washes, according to the manufacturer's protocol, were with 0.4X SSC plus 0.3% Nonidet at 72°C for two minutes, followed by a rapid wash in 2X SSC plus 0.1% Nonidet at room temperature for 30 seconds. The slides were then drained, stained with DAPI/antifade, and observed with fluorescence microscope using suitable filters.

The standard cytogenetic analysis, performed on fibroblasts at first passage in culture, showed the presence of a supernumerary metacentric chromosome, consistent with an isochromosome for the short arms of one chromosome 12, i(12p), in 16/16 cells scored (Figure 2A). Subsequent FISH with the wcp(12) confirmed the origin of the isochromosome from chromosome 12 (Figure 2B). In the same preparation were also present metaphases at 46 chromosomes, lacking in the supernumerary i(12p), hence the karyotype was a mosaic: 46,XY/47,XY, +i(12p) with a percentage of abnormal cells of 94%. Interphase FISH with CEP12 detected three signals (cells with the supernumerary chromosome) in 290/310 nuclei 93%) (Figure 2C). Both parents had normal chromosomes.

Discussion

PKS is a rare, sporadic disorder caused by a mosaic supernumerary isochromosome 12p. Isochromosomes are uncommon chromosomal anomalies, which may occur with different mechanisms and more frequently involve 9p, 12p, 15q, 18p, 21q, 22q, Xp, and Xq [3,7-9]. The parental origin of i(12p) is maternal in nearly all cases [9-11]. Recently, Wilkens et al. [12] reported a comprehensive evaluation of 59 affected individuals and reviewed the previously reported cases. The authors reported that at least greater than 47% of the PKS pregnancies were associated with polyhydramnios which can be associated with preterm delivery (as in the present case) [12].

The variable mosaic distribution of i(12p) is characteristic of tetrasomy 12p; loss of i(12p) could be explained by
a selective advantage of the normal diploid cells [13]. This mechanism, which is likely active both in vivo and in vitro, may account for the difficulty of detect i(12p) mosaic in fibroblasts of adult patients and in cultured lymphocytes, which are rapidly proliferating cells, or in amniocytes after so many replications in culture [14].

In postnatal cases, tetrasomy 12p may be found in variable rates in skin fibroblasts of newborns or young patients, while it is typically absent in blood lymphocytes. In alternative, to skin biopsy, another tissue which seems to be informative is buccal smear [15].

Postnatal clinical manifestations of PKS are variable and may involve different organs and systems. The commonest symptoms are: coarse facies with a high forehead, sparse scalp hair, hypertelorism, broad nasal bridge, streaks of hypo-hyperpigmentation, hypotonia, congenital heart defects, and diaphragmatic hernia. Profound mental retardation is a constant feature.

The fetal phenotype is variable as well, therefore the ultrasonographic findings are inconstant or may be absent. The main ultrasound anomalies include: polyhydramnios, congenital diaphragmatic hernia, and micromelia, of predominantly rhizomelic type. Less frequently are reported: hydrops fetalis, hygroma colli, increased nucal translucency, fetal overgrowth, ventriculomegaly, dilatation of cavum pellicudium, absence of stomach visualization, and presence of a sacral appendix. Intrauterine growth retardation was never reported [14, 16]. Some authors suggest that the association of diaphragmatic hernia, polyhydramnios, and short femurs in a fetus with normal or increased growth is enough to suggest the PKS [17]. In addition, a fetal profile showing a small nose and a thin upper lip with a protruding lower one may be a further marker of the syndrome [18, 19].

Conclusions

This case suggests that, at the time of birth, diagnosis of PKS could be suspected even in absence of significant congenital malformations, when some dysmorphic signs suggesting the syndrome are noted, particularly in patients with normal chromosomes on peripheral lymphocytes. In these cases the chromosomal complement requires a further control in other tissues, e.g. in skin fibroblasts or in buccal smears. A correct cytogenetic diagnosis is indeed essential for genetic counselling, since the recurrence risk may be considered practically absent in PKS.

References


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Introduction

Endometriosis was first described by Rokitansky in 1860 and was defined as the presence of proliferation of endometrium (endometrial glands and stroma) outside the uterine cavity, with the most common site being the pelvis [1]. It is a common gynecological condition that affects up to 22% of all women, eight to 15% of women of reproductive age, and six percent of premenopausal women [2, 3], and commonly occurs in pelvic organs of women presenting with dysmenorrhea, menorrhagia, pelvic pain, and infertility [4, 5]. Furthermore, ectopic endometrioma occurs in the abdominal wall in 0.03% to 1.08% with anamnesis of obstetrics or gynecologic procedures [1]. However it could sometimes be found with no previous scar (iatrogenic or not) [6].

Primary (spontaneous) umbilical endometriosis (SUE) was first described by Villar in 1886 [6] and represents a rare condition, estimated in 0.5% to 1% of all extragenital endometriosis [5].

The authors present a case of umbilical painful skin nodule that presented first to the general surgeons, which was clinically diagnosed as umbilical papilloma but finally resulted histologically as an abdominal wall endometrioma. This is a rare case of primary umbilical spontaneous abdominal wall endometriosis.

Case Report

A nulliparous woman, 32 years of age, presented with a pigmented umbilical mobile mass, which was tender to palpation over a period of five years. Her lesion was associated with cyclic changes in size with worsening during menses and severe pain over the past eight months. There was no bleeding. The mass replaced the umbilicus entirely. She had never been pregnant nor had any abdominal surgery. She had no history of dysmenorrhea and never used hormonal contraception.

On physical examination, she had a hard, black umbilical mass that measured three by two cm, stiff, and painful and irreducible to palpation (Figure 1). The nodule was movable from all skin plans. Given the clinical history and the physical appearance of the lesion, the diagnosis of umbilical endometriosis was strongly suspected.

Ultrasound scan of the mass showed a well-defined, oval-shaped anechoic area. The preliminary diagnosis was incarcerated umbilical hernia. There were no other localizations. The determination of CA-125 came back normal at 13.2 IU/ml. Hysterorraphy had found no other site of endometriosis.

Surgical excision of the umbilicus nodule and reconstruction was performed using a purse-string suture technique. Histological examination of the surgical specimen confirmed the diagnosis of endometriosis (Figure 2). Surgical pathology revealed a 5.0 × 4.0 × 3.0 cm area of endometriosis with negative margins at the umbilicus. Characteristic of cutaneous endometriosis, endometrial glands in a fibrous eosinophilic stroma were noted within the dermis.

Discussion

Endometriosis is a very common gynecological disease which usually occurs in the pelvic cavity [1, 7]. Extrapelvic endometrioma is an uncommon gynecological problem [8] with an estimated incidence of 0.5% to 1% [5]. It is the presence of ectopic endometrial tissue in almost any organ and cavity of the female body, including the lung, bowel, ureter, and brain, but the most including location is the abdominal wall [4, 5, 6]. Endometriosis involving the abdominal wall is termed as cutaneous endometriosis, and it is mostly associated with surgical scars after abdominal or pelvic operations, or may rarely occur spontaneously [7]. The primary umbilical endometriotic lesion was firstly described by Villar in 1886. There is no systematic literature review on published cohorts of patients having umbilical endometrioma [6].

Summary

Umbilical endometriosis is a very uncommon condition which presents as a pigmented umbilical nodule, papular or cystic, with symptoms punctuated rhythmically by menses. The authors report the case of a 32-year-old with spontaneous umbilical endometriosis. Surgical resection was performed with a good cosmetic result and no recurrence at six months. A review of the literature allowed the authors to discuss the diagnosis difficulties and treatment in an underdeveloped country.

Key words: Endometriosis; Surgery; Extragenital.
For Papavramidis et al., the definition of wall endometriosis includes lesions that are not due to previous surgical procedures, and such cases are referred to as spontaneous abdominal wall endometriosis [4]. No large prospective or retrospective studies have investigated SUE [6]. However, Horton et al. found that it is less common than scar-related endometriosis, and represents only 20% of all the cases [9]. The most common locations of SUE appear to be the umbilicus and groin [4, 5].

There are several doubts concerning the etiopathogenesis of the condition during the decades [7]. Many theories have been put forward to explain pathogenesis of endometriosis [4, 9, 10]. They have been classified into three main categories, i.e., the embryonic rest theory, the coelomic metaplasia theory, and the migratory pathogenesis theory [4, 7]. The embryonic rest theory explains the pelvic endometriosis such as a stimulus to a Müllerian origin cell nest [4, 9-11]. The migratory pathogenesis by implantation or retrograde menstruation theory explains the implantation on surrounding pelvic structures [4, 9-11]. Direct transplantation can explain the endometriosis occurring on surgical scars, but does not explain the distant locations, therefore Halban advocated the dissemination theory of vascular migration through vascular or lymphatic channels and in also surgical procedures [5, 9]. Even if the actual mechanism of SUE remains unclear, none of the suggested theories should be excluded until convincing experimental data are obtained. Some authors advocate a combination of the aforementioned theories [9, 10]. Papavramidis et al. suggested that the dissemination theory through lymphatic or vascular spread can explain occurrence of spontaneous abdominal wall endometriosis [4] as in the case report herein.

As for many authors, extragenital endometriosis has various presentations and remains a difficult condition to diagnose and treat [4, 10]. Clinical diagnosis has varying features such as flesh colored nodule, black nodule, flesh colored bluish, and with a size range of up to several centimeters. Hence, malignant melanoma should be considered [7].

In primary cutaneous umbilical endometriosis, the chief symptom is usually a mass at the site of maximum tenderness, which varies in size following the menstrual cycle, while the typical characteristic is cyclic pain associated with menses [4, 10].

There are reports that the pain can be constantly present without any association with the menstrual cycle, but this is generally regarded as atypical, which may explain why umbilical endometriosis is often misdiagnosed clinically. In such atypical cases, and especially in cases of SUE, signs and symptoms may occur singly, which always hinders an accurate diagnosis. In published series, the reported preoperative diagnosis rate has varied between 20% and 50% [4].

This diagnostic failure could be due to general surgeons, who often make the diagnosis, not being sufficiently familiar with SUE. Another possible explanation is the atypical presentation of the disease along with the possible differential diagnoses, including lipoma, sarcoma, lymphoma, primary or metastatic cancer, cysts, and inguinal or incisional hernia [4].

Clinical diagnosis is often difficult and patients suffering from this condition are usually of reproductive age and often present with an umbilical mass associated with swelling, pain, discharge, or cyclical bleeding [5]. Cyclical pain in umbilicus with a palpable mass was most the presenting symp-
tom as in this case, as for many authors in literature review [1, 7]. Rare cases of cyclical bleeding discharge in umbilicus have been described from the umbilical mass during menstrual period [12]. The umbilical nodule has been described as being flesh-colored, brownish, dark-bluish, or simply a subcutaneous mass, with a size that typically varies from 0.5 cm to several centimeters, but can be enormous [4, 10]. There may be associated symptoms of coexistent pelvic endometriosis, although the incidence of pelvic disease in abdominal wall endometriosis is within the same range as the general population (8%–15%) [5, 9].

The possibility of co-existing genital-pelvic endometriosis should be excluded by ultrasonogram and or exploratory laparoscopy of abdominal cavity [7]. Due to the variable macroscopic appearance of umbilical endometriomas, the differential diagnosis of umbilical nodules includes: pyogenic granuloma, embryological rests, irreducible hernia, endometriosis, inclusion cysts, primary tumours or secondary metastatic tumours from intra-abdominal malignancy [7].

According to Catalina-Fernandez et al., dermoscopy can be helpful in cases of cutaneous or subcutaneous endometriosis, with cysticole smears revealing high cellularity with hemosiderin-laden macrophages and sheets of stromal and epithelial cells on a hemorrhagic background [10]. The histologic diagnosis of endometrioma requires two of the three following features: endometrial-like glands, endometrial stroma, or hemosiderin pigment [4].

Surgical excision is necessary for proper histological diagnosis as well as for therapeutic purpose. It is the preferred treatment in all cases of UE consisting in wide local excision of the mass.

In case, no additional of hormonal therapy was associated. Papavramidis et al. proposed it whenever severe pelvic disease is assumed or demonstrably present [4]. Therefore, surgical resection of an umbilical endometrioma with safety and clear margins is the treatment of choice, and offers the highest probability of both a definitive diagnosis and a favorable outcome. Preservation of the umbilicus is preferred, but if the umbilicus has to be completely removed in order to achieve radical excision, certain methods can provide adequate reconstruction [11].

Complete excision of the umbilical lesion with partial resection of the underlying fascia is recommended, to avoid local recurrence [4, 10]. Therefore, wide excision with a margin of at least one cm is considered the treatment of choice, even for recurrent lesions [4, 10].

Several authors have advocated the use of hormonal therapy with a gonadotropin-releasing hormone analog (eg, danazol or progesterone), with the aim of decreasing the size of the mass and facilitating surgery. Furthermore, these hormones can be added to surgical treatment in cases of severe pelvic disease [5].

Medical management cannot be enthusiastically recommended, due to its reported success rate being low, with it offering only temporary alleviation of the symptoms, and serious adverse effects often being followed by recurrence after cessation of drug intake [1,6]. It is also known that both abdominal wall and scar endometriosis are less responsive to hormonal therapy [6].

Malignant transformation of abdominal wall endometriosis is a very rare complication (in 1% of cases) [6]. Spontaneous abdominal wall endometriosis is usually diagnosed by pathology, especially in cases without the typical triad of mass, pain, and cyclic symptomatology, as in the case report presented herein.

Conclusion

Primary umbilical endometriomas is a rare event. Careful history-taking and physical examination are essential to making the correct diagnosis, although this can be difficult in atypical presentations, and so other causes of umbilical lesions should be considered. In underdeveloped countries, complete excision and histology is highly recommended for obtaining a definitive diagnosis and to rule out malignancy. Radical surgical resection is the treatment of choice.

References


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