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Aims and Scope

Journal of the Turkish-German Gynecological Association is an official journal of the Turkish-German Gynecological Education and Research Foundation, Turkish-German Gynecological Association and the Turkish Society of Reproductive Medicine and is published quarterly on March, June, September and December.

The target audience of Journal of the Turkish-German Gynecological Association includes gynaecologists and primary care physicians interested in gynecology practice. It publishes original work on all aspects of gynecology. The aim of Journal of the Turkish-German Gynecological Association is to publish high quality original research articles. In addition to research articles, reviews, editorials, letters to the editor and case presentations are also published.

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The "Journal of the Turkish German Gynecological Association" (ISSN 1309-0399; Abbreviated as "J Turkish German Gynecol Assoc") is the official journal of the Turkish-German Gynecological Association and the Turkish Society of Reproductive Medicine. Formerly named "ARTEMIS" is printed quarterly (March, June, September, December) and publishes original peer-reviewed articles, reviews, case reports, brief reports and commentaries in the fields of Gynecology, Gynecologic Oncology, Endocrinology & Reproductive Medicine and Obstetrics in English. The title, abstract, and key words (according to medical subject headings) are provided in English at the beginning of each article. Reviews will be considered for publication only if they are written by authors who have at least three published manuscripts in the international peer reviewed journals and these studies should be cited in the review. Otherwise only invited reviews will be considered for peer review from qualified experts in the area.

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Contents

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Editorial

Dear Colleagues,

It is my great pleasure to introduce you the first issue of the Journal of the Turkish - German Gynecological Association (JTGGA) in the year of 2013. Many interesting articles from different countries have been collected for this issue of our journal.

In this particular issue, an article is published about Pipelle that shows again that the endometrial sampling using Pipelle is a safe, accurate and cost effective outpatient procedure. This technique avoids general anaesthesia with a high sensitivity and specificity for detection of endometrial hyperplasia and endometrial malignancy. Another interesting paper about fetal MRI is designed to detect the role of magnetic resonance imaging in refining the diagnosis of suspected fetal renal anomalies during screening sonography. Another article showed that vaginal hysterectomy is a safe and efficient procedure. Advanced age, increased number of pregnancies, parities and occurrence of intra or postoperative complications may prolong the duration of hospitalization after surgery whereas increased experience, careful surgical technique and adherence to aseptic principles may improve the cost-effectiveness and decrease the duration of hospitalization. I hope you will find many other useful articles and case reports for your interest in this issue.

I would like to inform you about the next congress of our foundation - 10th Turkish German Gynecology Congress that will be held between the dates of April 30th and May 4th, 2014 in Antalya. TAJEV, (Turkish German Gynecological Education and Research Foundation), organizing the biggest congresses of Turkey since the last twenty years is working hard to organize a unique and memorable organization at its decennial anniversary. The Congress venue has been selected after an intensive research as **Titanic Deluxe Hotel - Belek**, which will be opened in Spring 2013 in Antalya claiming to be the best hotel of the region.

It is always our biggest pride that the interest of the gynecology and obstetrics community in our congress is increasing steadily. Our last (ninth) congress, which was held in Antalya, had great interest from the community with 1400 attendees. The congress held in three parallel halls received 360 papers from 15 different countries.

In addition to the pre-congress courses, hands-on training sessions, satellite symposiums and round table meetings taking place in our congresses regularly; we are planning this year to enrich our scientific program with **debates, live surgeries and lots of innovative sessions**. We will proceed to include awards in our 2014 Congress to increase the interest of young researchers and encourage scholarly activities. As well as our previous congresses, many several leading scholars are invited in order to share their knowledge and experiences with the participants in special themes.

It is a common wish that our congress bringing together many of our colleagues nationally and internationally since 1995, will find rather a lot of **twentieth** anniversaries. Please do not forget to mark **April 30th, 2014** on your calendars.

I wish a fruitful and successful academic spell for all obstetrics and gynecology community.

Best regards,

Prof. Dr. Cihat Ünlü
Editor in Chief of JTGGA
President of TAJEV

Pipelle endometrial sampling versus conventional dilatation & curettage in patients with abnormal uterine bleeding

Anormal uterin kanamalı hastalarda konvansiyonel dilatasyon ve küretaja karşı Pipelle endometrial örnekleme

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Abstract

Objective: This study was designed to compare the diagnostic accuracy of Pipelle endometrial sampling with conventional dilatation & curettage in patients with abnormal uterine bleeding.

Material and Methods: One hundred and forty patients with abnormal uterine bleeding were included in this comparative study; where endometrial sampling was carried out before cervical dilatation by Pipelle device followed by conventional dilatation & curettage (D&C). The histopathology report of the Pipelle sample was compared with that of the dilatation & curettage sample and the dilatation & curettage reports were considered as the gold standard.

Results: 100% of the samples obtained by conventional D&C, while 97.9% of the samples obtained by the Pipelle device were adequate for histopathological examination. The histolopathological examination of 140 samples obtained by conventional D&C revealed proliferative endometrium in 37 specimens, secretory endometrium in 33 specimens, endometrial hyperplasia in 49 specimens (45 without atypia & 4 with atypia), endometritis in 8 specimens, endometrial polyps in 3 specimens and malignant endometrium in 10 specimens.

In this study; the Pipelle device had 100% sensitivity, 100% specificity and 100% accuracy for diagnosing endometrial hyperplasia, endometrial carcinoma, proliferative and secretory endometrium. Also, it had 88.9% sensitivity, and 99.2% negative predictive value (NPV) and 99.3% accuracy for diagnosing endometritis and it had 60% sensitivity, 89.6% NPV and 98.6% accuracy for diagnosing endometrial polyps.

Conclusion: The endometrial sampling using Pipelle is a safe, accurate, cost effective outpatient procedure, which avoids general anesthesia and has a high sensitivity and specificity for detection of endometrial hyperplasia and endometrial malignancy.

(J Turkish-German Gynecol Assoc 2013; 14: 1-5)

Key words: Abnormal, dilatation & curettage, endometrial sampling, Pipelle, uterine bleeding

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Özet

Amaç: Bu çalışma anormal uterin kanaması olan hastalarda Pipelle endometriyal örnek alımının tanısal doğruluğunu geleneksel dilatasyon ve küretaj ile karşılaştırmak üzere tasarlandı.

Gereç ve Yöntemler: Bu karşılaştırmalı çalışmaya anormal uterin kanaması olan 140 hasta dâhil edildi; Pipelle aleti ile servikal dilatasyondan önce endometriyal örnek alınmasının ardından geleneksel dilatasyon ve küretaj (D&C) yapıldı. Pipelle örneğinin histopatoloji raporu dilatasyon ve küretaj örneğininki ile karşılaştırıldı ve dilatasyon ve küretaj raporları altın standart olarak kabul edildi.

Bulgular: Geleneksel D&C ile alınan örneklerin %100'ü, Pipelle aleti ile alınan örneklerin ise %97.9'u histopatolojik inceleme için yeterliydi. Geleneksel D&C ile alınan 140 örneğin histopatolojik incelemesi 37 örnekte proliferatif endometriyum, 33 örnekte sekretuar endometriyum, 49 örnekte endometriyal hiperplazi (45'inde atipi yok ve 4'ünde atipi var), 8 örnekte endometrit, 3 örnekte endometriyal polip ve 10 örnekte malign endometriyum gösterdi.

Bu çalışmada, endometriyal hiperplazi, endometriyal karsinoma, proliferatif ve sekretuar endometriyum tanısında Pipelle aleti; %100 sensitivite, %100 spesifisite ve %100 doğruluğa, ayrıca endometrit tanısında %88,9 sensitivite, %99.2 negatif prediktif değer (NPD) ve %99.3 doğruluğa ve endometriyal polip tanısında %60 sensitivite, %89.6 NPD ve %98.6 doğruluğa sahipti.

Sonuç: Pipelle kullanılarak yapılan endometriyal örnekleme, endometriyal hiperplazi ve endometriyal malignitenin saptanmasında yüksek sensitivite ve spesifisite ile birlikte genel anestezinin yapılmadığı, güvenli, doğru, maliyet etkin bir ayaktan hasta prosedürüdür.

(J Turkish-German Gynecol Assoc 2013; 14: 1-5)

Anahtar kelimeler: Anormal, dilatasyon ve küretaj, endometriyal örnekleme, Pipelle, uterin kanama

Geliş Tarihi: 06 Kasım 2012 **Kabul Tarihi:** 12 Aralık 2012

Introduction

Abnormal uterine bleeding is a major gynecological problem, accounting for 33% of outpatient referrals, including 69% of referrals in the peri-menopausal and postmenopausal age groups (1). Evaluation of the abnormal uterine bleeding in women ≥40 years or menopausal women is of critical importance to confirm the benign nature of the problem and to

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exclude endometrial carcinoma, so that medical or conservative treatment can be offered and unnecessary radical surgery can be avoided (2).
Dilatation & curettage (D&C) is the gold standard for endometrial sampling, but in 60% of cases, less than half of the uterine cavity is curetted, with the added risk of general anesthesia, infection and perforation (3, 4). This has led to the advent of new and simple methods for endometrial sampling. Various devices are on the market nowadays, including the Pipelle device (5, 6). The Pipelle can be used on an outpatient basis and is cost effective compared with D&C (7). However, there are still concerns regarding the adequacy of the sample obtained, non-sampling of focal intrauterine lesions (6). Therefore, this study was designed to compare the diagnostic accuracy of Pipelle endometrial sampling with conventional D&C in patients with abnormal uterine bleeding.

Material and Methods

Over one year, patients with abnormal uterine bleeding over 40 years, were included in this comparative study. Detailed clinical assessment of the patients was followed by transvaginal sonography and laboratory investigations (CBC, coagulation profile, prolactin, thyroid and liver function tests). Patients with local gynecological cause or possibility of pregnancy or history of contraception or endometrial thickness <4 mm were excluded from the study. One Hundred and Forty-three patients were included in this study after informed consent and approval of the study protocol by the institute ethics committee. Patients included in this study were euthyroid with normal liver function tests, normal activated partial thromboplastin time (APTT) and normal platelet count. The endometrial sampling was performed by the Pipelle device in the ward prior to premedication ordered by the anesthetist. The Pipelle (Endocurrette, Midvale, Utah, USA) was introduced without performing cervical dilatation and withdrawn outside the uterus with a rotatory movement to get the sample which was labeled as sample A. The patients were then transferred to the operative theatre for D&C and the obtained sample after D&C was labeled as sample B. Both samples were sent to a pathologist, who was blinded to the methods of sampling and patients' medical history for histopathology assessment. The histopathology reports of the Pipelle sample was compared with that of the D&C sample and the D&C report was considered as the gold standard.

Results

Failure of the procedure was inability to introduce the Pipelle without cervical dilatation in three attempts (3 patients were excluded due to failure to introduce the Pipelle through the cervix to get the endometrial sample and the samples were obtained in those patients by D&C). After exclusion of those 3 patients, 140 patients with abnormal uterine bleeding were included in this study, the median age of the studied population was 44.5 years and median age of menarche was 13.5 years, while the median parity was 3.5 and median endometrial thickness was 11 cm, Table 1.

The presenting symptoms of the studied cases were; menorrhagia (n=53), polymenorrhagia (n=37), metrorrhagia or irregular bleeding (n=26) and postmenopausal bleeding (n=24). The sample was labeled as inadequate by the histopathologist when no endometrial tissue was present in the specimen sent. 100% of the samples obtained by D&C, while 97.9% of the samples obtained by Pipelle device were adequate for histopathological examination. The histopathological examination of 140 samples obtained by conventional D&C revealed; proliferative endometrium in 37 specimens, secretory endometrium in 33 specimens, endometrial hyperplasia in 49 specimens, endometritis in 8 specimens, endometrial polyps in 3 specimens and malignant endometrium in 10 specimens (one endometrial intra-epithelial neoplasia (EIN), 5 adenocarcinoma, 2 adenosquamous carcinoma, one endometrial adenosaroma, one mixed mullerian tumour (MMT)), Table 2.
In this study; the Pipelle device had 100% sensitivity, 100% specificity and 100% predictive values for diagnosing endometrial hyperplasia, endometrial carcinoma, proliferative and secretory endometrium, also, it had 88.9% sensitivity, 100% specificity, 100% positive predictive value (PPV) and 99.2% negative predictive value (NPV) for diagnosing endometritis, while, it had 60% sensitivity, 100% specificity, 100% PPV and 89.6% NPV for diagnosing endometrial polyps, Table 3.
In this study; the Pipelle device was 100% accurate for diagnosing endometrial hyperplasia, endometrial carcinoma, proliferative and secretory endometrium, also, it was 99.3% accurate for diagnosing endometritis and it was 98.6% accurate for diagnosing endometrial polyps, Table 3.

Discussion

Endometrial biopsy is an important step in the assessment of abnormal uterine bleeding to rule out endometrial carcinoma, so that medical or conservative surgery can be offered and unnecessary radical surgery can be avoided. Various methods of endometrial sampling are used in practice, including invasive and non-invasive on an inpatient or outpatient basis (8, 9).
D&C is an invasive inpatient procedure performed under general anesthesia. Pipelle device is used as outpatient non-invasive method gives adequate endometrial sample in 98% of cases and the probability of getting an adequate sample increases when central endometrial thickness is more than 5 mm (10, 11), this is why patients with endometrial thickness <4 mm were excluded from this study, also, in this study, the samples obtained by Pipelle device were adequate for histopathological examination in 97.9%.

Table 1. The characteristics of the studied population

Variables	Median	Range
Age (years)	44.5	40-49
Age of menarche (years)	13.5	12-15
Parity	3.5	1-6
Endometrial thickness (mm)	11	10-12

Table 2. The histopathological results of the specimens obtained by conventional dilatation & curettage (D&C) and Pipelle device

Histopathological diagnosis	Histopathological results of the specimens obtained by conventional D&C	Histopathological results of the specimens obtained by the Pipelle device
Proliferative endometrium	37	37
Secretory endometrium	33	33
Endometrial hyperplasia without atypia	45	45
Endometrial hyperplasia with atypia	4	4
Endometritis	8	7*
Endometrial polyp	3	1**
Endometrial intraepithelial neoplasia (EIN)	1	1
Adenocarcinoma	5	5
Adenosquamous carcinoma	2	2
Endometrial adenosarcoma	1	1
Mixed Mullerian tumor (MMT)	1	1

* One case of endometritis could not be diagnosed by Pipelle sampling, because the tissue sent was inadequate for histopathological examination
** Two cases of endometrial polyps could not be diagnosed by Pipelle sampling, because the tissue sent was inadequate for histopathological examination

Table 2. The sensitivity, specificity, predictive values and accuracy of the Pipelle device for diagnosing endometrial histology in patients with abnormal uterine bleeding

Variables	Proliferative endometrium	Secretory endometrium	Endometrial hyperplasia	Endometrial carcinoma	Endometritis	Endometrial polyps
Sensitivity =true positive/ true positive+false negative X 100	100%	100%	100%	100%	8/8+1 =88.9%	3/3+2 =60%
Specificity =true negative/ true negative+ false positive X 100	100%	100%	100%	100%	132/132+0 =100%	137/137+0 =100%
PPV =True positive/ (True positive+ false positive) X 100	100%	100%	100%	100%	8/8+0 =100%	3/3+0 =100%
NPV =True negative/ (True negative+ false negative) X 100	100%	100%	100%	100%	132/132+1 =99.2%	137/137+2 =89.6%
Accuracy =True positive+ true negative/ (True positive+ true negative+ false positive+ false negative) X 100	100%	100%	100%	100%	140/141 =99.3%	140/142 =98.6%

NPV: Negative predictive value, PPV: Positive predictive value

Pipelle sampling can be performed without anesthesia or analgesia during routine pelvic examination, in this study; the Pipelle sampling was done in the ward, followed by general anesthesia and D&C to maintain synchronization during sampling, which is needed during this comparative study.

Many authors concluded that the Pipelle is an accurate and acceptable outpatient sampling technique when compared with D&C (12-14). In this study; the Pipelle device had 100% sensitivity, 100% specificity and 100% predictive values, also it was 100% accurate for diagnosing endometrial hyperplasia (with or without atypia) and endometrial carcinoma.

A systematic quantitative review of published medical literature to determine the accuracy of outpatient endometrial biopsy in diagnosing endometrial hyperplasia in women with abnormal

uterine bleeding was carried by Clark et al. (15). Although, Clark et al. (15) concluded that outpatient endometrial biopsy has modest accuracy in diagnosing endometrial hyperplasia and additional endometrial assessment should be undertaken, especially if symptoms persist or intrauterine structural abnormalities are suspected, Sarwar et al. (16), concluded that the Pipelle had a 100% sensitivity, 98% specificity, and 100% NPV for detection of endometrial hyperplasia and atypia in women with postmenopausal bleeding.

Mechado and colleagues reviewed 1535 reports of endometrial biopsies taken from outpatients using the Cornier Pipelle, in pre- and postmenopausal patients with abnormal vaginal bleeding, to establish the accuracy of endometrial biopsy with the Cornier Pipelle in the diagnosis of endometrial cancer and atypical endometrial hyperplasia. The Cornier Pipelle was 84.2% sensitive, 99.1% specific, 96.9% accurate, with 94.1% PPV and 93.7% NPV for detection of endometrial carcinoma and atypical hyperplasia and they concluded that endometrial biopsy taken with the Cornier Pipelle is an accurate method for diagnosis of endometrial cancer and its precursor atypical hyperplasia (17).

Three hundred sixty endometrial cancer patients had preoperative endometrial sampling to evaluate the ability of preoperative endometrial sampling to accurately diagnose high-grade endometrial tumors were included in Gloria et al. (18) study. Gloria et al. (18) concluded that Pipelle endometrial sampling was 93.8% sensitive for diagnosing low-grade endometrial cancer and it was 99.2% sensitive for diagnosing high-grade endometrial cancer, also, they concluded that the endometrial sampling with Pipelle is sensitive and accurate for the diagnosis of high-grade endometrial tumors.

A meta-analysis to assess the accuracy of endometrial sampling devices in detection of endometrial carcinoma and atypical hyperplasia was done by Dijkhuijen et al. (19). They concluded that the endometrial biopsy with the Pipelle is superior to other endometrial techniques in detection of endometrial carcinoma and atypical hyperplasia in pre- and postmenopausal women.

In this study; the Pipelle had 88.9% sensitivity, 99.2% NPV and it was 99.3% accurate for diagnosing endometritis, also, it had 60% sensitivity, 89.6% NPV and it was 98.6% accurate for diagnosing endometrial polyps, because the accuracy is high when an adequate endometrial sample is obtained and in this study, 3 specimens were reported as inadequate for histopathological evaluation (two of them were diagnosed as endometrial polyps and the other one was diagnosed as endometritis by conventional D&C).

In this study, in spite of the low sensitivity of the Pipelle device for diagnosing endometritis and endometrial polyps (88.9% and 60%; respectively), it had a high negative predictive value (99.2% and 89.6%; respectively) and high accuracy (99.3% & 98.6%; respectively), also, Kuruvilla et al. (20), found that the most common histological diagnosis missed with an inadequate endometrial sample was endometrial polyp.

Three patients were excluded from this study due to failure to introduce the Pipelle through the cervix to get the endometrial sample (procedure failure), and the samples were obtained in those patients by D&C. No intra-operative or postoperative complications were recorded in this study, this leads to the conclusion that the endometrial sampling using Pipelle could replace the conventional D&C method of endometrial sampling, because, it is a safe, accurate, cost effective outpatient procedure, avoids general anesthesia with high sensitivity and specificity for detection of endometrial hyperplasia and endometrial carcinoma (6, 21).

Conflict of interest

No conflict of interest was declared by the authors.

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The role of magnetic resonance imaging in refining the diagnosis of suspected fetal renal anomalies

Şüpheli fetal renal anomali tanısını aydınlatmada manyetik rezonans görüntülemenin rolü

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Abstract

Objective: This prospective study was designed to detect the role of magnetic resonance imaging (MRI) in refining the diagnosis of suspected fetal renal anomalies detected during screening sonography.

Material and Methods: 54 pregnant women, with suspected fetal renal anomalies detected during routine ultrasound screening, were rescanned by MRI to refine the diagnosis of the suspected renal anomalies. The pregnancy outcome was examined externally and by postnatal ultrasonography.

Results: Fifty-four cases of suspected renal anomalies detected during screening sonography of 8400 pregnant women (0.6%), were rescanned by MRI in this study.

The MRI gave a similar diagnosis to postnatal ultrasound in 46 cases (16 cases of hydronephrosis, 14 cases of Polycystic Kidney Disease (PCKD), 9 cases of Multicystic Kidney Disease (MCKD), 2 cases of Renal Agensis (RA), 3 cases of single renal cyst and 2 cases of megacystis+hydroureter), while it gave a different diagnosis (false positive) in 6 cases (4 cases of hydronephrosis diagnosed by MRI confirmed to be PCKD by postnatal ultrasound, also, 1 case of MCKD diagnosed by MRI confirmed to be hydronephrosis by postnatal ultrasound and 1 case of RA diagnosed by MRI confirmed to be normal by postnatal ultrasound).

The prenatal ultrasound gave a similar diagnosis to postnatal ultrasound in 43 cases (14 cases of hydronephrosis, 13 case of PCKD, 9 cases of MCKD, 2 cases of RA, 3 cases of single renal cyst and 2 case of megacystis+hydroureter), while it gave a different diagnosis (false positive) in 9 cases; 4 cases of hydronephrosis diagnosed by prenatal sonography confirmed to be PCKD by postnatal ultrasound, one case of PCKD+one case of MCKD, and one case of megacystis+hydroureter confirmed to be hydronephrosis by postnatal ultrasound, while one case of MCKD diagnosed by prenatal sonography was confirmed to be PCKD by postnatal ultrasound and one case of RA diagnosed by prenatal ultrasound was confirmed to be normal by postnatal ultrasound.

Conclusion: The MRI can be used as a complementary adjunctive modality with excellent tissue contrast, especially in equivocal cases or inconclusive sonographic findings.

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Key words: The magnetic resonance imaging (MRI), refining diagnosis, suspected, fetal, renal anomalies

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Özet

Amaç: Bu prospektif çalışma, tarama sonografisi sırasında saptanan şüpheli fetal renal anomali tanısını aydınlatmada manyetik rezonans görüntüleme (MRG)'nin rolünü saptamak için tasarlandı.

Gereç ve Yöntemler: Rutin ultrason taraması sırasında şüpheli fetal renal anomalisi olan 54 gebe kadın şüpheli renal anomali tanısını aydınlatmak için MRG ile yeniden tarandı. Gebelik sonucu dışarıdan ve postnatal ultrasonografi ile incelendi.

Bulgular: Bu çalışmada 8400 gebe kadının sonografi taraması sırasında saptanan şüpheli renal anomalisi olan 54 vaka (%0.6) MRG ile yeniden tarandı.

MRG 46 olguda postnatal ultrason ile benzer tanı verirken (16 olguda hidronefroz, 14 olguda Polikistik Böbrek Hastalığı (PKBH), 9 olguda Multikistik Böbrek Hastalığı (MKBH), 2 olguda Renal Agenezi (RA), 3 olguda tek renal kist ve 2 olguda megakist+hidroüreter) 6 olguda farklı bir tanı (yalancı pozitif) verdi (4 olguda MRG ile teşhis edilen hidronefroz tanısının postnatal ultrason ile PKBH olduğu doğrulandı, ayrıca 1 olguda MRG ile teşhis edilen MKBH tanısının postnatal ultrason ile hidronefroz olduğu doğrulandı ve 1 olguda MRG ile teşhis edilen RA tanısının postnatal ultrason ile normal olduğu doğrulandı).

Prenatal ultrason 43 olguda postnatal ultrasona benzer tanılar verirken (14 olguda hidronefroz, 13 olguda PKBH, 9 olguda MKBH, 2 olguda RA, 3 olguda tek renal kist ve 2 olguda megakist+hidroüreter) 9 olguda farklı tanılar (yalancı pozitif) verdi; 4 olguda prenatal ultrason ile teşhis edilen hidronefroz tanısının postnatal ultrason ile PKBH olduğu doğrulandı, PKBH olan 1 olgu+MKBH olan 1 olgu+megakist+hidroüreter olan 1 olgunun postnatal ultrason ile hidronefroz olduğu doğrulandı, 1 olguda prenatal ultrason ile teşhis edilen MKBH tanısının postnatal ultrason ile PKBH olduğu doğrulandı ve 1 olguda prenatal ultrason ile teşhis edilen RA tanısının postnatal ultrason ile normal olduğu doğrulandı.

Sonuç: Özellikle belirsiz olgularda veya sonografik bulguları kesin olmayanlarda mükemmel doku kontrastı ile MRG tamamlayıcı bir ek yöntem olarak kullanılabilir.

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Anahtar kelimeler: Manyetik rezonans görüntüleme (MRG), tanının aydınlatılması, şüpheli, fetal, renal anomaliler

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Introduction

Ultrasound is the primary imaging method of fetal anomalies. When fetal renal anomalies are identified by prenatal ultrasound, other additional structural abnormalities should be excluded and when isolated renal anomaly is identified, the renal tract architecture and liquor volume should be monitored (1, 2).

Oligohydramnios is commonly associated with fetal urinary tract anomalies (3), however, oligohydramnios and maternal obesity or both may limit the diagnostic accuracy of ultrasound (1, 2).

Only 40-50% of cases of fetal malformations are detected prenatally by screening sonography (4). Therefore, the use of magnetic resonance imaging (MRI) is currently accepted as a valuable adjunctive technique for fetal imaging (5, 6). Fetal MRI was introduced in 1983, but the ultra-fast MRI sequences allows excellent detection of fetal anatomy without the need for maternal sedation (7-9). MRI as a complementary modality is more popular in such a setting because it enables the fetus to be viewed in multiple planes, irrespective of fetal lie and has excellent resolution (10, 11). This study was designed to detect the role of magnetic resonance imaging in refining the diagnosis of suspected fetal renal anomalies detected during screening sonography.

Material and Methods

Fifty-four pregnant women with suspected fetal renal anomalies, detected during screening ultrasound and more than 14 weeks gestation, were included in this study after informed consent of the patient and approval of the study by the institute ethics committee were obtained. A detailed history was taken from each patient regarding; the gestational age, exposure to possible teratogens and infections. Results of ultrasound or investigations carried out during this pregnancy, history of diabetes and past or family history of congenital fetal anomalies were also recorded. Patients with suspected fetal renal anomalies detected during screening ultrasound were rescanned by MRI to refine the diagnosis of suspected renal anomalies. Amniocentesis and chromosomal studies were performed for all cases with definite fetal renal anomalies.

Ultrasound examinations were made using Philips HD9 with trans-abdominal probe 2-5 MHz and data were stored in digital form on an external hard disk for rendering and re-analyzing. MRI was carried out using a Philips Interna 1.5 Tesla superconducting magnetic resonance system with a 30 mT/min gradient for fetal kidney imaging. Axial, coronal and sagittal T2-weighted images were obtained.

The complete MRI procedure was explained to the pregnant women, no sedation was used. Written informed consent was obtained from each case before MRI. The patients were positioned in the supine or left lateral position (9-10).

The assessment was focused on the type of renal anomalies, presence of the anomalies on one side or both sides; presence of other associated fetal anomalies and the amniotic fluid volume. MRI was interpreted by a professor of Radiology who was blinded to ultrasound findings. The MRI findings were compared to ultrasound findings and a professor of Obstetrics & Gynecology determined the impact of the information added by MRI on the obstetric management. The pregnancy outcome was examined externally and by postnatal ultrasonography which was interpreted by the professor of Radiology. Data were collected, and then analyzed using SPSS Statistical package version 15, to detect the role of MRI in refining the diagnosis of suspected fetal renal anomalies detected during screening sonography.

Results

Fifty-four cases of suspected renal anomalies, detected during screening sonography of 8400 pregnant women (0.6%) over two years, were rescanned by MRI to refine the diagnosis of suspected renal anomalies in this study. Forty-six (85.2%) cases of the antenatally diagnosed renal anomalies were unilateral and 8 (14.8%) cases were bilateral. The amniotic fluid volume was normal in 33 (61%) cases and decreased in 21 (39%) cases, Table 1.

Two extra-renal anomalies were detected in the studied cases; Arnold–Chiari malformation and congenital talipes equinovar-

Table 1. The fetal renal anomalies diagnosed by MRI

Renal anomalies	Number (%)	Unilateral or bilateral anomalies		Amniotic fluid volume		
		Unilateral N=46 (85.2%)	Bilateral N=8 (14.8%)	Normal N=33 (61%)	Oligohydramnios N = 21 (39%)	Polyhydramnios N=0 (0%)
Hydronephrosis	20 (37)	18	2	18	2	0
PCKD	14 (25.9)	14	0	0	14	0
MCKD	10 (18.5)	8	2	9	1*	0
RA	5 (9.3)	3	2**	3	2***	0
Single renal cyst	3 (5.6)	3	0	3	0	0
Megacystis + hydroureter	2 (3.7)	0	2	0	2	0

MRI: Magnetic resonance imaging, ***IUFD: Intrauterine fetal death, MCKD: Multicystic Kidney Disease, *NND: Neonatal death, PCKD: Polycystic Kidney Disease, RA: Renal agenesis, **Potter's syndrome

Table 2. Comparison between MRI and postnatal ultrasound findings

MRI findings	Postnatal ultrasound findings							Total
	Normal	Hydronephrosis	PCKD	MCKD	RA	Single renal cyst	Megacystis +hydroureter	
Normal	-	-	-	-	-	-	-	0
Hydronephrosis	-	16	4	-	-	-	-	20
PCKD	-	-	14	-	-	-	-	14
MCKD	-	1	-	9	-	-	-	10
RA	1	-	-	-	2	-	-	3
Single renal cyst	-	-	-	-	-	3	-	3
Megacystis+ hydroureter	-	-	-	-	-	-	2	2
Total	1	17	18	9	2	3	2	52

2 cases of bilateral RA: Potter's syndrome died in utero and excluded from postnatal ultrasound, MRI: Magnetic resonance imaging, MCKD: Multicystic Kidney Disease, PCKD: Polycystic Kidney Disease, RA: Renal agenesis

Table 3. Comparison between prenatal ultrasound and postnatal ultrasound findings

Prenatal ultrasound findings	Postnatal ultrasound findings							Total
	Normal	Hydronephrosis	PCKD	MCKD	RA	Single renal cyst	Megacystis +hydroureter	
Normal	-	-	-	-	-	-	-	0
Hydronephrosis	-	14	4	-	-	-	-	18
PCKD	-	1	13	-	-	-	-	14
MCKD	-	1	1	9	-	-	-	11
RA	1	-	-	-	2	-	-	3
Single renal cyst	-	-	-	-	-	3	-	3
Megacystis + hydroureter	-	1	-	-	-	-	2	3
Total	1	17	18	9	2	3	2	52

2 cases of bilateral RA: Potter's syndrome died in utero and excluded from postnatal ultrasound, MCKD: Multicystic Kidney Disease, PCKD: Polycystic Kidney Disease, RA: Renal agenesis

us, were both detected with bilateral hydronephrosis. Two cases of chromosomal aberration (3.7%) were detected in the studied cases. During antenatal follow up of the prenatal diagnosed cases with renal anomalies, one case of mild hydronephrosis due to Pelvi-Uretric Junction (PUJ) obstruction (renal pelvic diameter (RPD)<10 mm) had progressed to the severe form (RPD>15 mm) and 2 cases of bilateral RA (Potter's syndrome died in utero= Intra-uterine Fetal Death (IUFD)). Out of 52 live births 1 neonatal death occurred due to bilateral MCKD with trisomy 18 (Edwards syndrome), Table 1.

When the MRI findings were compared with postnatal ultrasound findings, it provided the same diagnosis in 46 cases, while it gave different diagnosis (false positive) in 6 cases (Table 2), and when the prenatal ultrasound was compared with postnatal ultrasound findings, gave the same diagnosis in 43 cases, while it gave a different diagnosis (false positive) in 9 cases (Table 3).

The MRI was 100% sensitive, 99.9% specific with 89.5% Positive Predictive Value (PPV) and accuracy in the diagnosis of suspected renal anomalies, while prenatal ultrasound was 100% sensitive, 99.9% specific with 85% PPV and accuracy (Table 4).

Discussion

Oligohydramnios is commonly associated with fetal urinary tract anomalies and the efficacy of ultrasound as a primary imaging tool in the diagnosis of fetal anomalies is decreased in the presence of oligohydramnios (12-15). Fifty-four (0.6%) cases of suspected renal anomalies, detected during screening sonography of 8400 pregnant women (0.6%) over two years, were rescanned by MRI to refine the diagnosis of suspected renal anomalies in this study. Literature reports that the frequency of congenital anomalies of the kidney and urinary tract (CAKUT), which can be detected sonographically in unselected

Table 4. The accuracy of the MRI and prenatal ultrasound in diagnosing fetal renal anomalies

Parameter	MRI	Prenatal ultrasound
Accuracy*	89.5%	85%
Sensitivity**	100%	100%
Specificity***	99.9%	99.9%
PPV (Positive predictive value)	89.5%	85%
NPV (Negative predictive value)	100%	100%

MRI: Magnetic resonance imaging, * True positive+true negative / True positive+ true negative+false positive+false negative X 100, ** True positive / True positive+False negative X 100, *** True negative / True negative+False positive X 100, PPV (Positive predictive value): True positive / True positive+False positive X 100, NPV (Negative predictive value): True negative / True negative+False negative X 100

populations, is about 0.1 to 0.7% (16) and the incidence of renal abnormalities detected by prenatal screening is 0.65% (17).

The MRI diagnosed 29 (53.7%) cases of parenchymal renal disease, 20 (37%) cases of hydronephrosis (Figure 1) due to PUJ obstruction, 3 (5.6%) cases of single renal cyst (Figure 2) and 2 (3.7%) cases of megacystis+hydroureter (Figure 3) due to a posterior urethral valve (PUV).

Twenty-seven fetuses with suspected renal anomalies on ultrasound (study group) were rescanned by MRI by Gupta et al. (10) and they found that a total of 10 (37%) cases were associated with severe oligohydramnios (10). It was reported that unilateral hydronephrosis is the most common fetal renal anomaly and normal amniotic fluid volume is the usual finding, but oligohydramnios is associated with bilateral renal anomalies (18, 19). Also, it was reported that the presence of a normal amount of amniotic fluid does not eliminate the possibility of a urinary tract abnormality nor guarantee normal renal function after birth (20, 21).

Two extra-renal anomalies were detected in the studied cases; Arnold–Chiari malformation and congenital talipes equinovarus and both were detected with bilateral hydronephrosis. Two cases of chromosomal aberration (3.7%) were detected in the studied cases; one case of numerical abnormality or trisomy 18 with bilateral MCKD and one case of structural abnormality or Cri du chat syndrome. Most of the fetal renal anomalies are isolated anomalies but the prognosis may be altered considerably by the detection of other anomalies which could indicate a genetic disorder or syndrome (22). Bilateral renal agenesis should be suspected when severe oligohydramnios is noted and with bilateral RA there is an increased incidence of chromosomal abnormalities, or multiple malformation syndromes such as VATER (vertebrae, anus, trachea, esophagus and renal) association or Potter's syndrome, the prognosis is uniformly lethal and the option of pregnancy termination should be offered (21).

During antenatal follow up of the prenatal diagnosed cases with renal anomalies, 2 cases of bilateral RA (Potter's syndrome) died in utero = IUFD. Out of 52 live births 1 neonatal death occurred due to bilateral MCKD with trisomy 18 (Edwards's syndrome). The most common type of fetal cystic kidney disease is MCDK (Potter type II), which is usually unilateral with normal amniotic fluid and good prognosis, but when bilateral MCKD is diagnosed, it is usually accompanied by oligohydramnios and the prognosis is very poor, because of pulmonary hypoplasia (21).

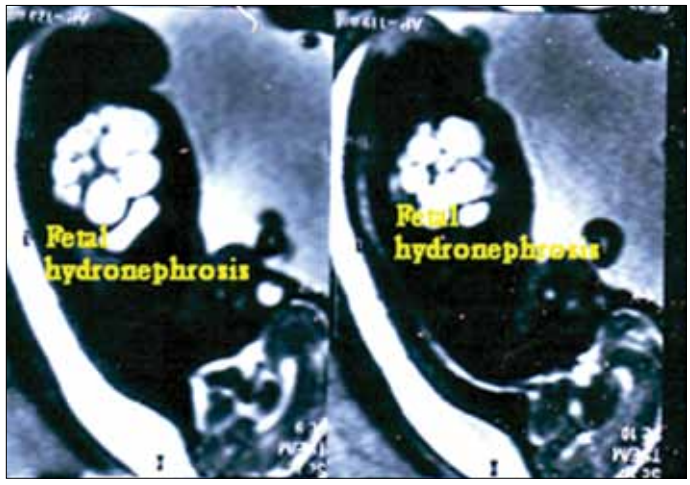

Figure 1. Fetal MRI shows fetal hydronephrosis

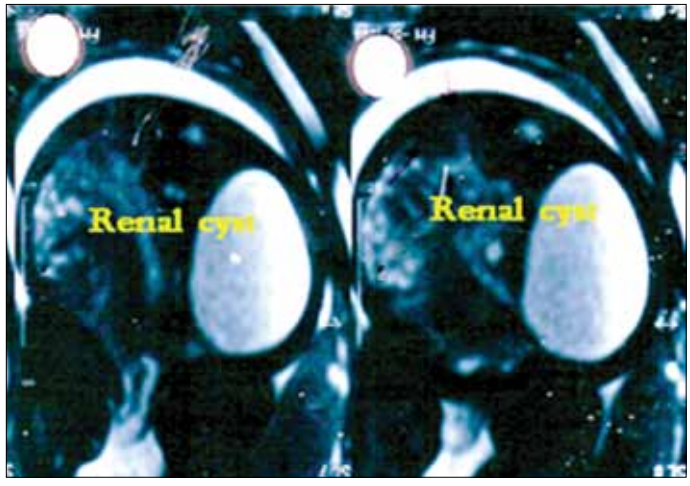

Figure 2. Fetal MRI shows single renal cyst

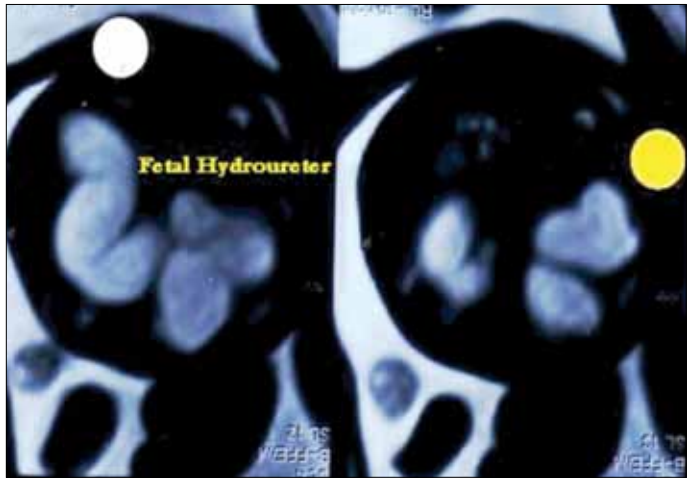

Figure 3. Fetal MRI shows fetal hydroureter

When the MRI findings were compared with postnatal ultrasound finding, it provided the same diagnosis in 46 cases, while it gave a different diagnosis (false positive) in 6 cases, and when

the prenatal ultrasound was compared with postnatal ultrasound findings; the same diagnosis was given in 43 cases, while it gave a different diagnosis (false positive) in 9 cases.

The MRI was 100% sensitive, 99.9% specific with 89.5% PPV and accuracy in the diagnosis of suspected renal anomalies; and gave a similar diagnosis to postnatal ultrasound in 46 cases, while it gave a different diagnosis (false positive) in 6 cases.

Using the postnatal findings as the gold standard of assessment and diagnosis; the suspected renal anomalies during prenatal screening were confirmed by MRI in 16 cases out of 18 (90% sensitivity) in the Ibrahim et al study and in 19 cases out of 27 in the Gupta et al. (10) study (70.4% accuracy) (3).

Twenty-six fetuses with sonographically suspected congenital anomalies (CNS, abdominal, musculoskeletal, renal and Meckel Gruber syndrome) were rescanned by MRI to evaluate the contribution of adding MRI findings to sonographic data when assessing fetal anomalies and to determine how this addition may affect the management of pregnancy by Behairy et al. They concluded that the MRI can be used as a complementary modality to ultrasound in diagnosing fetal abnormality in which ultrasound findings are inconclusive or equivocal (23).

The prenatal ultrasound was 100% sensitive, 99.9% specific with 85% PPV and accuracy in the diagnosis of suspected renal anomalies; it gave similar diagnosis to postnatal ultrasound in 43 cases, while it gave a different diagnosis (false positive) in 9 cases. Abdelazim et al. (3) concluded that the prenatal ultrasound failed to detect 6 cases out of 18 fetal renal anomalies (72% sensitivity), also they concluded that the hydronephrosis can be misdiagnosed by prenatal ultrasound as MCKD or PCKD.

Seventy-six (76) cases of Intrauterine Growth Retardation (IUGR) with oligohydramnios and sixteen cases out of 27 of structural defects represented bilateral renal agenesis were detected by Reuss et al. (24), 11 of them were diagnosed by prenatal ultrasound scanning (sensitivity of 76%). Shlossman et al. (21) reported that the MCKD can easily be diagnosed in utero by antenatal ultrasound with a 100% detection or accuracy rate. In this study, the MRI was more accurate (89.5%) than the prenatal sonography (85%) in diagnosing fetal renal anomalies,. It can be used as a complementary adjunctive modality with excellent tissue contrast especially in equivocal cases or inconclusive sonographic findings.

Although the MRI was more accurate than the prenatal sonography in diagnosing fetal renal anomalies in this study, it did not change the perinatal management of the studied cases.

Oligohydramnios is commonly associated with fetal urinary tract anomalies, however, oligohydramnios and maternal obesity or both may limit the diagnostic accuracy of the prenatal ultrasound.

Conflict of interest

No conflict of interest was declared by the authors.

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Increased psychological trauma and decreased desire to have children after a complicated pregnancy

Komplike gebelik sonrası artan psikolojik travma ve azalan çocuk isteği arzusu

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Abstract

Objective: Information about fertility desire and psychological sequelae after high-risk pregnancies are scarce in the literature. The aim of the present study is to investigate the psychological effects of high-risk pregnancies.

Material and Methods: The patients who had a history of severe preeclampsia, eclampsia or major hemorrhage during the peripartum period were enrolled as the study group and compared with the control subjects with respect to fear about new pregnancy, anxiety/depression and post-traumatic stress disorder (PTSD) scores. The study was carried out by submitting a questionnaire form to the participants. Numbers of planned children before and after the last delivery were evaluated in both groups.

Results: Fear about a new pregnancy was found to be significantly higher in the study group compared with the controls. There were no statistically significant difference between the two groups in terms of anxiety and depression. In terms of re-experience and avoidance in PTSD was significantly higher in the study group, however no significant difference was found for hyper-arousal.

Conclusion: Fear regarding new pregnancy is high and planning more children is decreased after high-risk pregnancies and PTSD symptom scores were higher after high-risk pregnancies.

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Key words: Pregnancy, fear of childbirth, depression, post traumatic stress syndrome, anxiety

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Özet

Amaç: Yüksek riskli gebelik sonrasında tekrar çocuk sahibi olma isteği ve psikolojik sekel riski literatürde yeteri kadar mevcut değildir. Bu çalışmanın amacı yüksek riskli gebelik sonrasında psikolojik etkileri incelemektir.

Gereç ve Yöntemler: Peripartum dönemde şiddetli preeklampsi, eklampsi veya doğuma bağlı majör kanama öyküsü olan hastalar; gebelik korkusu, travma sonrası stres bozukluğu (TSSB) ve anksiyete /depresyon skorları bakımından kontrol grubu ile karşılaştırıldı. Çalışmaya katılan hastalara birebir yüz yüze anket yöntemi ile formlar dolduruldu. Son doğum öncesi ve sonrası planlanan çocuk sayısı her iki grupta değerlendirildi.

Bulgular: Hasta grubunda tekrar gebe kalma korkusu kontrol grubuna göre önemli bir şekilde yüksek izlendi. Anksiyete ve depresyon skorları açısından iki grup arasında istatistiksel anlamlı fark izlenmedi. Hasta grubunda kontrol grubuna göre TSSB açısından; yeniden yaşam ve kaçınma belirtileri istatistiksel anlamlı yüksek iken, uyarılmışlık açısından fark gözlenmedi.

Sonuçlar: Komplike gebelik yaşamış hastalarda yeni bir gebeliğe karşı korku yüksek olmakta ve sonuç olarak planlanan çocuk sayısında azalmaya neden olmaktadır. Komplike gebelik sonrası hastalar TSSB semptomları gelişmesi yönünden risk altındadırlar.

(J Turkish-German Gynecol Assoc 2013; 14: 11-4)

Anahtar kelimeler: Gebelik, çocuk doğurma korkusu, depresyon, travma sonrası stres bozukluğu, anksiyete

Geliş Tarihi: 2 Kasım 2012 **Kabul Tarihi:** 15 Ocak 2013

Introduction

Every mother has significant memories about the course of the pregnancy/delivery (P/D) period. The mother and fetus could be exposed to complications and risks related to pregnancy and/or delivery, which can be described as high-risk pregnancies or complicated P/D. Maternal/fetal morbidity and mortality is high in complicated P/D (1). It has been reported that the most common pregnancy complications that require intensive care unit and the leading causes of maternal complications and mortality are preeclampsia/eclampsia and major peripartum hemorrhage (PPH) during the peripartum period (2-5). Past experiences of an individual have substantial effects on his or her future decisions. It could be anticipated that a complicated pregnancy that leads to life-threatening conditions, prolonged hospital stays and additional interventions may cause fear related to repeated pregnancy or delivery. The negative effects and the risk of a repetition of the experience may lead to reluctance to have a child. The desire to have a child may change based on various factors such as the number of children one has, the society, economic status, education and past experiences. To our knowledge, studies about the future desire of the patients with history of complicated P/D to have a child are lacking in the literature.

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In the present study, we aimed to investigate the desire for a new pregnancy and more children, also the anxiety/depression and post-traumatic stress disorder (PTSD) symptoms in patients with a history of complicated P/D, and to compare them with those of control subjects.

Material and Methods

This prospective study was conducted in the Obstetrics and Gynecology clinics of Dicle University Hospital, which is a tertiary referral center in the southeast Anatolian region, where complicated P/D cases are frequently referred. The patients who had severe preeclampsia or eclampsia or major hemorrhage during the peripartum period between January 2008 and December 2010 were enrolled as the study group. We used the term "complicated P/D" to simplify the analysis. The study and control groups included patients who were aged from 18 to 35 years, have no more than 3 children, have not reached her previously desired family size, had their last delivery within 6 months to 2 years and have completed at least primary school education and had no history of psychiatric disorder and psychotropic drug use. From patient records, 114 patients who were followed-up/treated in our clinic for complicated P/D were identified (Figure 1). These patients were interviewed via telephone calls and were informed about the study on January and February 2011. Forty patients who met the inclusion criteria and agreed to be enrolled in the study were invited to the clinic and participated in the study between January and April 2011. In the study group, 14 patients had severe preeclampsia, 14 patients had eclampsia and 12 patients had major hemorrhage histories during their peripartum period. Forty-one women, who were delivered at our clinic and did not have a history of complicated P/D, were enrolled as the control group.

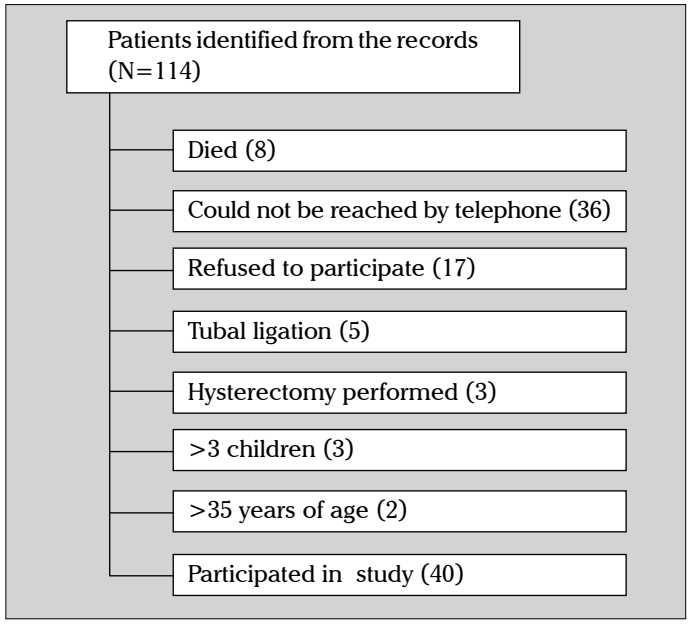

Figure 1. Distribution of the status of the patients identified from medical records at the time of recruitment to the study and selection of the study population

For each participant, hospital stay during the course of the last P/D, age, gravida, parity, number of living children, number of planned children before and after birth were identified. Their fear of a new pregnancy, depression/anxiety levels and PTSD symptoms were measured by questionnaires. All participants gave written informed consent. The study was approved by the Medical Ethics Committee of Dicle University.

Analog scale for evaluating the fear of a new pregnancy

The scale was developed by the investigators to measure the fear of getting pregnant again by rating. The scale was designed as a fear scale (FS) which is a 10 cm long horizontal straight line with 1 cm gaps between each rating, starting from 0 (not worried at all) and continuing up to 10 (very worried). It was adapted from a visual analogue scale (VAS) used to measure severity of pain subjectively (6). The patients could mark the level of fear they have regarding a repeat pregnancy by marking between 0 and 10 on the scale. It was a self-reported scale, that measured fear of a new pregnancy subjectively.

Hospital anxiety and depression scale (HADS)

The HADS was first developed by Zigmond at al. (7) 1983. It consists of 14 questions with multiple choices. It provides two subscores (anxiety and depression) and a total score. It is accepted as a reliable and valid scale for assessing clinically significant anxiety and depression (8). Higher scores reflect worse anxiety and depression. The HADS total score is also a valid measure of "emotional distress" or "psychological distress", so that the HADS can be used as a measure of overall psychiatric morbidity (9). The validity and reliability of the Turkish version of HADS was demonstrated by Aydemir et al. (10).

PTSD checklist-civilian version (PCL-C)

The PCL-C is an easily administered scale designed to assess the symptoms of posttraumatic stress disorder according to Diagnostic and Statistical Manual of Mental Disorders, 4th Edition DSM-IV criteria. It consists of 17 items with Liekert type answers ranging from 1 to 5. It is a self-report scale and provides three subscale scores (re-experience, avoidance, and hyper-arousal) and a total score. Higher scores reflect more severe symptoms of PTSD (11). The validity and reliability of the Turkish version of PCL-C was demonstrated by Kocabasoglu et al. (12).

Statistical analyses

Statistical analyses of the obtained data were conducted by using Statistical Package for Social Sciences (SPSS) version 15.0 (Chicago, IL, USA). Descriptive statistics were used to define the demographic data of the participants. Frequency and percentage were calculated if the data was categorical, whereas mean and standard deviation were calculated if they were continuous. For the comparison of continuous variables between groups, independent samples t test was used. The dependent samples t test was used to assess possible differences between any two repeated measures in a single group. Normality of variance was tested with the Kolmogorov-Smirnov test. Variables showing non-parametric distribution were compared between groups by using the Mann-Whitney U test. For the comparison

of categorical variables between groups, the Chi-square test was used. A P value less than 0.05 was accepted as statistically significant.

Results

The mean ages of the study and control groups were 26.98±4.45 and 28.07±4.44 years respectively (p=0.26). Demographical characteristics of patients showed no statistically significant difference between the groups (Table 1). In the study group, mean hospital stay due to complicated P/D was 11.73±11.42 days.

In the study group, 34 cases (85%) reported fear of having a new pregnancy, whereas 21 (51.2%) cases reported the same fear in the control group (p=0.001). Fear scale scores about a new pregnancy was 7.22±3.86 in the study group, whereas it was 4.12±3.80 in the control group (p<0.001). The mean number of planned children in the study group were 3.75±1.15 before the complicated P/D whereas it had declined to 1.60±1.41 afterwards. In the control group the planned number of children had also decreased after normal P/D (Table 2). Moreover, the decline in the study group was statistically greater than that of control subjects (p<0.001). No statistically significant difference was observed when the groups were compared in terms of anxiety and depression. PTSD scorings of re-experience and avoidance symptoms, and total scores were significantly higher in the patient group; however, no statistical difference was observed between the groups in terms of hyper-arousal symptoms (Table 3).

Discussion

The present study showed a statistically significant decline in desired family size after complicated P/D. In cases with major PPH, who had hypogastric artery ligation (13), uterine artery embolisation (14), or uterine devascularization (15) and whose fertility was preserved, when future pregnancy results were evaluated, it has been observed that the patients' future desire to have more children had declined. Investigators claimed that the women who have undergone serious risks tend to have reluctance to childbirth due to their anxiety of having the same risks again and that this decline is anticipated to have psychological reasons (13-15).

There were 85% patients in the study group and 51.2% patients in the control group who had a fear of having a new pregnancy, and the difference was statistically significant. We were unable to find a scale designed or recommended to measure fear caused by previous experiences. Therefore, we used a FS, which was modified from the VAS scale. While this method is open to discussion, understanding and application of this method is easy. The desire to become pregnant again might have decreased in complicated P/D cases due to prolonged hospital stay, exposure to additional trauma, life threatening nature of prior pregnancy, and the likelihood and fear of being exposed to the same risks again. The significantly higher degree in FS in the complicated P/D group, compared to the control group gives rise to the thought that this might be related to the experienced risk. The decrease in the desired family size after P/D in both groups makes it plausible that any pregnancy affects the patient's desire, and its impact increases with additional complications. The present study showed that desire to have more children after normal or complicated P/D has declined. However, the decline in the study group was higher when compared to the control group.

The groups were not different in terms of depression and anxiety levels. This condition can be explained in several ways. First, even if depression and anxiety symptoms had developed in patients, these might have healed in time due to various reasons. Second, even if the P/D experience was normal or complicated, it might lead to similar impact in terms of depression and anxiety symptoms. In addition, both conditions can lead to development of PTSD symptoms instead of depression and anxiety.

PTSD is defined as "one experiencing a direct exposure to a severe traumatic, stressing situation that may lead to a death

Table 1. Demographical characteristics of the groups (Mean±Standard Deviation)

	Study group (n=40)	Control group (n=41)	*p*
Age (years)	26.98±4.45	28.07±4.44	0.27
Gravidity	2.80±1.42	2.24±1.20	0.06
Parity	2.15±1.12	1.90±0.83	0.26
Number of living children	1.78±0.95	1.88±0.81	0.60

Table 2. Planned number of children in both groups before and after their last pregnancy (Mean±Standard Deviation)

	Planned number of children before last pregnancy	Planned number of children after last pregnancy	*p*
Study group (n=40)	3.75±1.15	1.60±1.41	<0.001
Control group (n=41)	2.78±0.96	1.98±1.37	0.001

Table 3. Anxiety/Depression and Posttraumatic stress disorder symptom scores in both groups (Mean±Standard Deviation)

	Study group (n=40)	Control group (n=41)	*p*
HADS Anxiety	8.55±4.31	8.15±4.15	0.66
HADS Depression	6.18±3.79	6.68±4.45	0.59
HADS Total	14.75±7.3	14.61±7.92	0.93
PTSD re-experience	15.00±4,12	12.24±5.55	0.013
PTSD avoidance	18.35±5.11	15.30±5.50	0.011
PTSD hyper-arousal	14.13±4.50	12.80±4.31	0.17
PTSD total	47.48±11.78	40.56±13.21	0.015

HADS: Hospital anxiety depression scale, PTSD: Posttraumatic stress disorder

risk or serious dysfunction, and he/she is responding to this experience with intense fear, helplessness and concern". Diagnosis of PTSD might be difficult in the postpartum period due to hormonal changes and adaptation mechanisms (16). Patients who have a history of general anxiety, incapacity to manage stress, fear inspired by delivery experience and psychiatric disorder may have a higher risk of developing PTSD (17). Olde et al. (18) have reported individuals who have poor social support, more obstetric intervention, perceived or true negative attitude of health-care personnel, and negative emotional state during pregnancy or postpartum period as a high-risk group in terms of PTSD. Although traditionally, childbirth is not considered as an event that initiates PTSD symptoms, Beck et al. (19) reported that it can lead to severe traumatic stress and can contribute to developing PTSD. Maggioni et al. (20) have reported that patients who perceive their normal delivery as being traumatic had developed PTSD and described that delusional fears can surpass reality at times. Compared to the control group, we found significantly higher levels of re-experience and avoidance symptoms and total scores in the patient group. Post-traumatic stress disorder hyper-arousal symptoms were similar in both groups.

This study has some limitations. The mall sample size of the study prohibits generalizability of the results. Additionally, it would be better if the evaluations of the patients were performed immediately after the obstetrical event and also in a second interview after a predetermined time period, which would give two scores and a better evaluation of the scales. Further studies are welcomed to clarify this issue.

As a result, fear of undergoing a new pregnancy was higher among those who had history of complicated P/D when compared to those with a history of normal P/D, and this condition appears to be associated with decreased desire to have more children. Although a decline is also observed in the number of children wanted in the normal P/D experiences, this decline appears to be lower compared with complicated P/D experiences. In addition to the P/D experiences, the number of children planned can be affected by other factors such as the number of children present, parental desire, socio-economic status, and religious and societal views. On the other hand, while normal and complicated P/D patients display similar traits in terms of depression and anxiety, those who have a history of complicated P/D report having more severe symptoms of post-traumatic stress disorder. Further work is needed to explain in detail how this condition impacts the number of planned children.

Conflict of interest

No conflict of interest was declared by the authors.

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Which parameters may influence the duration of hospitalization after vaginal hysterectomy?

Vajinal histerektomi sonrası hangi parametreler hastanede kalım süresini etkiler?

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Abstract

Objective: To estimate the variables that may affect the duration of hospitalization after vaginal hysterectomy.

Material and Methods: An 11-year retrospective analysis was performed on data derived from 197 patients who underwent vaginal hysterectomy due to non-malignant pathology at a tertiary care center between January 2000 to November 2011.

Results: The average age of the patients in our series was 60.9±11.1 with a duration of hospitalization of 11.6±6.1 days after vaginal hysterectomy. The grouping variables consisted of age, number of pregnancies, abortions, parities and the presence of intra or postoperative complications. Advanced age (>60), increased number of pregnancies (>5) and parities (>5) and occurrence of intra or postoperative complications were found to be correlated with the duration of hospitalization after vaginal hysterectomy. Categorical variables were analyzed by Pearson's chi square or the Fisher exact test. The Mann Whitney U test was used to compare groups, while the correlation of variables was assessed with the Spearman Correlation Analysis.

Conclusion: Vaginal hysterectomy is a safe and effective procedure. Advanced age, increased number of pregnancies and parities and occurrence of intra or postoperative complications may prolong the duration of hospitalization after surgery. Increased experience, careful surgical technique and adherence to aseptic principles may improve the cost-effectivity and decrease the duration of hospitalization.

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Key words: Pelvic prolapse, treatment, surgery, vaginal hysterectomy, duration of hospitalization

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Özet

Amaç: Vajinal histerektomi sonrası hastanede kalım süresini etkileyebilecek değişkenleri değerlendirmek.

Gereç ve Yöntemler: Bu 11 yıllık retrospektif çalışma Ocak 2000 ile Kasım 2011 yılları arasında tersiyer bir merkezde malign olmayan nedenlerle vajinal histerektomi gerçekleştirilmiş 197 hastanın bilgileri kullanılarak yapıldı.

Bulgular: Hastalarımızın ortalama yaşı 60.9±11.1 yıl ve vajinal histerektomi sonrası hastanede kalım süresi 11.6±6.1 gündü. Gruplandırmadaki değişkenlerimiz yaş, gebelik sayısı, abort sayısı, doğum sayısı ve operasyon sırası veya sonrasında ortaya çıkan komplikasyonları içermekteydi. İleri yaş (>60), artmış gebelik (>5) ve doğum (>5) sayısı, operasyon sırası veya sonrasında ortaya çıkan komplikasyonların vajinal histerektomi sonrası hastanede kalım süresi ile ilişkili olduğu bulundu. Kategorik değişkenler Pearson Ki Kare testi veya Fisher exact testi ile analiz edildi. Grupların karşılaştırılmasında Mann Whitney U testi, değişkenlerin korelasyonunda Spearman korelasyon analizi kullanıldı.

Sonuçlar: Vajinal histerektomi güvenilir ve etkili bir yöntemdir. İleri yaş, gebelik sayısı ve doğum sayısının fazla olması, operasyon esnasında ve sonrasında ortaya çıkan komplikasyonlar cerrahi sonrası hastanede kalım süresini uzatabilir. Artmış cerrahi deneyim, özenli bir cerrahi teknik ve asepsi kurallarına uymak fiyat-etkinliği arttırabilir ve hastanede kalım süresini azaltabilir.

(J Turkish-German Gynecol Assoc 2013; 14: 15-8)

Anahtar kelimeler: Pelvik prolapsus, tedavi, cerrahi, vajinal histerektomi, hastanede kalım süresi

Geliş Tarihi: 15 Ekim 2012 **Kabul Tarihi:** 08 Şubat 2013

Introduction

Hysterectomy may be performed through vaginal, abdominal or laparoscopic routes. Traditionally, vaginal hysterectomy (VH) is offered to women with symptomatic genital prolapse. It not only offers a lower complication rate, but also allows the repair of pelvic prolapse (1, 2). Reported benefits of vaginal hysterectomy compared to abdominal hysterectomy include shorter duration of hospital stay, more rapid return to normal daily activities, and fewer unspecified infections or febrile episodes (2). However, it is not still as popular as expected; possibly due to the relative lack of experience and shortage of technical facilities. Increased familiarity with outcomes of VH may help to eliminate this limitation (3).

The economic aspect of medical services cannot be ignored in the changing circumstances of the world. Duration of hospitalization constitutes an important component of cost-effectivity, which gains importance in provision of healthcare services. As far as we know, no published studies have investigated factors affecting the duration of hospitalization after VH in the literature.

Our aim was to outline parameters that may affect the duration of hospitalization after vaginal hysterectomy in our institution.

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Material and Methods

Medical records of 197 patients treated surgically with VH for benign gynecological diseases in the obstetrics and gynecology department of a tertiary care center between January 2000 to November 2011 were studied retrospectively. Approval of the local Institutional Review Board had been obtained. The indication for hysterectomy was based on the criteria proposed by Dicker et al. (4).

The demographics, occurrence of intra and postoperative complications and duration of hospitalization after surgery were noted. Patients were classified into three groups with regard to duration of hospital stay after surgery: Groups 1, 2 and 3 consisted of hospitalization for 0-10 days; 11-20 days and >20 days, respectively. Descriptive data and grouping variables such as age, number of pregnancies, parities, history of abortions and occurence of intra and postoperative complications are shown in Table 1 and Table 2.

The complications were classified according to Dicker's criteria (4): These criteria include febrile morbidity (oral temperature >38°C measured at least 4 hours apart on any 2 postoperative days excluding the first 24 hours after the operation), hemorrhage requiring operative or postoperative blood transfusion, unintended major surgical procedures (laparotomy, repair of a perforated viscous, or unplanned repair of a major blood vessel performed intraoperatively or postoperatively during the same hospitalization due to a problem related to the hysterectomy), life-threatening events such as intraoperative or postoperative cardiac or respiratory arrest, myocardial infarct or embolus or anaphylactic shock), re-hospitalization for a complaint or problem related to the hysterectomy and death or complication leading to death occurring intraoperatively or within 42 postoperative days.

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS Inc, Chicago, IL, USA) 11.0 software for Windows. Categorical variables were analyzed by Pearson's chi square or Fisher exact test. Mann Whitney U test was used to compare groups. Spearman Correlation Analysis was used to assess the correlation of variables.

Table 1. Descriptive data of our series

	average±SD	Range
Age	60.9±11.1	35-81
No. of pregnancies	6.8±2.2	0-14
No. of parities	7.1±3.0	0-13
No. of abortions	0.72±1.0	0-5
Duration of hospitalization after VH (days)	11.6±6.1	4-41

SD: standard deviation, VH: vaginal hysterectomy

Table 2. Distribution of variables

Variable		n	%
Age	≤60	78	39.6
	>60	119	60.4
Number of pregnancies	0-5	52	26.4
	6-10	108	54.8
	>10	37	18.8
Number of parities	0-5	72	36.5
	6-10	103	52.3
	>10	22	11.2
History of abortion	Yes	79	40.1
	No	118	59.9
Intra and postoperative complications	Yes	21	10.7
	No	176	89.3

Results

The duration of hospitalization after vaginal hysterectomy for the whole study group was 11.6±6.1 (range 4 to 41) days and was expressed in Table 1. The duration of hospitalization was 15.6±7.99 (range 8 to 41) days for the complicated group, and 9.82±3.97 (range 4 to 19) days for the uncomplicated group. Length of hospital stay was prolonged in our series because of the preoperative hospitalization of the patients for electrocardiography, chest radiography, and routine laboratory screening based on age, gender, and concomitant medical diseases. These procedures usually last for 2-4 days according to the underlying cardiovascular or respiratory diseases.

The distribution of complications according to Dicker's criteria was shown in Table 3. Five patients (23.8%) developed febrile morbidity, four (19.1%) operative blood transfusion, two (9.5%) postoperative blood transfusion, four (19.1%) unintended major surgical procedures, three (14.3%) life-threatening cardiac or respiratory events, and three (14.3%) re-hospitalization.

Table 3. The distribution of complications according to Dicker's criteria

Complications according to Dicker's criteria	n (%)
Febrile morbidity	5/21 (23.8%)
Hemorrhage requiring operative or postoperative blood transfusion	6/21 (28.6%)
Unintended major surgical procedures (laparotomy, repair of a perforated viscous, or unplanned repair of a major blood vessel performed intraoperatively or postoperatively during the same hospitalization due to a problem related to the hysterectomy)	4/21 (19.1%)
Life-threatening events such as intraoperative or postoperative cardiac or respiratory arrest, myocardial infarct or embolus or anaphylactic shock)	3/21 (14.3%)
Re-hospitalization for a complaint or problem related to the hysterectomy	3/21 (14.3%)
Death or complication leading to death occurring intraoperatively or within 42 postoperative days	0/21 (0%)

Analysis results showed that advanced age was correlated to the duration of postoperative hospitalization (rs=0.178, p=0.023). Duration of hospitalization was significantly prolonged in patients with >5 previous pregnancies (rs=0.225, p=0.001). No further difference was noted between durations of hospitalization of patients with 6-10 and >10 previous pregnancies (p=0.146).
Similar results were obtained for the number of parities. Patients with >5 parities were likely to be hospitalized for a longer time after surgery (rs=0.310, p<0.001). There was no difference between the durations of hospitalization of patients with 6-10 and >10 parities (p=0.426).
The presence of intra- or postoperative complications were strongly associated with the duration of hospitalization in this series (p<0.001), while a history of abortion seemed not to influence the interval for postoperative hospital stay (p=0.591). Previous surgeries were also not correlated to the duration of postoperative hospitalization (rs=0.478, p=0.267).

Discussion

Vaginal hysterectomy offers several advantages. In addition to the cosmetic benefit, the operating time is shorter, complications are rare, recovery is faster, and overall treatment costs are reduced (3, 5). The advent of laparoscopic hysterectomy has not changed these conclusions and it was concluded that specific guidelines should be established to replace abdominal hysterectomy not by laparoscopic hysterectomy but with vaginal hysterectomy (6, 7).
The most common indications for vaginal hysterectomy include stress urinary incontinence and pelvic prolapse. Although VH is advocated in many candidates for hysterectomy, it is not fully devoid of complications (5). In addition to complications, parameters that may affect the duration of hospitalization after VH are important for exploring the traps and pitfalls of this procedure.
Management of intraoperative and postoperative complications is important to improve the cost-effectivity of VH. We have included nulliparous patients and those with a history of caesarean section and other pelvic surgery in our study. In our series, febrile morbidity and bladder injury were common complications. Febrile morbidity may be due to infections of the urinary tract or vaginal cuff, pelvic abscess and pneumonia (6). Bladder injury can occur in the presence of adhesions in the vesicovaginal space (7). These adhesions may be attributed to previous caesarean sections. A previous caesarean section history can be associated with higher rates of bladder injury. Bladder injuries can occur more frequently in patients without pelvic prolapse or with first-degree pelvic prolapse than in those with second- or third-degree pelvic prolapse. This can be explained by the difficulty in dissection of the vesicouterine fold (6, 7). Maximum caution should be exercised to avoid penetration of the urinary bladder during dissection of the vesicouterine fold.
Large uterine size can constitute a mechanical difficulty in vaginal hysterectomy. It may prolong the duration of the operation and increase the rate of complications during surgery (5, 7). Therefore, a large uterus can represent a contraindication to vaginal hysterectomy and an indication for abdominal hysterectomy for some gynecological surgeons.
There is no consensus about whether nulliparity, history of pelvic surgery and excessive uterine size are contraindications for vaginal hysterectomy (3, 5-7). Vaginal hysterectomy may be technically more difficult in nulliparous than in multiparous women. The vagina is narrower and the uterus is less prolapsed in nulliparous women and the operative duration may therefore be longer (6).
According to our results, aging, multiparity and presence of complications were found to prolong the duration of hospitalization. Urinary tract and vaginal infections can be sources of febrile morbidity. Aseptic technique and strict use of prophylactic antibiotics can aid the elimination of infections. Structural changes in the uterus due to aging can prolong the duration of hospitalization and increase the likelihood of complications. Multiparity can result in similar impacts and cause anatomical and physiological alterations. Awareness of potential complications in older and multiparous patients is important in preoperative planning and operative performance of the procedure.
Hospitalization after surgery sometimes can be necessary for management of pain after the procedure. Improvement of pain control methods can reduce the rate of hospitalization and its cost (8). Vaginal hysterectomy is reported to result in lower costs and utilization and more favorable functioning, pain, and activity profiles than either abdominal hysterectomy or laparoscopically assisted vaginal hysterectomy (9).
Our study has several limitations. First, interpretation of retrospective data possesses some restrictions. Second, decisions to perform vaginal hysterectomy were made by individual surgeons. Third, cost-effectiveness cannot be evaluated by duration of hospitalization alone. Other aspects like radiology, laboratory, pharmacy, nursing, and operating room costs cannot be ignored. Further studies involving these dimensions are required to reveal the actual cost-effectivity of VH.
In conclusion, vaginal hysterectomy is an efficient treatment for uterovaginal prolapse with quick recovery and low complication rates. Advanced age, increased numbers of pregnancies and parities and occurrence of intra or postoperative complications may prolong the duration of hospitalization after surgery. Increased experience, careful surgical technique and adherence to aseptic principles may improve the cost-effectivity of this procedure and decrease the duration of hospitalization.

Conflict of interest

No conflict of interest was declared by the authors.

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Ultrasonographic endometrial thickness measurement is predictive for treatment response in simple endometrial hyperplasia without atypia

Ultrasonografik endometriyal kalınlık ölçümü atipisiz endometriyal hiperplazi tedavi cevabında öngörücüdür

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Abstract

Objective: We sought to determine the predictors of treatment response in simple endometrial hyperplasia without atypia.

Material and Methods: We prospectively treated 67 women with simple endometrial hyperplasia without atypia who were administered cyclic oral medroxyprogesterone acetate 10 mg/day for 12 days of luteal phase for 3 months and underwent control endometrial sampling after treatment. All subjects were evaluated in terms of age, gravidity, parity, body mass index (BMI), menstrual cycle, endometrial thickness, uterine fibroids, ovarian cysts, serum CA 125 levels, systemic disorders and cigarette smoking. All parameters were used to predict treatment success.

Results: Persistent hyperplasia was observed in 11 subjects. Endometrial thickness was significantly correlated with treatment failure (r=0.293, p=0.015). In ROC analysis, endometrial thickness was found to be predictive for persistent hyperplasia (area under curve: 0.724, P=0.019). Optimal cut off value was calculated to be 16.5 mm with 64% sensitivity, 72% specificity and 91% negative predictive value. The number of persistent hyperplasia in women with and without endometrial thickness greater than 16.5 mm was significantly different (7/23 vs. 4/45, p=0.029). Odds ratio of endometrial thickness higher than 16.5 mm for treatment failure was 4.4 (95% CI, 1.2-17.4, p=0.03).

Conclusion: Results of this study suggest treatment modification according to the baseline endometrial thickness in patients with simple endometrial hyperplasia without atypia.

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Key words: Endometrial hyperplasia, medroxyprogesterone acetate, endometrial thickness, ultrasonography, atypia

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Özet

Amaç: Bu çalışma ile atipisiz endometriyal hiperplazide tedaviye cevabı öngören faktörlerin belirlenmesi amaçlandı.

Gereç ve Yöntemler: Atipisiz endometrial hiperplazisi olup luteal fazın 12 günü boyunca 3 ay süreyle medroksiprogesteron asetat 10 mg/gün alan ve tedavi sonunda kontrol endometriyal örnekleme yapılan 67 hastayı prospektif olarak topladık. Tüm bireylerde yaş, gravida, parite, beden kitle indeksi, menstrüel siklusu, endometriyal kalınlık, uterin fibroidler, overyan kistler, serum CA125 değerleri, sistemik hastalıklar ve sigara içimi değerlendirildi. Tüm parametreler kullanılarak tedavi başarısı öngörülmesi amaçlandı.

Bulgular: Persistan hiperplazi 11 hastada izlendi. Endometriyal kalınlık tedavi başarısızlığı ile anlamlı korele idi (r=0.293, p=0.015). ROC analizinde, endometriyal kalınlık, persistan hiperplaziyi anlamlı öngörmekteydi (area under curve: 0.724, p=0.019). Optimal eşik değer %64 sensitivite, %72 spesifisite, %91 negatif prediktif değer ile 16.5 mm olarak hesaplandı. Persistan hiperplazi sayısı endometriyal kalınlığı 16.5 mm nin üstünde ve altında olan grupta anlamlı farklı idi (7/23 vs. 4/45, p=0.029). Endometriyal kalınlığın 16.5 mm'nin üstünde olması tedavi başarısızlığı ile ilişkiliydi [Odds oranı= 4.4 (%95CI, 1.2-17.4, p=0.03)].

Sonuç: Bu çalışmanın sonucu basit atipisiz endometriyal hiperplazide bazal endometriyal kalınlık ölçümünün tedavi modifikasyonunda etkili olabileceğini göstermiştir.

(J Turkish-German Gynecol Assoc 2013; 14: 19-22)

Anahtar kelimeler: Endometriyal hiperplazi, medroksiprogesteron asetat, endometriyal kalınlık, ultrason, atipi

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Introduction

Endometrial hyperplasia is defined as a proliferation of endometrial glands that may progress to or coexist with endometrial cancer. Endometrial hyperplasia considered to result from unopposed chronic estrogen stimulation. The treatment of endometrial hyperplasia is managed according to the risk of endometrial carcinoma. The classification system that correlates most closely with the risk of malignancy was suggested by the World Health Organization system (WHO) (1). This classification system includes four categories:

- Simple without atypia
- Complex without atypia
- Simple with atypia
- Complex with atypia

A cyclic regimen of medroxyprogesterone acetate (MPA, ie. 10 mg/day for 12 to 14 days each month) is a widely accepted regimen for treatment (2).

A previous study reported that regression was noted in 52 of 65 patients (80%) with hyperplasia without atypia treated with MPA (3).

If regression to normal endometrium does not occur after three to six months, it was suggested that the progestin dose be increased, or a combination of a systemic progestin and the levonorgestrel intrauterine device may be used.

Usually obese women are encouraged to lose weight, which has multiple health benefits in addition to reduction of estradiol and estrone production by adipocytes. In a previous study it was concluded that cigarette smoking specifically affects the control mechanisms of intraovarian processes which are responsible for normal luteal function (4). Body mass index (BMI) was reported to be predictive of sonographic endometrial stripe thickness, which in turn is predictive of endometrial hyperplasia in patients with polycystic ovary syndrome. For every 1mm increase in endometrial stripe in ultrasonographic evaluation, the odds ratio of hyperplasia increased by 1.48 (95% confidence interval, 1.04-2.10) (5).

The aim of this study is to assess the predictors of treatment response in women with simple endometrial hyperplasia without atypia.

Material and Methods

Sixty seven premenopausal women diagnosed with simple endometrial hyperplasia between 2010 and 2012 at Dr. Sami Ulus Maternity and Women's Health Teaching and Research Hospital were enrolled for the study. Local ethics committee approval with subjects' informed consent were obtained before the study. Women were administered cyclic oral MPA 10 mg/day for 12 days of the luteal phase for 3 months and underwent control endometrial sampling after treatment. MPA was preferred in order to make the results easily compared with previous studies in which MPA was the drug of choice. All subjects were evaluated in terms of age, gravidity, parity, BMI, menstrual cycle, endometrial thickness, uterine fibroids, ovarian cysts, serum CA 125 levels, systemic disorders, cigarette smoking. All parameters were used to predict treatment success.

Inclusion criteria were a diagnosis of simple endometrial hyperplasia in premenopausal women with abnormal vaginal bleeding or thickened endometrium, followed by progestin therapy for three months and post treatment endometrial samplings and without previous medical or surgical intervention for any endometrial pathology. Endometrial polyps were ruled out by an office hysteroscopic procedure in women with thickened endometrium. Premenopausal women without any symptoms underwent imaging at least twice, and persistence of an early–proliferative-phase endometrium thicker than 12 mm was an indication for office hysteroscopy and endometrial sampling (6). The final outcome was categorized as resolution, persistence, or progression based on the findings either at hysterectomy or in the two final, consecutive endometrial samples. Post-treatment specimens were obtained within 3 weeks of discontinuing progestins. Control endometrial samplings were obtained just after menstruation.

Patients were excluded if they were postmenopausal, if they had a history of other genital tract cancer, pelvic radiation, or hormonal therapy for breast cancer; or if either pretreatment or first follow-up specimen was unavailable for review. A pathologic review of the pretreatment and first follow-up endometrial specimens was performed independently by two gynecologic pathologists. When the two pathologists differed as to diagnosis, a third gynecologic pathologist was consulted; the majority diagnosis was used. Pathologists were blinded to the final outcome. The pretreatment and first follow-up endometrial specimens were classified based on the WHO criteria for the diagnosis of endometrial hyperplasia and carcinoma (7). Subject data were collected until resolution, hysterectomy, or loss to follow-up. Resolution was defined as the absence of hyperplasia or carcinoma in a hysterectomy specimen or in a minimum of two sequential endometrial specimens. Persistence was defined as any continued simple hyperplasia during treatment. During transvaginal sonography (TVS), the thickest part of the anteroposterior bilayer endometrial thickness was measured in the sagittal plane. Body mass index was calculated by body weight divided by height squared. Serum levels of carbohydrate antigen-125 (CA-125) were determined with use of the commercially available Tumor Markers CA 125 AxSYM® System (Abbott Laboratories; Abbott Park, IL, USA). All subjects were questioned about cigarette addiction, menstrual cycle, gravidity and parity. A blood loss of greater than 80 mL or lasting longer than 7 days constitutes menorrhagia. Metrorrhagia was defined as light bleeding from the uterus at irregular intervals. Menometrorrhagia was diagnosed in subjects with heavy bleeding from the uterus at irregular intervals. The subjects' smoking habits were obtained from the questionnaire, including current smoking habits, history of giving up smoking, duration of smoking habit and average daily cigarette consumption. A current smoker was defined as a subject who had smoked more than 100 cigarettes and was still smoking (8). An ex-smoker was defined as having stopped smoking for more than half a year (8).

An ovarian cyst was defined as any collection of fluid, surrounded by a very thin wall, within an ovary larger than about two centimeters. Diagnosis of adenomyosis was considered

according to the clinical and imaging findings after ruling out other possible uterine pathologies.
Women with refractory hyperplasia were administered 20 mg/day of metroxyprogesterone acetate for 12 days of the luteal phase for 3 months and underwent endometrial sampling.

Statistical analysis
The statistical analyses were performed using the Statistic Package for Social Sciences (ver. 12.0; SPSS Inc., Chicago, USA). Categorical variables were compared by Chi square test. Correlation analysis was used to show associations. p value <0.05 was accepted as statistically significant. ROC analysis was used to calculate cut off value. Binary logistic regression analysis was used to calculate the odds ratio.

Results

Mean age, gravidity, parity, BMI, endometrial thickness was 44.2±7.2 years, 3.2±1.8, 2.8±1.3, 27.8±5.1 kg/m^2, 14.1±6 mm respectively (Table 1). Mean number, size of myoma, CA125 levels were as follows; 1.6±0.9 (range 0-5), 20.1±12 mm (range 6-57), 17.4 U/mL (range 5-104). Persistent hyperplasia was observed in 11 (16.4%) subjects. The symptoms at the time of admission were menorrhagia (n=10), metrorrhagia (n=19), menometrorhagia (n=28), vaginal spotting (n=2) and without any symptom (n=8). There were 35 women without any fibroids, 25 women had at least one fibroid, 7 women had adenomyosis. Endometrial polyp was not observed in any case. Forty-seven women had an ovarian cyst. Seven women had hypertension, 2 women had diabetes mellitus and 2 women had both disorders. Out of 67 women, 8 were smokers. Endometrial thickness was significantly correlated with treatment failure (r=0.293, p=0.015). In the ROC analysis, endometrial thickness was found to be predictive for persistent hyperplasia (area under curve: 0.724, p=0.019, Figure 1). Optimal cut off value was calculated to be 16.5 mm with 64% sensitivity, 72% specificity and 91% negative predictive value. The number of persistent hyperplasia in women with and without endometrial thickness greater than 16.5mm was significantly different (7/23 vs. 4/45, p=0.029, Table 2). Mean age, BMI and serum CA125 levels were similar between subjects with endometrial thickness of greater and lower than 16.5 mm (p>0.05). The number of smokers and subjects with fibroids and ovarian cysts were similar between groups (p>0.05). Other parameters did not show any significant association with treatment success. The odds ratio of endometrial thickness greater than 16.5 mm for treatment failure was 4.4 (95% CI, 1.2-17.4, p=0.03). All persistent hyperplasia cases responded to higher doses of progesterone therapy.

Table 1. Some demographic and clinical parameters of groups with and without thickened endometrium

	Endometrial thickness <16 mm (N=56)	Endometrial thickness >16 mm (N=11)	
Age (years)	44.3±6.8	44.1±9.9	NS
Gravidity	3.1±1.7	3.7±2.2	NS
Parity	2.7±1.3	3.2±1.6	NS
BMI (kg/m^2)	27.9±5.1	27.8±6.2	NS
ET (mm)	13.4±5.7	18.1±6.1	0.015

BMI: Body mass index, ET: Endometrial thickness

Discussion

In this study we tried to assess some parameters to predict treatment response in women with simple endometrial hyperplasia and we found that solely ultrasonographic endometrial thickness measurement was significantly predictive for treatment response. Cigarette addiction, menstrual cycle, gravidity, parity and pelvic pathologies (i.e. myomas, ovarian cysts) were not found to be predictive for treatment response.
Based on the systematic review of the contemporary literature, 66% of endometrial hyperplasia cases respond to hormonal therapy. Disease persistence was found in 14% of cases (9). In our study population, 16.4% cases were refractory to the treatment.
A recently published study questioned the value of endometrial thickness measurement to predict histeroscopic findings and concluded that hysteroscopy should be offered when thickened endometrial is found (10). In addition to this ,although attempts to introduce noninvasive new diagnostic tools have beenmade, transvaginal ultrasound remained one of the most effective methods to screen endometrial pathologies (11).

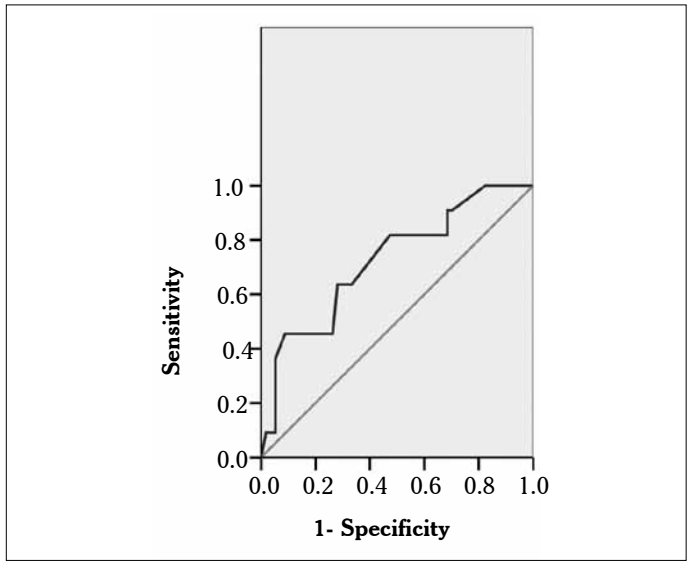

Figure 1. Receiver operator curve of endometrial thickness to predict persistent hyperplasia

Table 2. Number of persistent hyperplasia cases between women with higher and lower than 16.5 mm endometrial thickness

Endometrial Thickness	<16.5 mm	>16.5 mm	Total	p Value
Non persistent	41	16	57	
Persistent	4	7	11	0.029
Total	45	23	68	

In another study on endometrial hyperplasia, it was concluded that endometrial hyperplasia can be effectively excluded when the endometrial thickness is less than 7 mm (12). This data also confirms our hypothesis that endometrial thickness measurement directly gives information about the possibility of endometrial pathology.

There are still concerns about the treatment of endometrial hyperplasia without atypia, previous study concluded that the majority of women with atypical endometrial hyperplasia were managed by hysterectomy and the substantial risk of diagnostic under-call supports this approach to treatment. However, there is no consensus regarding the initial management of women with endometrial hyperplasia without cytological atypia (13).

In another study with an aimsimilar to ours, it was found that among 13 clinical non-responders, 84.6% might have associated pelvic pathology. Significant factors predicting clinical non-responders included a history of prior bleeding, the presence of associated pelvic pathology and treatment using progestins other than MPA. The study concluded that the current regimens of progestin therapy for non-atypical endometrial hyperplasia have high response rates. Patients who fail to have a clinical response should be evaluated for associated pelvic pathology. Follow-up endometrial biopsy should be offered to the patients, because 7.5% have persistent or progressive lesions, necessitating aggressive treatment (14). In our study, the most commonly seen pelvic pathologies were not found to be associated with disease persistence.

A study estimated the clinical value of CA-125 in the diagnosis of endometrial carcinoma. It was found that there is an important correlation between serum levels of CA-125 and endometrial cancer (15). Based on this data, we assessed CA125 levels but did not find any significance.

Body mass index was found to be predictive of sonographic endometrial stripe thickness, which in turn is predictive of endometrial hyperplasia in patients with polycystic ovary syndrome. For every 1mm increase in endometrial stripe, the odds ratio of hyperplasia increased by 1.48 (95% confidence interval, 1.04-2.10) (5). This data shows the value of endometrial thickness measurement in hyperplasia.

Of the known risk factors for endometrial hyperplasia, obesity is the most preventable. Data suggest that higher BMI is associated with endometrial hyperplasia as compared to women with lower BMIs and abnormal bleeding (16). Contrary to this conclusion, our study did not reveal an association between BMI and disease persistence.

Although endometrial thickness measurement is a widely used simple and cheap method, in our literature search we have not encountered a study assessing its predictive value for treatment response in women with endometrial pathologies. This is the first study which shows a significant value of endometrial thickness in predicting treatment response in endometrial hyperplasia cases.

In conclusion, there are concerns about the optimal treatment for simple endometrial hyperplasia without atypia, and this study suggests that endometrial thickness measurement alone may predict response to therapy and this can be used to modify treatment.

Conflict of interest

No conflict of interest was declared by the authors.

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Microarray detection of human papilloma virus genotypes among Turkish women with abnormal cytology at a colposcopy unit

Bir Kolposkopi merkezine başvuran anormal sitolojili Türk kadınlarındaki human papilloma virus tiplerinin mikroarray analizi

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Abstract

Objective: There is a well-known association between human papilloma virus (HPV) and cervical neoplasia. The aim of this study was to investigate the types of HPV DNA and to compare the results with colposcopic findings among women with abnormal cytology.

Material and Methods: A series of 76 consecutive women attending the clinic with the usual referral indications (ASC-US or higher in Pap) were examined by the conventional diagnostic tools (PAP smear, colposcopy,punch biopsy) and subjected to HPV testing. For HPV genotyping, we used a commercially avaliable HPV DNA chip (Genomica-CLART) which is a PCR based microarray system.The HPV test detected 35types of HPV (HPV-6/-11/-16/-18/-26/-31/-33/-35/-39/-40/-42/-43/-44/-45/-51/-52/-53/-54/-56/-58/-59/-61/-62/-66/-70/-71/-72/-73/-81/-83/84/-85/-89).

Results: Overall, 44.7% of all patients were HPV positive. HPV was positive in 35%, 51.9%, 77.7% of the ASCUS, LSIL and HSIL groups respectively and HPV 16 was the most prevalent type in all groups. 6 %of patients had mutiple infections. 57.8% of biopsy proven SIL's were HPV positive. The most prevalent HPV type was HPV 16 (54.5%).Colposcopic assessment revealed pathologic findings in 94.7% of biopsy proven SIL cases.

Conclusion: Although it has been reported that the prevalence of HPV in the general population is lower than Western countries, and the prevalence and distribution of genotypes are smilar in patients with abnormal cytology. Further population based studies are needed to determine the prevalance and type distribution of HPV with normal and abnormal cytology in Turkish women. Despite the new technological progress in HPV virion, colposcopy is still very important diagnostic tool in the management of abnormal smears.

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Özet

Amaç: Human Papilloma Virus (HPV) ile servikal neoplaziler arasında iyi bilinen bir ilişki mevcuttur. Bu çalışmanın amacı anormal servikal sitolojili kadınlarda HPV DNA tiplerini araştırmak ve sonuçları kolposkopik bulgularla karşılaştırmaktır.

Gereç ve Yöntemler: Genel referans endikasyonlarıyla (ASCUS ve üstü smear sonucu) başvuran 76 kadın, sırasıyla geleneksel tanı araçlarıyla (PAP-smear, kolposkopi, punch biyopsi) değerlendirmeye alındı ve tüm hastalar HPV DNA testine tabi tutuldu. HPV DNA tiplemesi için piyasada bulunan PCR bazlı mikroaarray (Genomica-CLART) sistemi kulanıldı. HPV testi, 35 tipi belirleyebiliyordu. (HPV-6/-11/-16/-18/-26/-31/-33/-35/-39/-40/-42/-43/-44/-45/-51/-52/-53/-54/-56/-58/-59/-61/-62/-66/-70/-71/-72/-73/-81/-83/84/-85/-89).

Bulgular: Tüm hastaların %44.7 sinde HPV pozitifliği saptandı. HPV pozitifliği yüzdeleri ASCUS; LSIL ve HSIL hastalarında sırasıyla %35, %51.9 ve %77.7 idi. HPV 16 en sık tip olarak bulundu. Hastaların %6 sında multipl infeksiyon tespit edildi. Biopsi ile ispatlanmış servikal neoplazi olgularının %57.8 inde HPV pozitifliği saptandı. En sık rastlanan tip HPV 16 (%54.5) olarak bulundu. Biyopsi ile ispatlanmış sevikal neoplazi vaklarının %94.7 sinde kolposkopi patolojik olarak değerlendirildi.

Sonuç: Batı ülkelerine kıyasla HPV sıklığının ülkemizde daha düşük olduğu yayınlanmış veri olmakla birlikte, anormal sitolojili kadınlarda HPV sıklık ve dağılımı batı ülkeleriyle benzerlik göstermektedir. Anormal ve normal sitolojili Türk kadınlarındaki HPV sıklık ve dağılımının belirlenmesi için daha ileri ve popülasyon bazlı çalışmalara gereksinim vardır. HPV virüsünün tanımlanmasıyla ilgili teknolojik ilerlemelere rağmen kolposkopik değerlendirme anormal sitolojili kadınlarda hala çok önemli bir tanı aracıdır.

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Anahtar kelimeler: Microarray, HPV, kolposkopi, anormal smear, PCR

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Introduction

Cervical cancer is the second most common cancer and one of the leading causes of cancer-related deaths among women worldwide. Epidemiological studies have shown that there is a strong association, consistent in several countries, between human papilloma virus (HPV) and cervical neoplasia, independent of other risk factors (1, 2).
According to the statistics of the Ministry of Health and GLOBOCAN 2008, cervical cancer is the 8th most common cancer among women in Turkey (3, 4). It has been reported that the range of HPV prevalence among low risk women is between 2-20% in Turkey (5, 6).
The aim of this study is to investigate the prevalance and distribution of HPV genotypes, utilising a microarray system which can define 35 different types of HPV among Turkish women with abnormal cervical cytology and to compare the HPV DNA results with colposcopic findings.

Material and Methods

Specimens were obtained from 76 patients who were referred to our referral colposcopy clinic at the Department of Obstetrics and Gynecology, İstanbul Medical Faculty, İstanbul University between January 2007 and January 2008. Each participiant gave written informed consent before she was enrolled and the study was approved by the institution. Seventy-six patients with pathological smears were classified into three groups according to their cytological diagnoses: Atypical squamous cells of undetermined significance (ASCUS), Low grade squamous ıntra epithelial lesions (LGSIL), High grade intraepithelial lesions (HGSIL). For HPV genotyping, we used a commercially avaliable HPV DNA chip (Genomica-CLART®) which detects the HPV genotypes by highly specific and sensitive polimerase chain reacton (PCR) with a new technological platform based on low density arrays.
Cervical biopsy samples were taken from patients with abnormal colposcopic findings in Group I (ASCUS) and Group II (LGSIL), and from all patients in Group III (HGSIL) regardless of the colposcopic findings.

Cytological and histological diagnoses

Classification of each cytological diagnosis was based on the Bethesda system. Cervical Intraepithelial neoplasia (CIN I, CIN II, CIN III), in situ carcinoma and invasive carcinoma were used for histological diagnosis of cervical lesions to unify the terminology.

HPV tests

Microarray HPV test (Genomica-CLART®) was used for HPV genotyping. The HPV microarray system contains 35 type specific probes: HPV 6, HPV 11, HPV 16, HPV 18, HPV 26, HPV 31, HPV 33, HPV 35, HPV 39, HPV 40, HPV 42, HPV 43, HPV 44, HPV 45, HPV 51, HPV 52, HPV 53, HPV 54, HPV56, HPV 58, HPV 59, HPV 61, HPV 62, HPV 66, HPV 70, HPV 71, HPV 72, HPV 73, HPV 81, HPV 82, HPV 83, HPV 84, HPV 85, HPV 89. Detection of different HPV genotypes was achieved by PCR amplification of a 450 bp fragment within the highly conserved L1 region of the virus.
Cervical samples for HPV testing were taken at the beginning of colposcopy with a clean, dry cotton or alginate swab large enough to obtain a good sized sample. No device that could cause bleeding was used, as blood might interfere with the assay. The swab was placed in its tube without any kind of preservation medium and was maintained at 4°C if it was to be processed within seven days or at -20°C when processed later. The samples were fixed in buffered formol for the shortest time possible (never more than 24 hours) to avoid DNA degradation. Before and after cutting the sample, the blade was carefully cleaned with xylene to avoid any cross contamination of the samples cut.

Colposcopic evaluation and punch biopsy

Colposcopic evaluation and HPV test were performed in all patients. Colposcopic biopsy was performed for pathological colposcopic findings. Furthermore, loop electrosurgical excision procedure (Leep) biopsy was performed in all HGSIL (Group III) patients regardless of the colposcopic findings.

Statistical analyses

The statistical analyses were performed using the SPSS version 15.00. Chi-square and Fisher's exact tests were used to assess the statistical significiance of differences in the prevalence of HPV infection and to evaluate differences in the frequency of multiple infections among various cervical lesions, as well as to compare the other variables. p values <0.05 were considered statistically significant.

Results

During the one year period, 76 women with pathological cytology were referred to our colposcopy unit. The mean age of the patients was 35.5 (range: 19-62 years). There were no significant differences with respect to decades of life and HPV positivity. Also, menopausal status had no effect on HPV positivity. The patients were classified into three groups according to their cytological diagnoses, such as Group 1 (atypical squamous cells of undetermined significance=40), Group 2 (low grade squamous intraepithelial lesion=27) and Group 3 (high grade squamous intraepithelial lesion=9).
Overall, 44.7% of all patients were HPV positive. HPV was positive in 35%, 51.9%, 77.7% of the ASCUS, LSIL and HSIL groups, respectively. HPV 16 was the most prevalent type in all groups. HPV 16 and HPV 84 was found in higher prevalence in high grade squamous intraepithelial lesions (HSIL) when compared to other groups ($p<0.01$). The rate of HPV types were as follows: 5.8% for HPV 11, 20.5% for HPV 6, 32.3% for HPV 16, 20.5% for HPV 18, 2.9 % for HPV 31, 2.9% for HPV 51, 11.7% for HPV53, 5.8% for HPV 58, 2.9% for HPV 59, 8.8% for HPV 61, 11.7% for HPV 66, 2.9% for HPV 70 and 2.9 % for HPV 84 (Table1). Multiple infections were detected in 5/76 (6%) women (Table 2).
Colposcopic examination was made in all patients. Abnormal colposcopic findings were found in 20% (n: 8), 40.7% (n: 11) and 77.8% (n: 7) of the ASCUS, LGSIL, HGSIL groups, respectively.

Cervical biopsy specimens were taken from the patients with abnormal colposcopic findings in the ASCUS and LSIL group. Cervical biopsy samples were taken from all patients in the HSIL group regardless of colposcopic findings.
Of the biopsy proven Squamous ıntraepithelial lesion's (SIL's), 94% had colposcopic findings and 57.8% of biopsy proven SILs were HPV positive. The most common HPV type was HPV 16 (54.5%). There was a statistically significiant correlation between the HPV positivity and biopsy positivity ($p< 0.05$) (Table 3).

Table 1. Smear results-HPV types

	LGSIL (n:27)	ASCUS (n:40)	HGSIL (n:9)	p value
HPV	14 (51.9%)	14 (35.0%)	7 (77.7%)	0.147
Type 6	3 (11.1 %)	3 (7.5%)	1 (11.1%)	0.863
Type 11	0 (0%)	2 (5.0%)	0 (0%)	0.397
Type 16	3 (11.1%)	4 (10%)	4 (44.4%)	0.024*
Type 18	1 (3.7%)	5 (12.5%)	1 (11.1%)	0.464
Type 31	1 (3.7%)	0 (0%)	0 (0%)	0.399
Type 51	1 (3.7%)	0 (0%)	0 (0%)	0.399
Type 53	2 (7.4%)	2 (5.0%)	0 (0%)	0.686
Type 58	1 (3.7%)	1 (2.5%)	0 (0%)	0.832
Type 59	1 (3.7%)	0 (0%)	0 (0%)	0.399
Type 61	0 (0%)	2 (5.0%)	1 (11.1%)	0.295
Type 66	2 (7.4%)	2 (5.0%)	0 (0%)	0.686
Type 70	0 (0%)	1 (2.5%)	0 (0%)	0.634
Type 84	0 (0%)	0 (0%)	1 (11.1%)	0.023*

*: $p<0.05$, HPV: Human papilloma Virus, LGSIL: Low Grade Sguamous intraepithelial lesion, HGSIL: High Grade Squamous intraepithelial lesion, ASCUS: Atypical squamous cells of undetermined significance

Table 2. Multiple infections

AGE	SMEAR	HPV TYPES	COLPOSCOPY	HISTOPATHOLOGIC DIAGNOSIS
26	ASCUS	HPV6, HPV53, HPV 58	NEGATIVE	NEGATIVE
25	ASCUS	HPV 6, HPV 11, HPV18, HPV 53	AWE	CIN III
41	LGSIL	HPV16, HPV18	NEGATIVE	NEGATIVE
34	HGSIL	HPV16, HPV18	NEGATIVE	IN SITU CARCINOMA
46	LGSIL	HPV6, HPV 59	NEGATIVE	NEGATIVE

AWE: Acetowhite epithelium, HPV: Human papilloma Virus, LGSIL: Low Grade Sguamous intraepithelial lesion, HGSIL: High Grade Squamous intraepithelial lesion, ASCUS: Atypical squamous cells of undetermined significance, CIN: Cervical intraepithelial neoplasia

Discussion

Epidemiological studies and experimental research have established a causal link between the presence of HPV 16, HPV 18, HPV 31, HPV 33, HPV 35, HPV39, HPV 45, HPV 51, HPV 52, HPV 56, HPV 58, HPV 59, HPV 66 and the development of invasive cervical cancer (7, 8). It has also been estimated that HPV is responsible for 5.2% of all cancers worldwide (9).
The HPV microarray system is a newly developed biotechnology that can be applied to clinical practice for the detection and genotyping of HPV. The application of microarray technology as a diagnostic tool shows great advantages since microarrays can discriminate the HPV genotype and identify multiple infections. In our study, the microarray system (microarray genomica) could detect 35 types of HPV.
It has been reported that the HPV detection rates of the microarray technique is comparable to hybrid capture II (HCII) and it is also able to determine multiple lesions (10, 11). Kim et al. (10) reported that the HPV testing methods have comparable sensitivities (94.9% for HC-II and 93.7% for HPV microarray) for detection of SIL. The sensitivity, specificity, positive and negative predictive values of HPV testing by HC-II and HPV microarray methods were not significantly different.

Table 3. HPV types and colposcopic results of biopsy proven lesions

Smear	Colposcopy	HPV	Biopsy
ASCUS	Mosaic pattern	Negative	CIN II
ASCUS	AWE	Negative	CIN III
ASCUS	Mosaic pattern	Negative	CIN II
LGSIL	Mosaic pattern	Negative	CIN II
LGSIL	Mosaic pattern	Negative	CIN II
LGSIL	AWE	HPV type 6	CIN II
LGSIL	AWE	HPV type 31	CIN II
LGSIL	AWE	Negative	CIN II
LGSIL	Mosaic pattern	HPV type 51	CIN III
LGSIL	Mosaic pattern	HPV type 16	CIN III
LGSIL	AWE	HPV type 16	CIN II
HGSIL	Mosaic pattern	HPV type 16	CIN III
HGSIL	Mosaic pattern AWE	HPV type 16,18	CIN III
HGSIL	AWE	Negative	CIN III
HGSIL	Mosaic pattern	HPV type 61,84	CIN III
HGSIL	AWE	HPV type 6	CIN III
HGSIL	Lesion positive	Negative	İnvasive ca
HGSIL	Mosaic pattern	HPV type 16	CIN III
HGSIL	Negative (normal colposcopic finding)	HPV type 16	In situ ca,

AWE: Acetowhite epithelium, HPV: Human papilloma Virus, LGSIL: Low Grade Sguamous intraepithelial lesion, HGSIL: High Grade Squamous intraepithelial lesion, ASCUS: Atypical squamous cells of undetermined significance, CIN: Cervical intraepithelial neoplasia

In women with abnormal cytology results, the presence of HPV infection has been reported in 28.8-61.3% of cases wordwide (12, 13).

In a Turkish study, the HPV prevalence has been reported in 36% of cases with abnormal cytology (6). Inal et al. (5) performed a HC-II study in 1353 women from the Izmir region, which has the highest cervical cancer incidence in Turkey, and reported that all the women with cytological abnormalities had positive HPV DNA. In our study, HPV was positive in 44.7% of the women with abnormal cytology and HPV 16 was the most prevalent type.

The published data from Turkey reveals us that the HPV prevalence is 3-20% in a low risk population (5, 6). Although it has been reported that the HPV prevalence is lower than reported worldwide in the low risk population, HPV prevalence and type distribution with abnormal cytology in our study was similar to that reported worldwide. It should be borne in mind that there is no population based study investigating HPV prevalence in Turkish women and the published data for HPV prevalence is limited.

International prevalence surveys by the International agency for Research on Cancer (IARC) have shown that the most prevalent HPV types of invasive cervical cancer were HPV 16 (53%), HPV 18 (15%), HPV 45 (9%), HPV 31 (6%) and HPV 33(3%) (14). In various studies, HPV 51, HPV 52, HPV35, HPV 56 and HPV 58 were found to be the common types in premalignant conditions (10, 15). Dursun et al. from Turkey reported that the most common HPV types in cytologically abnormal women were HPV 16 (35%), HPV 6 (19%) and HPV 18 (8.8%) (6).

In our sudy, the prevalence of HPV 16 and HPV 18 was found to be lower than in other reports, whereas HPV 53 and HPV 66 were found to be the second common type in pathological smears. In addition, HPV 16 and HPV 84 were significantly higher in the HSIL group. However, the number of our patients is inadequate to make a a comment.

HPV-84 was more commonly detected than HPV-16 or any other HPV genotype in people with incidental HPV infection in men genital specimens (16). HPV 84 has been considered as a low-risk HPV type and was detected in 3.3% of females aged between 14-59 in United States (17).

Although HPV 84 has been considered as a low risk HPV type, recent studies showed that it was detected in 13.9 % of biopsy proven cervical intraepithelial lesions and was more associated with HSIL or worse as compared to all other types together (18).

A study for the association between HPV DNA positivity and the subsequent development of cervical cancer showed that the HPV DNA type in all women with cervical cancer was the same in the baseline smear and in the biopsy specimen. None of the control women had the same type of HPV in both smears (8). The stong concordance between the type of HPV found in the baseline smears and that found in the biopsy specimen of the invasive cancer further supports the importance of viral subtyping.

Colposcopic evaluation and guided biopsy are important diagnostic steps and standards of management for abnormal cytology smears The performance and accuracy of colposcopy depend largely on the training, experience, and skills of the colposcopist. Hence, accuracy of colposcopy varies widely among studies in different parts of the world. In a meta-analysis, it has been reported that the sensitivity of colposcopy varies between 87-99% (19). The sensitivty of HPV DNA test to detect high grade lesions in ASCUS and LSIL groups ranges between 92.5-97.5% (20). According to an American Society for Colposcopy and Cervical Pathology (ASCCP) concensus in 2006, HPV testing and colposcopy are reasonable options for the management of patients with ASCUS and LSIL cytology.

In our study, 94.7% of biopsy proven SILs had abnormal findings at colposcopic evaluation. Statistically significant correlations were found between smear and colposcopic results. For ASCUS, LSIL and HSIL groups, 20%, 40% and 77.8% of the colposcopic evaluation were positive, respectively. Overall, 57.8 % biopsy proven cervical neoplastic lesions were HPV positive. Three cases with ASCUS cytology who had biopsy proven SIL were negative for HPV. In the LSIL group, 62.5% of the biopsy proven SILs were HPV positive.

Our data is limited to making a recommendation. Nevertheless, the HPV DNA test without colposcopic evaluation could be the cause of misdiagnosis in our cases, particularly in the ASCUS group. In our study, all of the colposcopic evaluations were made by experienced colposcopists. This could explain the strong correlation between colposcopy and biopsy.

Conclusion

Although it has been reported that the prevalence of HPV in the general population is lower than Western countries, the prevalance and genotypes are smilar in patients with abnormal cytology. This could be attributed to the limitations of the studies from Turkey, methodology and hospital based patient population. Further population based studies are needed to determine the prevalence and distribution of the HPV types with normal and abnormal cytology in Turkish women.

Colposcopic evaluation is a very important diagnostic tool for the detection of cervical intraepithelial lesions. Despite the major advances in the development of new technologies, the value of colposcopy in the management of abnormal smears remains stable.

Conflict of interest

No conflict of interest was declared by the authors.

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A randomized comparative study on modified Joel-Cohen incision versus Pfannenstiel incision for cesarean section

Sezaryen ameliyatı için Pfannenstiel insizyonuna karşı modifiye Joel-Cohen insizyonu üzerine randomize karşılaştırmalı çalışma

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Abstract

Objective: Pfanennstiel incision is the most commonly used incision for cesarean section, but may not be the best. This study compared the modified Joel-Cohen incision with the Pfannenstiel incision to evaluate whether techniques to open the abdomen might influence operative time, and maternal and neonatal outcomes.

Material and Methods: In a randomized comparative trial, 302 women with gestational age >34 weeks, requiring cesarean section, were randomly assigned to either modified Joel-Cohen incision or Pfannenstiel incision for entry into the peritoneal cavity. The primary outcome measure was total time required for performing operation and secondary outcome measures were baby extraction time, number of haemostatic procedures used in the abdominal wall, postoperative morbidity, postoperative hospital stay and neonatal outcome.

Results: Mean total operative time was significantly less in the modified Joel-Cohen group as compared to the Pfannenstiel group (29.81 vs 32.67 min, p<0.0001, 95%CI=2.253 to 3.467). Time taken to deliver the baby and haemostatic procedures required during operation were also significantly less in the modified Joel-Cohen group as compared to the Pfannenstiel group. Requirement of strong analgesics was higher in the Pfannenstiel group (53.64% vs 21.85%, p<0.0001). There was no statically significant difference in the incidence of postoperative wound complications but postoperative stay in hospital was significantly less in the modified Joel-Cohen group (p=0.002). Neonatal outcomes were similar in both groups.

Conclusion: The modified Joel-Cohen incision for entry into peritoneal cavity during cesarean section is associated with reduced mean total operative and baby extraction times with less postoperative pain and shorter hospital stay, which may be beneficial and cost effective.

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Key words: Cesarean section, modified Joel-Cohen, Pfannenstiel, incision, operative time

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Özet

Amaç: Pfannenstiel insizyonu sezaryen ameliyatında en yaygın kullanılan insizyondur ancak en iyisi olmayabilir. Bu çalışmada abdomeni açmak için kullanılan tekniklerin operasyon süresini, maternal ve neonatal sonuçları etkileyip etkilemediğini değerlendirmek için modifiye Joel-Cohen insizyonu Pfannenstiel insizyonu ile karşılaştırıldı.

Gereç ve Yöntemler: Randomize karşılaştırmalı çalışmada gestasyon yaşı >34 hafta olan ve sezaryen ameliyatı gerektiren 302 kadın periton kavitesi içine giriş için modifiye Joel-Cohen insizyon veya Pfannenstiel insizyon gruplarından birine rastgele atandı. Birincil sonuç ölçütü operasyonun yapılması için gerekli olan toplam süreydi ve ikincil sonuç ölçütleri bebek çıkım zamanı, karın duvarında kullanılan hemostatik işlemlerin sayısı, postoperatif morbidite, postoperatif hastanede kalış ve neonatal akıbet idi.

Bulgular: Ortalama toplam operasyon süresi modifiye Joel-Cohen grubunda Pfannenstiel grubuna kıyasla anlamlı şekilde daha kısaydı (32.67'ye karşılık 29.81 dk, p<0.0001, %95 GA=2.253-3.467). Ayrıca, Pfannenstiel grubuna kıyasla modifiye Joel-Cohen grubunda bebeği doğurtma süresi ve operasyon sırasında gerekli olan hemostatik işlemler anlamlı olarak daha azdı. Güçlü analjezik gereksinimi Pfannenstiel grubunda daha yüksekti (%21.85'e karşılık %53.64, p<0.0001). Postoperatif yara insidansı açısından istatistiksel olarak anlamlı farklılık yoktu ancak postoperatif hastanede kalış modifiye Joel-Cohen grubunda anlamlı şekilde daha kısaydı (p=0.002). Neonatal akibetler her iki grupta benzerdi.

Sonuç: Sezaryen ameliyatı sırasında periton kavitesi içine giriş için modifiye Joel-Cohen insizyonu ortalama toplam operasyon süresinde ve bebek çıkım süresinde azalma, daha az postoperatif ağrı ve daha kısa hastanede kalış ile ilişkili olup faydalı ve maliyet etkin bir yöntem olabilir. (J Turkish-German Gynecol Assoc 2013; 14: 28-34)

Anahtar kelimeler: Sezaryen ameliyatı, modifiye Joel-Cohen, Pfannenstiel, insizyon, operasyon süresi

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Introduction

Cesarean section (CS) is the commonest major operation in women all over the world. Approximately 18.5 million cesarean sections are performed yearly worldwide. About 40% of the countries have CS rates <10%, about 10% have CS rates between 10 and 15%, and approximately 50% have CS rates >15% (1). There have been different methods of opening the peritoneal cavity for Cesarean section and each has its own merits and demerits. There are vertical incisions like midline and paramedian. There are different transverse incisions like Pffanenstiel, Maylard, Cherney, Joel-Cohen, named according to the introducer.

Vertical midline incision was the preferred method for opening the abdomen during cesarean section. It has the advantage of rapid entry with ease. After that came the vertical paramedian incision. The paramedian incision is not used widely even in general surgery due to its limitations, and it is not an accepted method to use the paramedian incision for CS. Nowadays, a lower abdominal transverse incision is used for most cesarean sections. In the early days, transverse incision was avoided because it was time consuming. In 1900, classically the transverse incision was described by Pffanenstiel et al. (2). When exposure is limited and additional space is required, Maylard (3) and Cherney (4) procedures may be used. The Mouchel (5) transverse incision runs at the upper limit of the pubic hair. In the Pelosi (6) technique for caesarean delivery, the skin is cut in a low transverse fashion with a knife; the subcutaneous tissues and fascia are incised with electrocautery. Joel-Cohen et al. (7) described a transverse skin incision particularly for hysterectomy, which was subsequently adapted for cesarean sections. This incision is placed about 3 cm below the line joining the anterior superior iliac spines. This incision has another modification regarding opening of the peritoneum. In the classical type, the peritoneum used to be opened by finger traction laterally along with subcutaneous tissue, rectus sheath and rectus muscle. However, in the modified Joel-Cohen variety as described by Stark et al. (8), the peritoneum is not opened during separation of the structure superficial to it. Rather, it is opened in the next step by a small transverse incision in the midline which is then extended by applying finger traction both upward and downward to avoid injury to the bladder wall.

The modified Joel-Cohen incision is claimed to be associated with some immediate benefits for women undergoing cesarean delivery in comparison to the Pfannenstiel incision. Postoperative morbidity is lower following this incision as indicated by fever, postoperative pain and analgesic requirements. Although measurements are subjective, estimated intraoperative blood loss is reportedly less with the modified Joel-Cohen incision compared to Pfannenstiel and vertical incisions. The clinical significance of the reported difference (less than 100 mL) in estimated blood loss is probably less important in non-anemic women but may be of greater significance in anemic women.

It is also stated that cesarean delivery using the modified Joel-Cohen incision takes less time than cesarean delivery by the Pfannenstiel incision. The time from skin incision to delivery of the baby and the total duration of surgery are both shorter. Less time taken for surgery may be significant in situations where there is a shortage of operation theatre facilities and staff availability. Women having the modified Joel-Cohen incision have shorter periods of hospitalization compared to the Pfannenstiel incision. Nabhan et al. (9) in his study proposed that a modified cesarean delivery technique, including Joel-Cohen incision, exteriorized full thickness suturing of the uterine incision, and non-closure of the peritoneum may reduce long-term morbidities of the procedure.

This study compared the modified Joel-Cohen incision with Pffanenstiel incision for opening abdomen in Cesarean section. The aim of the study was directed to compare the modified Joel-Cohen incision with Pfannenstiel incision with the objective to evaluate whether the technique to open the abdomen might influence operative time and maternal and neonatal outcomes.

Material and Methods

This was a prospective randomized comparative trial. We conducted the study over a period of one and half years, from July, 2010 to December, 2011 in two teaching institutions of West Bengal, India viz. R.G. Kar Medical College and Hospital, Kolkata and North Bengal Medical College and Hospital, Darjeeling, simultaneously.

Three hundred and fifty pregnant women, who were carrying more than 34 weeks of gestation, requiring cesarean sections for different indications, were assessed for enrolment in the study. After undergoing through exclusion criteria a total of 302 women were ultimately included in the study. Exclusion criteria were (a) post cesarean section pregnancy; (b) history of any other previous abdominal surgery which may have produced adhesion internally; (c) very obese patient; (d) multifetal gestation and (e) patients with a history of antepartum hemorrhage. A thorough search of the medical literature did not reveal any research that has addressed repeat cesarean section in terms of previous incision type. In our clinical experience, we had observed that there was thickening and fibrosis formation in the anterior abdominal wall in a considerable number of cases of post cesarean section pregnancy, which was a hindrance to blunt dissection of tissue plane at the time of repeat cesarean section. Haacke Karl Olaf (10), in his dissertation submitted to the University of the Witwatersrand, Johannesburg (2009), had shown that severe adhesion formation in the anterior abdominal wall detected at the time of repeat cesarean section was 51% and 36% following Pfannensteil and subumbilical midline skin incisions respectively during previous CS. In our view, use of the modified Joel Cohen incision in such cases is technically not a wise choice and so we excluded the post CS pregnancy cases from our study.

Three hundred and two women with a period of gestation over 34 weeks and scheduled to have a caesarean section, were included in the study. Patients were divided into two groups (A and B) using a computer-generated randomization protocol having 151 women in each arm. We used a computer-generated randomization sequence to assign participants

into two treatment groups and the allocation was concealed in sealed, sequentially numbered, brown envelopes (opaque), which had been prepared by the statistician of each centre and handed over to the sister-in-charge of the operation theatre, department of Obstetrics and Gynecology of respective Institutions. The researchers responsible for treating the pregnant women allocated the next available number on entry into the trial in the department of Obstetrics and Gynecology and the operating surgeons collected the corresponding sealed envelope directly from operation theater sister-in-charge. Four surgeons, two in each centre, were involved for performing CS. The envelope was opened just before performing the caesarean section and the technique for entry into the peritoneal cavity was selected as per code. Because of the nature of the study, the patients were blinded but doctors responsible for performing operations were not blinded to the randomization allocation.

After allocation, relevant history and patient particulars were recorded for each patient. In group A (study group) the modified Joel-Cohen method and in group B (control group) the Pfannenstiel method were chosen for entry into the peritoneal cavity. Doctors who performed caesarean sections did not assess procedure outcomes. Assessors of the study outcomes were blinded to the techniques of caesarean sections. Before cesarean section, preoperative blood sample was taken from each patient for hemoglobin estimation.

In the Pfannenstiel group, the incision of about 15 cm length was made at the lowermost transverse crease (2 cm above symphysis pubis) with a gentle curve upwards. After the skin was entered, the subcutaneous tissue was incised sharply with a scalpel. Once the fascia was exposed the rectus sheath, separation of rectus muscles and opening of peritoneum were carried out in the traditional way. In the modified Joel-Cohen group, a straight transverse incision deep enough to cut the cuticle of about 12 cm length was made 3 cm below the arbitrary line joining two anterior superior iliac spines. The incision in the midline was deepened with the scalpel in a short transverse cut of about 2-3 cm through the fat, down to the rectus sheath. A small transverse incision was made in the midline over the rectus sheath and the incision was enlarged bilaterally about 2 cm on either side underneath the fat and subcutaneous tissue without disturbing them. The fascial borders were gently separated caudally and cranially, using the fingers to make room for the next step. That made an oval opening of about 4cm by exposing the rectus muscle underneath. Following this, the surgeon and assistant pulled the rectus muscles on their corresponding side by pushing their index and middle fingers in the midline between the rectus muscles, encircling the whole muscle bellies by smooth, balanced and increasing force. It was often necessary for both to place their other index and middle fingers over the two fingers initially placed in order to attain the force needed to make a large enough opening. The pulling force was mostly from the wrists. The parietal peritoneum was opened transversely , using the surgeon's fingers to stretch the tissues until a small hole was made. The hole was enlarged by stretching with the surgeon's two index fingers in a caudal and cranial direction simultaneously. The rest of the procedures were similar in both groups. The placenta was removed by a controlled cord traction method in both groups. The uterus was closed in two layers using No.1-0 polygygolic suture material (polygalactin 910) with atraumatic 40mm half circle round bodied needle. An abdominal retractor was used while making an incision on the lower uterine segment and also during closure of uterine incision. The peritoneum (both visceral and parietal) was not stitched. In a few cases, haemostatic sutures using chromic catgut had to be applied (in both groups) where we could detect significant oozing or bleeding from exposed peritoneal margins or separated rectus muscles. The fascial sheath was stitched using No.1-0 polygygolic suture material. the skin in both groups was sutured by interrupted stitches using synthetic non absorbable nylon suture (2-0) with half circle 50mm taper cutting needle.

The primary outcome measure was total time required for performing operation (skin to skin), and the secondary outcome measures were time taken to deliver the baby, number of haemostatic procedures used during closure of abdominal wall, requirement of postoperative analgesia, wound complication if any, postoperative stay in hospital, Apgar score at 5 minutes, birth trauma if any and appearance of scar at 12 weeks postoperative period.

From the hospital record of our institutions, we observed that 75% of women required more than 30 minutes time for completion of operation when the Pfannenstiel incision was used to enter the peritoneal cavity during cesarean section. A 25% difference in proportion of women who required more than 30 minutes time for completion of operation, between two procedures (Modified Joel-Cohen and Pfannenstiel incisions) was used to calculate the sample size having a power of 90, setting alpha error at 0.05. The minimum sample size thus calculated was 74 in each arm for the study to have a statistical significance.

All data entries were visually double checked by an independent second investigator. The data were analysed using MedCalc (Version 12.2.1.0, MedCalc Software) statistical software. Statistical analysis included Chi-square test, 'z' statistics and 't' test to compare the outcomes between the study group and the control group. A p-value less than 0.05 was considered as statistically significant.

The study was approved by "The Committee for Ethical Consideration and Approval for Human Research", R G Kar Medical College & Hospital, and "The Medical Ethical Committee for Human research", North Bengal Medical College & Hospital as required by Indian law.

Results

Initially, 350 women were assessed for eligibility criteria to be included in this study. 48 women were excluded from the study due to either not meeting the inclusion criteria (n= 28) or refusal to participate (n=20). 302 women were thus randomized into two groups (A and B) having 151 patients in each arm. Modified Joel–Cohen and Pfannensteiel incisions were used for entry into the peritoneal cavity during the caesarean section

in group A and B respectively. Subsequently, 7 women from group A and 10 from group B were lost in follow up. Hence, 144 women in group A and 141 in group B completed the study. However, 151 women in each group who received allocation intervention were analyzed as we adopted the intention to treat protocol (Figure 1).

Demographic profiles of the patients in both groups were comparable in relation to age, parity, gestational age and indication for cesarean sections (Table 1). From Table 2, it is evident that the mean time taken to complete the operation (skin to skin) was significantly lower in the group who had the modified Joel-Cohen incision as compared to the Pfannenstiel incision group (29.81 min vs 32.67 min, p<0.0001, 95% CI=2.253 to 3.467). Time taken to deliver the baby and haemostatic procedures required during operation were also significantly lower in group A as compared to group B. Requirement of strong analgesics (other than paracetamol) was higher in group B (Table 3) and statistically significant when compared to group A (53.64% vs. 21.85%, p<0.0001). Postoperative fall in hemoglobin (Hb) level and time taken for ambulation were also significantly higher in group B (p<0.0001). There was no statistically significant difference in the incidence of postoperative wound complications between the two groups (Table 4) but postoperative stay in hospital was significantly shorter in group A (p=0.002). Neonatal outcomes were similar in both groups (Table 5). There were no significant differences in appearance of scar at 12 weeks post-surgery (Table 6).

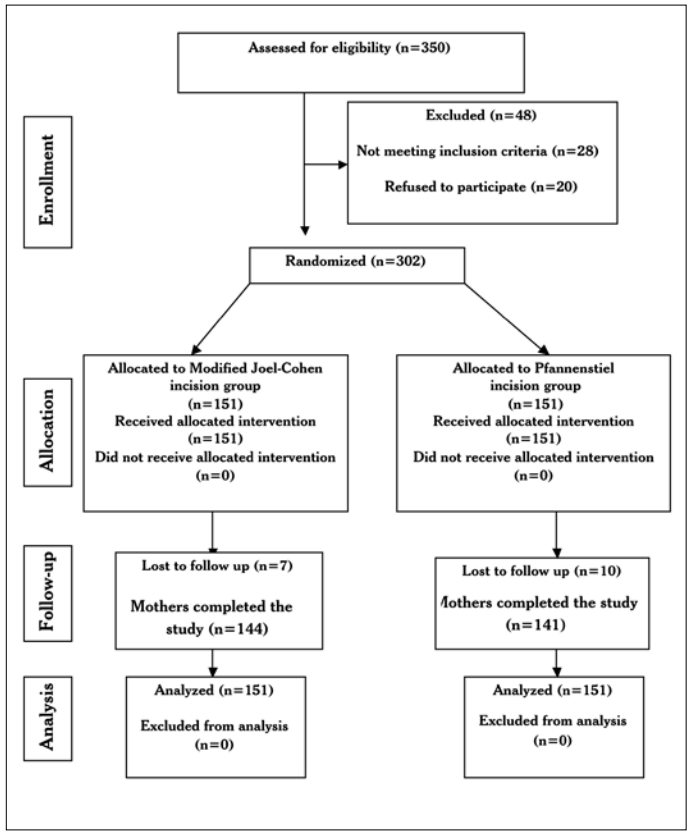

Figure 1. Patients' flow through chart.

Table 1. Demographic profile of patients

Characteristics		Study Group (Joel-Cohen) (n=151)	Control Group (Pfannenstiel) (n=151)	p value
Age in yrs (mean±SD)		23.08±3.48	23.24±4.69	0.736
Parity				
	Primi	118 (78.15%)	121 (80.13%)	0.778
	Multi	33 (21.85%)	30 (19.87%)	0.778
Gestational age in weeks (mean±SD)		38.7±1.63	38.4±1.6	0.107
Indication				
	Emergency	107 (70.86%)	112 (74.17%)	0.606
	Elective	44 (29.14%)	39 (25.83%)	0.606

Table 2. Operative findings and outcomes

Characteristics	Study Group (n=151)	Group (n=151)	95% CI of difference	p value
Abdominal fat thickness in cm (mean±SD)	2.22±0.63	2.45±0.85	-1.478 to 1.938	0.791
No. of haemostatic procedures used (mean±SD)	0.55±0.62	1.18±0.8	0.468 to 0.792	<0.0001
Time taken for operation (skin-skin) in minutes (mean±SD)	29.81±2.58	32.67±2.78	2.253 to 3.467	<0.0001
Time taken to deliver baby in seconds (mean±SD)	142.16±13.24	163.94±14.26	18.664 to 24.896	<0.0001
CI: Confidence interval				

Table 3. Postoperative outcomes

Characteristics	Study Group (n=151)	Control Group (n=151)	Odds Ratio (95% CI)	p value (95% CI of difference)
Postoperative analgesic requirement other than paracetamol	33(21.85%)	81(53.64%)	0.241 (0.146 to 0.399)	<0.0001
Postoperative fall in Hb after 48 hrs in gm/dl (mean±SD)	0.57±0.1	0.82±0.13		<0.0001 (0.224 to 0.276)
Time taken for ambulation in hrs (mean±SD)	9.6±1.64	12.13± 2.21		<0.0001 (2.089 to 2.971)
CI: Confidence interval				

Table 4. Wound complications

Characteristics (n=151)		Study Group (n=151)	Control Group (95% CI)	Odds Ratio	p value
No wound complication		146 (96.69%)	139 (92.05%)		0.133
Wound complication if any		5 (3.31%)	12 (7.95%)	0.396 (0.136 to 1.155)	0.133
	a) Serosanguinous discharge	3 (1.99%)	6 (3.97%)	0.489 (0.120 to 1.996)	0.5
	b) Purulent discharge	2 (1.32%)	2 (1.32%)	1.0 (0.139 to 7.192)	0.614
	c) Hematoma formation	0	4 (2.64%)		0.131
	d) Wound gaping	2 (1.32%)	5 (3.31%)	0.391 (0.074 to 2.052)	0.444
Postoperative stay in hospital (in days) (mean±SD)		4.36±0.78	4.7±1.1		0.002
CI: Confidence interval					

Table 5. Neonatal outcome

Characteristics	Study Group	Control Group	95% CI of difference	p value
Apgar score at 5 minutes (mean±SD)	7.77±1.38	8±1.1	0.0526 to 0.513	0.110
Birth trauma if any (mean±SD)	Nil	Nil		
CI: Confidence interval				

Table 6. Appearance of scar at 12 weeks postoperative period

Characteristics	Study Group (n=151)	Control Group (n=151)	95% CI of difference	p value
Fine	129 (85.43%)	122 (80.79%)	-4.287% to 13.525%	0.356
Broad	6 (3.97%)	10 (6.62%)	-2.969% to 8.437%	0.440
Thick	2 (1.32%)	3 (1.99%)	-3.056% to 4.558%	0.995
CI: Confidence interval				

Discussion

In this prospective, randomized study, we compared the outcomes of cesarean section carried out by the Modified Joel-Cohen incision and Pfannenstiel incision for entering the peritoneal cavity. Different studies done at different times showed that there is some advantage in making the Modified Joel-Cohen incision in respect of operative time, operative blood loss, postoperative pain and analgesic requirement, wound complication, postoperative hospital stay etc. Less time taken to complete the operation is of benefit in places where there is shortage of operation theater facilities or trained staff. Reduced operative blood loss is beneficial in women who are anemic due to poor nutrition or any other disease, particularly

in countries like India. More wound complications and subsequent longer hospital stay have a significant effect in those health institutions where there is paucity of adequate beds, in addition to financial burden.

In 1998, Franchi et al. (11) did a randomized controlled trial with the objective to compare intra and postoperative morbidity between the Joel-Cohen incision followed by nonclosure of pelvic and parietal peritoneum (n=149) as an alternative to the Pfannenstiel incision with peritonealization (n=150) at cesarean section. A shorter median opening time and a shorter median operative time (p<0.01) were observed in the former group.

In 2008 Hofmeyr et al. (12) searched the Cochrane Pregnancy and Childbirth Group's Trials Register (August 2007), the Cochrane Central Register of Controlled Trials (The Cochrane Library 2007, Issue 3) and found the Joel-Cohen incision for cesarean section compared with Pfannenstiel incision was associated with: less blood loss, (five trials, 481 women; weighted mean difference (WMD) -64.45 mL; 95% confidence interval (CI) -91.34 to -37.56 mL); shorter operating time (five trials, 581 women; WMD -18.65; 95% CI -24.84 to -12.45 minutes) and shorter time from skin incision to birth of the baby (five trials, 575 women; WMD -3.84 minutes; 95% CI -5.41 to -2.27 minutes). In our study, we found that there was significant difference in mean time taken for completion of cesarean section between the two methods, 29.81 minutes for modified Joel-Cohen incision vs 32.67 minutes for Pfannenstiel incision (p<0.0001, 95% CI=2.253 to 3.467). These findings were similar to the findings of studies by Wallin et al. (13) (1999) and Ferrari et al. (14) (2001). In 2002, Franchi et al. (15) in their study did not find any difference in total operative time between the two groups for performing cesarean section by using either the Joel-Cohen or Pfannenstiel incisions. We also observed that the mean time taken for baby extraction (from skin incision to delivery of baby) was significantly less in cases of the Modified Joel- Cohen incision group compared to Pfannenstiel incision group in our study (142.16 sec vs. 163.94 sec, p<0.0001, 95% CI=18.664 to 24.896). Franchi M et al. (15) (2002) and Zienkowicz et al. (16) (2000) had similar opinions in their studies.

The Cochrane Pregnancy and Childbirth Group's Trials Register (17), when searched by Mathai M and Hofmeyr GJ in 2007, showed reduced estimated blood loss for the Joel-Cohen incision as compared to the Pfannenstiel incision (weighted mean difference (WMD)=58.00, 95% CI = -108.51 to -7.49 mL). In our study we could not directly measure the blood loss from abdominal wall incision sites due to mixing of blood with amniotic fluid and uterine blood. However, indirect methods, like the number of hemostatic procedures used and postoperative fall in hemoglobin concentration after 48 hrs, were used to assess the blood loss. We found that there was significantly less use of hemostatic procedures in case of the Modified Joel-Cohen incision compared to Pfannenstiel incision (p<0.0001, 95% CI=0.468 to 0.792). Similarly there was a significant fall in postoperative hemoglobin level in the control group compared to the study group (p<0.0001, 95% CI=0.224 to 0.276).

Data analysis in our study showed that the Modified Joel-Cohen method needed less use of stronger analgesics in the postoperative period to relieve pain compared to the Pfannenstiel method which was statistically significant (RR=0.407, 95% CI=0.291 to 0.570, p<0.0001). Postoperative discomfort at the abdominal incision site was evidently less in the study group as seen from time taken for ambulation of patient when both groups were compared (p<0.0001). Mathai et al. (16) on searching The Cochrane Pregnancy and Childbirth Group's Trials Register in 2007, observed that Joel-Cohen incision was associated with lower total dose of analgesia in the first 24 hours (WMD=0.89, 95% CI=-1.19 to -0.59) and increased time to the first dose of analgesia (WMD=0.80, 95% CI=0.12 to 1.48) compared to the Pfannenstiel group.

Franchi et al. (11), in their study, compared intra- and postoperative morbidity between the two techniques. No difference was found in terms of intraoperative complications, proportion of patients who required transfusion, endometritis, sepsis, febrile morbidity, and urinary tract infections. A higher rate of wound infections was found in the Pfannenstiel group than that in the Joel-Cohen group (14 of 150 (9.3%) vs. 2 of 149 (1.3%), respectively, p<0.01). Mathai et al. (16) on searching Cochrane Pregnancy and Childbirth Group's Trials Register, found that there was a 65% reduction in reported postoperative morbidity (Relative Risk=0.35, 95% CI=0.14 to 0.87) and short postoperative hospital stay for the mother with the Joel-Cohen incision (WMD=1.50, 95% CI=-2.16 to -0.84). In our study, although in absolute number, wound complication was greater in cases of the Pfannenstiel incision, that was not statistically significant. However, postoperative hospital stay was significantly shorter in the modified Joel-Cohen group. Regarding appearance of scar after 12 weeks, we did not find any comparative study. In our study we found no significant difference in the nature of scar when both groups were compared.

In the study conducted by Franchi et al. (10) no difference was found in the neonatal neurodevelopmental assessment at 6 months of age in relation to the abdominal incision performed. In our study, we did not follow the neonates after their discharge from hospital, but immediate neonatal outcomes did not vary with the type of incisions.

This study could analyse a reasonably adequate sample size for comparison of feto-maternal outcomes between modified Joel-Cohen and Pfannenstiel incisions for perfoming cesarean sections. In this study, there was not a single case of discontinued intervention after randomization and only a few cases were lost during follow up in both groups (7 in group A and 10 in group B). We also adopted the intention to treat principle for analyzing results. The only weakness of this study was non measurement of actual blood loss from the abdominal incision sites.

The modified Joel-Cohen incision for entry into the peritoneal cavity during cesarean section is associated with reduced mean total operative and baby extraction times, with less postoperative pain and shorter hospital stay which may be beneficial and cost effective.

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Conflict of interest

No conflict of interest was declared by the authors.

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Medicine in stamps-Ignaz Semmelweis and Puerperal Fever

Pullardaki tıp-Ignaz Semmelweis ve Lohusalık Humması

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Abstract

Puerperal fever was common in mid-19th-century hospitals and often fatal, with mortality at 10%-35%. Ignaz Philipp Semmelweis was a Hungarian gynecologist who is known as a pioneer of antiseptic procedures. Semmelweis discovered that the incidence of puerperal fever could be drastically cut by the use of hand disinfection in obstetrical clinics. He is also described as the "savior of mothers" and "father of infection control". This paper provides an overview on the process of preventing puerperal fever and the life story of the physician behind this attempt, Ignaz Semmelweis, through philately.

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Key words: Ignaz Semmelweis, puerperal fever, infection, history, philately

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Özet

19. yüzyıl ortalarında, hastanelerde lohusalık humması oldukça sık görülen, %10-35 arasındaki ölüm oranlarıyla genellikle fatal seyreden bir hastalıktı. Ignaz Philipp Semmelweis, antiseptik uygulamaların öncüsü olarak bilinen Macar jinekologtur ve jinekoloji kliniklerinde el dezenfeksiyonunun sağlanmasıyla birlikte lohusalık humması oranlarının düşürülebileceğini keşfetmiştir. Kendisi aynı zamanda "annelerin kurtarıcısı" ve "enfeksiyon kontrolünün babası" olarak da tanınır. Bu çalışma,filateli aracılığıyla lohusalık hummasının önlenmesi sürecine ve bu sirecin arkasındaki hekim olan Ignaz Semmelweis'ın hayatına genel bir bakış sunmayı hedeflemektedir.

(J Turkish-German Gynecol Assoc 2013; 14: 35-9)

Anahtar kelimeler: Ignaz Semmelweis, lohusalık humması, enfeksiyon, tarih, filateli

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Introduction

Worldwide, sepsis is the cause of death in about 1400 people each day. Many of these people develop sepsis from infections acquired as patients while in hospital. Infections acquired in the hospital are called nosocomial infections. They are the most common complications of hospitalized patients, with 5–10% of patients in acute care hospitals acquiring at least one infection (1). Nosocomial infections occur in 2 million patients per year in the United States, causing 90.000 deaths and resulting in $4.5–5.7 billion in additional patient care costs. Infection control is essential in order to limit the spread of these diseases. Cross-infection of patients by the contaminated hands of healthcare workers is a major method of spreading infectious agents. Hand hygiene is noted to be the single most important factor for infection control. Even today, hand washing is performed only one third to one half as often as it should be (2).

Ignaz Semmelweis (Figure 1) was the first physician in medical history who demonstrated that puerperal fever (also known as "childbed fever") was contagious and that its incidence could be drastically reduced by enforcing appropriate hand washing by medical care-givers (3). Although hugely successful; Semmelweis' discovery directly confronted the beliefs of science and medicine in his time.

Early Years

Ignaz Semmelweis was born on July 1, 1818 in the Tabán, an area of Buda, part of present Budapest, Hungary (then part of the Austrian Empire). He was the fifth child of ten of the family of grocer Josef and Teresia Müller Semmelweis. Ignaz Semmelweis began studying law at the University of Vienna in the autumn of 1837, but by the following year, for reasons that are no longer known, he had changed to medicine. He was awarded his doctorate degree in medicine in 1844. After failing to obtain an appointment in a clinic for internal medicine, Semmelweis decided to specialize in obstetrics. Semmelweis was appointed assistant to Professor Johann Klein in the First Obstetrical Clinic of the Vienna General Hospital on July 1, 1846 (3) (Figure 2).

His duties were to examine patients each morning in preparation for the professor's rounds, supervise difficult deliveries, teach students of obstetrics and be 'clerk' of records. Maternity institutions were set up all over Europe to address

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problems of infanticide of illegitimate children. They were set up as *gratis* institutions and offered to care for the infants, which made them attractive to underprivileged women, including prostitutes. In return for the free services, the women would be subjects for the training of doctors and midwives (4). There were two maternity clinics at the Viennese hospital. The First Clinic had an average maternal mortality rate due to puerperal fever of about 10%. The Second Clinic rate was considerably lower, averaging less than 4%. This fact was known outside the hospital. The two clinics admitted on alternate days but women begged to be admitted to the Second Clinic, due to the bad reputation of the First Clinic. Some women even preferred to give birth in the streets, pretending to have given sudden birth, which meant they would still qualify for the child care benefits without having been admitted to the clinic. Semmelweis was puzzled that puerperal fever was rare among women giving street births. "To me, it appeared logical that patients who experienced street births would become ill at least as frequently as those who delivered in the clinic. What protected those who delivered outside the clinic from these destructive unknown endemic influences?"(5).

Figure 1. Semmelweis from the German series of welfare, which was issued in 1956

Figure 2. A stamp showing Semmelweis issued in Austria in 1965

Semmelweis was severely troubled that his First Clinic had a much higher mortality rate due to puerperal fever than the Second Clinic. It "made me so miserable that life seemed worthless". The two clinics used almost the same techniques, and Semmelweis started a meticulous process of eliminating all possible differences, including even religious practices. The only major difference was the individuals who worked there. The First Clinic was the teaching service for medical students, while the Second Clinic had been selected in 1841 for the instruction of midwives only (3) (Figure 3).

Prevention of Puerperal Fever

He excluded "overcrowding" as a cause, since the Second Clinic was always more crowded and yet the mortality was lower. He eliminated climate as a cause because the climate was the same. The breakthrough occurred in 1847, following the death of his good friend Jakob Kolletschka, who had been accidentally poked with a student's scalpel while performing a postmortem examination. Kolletschka's own autopsy showed a pathology similar to that of the women who were dying from

Figure 3. A stamp showing Semmelweis issued in East Germany in 1965

puerperal fever. Semmelweis immediately proposed a connection between cadaveric contamination and puerperal fever (6). He concluded that he and the medical students carried "cadaverous particles" on their hands from the autopsy room to the patients they examined in the First Obstetrical Clinic. This explained why the student midwives in the Second Clinic, who were not engaged in autopsies and had no contact with cadavers, saw a much lower mortality rate (7).

Thus, Semmelweis concluded some unknown "cadaverous material" caused puerperal fever known as childbed fever. He instituted a policy of using a solution of chlorinated lime (modern calcium hypochlorite, the compound used in today's common household chlorine bleach solution) for washing hands between autopsy work and the examination of patients. He did this because he found that this chlorinated solution worked best to remove the putrid smell of infected autopsy tissue, and thus perhaps destroying the causal "poisonous" or contaminating "cadaveric" agent which were hypothetically being transmitted by this material (6).

The result was that the mortality rate in the First Clinic dropped 90%, and was then comparable to that in the Second Clinic. The mortality rate in April 1847 was 18.3%. After hand washing was instituted in mid-May, the rates in June were 2.2%, July 1.2%, August 1.9% and, for the first time since the introduction of anatomical orientation, the death rate was zero in two months of the year following this discovery (5) (Figure 4).

Semmelweis discovered that cases of puerperal fever, a form of septicemia, could be cut drastically if doctors washed their hands in a chlorine solution before gynaecological examinations. Semmelweis's observations conflicted with the established scientific and medical opinions of the time. The theory of diseases was highly influenced by ideas of an imbalance of the basic "four humours" in the body, a theory known as dyscrasia, for which the main treatment was bloodletting. His findings also ran against the conventional wisdom that diseases spread in the form of "bad air", also known as miasmas or vaguely as "unfavourable atmospheric-cosmic-terrestrial influences". Semmelweis's groundbreaking idea was contrary to all established medical understanding (4).

As a result, his ideas were rejected by the medical community. Other more subtle factors may also have played a role. Some doctors, for instance, were offended at the suggestion that they should wash their hands, feeling that their social status as gentlemen was inconsistent with the idea that their hands could be unclean (4).

In 1848, despite all these rejections, Semmelweis widened the scope of his washing protocol to include all instruments coming in contact with patients in labour, and used mortality rates time series to document his success in virtually eliminating puerperal fever from the hospital ward (5) (Figure 5).

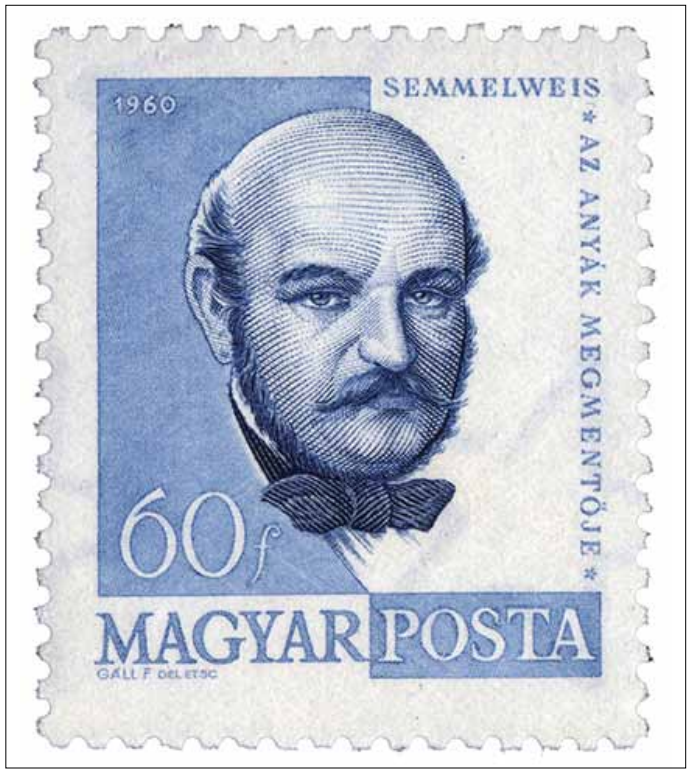

Figure 4. A stamp showing Semmelweis issued in Hungary in 1960

Personal Life

Semmelweis had very difficult times especially after announcing his hand washing protocol and emphasising the importance of cleanliness. His claims were thought to lack scientific basis, since he could offer no acceptable explanation for his findings. Such a scientific explanation was made possible only some decades later, when the germ theory of disease was developed by Louis Pasteur, Joseph Lister, and others. In 1848 a series of tumultuous revolutions swept across Europe. The resulting political turmoil would affect Semmelweis's career. In Vienna on March 13, 1848, students demonstrated in favor of increased civil rights, including trial by jury and freedom of expression. The demonstration was led by medical students and young faculty members and were joined by workers from the suburbs. Two days later in Hungary, demonstrations and uprisings led to the Hungarian Revolution of 1848 and a full-scale war against the ruling Hapsburgs of the Austrian Empire. In Vienna,

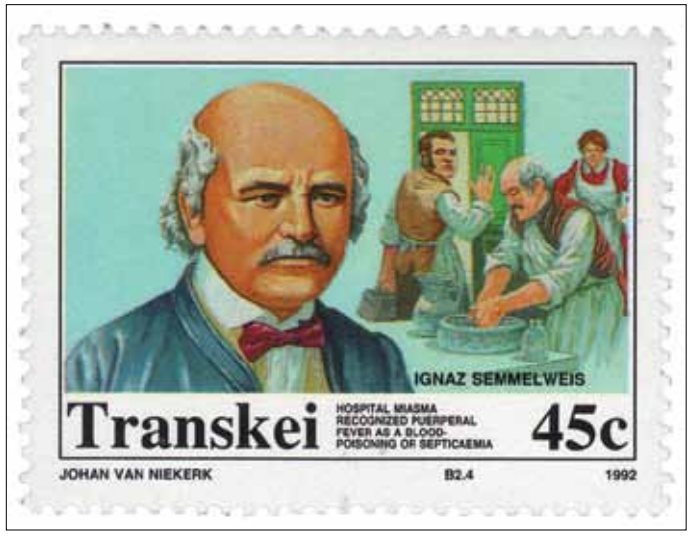

Figure 5. A stamp showing Semmelweis issued in Transkei in 1992

the March demonstration was followed by months of general unrest (8) (Figure 6).

There is no evidence that Semmelweis was personally involved in the events of 1848. It is known that some of his brothers were punished for active participation in the Hungarian independence movement, and it seems likely that the Hungarian-born Semmelweis was sympathetic to the cause. Semmelweis's superior, Professor Johann Klein, was a conservative Austrian, probably uneasy with the independence movements and alarmed with the other revolutions of 1848 in the Hapsburg areas. It is known that Klein mistrusted Semmelweis. After having some serious personal conflicts with Klein, Semmelweis left Vienna abruptly and returned to Pest. In 1851, Semmelweis took the relatively insignificant, unpaid, honorary head-physician position of the obstetric ward of Pest's small St. Rochus Hospital. He held that position for six years, until June 1857. Childbed fever was rampant at the clinic and on a visit in 1850, just after returning to Pest, Semmelweis found one fresh corpse, another patient in severe agony, and four others seriously ill with the disease. After taking over in 1851, Semmelweis virtually eliminated the disease. During 1851-1855 only 8 patients died from childbed fever out of 933 births (0.85%) (5).

Despite the impressive results, Semmelweis's ideas were not accepted by the other obstetricians in Budapest. The professor of obstetrics at the University of Pest, Ede Flórián Birly, never adopted Semmelweis's methods. He continued to believe that puerperal fever was due to uncleanliness of the bowel. Therefore, extensive purging was the preferred treatment (6).

In 1857, Semmelweis married Maria Weidenhoffer (1837-1910) and they had five children (3).

In 1858, Semmelweis finally published his own account of his work in an essay entitled, "The Etiology of Childbed Fever". Two years later he published a second essay, "The Difference in Opinion between Myself and the English Physicians regarding Childbed Fever". In 1861, Semmelweis finally published his main work *Die Ätiologie, der Begriff und die Prophylaxis des Kindbettfiebers* (German for *The Etiology, Concept and Prophylaxis of Childbed Fever*) (7).

In his 1861 book, Semmelweis lamented the slow adoption of his ideas: "Most medical lecture halls continue to resound with lectures on epidemic childbed fever and with discourses against my theories. The medical literature for the last twelve years continues to swell with reports of puerperal epidemics, and in 1854 in Vienna, the birthplace of my theory, 400 maternity patients died from childbed fever. In published medical works, my teachings are either ignored or attacked. The medical faculty at Würzburg awarded a prize to a monograph written in 1859 in which my teachings were rejected (7) (Figure 7).

Death

In 1861, Semmelweis started to suffer from various nervous complaints. He suffered from severe depression and became excessively absentminded. He turned every conversation to the topic of childbed fever. It was impossible to appraise the nature of Semmelweis's disorder. It might have been Alzheimer's disease, a type of dementia, which is associated with rapid cognitive decline and mood changes. It might have been third stage syphilis, a then-common disease of obstetricians who

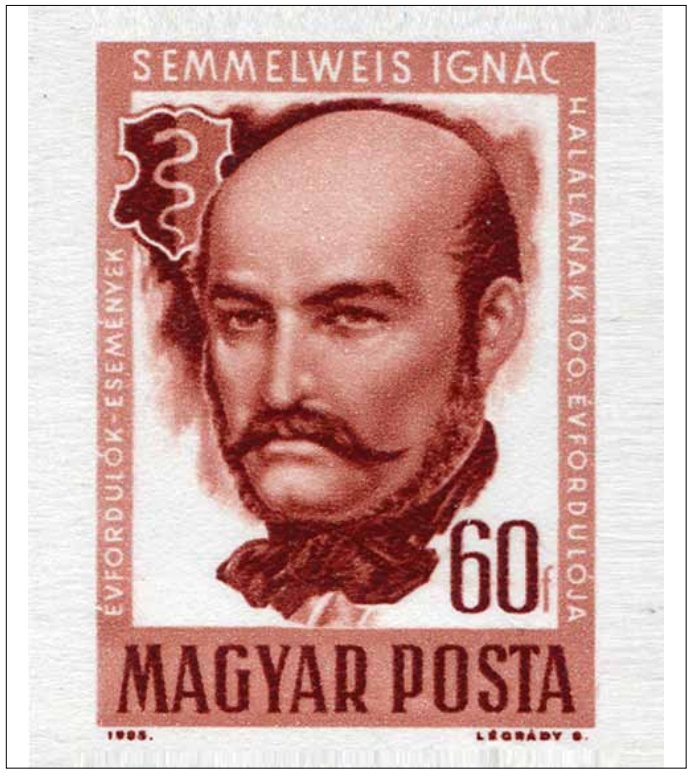

Figure 6. A stamp showing Semmelweis issued in Hungary in 1965

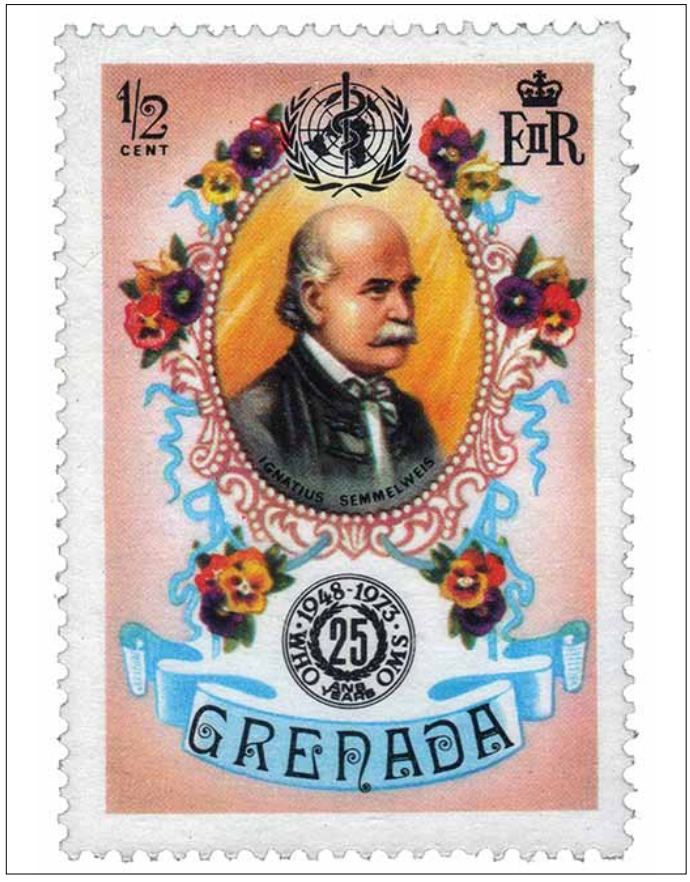

Figure 7. A stamp showing Semmelweis issued in Grenada in 1973

examined thousands of women at gratis institutions. Or it might have been emotional exhaustion from overwork and stress. In 1865, Semmelweis was referred to a mental institution (4). He died after two weeks in that clinic, on August 13, 1865, aged 47. Years after his death, especially with the discovery of germ theory and the nature of infectious agrnts, his great contribution to medicine was understood (5). Now, there is a university for medicine and health-related disciplines (located in Budapest, Hungary), called Semmelweis University and many other honorary establishments were organised after his name, like The Semmelweis Klinik, a hospital for women located in Vienna, Austria and The Semmelweis Hospital in Miskolc, Hungary. His house in Budapest is now a historical museum and a library called the Semmelweis Medical History Museum.

Conflict of interest

No conflict of interest was declared by the authors.

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Uterine fibroids and current clinical challenges

Uterin fibroidler ve güncel klinik tartışmalar

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Abstract

Uterine fibroids (UF) are the most common gynecological tumors in premenopausal women. Hysterectomy remains the major and definitive therapeutic option. Minimally invasive surgical techniques for performing hysterectomy have many advantages over laparotomy. Current drug therapies for UF remain unsatisfactory. Unquestionably, continued investigation of novel agents is necessary. The currently used drugs for UF treatment which exclusively modulate a single target, typically either the estrogen or progesterone signaling pathways, are limited in their therapeutic effects. By contrast, multi-target drugs which simultaneously modulate multiple critical hubs in the network of the signaling pathways underlying UF pathogenesis should achieve robust and durable therapeutic effects.

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Key words: Uterine fibroids, hysterectomy, pathogenesis, drug therapy, multi-target drugs

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Özet

Uterin fibroidler (UF) premenopozal kadınlarda en yaygın görülen jinekolojik tümörlerdir. Histerektomi başlıca tedavi seçeneğidir. Histerektomi uygulamasında minimal cerrahi yaklaşımların laparotomiye göre avantajları mevcuttur. UF tedavisinde kullanılan güncel ilaç tedavileri ise tatmin edici olmaktan uzaktır. Şüphesiz, yeni ajanlar için çalışmalar devam etmelidir. UF tedavisinde kullanılan, ya östrojen ya da progesteron yolakları gibi tek bir hedef üzerinden etki eden güncel tedaviler terapötik etkinlik konusunda yetersiz kalmaktadır. Bunların yanında, UF patogenezinde rol alan yolaklardaki birden çok kritik noktayı değiştiren çok hedefli ajanlar etkin ve uzun süreli terapötik etki sağlayacaktır.

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Anahtar kelimeler: Uterin fibroid, histerektomi, patogenez, ilaç tedavisi, çok hedefli ilaçlar.

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Introduction

Uterine fibroids (UF) are the most common gynecological tumors in premenopausal women (1, 2). The direct healthcare costs for UF management are estimated to be over $2 billion annually in the United States. Hysterectomy remains the major and definitive therapeutic option, performed in more than 200,000 cases per year in the United States alone (3, 4). Unfortunately, hysterectomy results in permanent infertility of reproductive-age women. Surgical removal of fibroids alone, myomectomy, is associated with significant risks, such as massive intra-operative hemorrhage and distortion of the uterine cavity. In addition, the scar left on the uterus after myomectomy increases the chance of uterine rupture in future pregnancies. Even with myomectomy, UF have up to a 50% recurrence rate (5). Two relatively new modalities have been utilized for treatment of UF: myolysis and uterine artery embolization. Myolysis disrupts or abolishes the blood supply to the fibroid using bipolar or monopolar electrosurgery (6). The procedure is rarely performed and is not recommended for women who wish to become pregnant (7). Uterine artery embolization (UAE) is a procedure that uses radiologically directed injection of microspheres to block the blood supply to specific fibroids (8). At this point this method is also not recommended for women seeking future fertility. In addition, not all fibroids respond to UAE and it does not prevent recurrence of UF (9, 10).

Current medical therapies

The current therapeutic approaches for UF treatment include gonadotropin-releasing hormone (GnRH) agonists which may reduce tumor volume by up to 40% in 3 months, with significant improvement in clinical symptoms (11, 12). However, GnRH agonists also cause a hypoestrogenic environment, which leads to serious side effects. Therefore, the use of GnRH agonists is limited to preoperative treatment of UF, both for myomectomy and hysterectomy in selected cases (13-16) Regrettably, the effects of GnRH agonists are short-lived and UF tend to rapidly re-grow, with recurrence of clinical symptoms after cessation of treatment (17). Another therapeutic strategy for UF treatment is inhibition/modulation of progesterone receptor (PR) transcriptional activity. This approach has been validated in preclinical and clinical studies and both antiprogestins and selective progesterone recep-

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tor modulators (SPRMs) have been shown to reduce tumor volume, control bleeding, and reduce pelvic pressure (18, 19). Unfortunately, there are adverse effects of long-term use of SPRMs, even at low doses, which include abnormal endometrial morphology, endometrial hyperplasia, and liver damage (20-22). These side effects have emerged as an impediment to the use of antiprogestins and SPRMs for all but short-term use as UF treatments. Recently, aromatase inhibitors (AIs) have been introduced as potential treatments; two case series have documented improved symptoms and reductions in the size of the tumors with the use of AIs (23, 24). In premenopausal women, AIs can be used for a short time before myomectomy or hysterectomy (25). Combined oral contraceptives, steroid-delivering vaginal rings, skin patches, Levonorgestrel-releasing intrauterine devices, progestin implants/injections, and progestin-only pills are currently used for improving symptoms in clinical settings. All of the current options have their limitations and contraindications for patient selection and efficacy (26, 27). Thus, current drug therapies for UF remain unsatisfactory. Unquestionably, continued investigation of novel agents is necessary.

Current surgical therapies

The first successful selected hysterectomy operation was performed in 1813 by Conrad Langenbeck via the vaginal approach, and today, after nearly two centuries, hysterectomy is the second most frequent surgery in women of reproductive age, with the first being cesarean section (28). Approximately 80000 hysterectomies are performed each year in the United Kingdom (UK), and over 600.000 in the United States (USA) (29, 30). Vast majority of these numbers (more than 70%) are for benign indications such as menorrhagia (%21), fibroids (33%), pelvic pain (3%) and uterine prolapse (28%) (30).

The traditional surgical approach to hysterectomy involves a large abdominal incision, two to four day hospital stay and significant requirements for postoperative analgesia. Minimally invasive surgical (MIS) techniques for performing hysterectomy have many advantages over laparotomy, including reduced postoperative pain, shorter length of hospital stay, better cosmesis and quicker resumption of regular activity (31-38). The Nationwide Inpatient Sample of the Healthcare Cost and Utilization Project recently reported that abdominal hysterectomy was performed in 64% of cases, followed by the vaginal route in 22% of cases and the laparoscopic route in 14% (34).

Improvements in minimally invasive techniques were introduced with 2005 Federal Drug Administration (FDA) approval of the da Vinci® Surgical System (Intuitive Surgical, Inc., Sunnyvale, CA) for use in gynecologic procedures. The da Vinci® Surgical System has some advantages compared to conventional laparoscopic surgery, such as three-dimensional (3D) vision, wristed instrumentation, improved dexterity, ergonomic positioning allows surgeon comfort with less hand fatigue and frustration, and eliminates the hand tremors (35-38). Currently, robotic-assisted hysterectomy is emerging as a new technique for hysterectomy and many of the general gynecologists have become to prefer robotic surgery for hysterectomy. For both general gynecologist and subspecialist including gynecologic oncologists and urogynecologists introduce to the robotic surgery usually through simple hysterectomies. In this chapter we aimed to describe the step by step approach to the simple hysterectomy performed with the da Vinci® Surgical System.

The AAGL Advancing Minimally Invasive Gynecology Worldwide (formerly known as the American Association of Gynecologic Laparoscopists) released a statement in 2010 advising that ''most hysterectomies for benign disease should be performed either vaginally or laparoscopically and that continued efforts should be taken to facilitate these approaches. Surgeons without the requisite training and skills required for the safe performance of vaginal hysterectomy (VH) or laparoscopic hysterectomy (LH) should enlist the aid of colleagues who do or should refer patients requiring hysterectomy to such individuals for their surgical care'' (39). In calling for a dramatic reduction in the number of abdominal hysterectomies, the AAGL position is in line with that of the American College of Obstetricians and Gynecologists (ACOG), issued in a committee opinion paper "Choosing the Route of Hysterectomy for Benign Disease" in November 2009 (39). ACOG supports the notion that LH and VH offer substantial advantages over abdominal hysterectomy (AH) (40). Taking these points into account, vaginal hysterectomies should be preferred for simple hysterectomies. In case vaginal hysterectomy is not feasible minimally invasive approach should be preferred. Gynecologist who cannot offer vaginal or MIS should consider referring the patients to surgeon who can perform these before offering open AH.

After introducing robotic technology, hysterectomies performed utilizing MIS increased significantly in the last 5 years (41, 42). In our experience after introducing robotic program it takes one year to see switching number of cases from open to MIS hysterectomies which seems to be common trend nationwide (43). Currently there is a great deal of overlap in the indications of hysterectomies between laparoscopy and robotic surgery. However robotic surgery seems to have certain advantage over laparoscopy in obese patients and surgeries requires more dissection (endometriosis, pelvic-abdominal severe adhesions) (44, 45). Our prospective comparative study focused on the intra- and perioperative outcomes of 208 obese [Body mass index (BMI) $> 30 kg/m^2$) patients who underwent robotic-assisted hysterectomy (n: 51), laparoscopic hysterectomy (n: 24), and abdominal hysterectomy (n: 133) for benign indications at our institution (Unpublished data). We found that robot-assisted hysterectomy was associated with fewer intraoperative complications and estimated blood loss (EBL) and shorter length of hospital stay; there were no differences in postoperative complications, conversions to laparotomy. In our conclusion, we mentioned that robotic-assisted hysterectomy is safely and feasible procedure for obese patients with low morbidity, a shorter hospital stay, and comparable blood loss. Robotic surgery provides shorter learning curve commonly accepted opinion is approximately 20 cases required to reach to the steady state (46, 47). Compare to this steep learning curve in robotic surgery laparoscopy demands to higher number of cases to reach to the same level (48, 49). Conversely, the main disadvantages of the robotic surgery across applications are the cost, the large size of the robot and console and lack of tactile feedback or habits (50).

A Cochrane review for surgical approaches to hysterectomy for benign gynecological disease found no definite evidence for favoring technique and stated that the surgical approach should be decided by the woman in discussion with her surgeon in light of the relative benefits and hazards (51). Recently, a new review was published by Cochrane about robotic surgery for benign gynecological disease and indicated that robotic surgery did not benefit women in effectiveness or in safety. However, this statement was limited by the small sample size (52). In literature, some authors have suggested vaginal approach primarily for hysterectomy (11, 12), some studies have showed the superiority of the MIS (53) and some have focused on robotic-assisted hysterectomy and advised this approach for special individual cases (17, 54). There are only few comparative studies about robotic-assisted hysterectomy for benign indications and most of them are retrospective. Only three prospective comparative studies were published in the literature. The first one by Sarlos et al., second by Geppert et al., and last one was published by our group. The safety and feasibility of the robotic approach were reported in all three studies (55-58). The sample sizes were low in most series except for the study by Pasic et al. (42). They analyzed data from the Premier hospital database of 358 hospitals in USA and found the use of robotic assistance was consistently associated with higher per-patient average hospital costs (14). Recently, Landeen et al. (59) analyzed the clinical and cost comparisons for hysterectomy via abdominal, standard laparoscopic, vaginal and robot-assisted approaches and demonstrated the highest complication rates for abdominal procedure and significantly greater blood loss and longer hospital stay with standard laparoscopic hysterectomy compared to robotic-assisted. Scandola et al. (60) in 2011 also reported a metaanalyses about robotic-assisted hysterectomy versus traditional laparoscopic hysterectomy and concluded that robotic-assisted hysterectomy has less deleterious effect on hospital, society, and patient stress and leads to better intervention quality. No randomized controlled trial has been published to date and current medical data is immature to draw concrete conclusion for robotic-assisted hysterectomy. The need for randomized controlled trials to compare outcomes of robotic technology to other forms of MIS is a topic of debate.

The complex and multifactorial nature of UF

Clinical and molecular studies have demonstrated that UF are not a single entity but a clinically and genetically heterogeneous disease (56-59). Although earlier studies have traditionally focused on estrogen and progesterone as major risk factors, compelling evidence indicates that multiple etiological factors such as growth factors, profibrotic cytokines, and proinflammatory mediators also contribute to UF pathogenesis (45, 60-67). In addition, complex interlocking networks of signaling pathways that regulate cell proliferation and differentiation, apoptosis, angiogenesis, and ECM synthesis and remodeling are aberrantly regulated in UF and are characterized by built-in redundancy and biological buffering capacity. For instance, it has been reported that progesterone can function through activating the PI3K/Akt pathway independent of the classical PR pathway (68). Similarly, activation of the PI3K/Akt pathway leads to estrogen-independent activation of ER-α, with phosphorylation of ER and subsequent upregulation of estrogen-regulated genes and resistance to aromatase inhibitors (69).

Successful treatment of a complex disease such as UF requires effective means to control the full biological network underlying the disease. However, these networks are typically robust to external perturbations, making it difficult to beneficially alter the dynamics by controlling a single target. In fact, multi-target therapeutics are often more effective compared to monotherapies, and combination drugs are commonly used for treating various complex diseases (70). Consequently, the currently used drugs for UF treatment which exclusively modulate a single target, typically either the estrogen or progesterone signaling pathways, are limited in their therapeutic effects. By contrast, multi-target drugs which simultaneously modulate multiple critical hubs in the network of the signaling pathways underlying UF pathogenesis should achieve robust and durable therapeutic effects. Thus, it is logical to rethink the current treatment paradigm for UF in the context of multi-target drugs. These agents would have improved therapeutic efficacy by their collective effects on multiple primary and compensatory or alternative pathways. In addition, these multi-target drugs will affect not only the fibroid cells, but also the tumor microenvironment which is a crucial regulator of tumor growth.

Microtubules: master regulators for multiple signaling pathways in UF

Identification of a “druggable target” that regulates multiple biological processes and signaling pathways involved in UF pathogenesis is the gateway for developing a multi-target polypharmacological drug for UF treatment. Compelling evidence indicates that almost every pathway critically involved in UF development and progression is functionally regulated by microtubule (MT) dynamics. MT serve as master scaffolds for a variety of active molecules and transcription factors involved in cell proliferation, differentiation, apoptosis, angiogenesis, and ECM synthesis and remodeling. In addition, MT function as molecular “rails” which regulate the intracellular localization and the activities of many transcription factors, including ERα, PR, TGF-β, growth factors, and profibrotic cytokines (71-78). Studies from my laboratory and others have demonstrated that drugs which target MT dynamics dampen the signaling pathways of ERα (74, 75), PR (75), TGF-β (79,80), connective tissue growth factor (CTGF) (81-84), proangiogenic factors, (85) and anti-apoptotic factors (86) by sequestering these transcription factors or their downstream effectors in a ‘‘repressive state” in the cytoplasmic compartment of the cells. Thus, owing to their crucial role in orchestrating many biological processes and signaling pathways relevant to UF development and growth, MT represent appealing targets for innovative development of anti-UF drugs. Without a doubt, MT-targeting drugs have met with excellent clinical success in the treatment of many fibrotic diseases (72, 79).

Conclusion

This review article addresses an important risk to women’s health, as UF occur in 70-80% of women. UF are also a major

health disparity issue, occurring 3-4 times more frequently in African Americans as compared to white women. UF substantially increase the risk of a number of significant health outcomes, such as pain, preterm labor, placental abruption, postpartum hemorrhage, and cesarean section (87). Despite the magnitude of the problem, there are currently no effective therapies for UF and hysterectomy remains the major and definitive treatment option, resulting in direct healthcare costs of over $2 billion annually (3, 4) In addition, for women who desire to preserve their fertility, hysterectomy is not a viable option.

Conflict of interest

No conflict of interest was declared by the authors.

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Vaginal foreign body: Successful management with vaginoscopy

Vajende yabancı cisim: Vajinoskopi ile başarıyla yönetimi

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Abstract

The etiology of chronic vaginal discharge in children varies and can be seen as infection, sexual abuse, congenital malformations, vulvar skin disease, vaginal neoplasms and a foreign body. A vaginal foreign body is not a common problem in childhood but it should always be considered when a little girl consults a physician with a chronic vaginal discharge problem. We present the diagnosis and treatment management via vaginoscopy applied to a 6 year old girl who complained of a foul smelling vaginal discharge that had been resistant to medical treatment for the last two years. (J Turkish-German Gynecol Assoc 2013; 14: 46-7)

Key words: Chronic vaginal discharge, foreign bodies, vaginoscopy, diagnosis, treatment

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Özet

Çocuklarda kronik vajinal akıntı nedenleri arasında enfeksiyon, cinsel istismar, konjenital malformasyonlar, vulvar deri hastalıkları, vajinal neoplazmlar ve yabancı cisim yer alır. Vajinal yabancı cisim çocukluk çağında yaygın bir neden değildir ancak kronik vajinal akıntı ile başvuran bir kız çocuğunda her zaman akılda tutulmalıdır. Bu yazıda, son 2 yıldır medikal tedaviye dirençli kötü kokulu vajinal akıntısı olan 6 yaşındaki bir kız çocuğunun vajinoskopi ile tanı ve tedavi yönetimini sunduk. (J Turkish-German Gynecol Assoc 2013; 14: 46-7)

Anahtar kelimeler: Kronik vajinal akıntı, yabancı cisim, vajinoskopi, tanı, tedavi

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Introduction

The etiologies of chronic vaginal discharge in children are various such as infection, sexual abuse, congenital malformations, vulvar skin disease, vaginal neoplasms and a foreign body (1). A vaginal foreign body is not a common problem in childhood, but it should always be considered when a little girl consults a physician with the chronic vaginal discharge problem. We present the diagnosis and treatment management via vaginoscopy applied in a 6 year old girl who complained of a foul smelling vaginal discharge that had been resistant to medical treatment for the last two years.

Case Report

A 6 year old girl was referred to our clinic with persistant vaginal discharge. She had been treated several times with antibiotics by gynecologists. The girl and her mother denied foreign body insertion or sexual abuse. The discharge was intermittently purulent and smelly. Physical examination revealed normal external genitalia. A mild amount of discharge and erythema of vulva was seen (Figure 1). Without any scars or rupture, the hymen was not disturbed. A vaginal swab was sent for microbial culture, which revealed Escherichia coli. Urine analysis revealed leukocyturia. Pelvic ultrasound showed normal findings. In addition, the urine culture result was not significant. It was decided that the patient should be admitted to the gynecological department for examination under general anesthesia. A hysteroscope was inserted into the vagina without disrupting the hymen. Vaginoscopy with 'no-touch technique' was performed with a 5 mm operative office hysteroscope (Karl-Storz, Tutlingen, Germany) and the foreign bodies were revealed. The foreign bodies were removed by forceps with gentle traction. There were two parts of a pencil and a hairgrip (Figure 2). She was discharged on the first postoperative day. In subsequent visits, the girl and her mother reported the cessation of discharge and physical examinations revealed normal findings.

Discussion

The prevalence of vaginal foreign bodies in girls under 13 years of age with gynecological disorders was found to be 4.0% (2). Foreign body insertion into the vagina in childhood is uncommon but it is very interesting. Such foreign bodies are introduced into the vagina either due to the curiosity of the child or for sexual satisfaction. Small pieces of toilet paper that are found in the vagina are the most common (3). An interesting variety of foreign bodies, such as safety pins, pencils, toys, sweets, seeds, fruits were found in the vagina.

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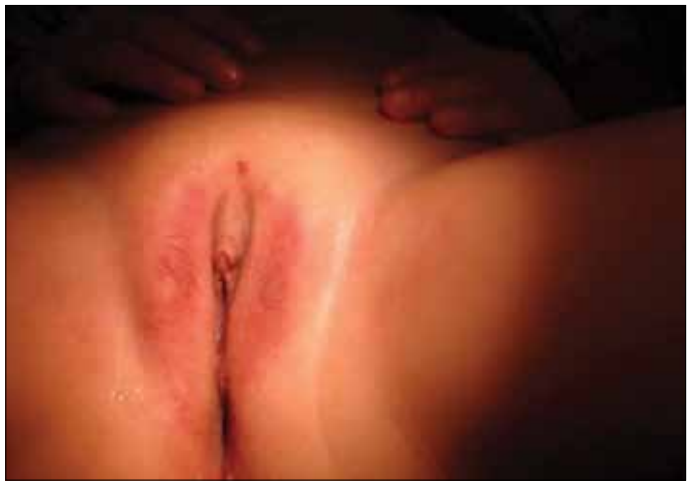

Figure 1. Erythema of vulva
Written informed consent was obtained from the parent of the patient for publication of this case report and any accompanying images

Figure 2. Vaginal foreign bodies

When a child presents with persistent or relapsing foul smelling vaginal discharge, one should always look for a foreign body in the vagina (4). Stricker et al. (5) reported that 49% of girls with a vaginal foreign body had presented with vaginal discharge. Also, a study review performed by Striegel et al. (6) reported that the etiology of vaginal discharge in girls younger than 6 years who underwent examination under general anesthesia in 45% of the cases was foreign bodies in the vagina.

Diagnosis of foreign bodies in the vagina includes careful history taking, genital examination, pelvic ultrasound, pelvic radiography and Magnetic Resonance Imaging (MRI). MRI is regarded as the best technique for evaluating vaginal foreign bodies in young children (7). However, it is not always available or necessarily conclusive. Vaginoscopy with 4 mm hysteroscope under general anesthesia is very useful for detection and treatment of vaginal foreign bodies (8).

In our case, we managed the patient with vaginoscopy without disrupting the hymen. We believe that examination under anesthesia should be the first line of investigation in cases of resistant chronic vaginal discharge because pelvic ultrasound, plain radiography and MRI are not always helpful in detecting foreign bodies in the vagina.

In conlusion, if a child presents with chronic vaginal discharge, the possibility of a vaginal foreign body should be considered. Diagnostic procedures may be more available and helpful, but vaginoscopy is a very important means of diagnosis and treatment of vaginal foreign bodies in childhood.

Conflict of interest

No conflict of interest was declared by the authors.

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Case report: Methotrexate-induced pericardial effusion

Olgu sunumu: Metotreksata bağlı perikardiyal efüzyon

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Abstract

We report a case of pericardial effusion induced by methotrexate in a patient with low risk gestational trophoblastic neoplasia, who had been taking the first course of sequential methotrexate-folinic acid treatment. After aspiration of pericardial effusion another methotrexate-folinic acid course was given and the pericardial effusion did not relapse. (J Turkish-German Gynecol Assoc 2013; 14: 48-9)

Key words: Methotrexate, toxicity, pericardial effusion, gestational trophoblastic neoplasia, treatment

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Özet

Ardışık metotreksat-folinik asit tedavisi verilen düşük riskli gestasyonel trofoblastik neoplazi olgusunda ilk kemoterapi kürü sonrasında perikardiyal efüzyon gelişti. Perikardiyal efüzyon aspire edildikten sonra ikinci kür kemoterapi verildi ve olgumuzda perikardiyal efüzyonun tekrar etmediği gözlendi.

(J Turkish-German Gynecol Assoc 2013; 14: 48-9)

Anahtar kelimeler: Metotreksat, toksisite, perikardiyal efüzyon, gestasyonel trofoblastik neoplazi, tedavi

Geliş Tarihi: 07 Ağustos 2012 **Kabul Tarihi:** 18 Eylül 2012

Introduction

In gynecologic oncology methotrexate is an important agent for treatment of gestational trophoblastic neoplasia (GTN). It is used as a single agent in the treatment of low risk GTN and also in high risk GTN as a component of multi-agent chemotherapy. It is possible to provide nearly 100% survival rates in the case of non-metastatic GTN and in low risk metastatic GTN with single agent methotrexate chemotherapy (1). During methotrexate chemotherapy mucositis and hematological adverse effects are common (2). Also serositis is an important component of methotrexate induced toxicity profile. Serositis usually presents itself as pneumonia and pleural effusion. Pericarditis and pericardial effusion which are also serositis complications are quite uncommon ones.

We report a case of pericardial effusion induced by methotrexate treatment in a patient with low risk GTN.

Case Report

A 33 year old woman was diagnosed histopathologically as partial hydatidiform mole after evacuation. During the follow up period careful monitoring of the patient revealed levelling of β-hCG levels, which means gestational trophoblastic neoplasia and the appropriate treatment is planned for the patient.

The β-hCG level before the treatment was 75 mIU/mL and there was no tumoral mass revealed by the imaging methods except in the uterus. The tumoral mass in the uterus was 3cm in diameter and there were no metastases in the upper abdomen, lungs and brain. According to the modified World Health Organization (WHO) prognostic scoring criteria, the case was a low risk GTN and the treatment plan was sequential methotrexate-folinic acid chemotherapy. On the 1st, 3th, 5th and 7th days of chemotherapy 1mg/kg methotrexate was given by intramuscular injection, on the 2nd, 4th, 6th and 8th days 0.1mg/kg folinic acid was given by intramuscular injection also. After the β-hCG levels returned to normal ranges, a second cure of methotrexate-folinic acid chemotherapy was planned. Following the first course of methotrexate-folinic acid chemotherapy according to WHO toxicity criteria, grade 2 hepatotoxicity had developed. Before the 2nd cure, because of sinusitis, the patient was given antibiotherapy. In the following time period chest pain and shortness of breath developed and therefore electrocardiography, chest X-ray, thoracic computerized tomography and echocardiography were performed. The echocardiography revealed massive pericardial effusion of 2.8 cm depth posteriorly and 0.8cm depth anteriorly. Meanwhile, the β-hCG was 4.55 mIU/mL, aspartate aminotransferase (AST) was 52U/L (normal 5-40), alanine aminotransferase (ALT) 88U/l (normal 5-40) and CA 125 was 99.5 IU/L, complete blood count and other biochemical tests were normal. The patient was hospitalized and the pericardial effusion was aspirated. Pericardial fluid was examined microbiologically, cytologically and biochemically,

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which did not reveal any abnormalities explaining pericardial effusion. The second course of methotrexate chemotherapy was given 14 days later than the planned date. Methotrexate induced pericardial effusion did not relapse after the second course of chemotherapy. Three months after the diagnosis of pericardial effusion CA 125 levels returned to normal ranges. In the following twelve months cardiological or oncological problems did not develop.

Discussion

It is known that serositis is a component of the methotrexate induced toxicity profile. The etiology and pathophysiology is unknown. However it is thought that this process is due to a specific cellular immune response developing against the drug (3, 4). Therefore, serositis is not a direct toxic effect of the drug. The serositis commonly presents itself in the form of pneumonitis and pleural effusion. The frequency of methotrexate induced serosal symptoms is 5-12% with doses used in oncology clinics (5, 6). However, in persistent cases where repetitive doses are used, the serosal symptoms reach 20-25% (7, 8). Sharma et al. (8) reported the rate of serosal symptoms as 25% in 168 patients who received low dose sequential methotrexate-folinic acid treatment. It is thought that the risk of developing serositis increases as the frequency of doses applied increases (9).

Since serositis commonly presents itself in the form of pleurisy in these patients, respiratory system findings and chest pain of varying degrees of severity are prominent. However it is possible to observe findings of peritonitis and pericarditis according to the site of serosal involvement. Generally, symptoms are easily controlled by analgesia, but in 12% of patients symptoms may be severe enough to, cause some variations in the treatment (8, 10)

Methotrexate induced pericardial effusion and pericarditis was first reported by Forbat et al. (10) The case was a 22 year old low risk GTN, receiving methotrexate chemotherapy. The patient tolerated methotrexate chemotherapy well until the seventh cure. During the seventh cure minimal pleuritic chest pain on the left side had developed and by auscultation a pleural friction sound was heard. Because of these findings the diagnosis was methotrexate induced pleurisy. The patient in this case responded to analgesic treatment rapidly and the methotrexate chemotherapy was continued until the ninth cure was completed. Two months after chemotherapy the patient developed chest pain again and also dyspnea induced by exercise. Chest X-ray and echocardiography revealed a large pericardial effusion of 5cm depth posteriorly and 2cm depth anteriorly. The electrocardiography and routine blood tests were normal and the clinical findings became normal after aspiration of 650cc pericardial fluid. The aspirated fluid was in the form of inflammatory exudate and the tests for viral and bacterial agents, including tuberculosis, and cytology were negative. It was observed that in the follow up of the patient serositis did not develop.

Although peritonitis is an infrequent type of serositis, it was first reported by Sharma et al. (8) in 1999. The reported case was a 27 year old patient receiving methotrexate chemotherapy for persistent GTN. The patient developed relapsing peritonitis after each methotrexate course. This clinical finding was thought to be methotrexate induced and the treatment protocol was changed. During the clinical follow up of this patient, symptoms of peritonitis did not recur .

It is thought that in the case of methotrexate induced peritonitis, it is not necessary to interupt the treatment since it does not increase the relapses (8). However it is equivocal for very infrequent cases of pericarditis and peritonitis. In the case we reported, after the cardiologic consultation and intervention we continued methotrexate chemotherapy. In the following cure cardiac symptoms did not recur.

Serositis induced by methotrexate is very common, but pericarditis and pericardial effusion are very infrequent adverse effects of the drug. Although pericardial effusion is a result of methotrexate chemotherapy we kept on giving methotrexate until remission was provided in this case. At the end we observed that a further attack of pericardial effusion did not occur. On the other hand, there is no consensus about the safety of the use of methotrexate after an episode of serositis. Other treatment modalities could be considered for these patients.

Conflict of interest

No conflict of interest was declared by the authors.

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Prenatal diagnosis of frontonasal dysplasia with anterior encephalocele

Anterior ensefaloselin eşlik ettiği frontonazal displazinin prenatal tanısı

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Abstract

Frontonasal dysplasia is a rare congenital anomaly affecting the eyes, nose and forehead, and occurs sporadically in most of the cases. A 24-year-old woman was referred to our unit at 27 weeks gestation due to the preliminary diagnosis of encephalocele. The sagittal and axial sonography of the fetal face depicted a midline mass measuring 3.8 x 4.2 cm, projecting anteriorly between the fetal orbits and extending from the the upper aspects of the forehead to the nasal bridge, which was consistent with the frontal (anterior) encephalocele. There were prominent hypertelorism and two facial clefts, and the nostrils were extremely separated. Following genetic counseling, the couple requested termination of pregnancy. Fetal pathologic examination confirmed the diagnosis of frontonasal dysplasia and anterior encephalocele with no additional major malformation. The fetal karyotype was normal and no mutation in the ALX1 gene was found, excluding ALX1-related frontonasal dysplasia in the differential diagnosis. Fetuses with neural tube defect may suffer from associated syndromes and disorders, as with our case. The presence of frontonasal dyplasia should be considered when an anterior encephalocele is detected by ultrasonography. (J Turkish-German Gynecol Assoc 2013; 14: 50-2)

Key words: Frontonasal dysplasia, anterior encephalocele, prenatal diagnosis, ultrasound, congenital anomaly

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Özet

Frontonazal displazi gözleri, burnu ve alnı etkileyen nadir bir konjenital anomalidir ve çoğunlukla sporadik olarak meydana gelir. 24 yaşındaki bir kadın 27. gestasyonel haftada ensefalosel ön tanısıyla kliniğimize refere edildi. Fetal yüzün sagital ve aksiyal ultrason kesitlerinde 3.8 x 4.2 cm büyüklüğünde, fetal orbitaların arasından öne doğru bir çıkıntı oluşturan ve alnın üst kısmından burun köküne kadar uzanan frontal (anterior) ensefalosel ile uyumlu orta hat yerleşimli bir kitle saptandı. Belirgin hipertelorizm ve iki tane fasiyal kleft mevcuttu ve burun delikleri aşırı derecede ayrık duruyordu. Genetik danışmanlık verildikten sonra çift gebeliğin sonlandırılmasını talep etti. Fetusun patolojik değerlendirmesinde frontonazal displazi ve anterior ensefalosel tanısı doğrulandı ve ek bir majör bulgu saptanmadı. Fetal karyotip normaldi ve ALX1 genininde mutasyon olmaması nedeniyle ayırıcı tanıda ALX-1 ile ilişkili frontonazal displazi dışlandı. Nöral tüp defekti olan fetuslarda bizim olgumuzda olduğu gibi eşlik eden sendrom ve hastalıklar görülebilir. Ultrason ile anterior ensefalosel tanısı koyulduğu zaman, frontonazal displazinin de beraberinde bulunma olasılığı akla getirilmelidir. (J Turkish-German Gynecol Assoc 2013; 14: 50-2)

Anahtar kelimeler: Frontonazal displazi, anterior ensefalosel, prenatal tanı, ultrason, konjenital anomali

Geliş Tarihi: 30 Temmuz 2012 **Kabul Tarihi:** 22 Ağustos 2012

Introduction

Frontonasal dysplasia, also known as median cleft syndrome, frontonasal syndrome and frontonasal dysostosis, is a rare congenital anomaly affecting the eyes, nose and forehead (1). A spectrum of abnormalities can be seen, ranging from mild hypertelorism to cleft face malformation (2). Frontonasal dysplasia is defined as the presence of two or more of the following symptoms: 1) true ocular hypertelorism, 2) anterior cranium bifidum occultum (a skin-covered gap in the bones of the forehead), 3) broadening of the nasal root, 4) median facial cleft affecting the nose, upper lip and palate, 5) unilateral or bilateral clefting of alae nasi, 6) lack of formation of nasal tip, 7) a V-shaped or widow's peak frontal hairline (3). Hypertelorism is the main and invariable component (4), and the male:female ratio has been reported to be 2:1 (5). There are several variations of frontonasal dysplasia, such as cranio-frontonasal dyplasia, oculoauriculofrontonasal dysplasia, acrofrontofacionasal dysostosis 1, acrofrontofacionasal dysostosis 2, Teebi type hypertelorism, acromelic frontonasal dysplasia, frontofacionasal dysplasia, cerebrofrontofacial syndrome, Pai syndrome and Shanske syndrome (2).

Only a few prenatally diagnosed cases have been reported in the literature (4, 6, 7). In this paper, we aimed to present a prenatally diagnosed case of frontonasal dyplasia with anterior encephalocele.

Case Report

A 24-year-old woman, gravida 4 para 1, was referred to our unit at 27 weeks gestation due to the prenatal diagnosis of encephalocele. The sagittal and axial sonography of the fetal

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face depicted a midline mass measuring 3.8 x 4.2 cm, projecting anteriorly between the fetal orbits and extending from the the upper aspects of the forehead to the nasal bridge, which was consistent with the frontal (anterior) encephalocele (Figure 1a and 1d). There were two facial clefts and the nostrils were extremely separated (Figure 1b). There was hypertelorism with an external orbital diameter measuring 51 mm and an internal orbital diameter measuring 23 mm (Figure 1c). Aside from the aforementioned malformations, there were no additional fetal abnormalities and the size of fetus was appropriate for gestational age.

Following genetic counseling, the couple requested a termination of pregnancy. A fetal blood sample was obtained via cardiocentesis and feticide was applied in the same session because of advanced gestational age. Termination of pregnancy was induced with intravaginal prostaglandin and a 1250 g male fetus was delivered. The postmortem examination revealed a soft-tissue mass measuring 4.5 x 5 cm and extending from the hairline to the nasal tip with a palpable bone defect (Figure 2a and 2b). The hypertelorism was prominent due to the encephalocele. The eyes were asymmetrical, with the left eye located more superiorly than the right eye, and the palpebral fissures were short. Two clefts were noted. The nasal root was broad and the nostrils were separated by the cleft on the left-hand side (Figure 2c) The distance between the two alae nasis measured 3.1 cm. The frenulum extended to the tip of the tongue, restricting lingual movement. 3D fetal CT depicted the bone defect between the frontal, nasal and etmoidal bones (Figure 2d). The fetal karyotype was normal and sequencing of ALX1 gene revealed no mutation.

Discussion

Embryologically, frontonasal dysplasia is suggested to be a result of the migration arrest of olfactory epithelium into the nasal capsule between the 4th and 6th weeks of embryogenesis (5). The nasal capsule does not form normally, leaving a central defect in which the forebrain area protrudes forming the anterior encephalocele (4). Anterior encephalocele is a rare condition and diagnosed as a soft-tissue mass overlying the lower aspect of the frontal bone (8). Fetuses with neural tube defects may suffer from associated syndromes and disorders, as with our case in which anterior encephalocele was associated with frontonasal dysplasia. The diagnosis of associated anomalies plays an important role in prenatal care, because the risk of neural tube defect in subsequent fetuses and the preventive effect of maternal folic acid intake in these cases may be different from those of nonsyndromic multifactorial neural tube defects (9).

Frontonasal dysplasia can be isolated or associated with other malformations (5). Distal limb abnormalities such as syndactyly, polydactyly, clinodactyly or tibial/fibular hypoplasia are associated sonographic findings in craniofrontal dysplasia, acrocallosal syndrome, acromelic frontonasal dysplasia, acrofrontofacionasal dysostosis 1 and 2, oral-facia-digital syndromes and Greig acrocephalopolysindactyly (4). Also, an association between frontonasal dysplasia and severe anomalies of the calvarium and central nervous system has been described (4). Therefore, a thorough search for cranial and limb malformations is recommended for the differential diagnosis (4). In our

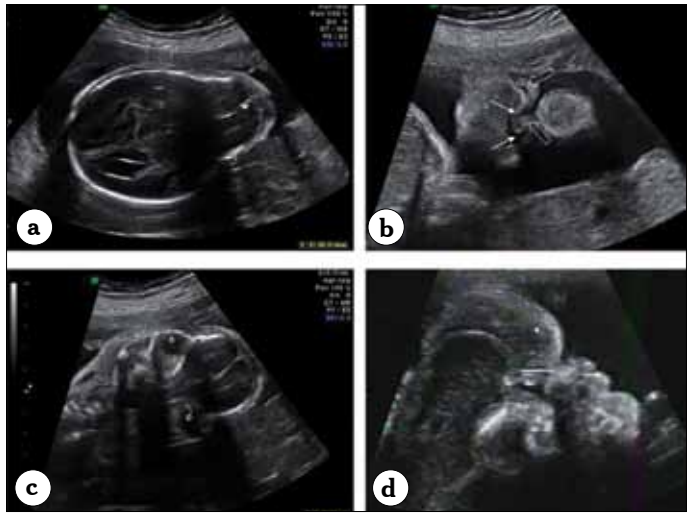

Figure 1. Fetal ultrasonography at 27 weeks gestation. (a) Axial scan of the fetal head showing anterior cephalocele (asterix). (b) Frontal view showing bilateral facial clefts (arrow) and nostrils widely separated (double arrow). (c) Frontal view depicting severe hypertelorism (O, orbits). (d) Sagittal scan showing the abnormal profile and cephalocele (asterix)

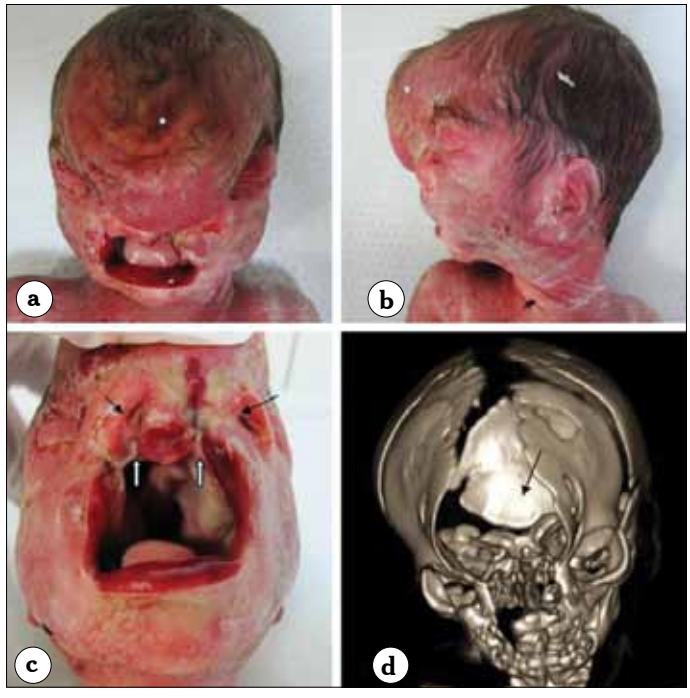

Figure 2. Postnatal appearance of the fetus. (a) Frontal view of the specimen showing anterior cephalocele (asterix). (b) Lateral view of the specimen showing anterior cephalocele (asterix). (c) Frontal view showing two facial clefts (white arrows) and the nostrils extremely separated from each other (black arrows). (d) 3D CT scan showing the cranium bifidum (arrow)

Written informed consent was obtained from the patient for publication of this case report and any accompanying images

case, encephalocele was the only associated finding and there were no extracranial malformations.

Genetic aspects of frontonasal dysplasia are not well-defined. Although frontonasal dysplasia occurs sporadically in most of the cases, autosomal dominant and X-linked patterns, as well as 22q11 microdeletion have been reported in the literature (1,10,11). In general, the possibility of this syndrome occurring in the next sibling is suggested to be 25% (12). Recently, autosomal-recessive mutations in aristaless-like homebox genes ALX1 (13), ALX3 (14) and ALX4 (15) have been described. While ALX3 and 4 predominantly play a role in the formation of the final shape of the nose, ALX1 expression is essential for building oral and nasal cavities as well as proper eye development during early embryogenesis (13). Therefore, ALX1-related frontonasal dysplasia is the most severe form, with a phenotype similar to the fetus in the present report. For this reason, the presence of a mutation in ALX1 gene was investigated but no mutation was found, excluding ALX1-related frontonasal dysplasia in the differential diagnosis.

In this report, we have presented a rare case of prenatally diagnosed frontonasal dyplasia associated with anterior encephalocele. Frontonasal dyplasia should be considered in the differential diagnosis when an anterior encephalocele is detected by ultrasonography.

Conflict of interest

No conflict of interest was declared by the authors.

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Ferritin and bile acid levels during the intrauterine pre-treatment of gastroschisis by serial amnioexchange

Seri amniotik sıvı değişimi ile gastroşizisin intrauterin ön-tedavisinde ferritin ve safra asidi düzeyleri

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Abstract

We present a case of gastroschisis managed with serial amnioexchanges. Marked decreases were detected in both ferritin and bile acid levels following the procedure. The bowels were not severely affected, as expected. After delivery, single primary closure of the defect was performed. Early enteral feeding and shorter hospital stay were the main outcome measures. Intrauterine pre-treatment of gastroschisis by serial amnioexchange may provide benefits by decreasing the levels of inflammatory products in the amniotic fluid in order to lower the possible risk of bowel damage, and this may help to achieve better surgical and postnatal outcomes.

(J Turkish-German Gynecol Assoc 2013; 14: 53-5)

Key words: Gastroschisis, amnioexchange, ferritin, bile acid, intrauterine treatment

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Özet

Seri amniotik sıvı değişimleri ile yönetilen bir gastroşizis olgusu sunduk. İşlem sonrası ferritin ve safra asidi düzeylerinde belirgin azalmalar saptandı. Bağırsaklar beklenildiği kadar çok etkilenmemişti. Doğumdan sonra, defektin tek primer kapatılması uygulandı. Ana ölçütler, erken enteral beslenme ve daha kısa hastanede kalış süresiydi. Seri amniotik sıvı değişimi ile gastroşizisin intrauterin ön-tedavisi amnion sıvısındaki enflamasyon ürünlerini azaltarak olası bağırsak hasarı riskini azaltarak yarar sağlayabilir ve bu daha iyi cerrahi ve doğum sonrası sonuçlara ulaşmak için yardımcı olabilir.

(J Turkish-German Gynecol Assoc 2013; 14: 53-5)

Anahtar kelimeler: Gastroşizis, amniotik sıvı değişimi, ferritin, safra asidi, intrauterin tedavi

Geliş Tarihi: 22 Temmuz 2011 **Kabul Tarihi:** 20 Eylül 2012

Introduction

Gastroschisis is a congenital anomaly, in which the fetal intestines herniate through a paraumbilical (usually right sided) full thickness abdominal wall defect without any covering membrane (1). The direct interaction of intestines with the amniotic fluid leads to an inflammatory reaction due to the amount of intestinal waste products, inflammatory mediators or both. The effect of inflammation on the bowel serosa, denoted as ''perivisceritis'', results in the formation of a fibrous peel and intestinal edema after 30 gestational weeks (2).

Previously, it has been shown that repeated amniotic fluid exchange procedures may help to reduce the concentration of inflammatory products that could damage the intestines (3). The aim of this report is to show that repeated amniotic fluid exchange may help to lower the effect of a negative impact of gastrointestinal products, including amniotic fluid ferritin and bile acids, on the intestines and may help to slow the development of a less fibrous peel surrounding the intestines at birth.

Case Report

A 24 year-old primigravida was detected with a right-sided paraumbilical defect with protruding intestines at 14 weeks of her pregnancy (Figure 1). The case was diagnosed as an isolated gastroschisis. Amniocentesis was performed at 19 gestational weeks and a male fetus with a normal karyotype was detected. The parents were informed about the amnioexchange procedure; they opted to undergo the technique and provided their informed consent. The local ethics committee approved the procedure. The technique used for the amnioexchange procedure was that previously described by Aktug et al. (4). Serial amnioexchange procedures were performed every four weeks until birth, starting at 24 gestational weeks. Overall, a total of four procedures were performed. The total amnioexchange volume was determined empirically and according to previous reports (4). Amniotic fluid volume (AFV) was restored to normal levels of 11-13cm

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if oligohydroamnios was present. A single dose of antibiotic prophylaxis was administered before each procedure. There was no need for hospitalization or tocolytic therapy. Amniotic fluid samples were assayed for ferritin and bile acids. Table 1 summarizes the amount of fluid, ferritin and bile acid levels before and after pre-treatment and fetal intestinal diameters and wall thicknesses at the time of the procedure.

A caesarean section was performed at 37 weeks gestation due to late decelerations. A male infant of 2870 g with Apgar scores of 8 at 1min and 10 at 5 min was delivered. There were small and large bowel loops protruding through the paraumbilical defect with little fibrous peel or edema (Figure 2). Intestines were separated easily and placed into the abdomen; primary closure of the defect was performed immediately after birth. Oral feeding was started at postoperative day 5; at postoperative day 7 oral feeding was cancelled due to some vomiting and restarted at postoperative day 13. The patient was discharged on the 20th postoperative day. After 1 year of follow-up, the baby was normal.

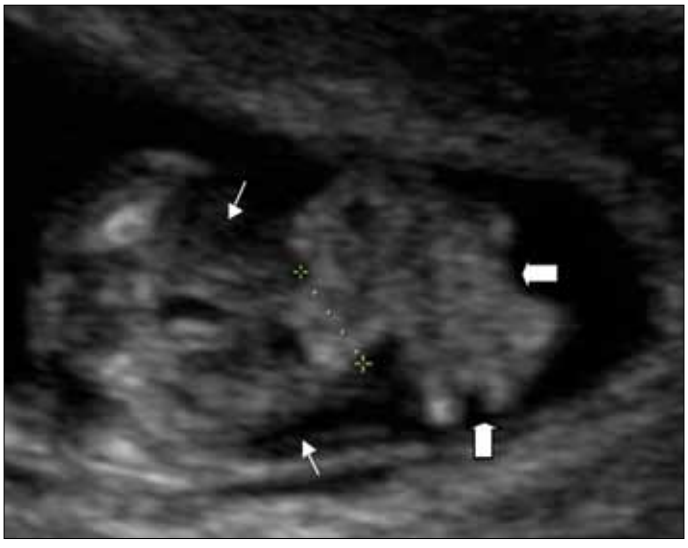

Figure 1. Thin arrows indicate the abdomen of 14th week fetus. Thick arrows indicate the protruding fetal intestines. Two plus signs indicate the distance of the paraumbilical defect

Discussion

Fetuses with gastroschisis will suffer from complications mostly associated with intestinal damage due to direct contact with inflammatory products in the amniotic fluid (5). This inflammation is supposed to cause bowel edema and induce the creation of fibrous peel, which may lead to intestinal atresia, malrotation, intestinal wall thickening, hypoperistaltism, and necrotising enterocolitis (1). All of these issues may cause difficulties in primary closure, increased length of stay in the neonatal intensive care unit, lower tolerance of enteral feeding and prolonged hospital stay.

Perivisceritis of the intestines was expected to occur due to inflammatory mediators and intestinal products (interleukin 8, matrix metalloproteinases, protein, ferritin, amino acids, γ-glutamyl transferase, amylase, lipase and meconium staining of the liquor) only after 30 weeks' gestation (2, 6). However, it was previously shown that ferritin levels were higher in the second trimester than the third trimester (3). Therefore, in this case we started the first exchange procedure at 24 gestational weeks. In this way, we aimed to reduce the possible risk of early development of intestinal damage. This implication should be

Figure 2. The intestines were seen, immediately after the birth and before the primary closure surgery. It is seen that, the small and large bowels were almost in normal appearance

Table 1. Exchange, infusion and amniotic fluid volume, ferritin and bile acid levels and fetal intestinal measurements before, after or at the time of the procedure

	Week 24		Week 28		Week 32		Week 36	
	pre	post	pre	post	pre	post	pre	post
Exchange volume (mL)	500		500		750		750	
Infusion Volume (mL)	-		150		150		150	
AFV (cm)	13	13	8	13	9	11	8	11
Ferritin (ng/mL)	98	38	245	21	171	28	191	51
Bile acids (μmol/L)	1.6	<1	2.8	<1	1.5	<1	1.1	<1
İntestinal loop diameter (mm)	10		11		14		16	
İntestinal wall thickness (mm)	0.9		1.2		2		2.3	

AFV: amniotic fluid volume

confirmed with case series or randomized controlled trials.

Bile acids, which might directly disrupt intestinal function and/or might increase the inflammatory reaction in the amniotic fluid, were also studied (7). In the present study, ferritin and bile acid levels peaked at 28 gestational weeks. Additionally, bile acid levels were as high at 24 gestational weeks as they were at 32nd gestational week. There were marked decreases in both ferritin and bile acid levels following the amnioexchange procedure.

It was previously reported that mean hospital stay for gastroschisis patients was 41 days (8). The amnioexchange procedure reduced the hospital stay time almost by half in the present study. Additionally, in term deliveries of fetuses with gastroschisis, the mean time to achieve enteral feeding was 17 days (9). In our study, the amnioexchange procedure seemed to reduce this value.

Previously, Midrio et al. (7) reported that the amnioexchange procedure did not have much benefit in gastroschisis. In that study, a total of 8 gastroschisis cases were evaluated. In some cases, they only performed amnioinfusion without amnioexchange. Their study did not include a control group. Additionally, most of their concerns were related to infection and preterm premature rupture of membranes caused by the invasive procedure. However, it was previously reported that the amnioexchange procedure did not have any side effects in humans (10).

Although our case might be important in order to give an idea about serum ferritin and bile acid levels during the intrauterine pre-treatment of gastroschisis by serial amnioexchange, a single case report might not be adequate to sustain our conclusions. Therefore, large clinical randomized controlled trials are necessary to make definite conclusions regarding on the pros and cons of the amnioexchange procedure in gastroschisis.

Conflict of interest

No conflict of interest was declared by the authors.

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Diagnosis and management of female adnexal tumor of probable Wolffian origin (FATWO) arising from ovary: a case report

Overlerden gelişen olası Wolffian kökenli adnexal tümörün tanı ve tedavisi: Olgu sunumu

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Abstract

Female adnexal tumor of probable Wolffian origin (FATWO) is a rare neoplasm which is usually considered as benign, although in some cases metastasis or recurrences have been reported even after a long interval following the initial diagnosis. Preoperative diagnosis of FATWO is very difficult because of the rarity of the disease and the limited literature available. In this case report, we present a case of FATWO arising from the ovary and review the literature based on the clinical characteristics and management of this rare condition. A 51- year- old postmenopausal woman was referred to our clinic for evaluation of an adnexal mass. After diagnostic evaluation, the patient underwent explorative laparotomy. Intra-operatively, a solid- cystic mass was found in the right ovary, the rest of the abdomen and the pelvis were normal. The ovarian mass was removed and examined with frozen-section (FS). When the frozen section proved negative for malignancy, total abdominal hysterectomy and bilateral adnexectomy were performed. The anatomic study revealed a well-capsulated mass which was 3.5×1.5 cm in diameter. Based on pathological and immunohistochemical results, the final diagnosis was concluded to be FATWO. Adjuvant therapy was not administered. Te patient was followed up after discharge from the hospital. One year after surgery she was asymptomatic. No evidences of recurrence were observed throughout this period. Although FATWOs are rare tumors, they should be kept in mind in women with an abdominal mass. They can present diagnostic difficulties and the diagnosis is based on the exclusion of other neoplasms. FATWO has malignant potential, after the initial surgical treatment patients should be appropriately followed up for possible recurrence and metastasis.

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Key words: Neoplasm, Wolffian adnexal tumor, FATWO, ovary, benign

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Özet

Olası wollfian kökenli kadın adneksal tümörü (FATWO) genellikle benign doğada olan nadir bir neoplazmdır. Bununla beraber ilk tanı konulmasından uzun zaman sonra bile bazı vakalarda metastaz ve yinelemeler bildirilmiştir. Preoperatif olarak FATWO tanısı konulması bu hastalığın çok nadir ve literatürün sınırlı olması nedeniyle çok güçtür. Bu yazıda overden gelişen FATWO tanısı almış bir kadın olgu sunulacak, ve bu nadir görülen durumun tanı ve tedavisiyle ilgili literatür gözden geçirilecektir. Elli bir yaşındaki postmenapozal kadın hasta kliniğimize adneksal kitlenin değerlendirilmesi için gönderildi. Tanısal incelemeden sonra, hastaya eksploratif laparotomi uygulandı. Operasyon esnasında sağ overde solid kistik bir kitle bulundu, bunun dışında abdomen içinde herhangi bir başka anomali saptanmadı. Ovaryan kitle cerrahi olarak çıkarıldı ve frozen kesi ile incelendi. Frozen kesilerde malignansi negatif olarak gelince, total abdominal histerektomi ve bilateral adneksektomi gerçekleştirildi. Anatomik olarak iyi kapsüle olmuş 3.5x1.5 cm çapında bir kitle idi. Patolojik ve immüno histokimyasal tetkik sonucunda nihai tanı FATWO olarak teyid edildi. Adjuvan terapi uygulanmadı. Hasta daha sonra taburculuk sonrası klinik izleme alındı. Halihazırda bir yıldır takipte olan hastada herhangi bir yineleme gözlenmedi. FATWO nadir bir tümör olmasına rağmen kadınlarda karın içi kitlede akılda bulundurulması gereken bir durumdur. Tanısı diğer diğer neoplasm nedenlerinin ekarte edilmesini gerektirdiği için zorluk taşıyabilir. FATWO malign olma potansiyeline sahip bir neoplasm olduğu için olası tekrarlama ve malignansi nedeniyle uygun bir biçimde takip edilmesi gereklidir.

(J Turkish-German Gynecol Assoc 2013; 14: 56-9)

Anahtar kelimeler: Neoplazm, Wollfian adneksal tümör, FATWO, over, benign

Geliş Tarihi: 23 Nisan 2012 **Kabul Tarihi:** 20 Ağustos 2012

Introduction

Female adnexal tumor of probable Wolffian origin (FATWO) is a rare, poorly understood lesion first described in 1973 (1). It is defined as a tumor of presumptive mesonephric (Wolffian duct) origin characterized by a variety of epithelial patterns and occurs most commonly in the broad ligament, but is also known to occur in mesosalpynx, fallopian tube, ovary, and peritoneum (2, 3). FATWO is usually regarded as a benign lesion, although in some instances more aggressive behavior is encountered with a tendency to distant metastases and recurrences (4, 5).

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Preoperative diagnosis of FATWO is very difficult because of the rarity of the disease and the limited literature available. There are no comprehensible recommendations regarding its preoperative workup and optimal treatment (6). Here, we report a case of FATWO arising from the ovary and review the literature based on the clinical characteristics and management of this rare situation.

Case Report

A 51-year-old postmenopausal woman gravida 5, para 3, was referred to our clinic for evaluation of a right adnexal mass suspected to be malignant. Her previous gynecological history included cesarean section and appendectomy. Pelvic transvaginal ultrasound revealed a normal sized uterus, with a thin and regular endometrial layer. The left ovary was normal, but the right ovary was enlarged and there were two masses, 2.5 and 2 cm, which contained solid and cystic areas. No traces of ascites were found. In the color Doppler examination of these solid- cystic masses, it was found that Resistance Index (RI) value was 0.55 and Pulsatility Index (PI) value was 0.85. Because the sonographic findings suggested an ovarian malignancy, magnetic resonance imaging (MRI) was performed. The T_1 weighted images showed a hypointense bi-lobule solid mass probably originating from the right ovary. On T_2 weighted images, the mass was heterogenic and hyperintense. A chest X-ray was unremarkable. Serum tumor markers were CA-125=5.8 U/mL (nL<35U/mL), CA 15-3=4.1 U/mL (nL<38.6 U/mL), CA 19-9=7.25 U/mL (nL<37 U/mL) and CEA=0.76 ng/mL (nL<10 ng/mL). The patient underwent explorative laparotomy. Intra-operatively a 3×4 cm solid- cystic mass was found in the right ovary. The rest of the findings in the abdomen and the pelvis were normal. The ovarian mass was removed and examined with frozen-section (FS). When the FS proved negative for malignancy, total abdominal hysterectomy and bilateral salpingo-oopherectomy were done. The postoperative period was uneventful and the patient was discharged on day 5 after the surgery.

The anatomic study revealed a well-capsulated mass which was 3.5×1.5 cm in diameter. The cut section of the tumoral mass contained solid and microcystic parts and had a sponge-like, yellow appearance. Microscopically, the lesion was well distinguished from ovarian tissue. The tumor, composed of sheets of epithelial like cells, contained oval, polygonal nuclei with regular chromatin and thin- pale cytoplasm (Figure 1a). There wereseparate retiform areas like tubules (Figure 1b). In the stromal tissue some hyalinization and hyalinized vasculature were seen. There were no nuclear atypia or necrosis. The mitotic activity was 0-1 per 10 high-power fields.
Immunohistochemically, the tumor cells were positive for pancytokeratine (Figure 2a), vimentin (Figure 2b) and calretinin (Figure 2c) but negative for inhibin, Factor 8 and epithelial membrane antigen (EMA). Based on pathological and immunohistochemical results, the diagnosis of FATWO was confirmed. The patient was informed about the malignancy risk of this tumor and was recommended close follow up which included clinical examination, tumor markers, abdominal and pelvic ultrasound and MRI. One year after surgery she was asymptomatic. No evidence of recurrence was observed throughout this period.

Discussion

Female adnexal tumor of probable Wolffian origin (FATWO) arises by the rare persisting remnants of the mesonephric duct. FATWO is an uncommon lesion and approximately 80 cases have been reported in the literature including case reports (3). The age at diagnosis ranged from 18 to 81 years, with a mean of 50 years (7). These tumors usually express a benign behavior. However they have recently been considered to have malignant potential. Some of the tumors follow a malignant course with metastasis and recurrence (4, 5). In the review of the literature, it has been reported that almost one-fifth of the cases is associated with an adverse outcome (3). The prognosis of this tumor does not correlate with their clinical presentation and their cytology (4). However, the presence of necrosis, capsular

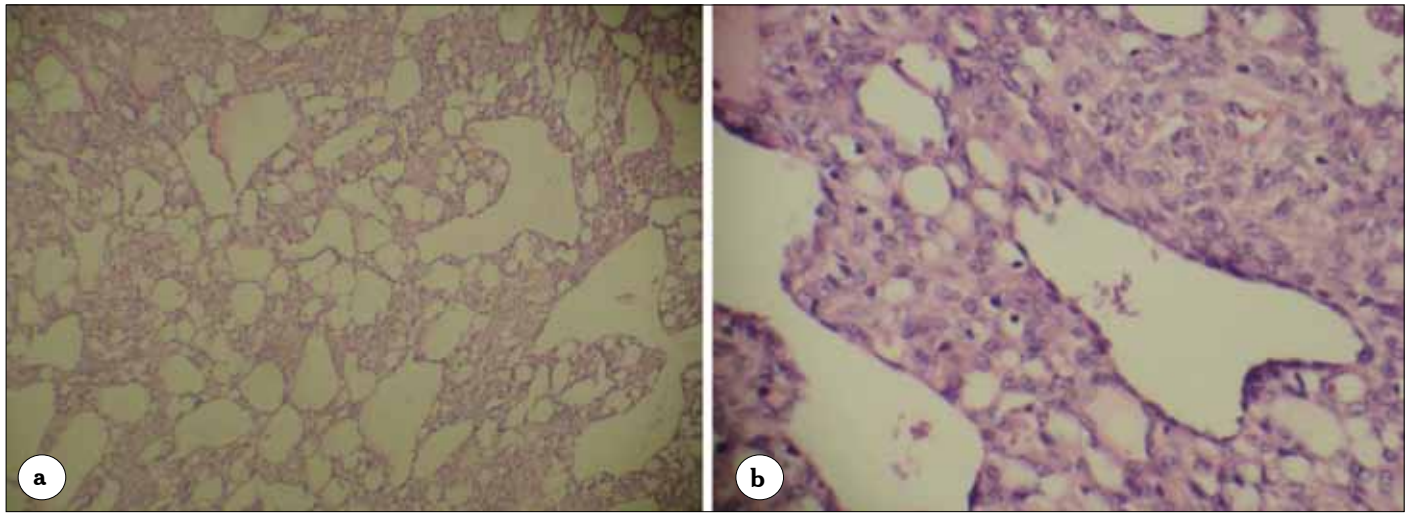

Figure 1. Histological section showing a) solid pattern with sieve-like cystic areas, b) the presence of tumor cells with oval- polygonal nuclei, small nucleoli and scanty- pale cytoplasm (Hematoxylin and eosin, x20)

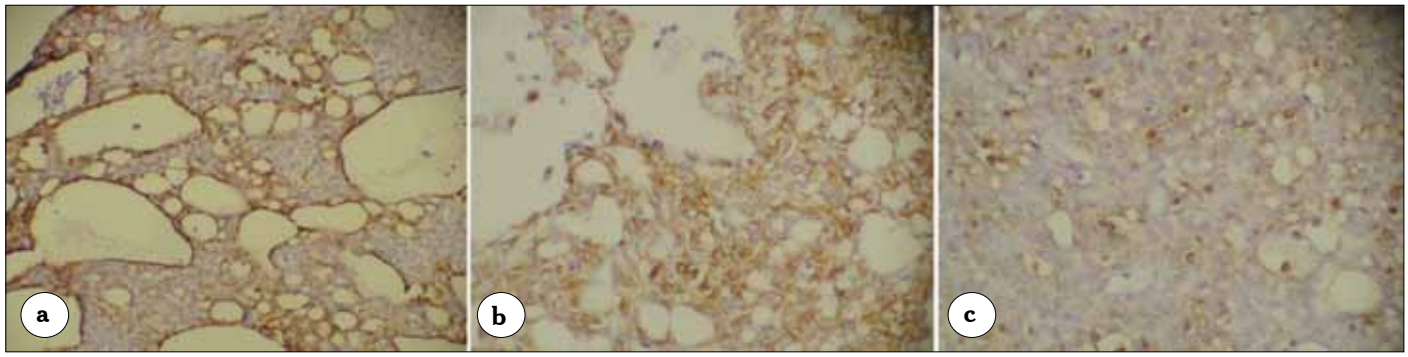

Figure 2. Immunohistochemical finding showing the positive immunoreactions for a) pan- cytokeratin, b) vimentin and c) calretinin (x40)

invasion and especially a high number of mitoses are elements justifying caution regarding their prognosis (4, 8, 9). However, recurrence could occur in the absence of the aggressive histological character and even after several years following the initial diagnosis (8, 10). In the literature, recurrence median time was 48 months with a range from 13 to 96 months, and in some cases recurrences occurred even after a long interval following the diagnosis (4, 9).

The rarity and variable location of FATWO make the diagnosis difficult. Its diagnosis depends largely on histological features which are characterized by a tubular pattern with either closely packed tubules or even solid cords, a sieve-like growth pattern produced by cysts of varying sizes lined by flattened cells and a diffuse growth composed of spindle or polygonal cells (11).

Usually, an ultrasound examination shows a pelvic semisolid mass with high vascularization in these cases. The MRI findings of this tumor were described by Matsuki et al. (7) as a slightly hyperintense mass with cystic degeneration in the adnexa, which were difficult to differentiate from a subserosal leiomyoma or an ovarian tumor. According to the Ramirez et al. (9) review, it has been found that pre-operatively the serum CA-125 levels were normal in all of the patients.

The main differential diagnosis includes well differentiated endometrioid ovarian adenocarcinoma, endometrioid adenocarcinoma of the fallopian tube and Sertoli Leydig cell tumor (3, 12, 13). Endometrioid adenocarcinoma arises from the fallopian tube, whereas FATWO usually arises outside the tube within the broad ligament and ovary (1). The degree of nuclear atypia and mitotic activity is more impressive in endometrioid adenocarcinoma (12). Sertoli-Leydig cell tumors may bear a strong morphological resemblance to FATWO, but FATWO tends not to be associated with the endocrine symptoms that are features of Sertoli Leydig cell tumors (13). Also, Sertoli–Leydig cell tumors have not been reported in the paratubal site or in the broad ligament and the presence of a sieve-like pattern, the absence of Leydig cells, may be useful for the diagnosis of FATWO (10). It is not always possible to differentiate between the broad ligament GCT and female adnexal tumor of probable Wolffian origin (FATWO). Nuclear grooving is not an exclusive feature of GCT and can be seen in a variety of other neoplasms, in the context of the differential diagnosis between broad ligament GCT and FATWO, but the presence of this feature may be very useful in establishing the diagnosis of broad ligament GCT (14).

Specific antibodies for use in immunohistochemistry have become available in the last few decades and immunohistochemical investigations have been performed for the diagnosis of these tumors (11). Positive immunoreactions to pan-cytokeratin, CAM 5.2, cytokeratin 7 (CK7) and vimentin support diagnosis of FATWO (4) .These tumors are generally EMA negative (11, 12). Positive staining for α-inhibin in nine of 10 tumors of probable Wolffian origin has been demonstrated by Kommos et al. (15), but they have also reported that positive staining for α-inhibin is not a useful marker to distinguish between Sertoli cell and Wolffian tumors.

Therapeutic options in these tumors remain ill defined due to the rarity of the disease. It has been considered that the most effective therapy is complete surgical resection with hysterectomy and bilateral adnexectomy (4, 7). Most of the tumor relapses have occurred in patients initially treated with only tumor resection (4). Some authors asserted that the most suitable initial treatment for FATWO was surgical debulking with hysterectomy and bilateral adnexectomy (16). The role of adjuvant chemotherapy or radiation therapy is controversial (7). Also, there are limited options in treating recurrent or metastatic disease. In recurrent or metastatic FATWO, molecular targeted therapy, such as tyrosine kinase inhibitor, could be considered. However, to determine the effectiveness of this option, collective data are needed from multiple centers (17).

In our case, ovarian malignancy was suspected preoperatively. Pathological and immunohistochemical analysis revealed the lesion to be a FATWO. Immunohistochemical findings of the case reported are similar to those described by other authors except for inhibin which has not been detected by us (11, 12, 15). After the surgery, chemotherapy and radiation therapy were not administered and she was scheduled for clinical follow-up.

In conclusion, FATWOs are rare tumors arising from the remnants of the mesonephric duct. Although most of them behave as benign lesions, some cases have the potential for malignant behavior. They can present diagnostic difficulties and the diagnosis is based on the exclusion of other neoplasms. It should be differentiated from other possibilities with careful pathological and immunohistochemical examination. Because the role of adjuvant therapies is questionable, they are not routinely administered. After the initial surgical treatment, patients should be appropriately followed up during a long-term period.

Conflict of interest

No conflict of interest was declared by the authors.

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What is your diagnosis?

Case

A 27-year-old G2 P1 woman at 20 weeks 3 days of gestation by her last menstrual period was referred to our clinic with an abnormal result in the four chamber view at obstetric ultrasonographic evaluation. At our clinic, detailed fetal ultrasonographic cardiac examination was performed (Figure 1). In order to detect the associated fetal abnormalities, a detailed ultrasonography was made and amniocentesis was performed simultaneously. These investigations of the fetus were otherwise unremarkable. What is your diagnosis?

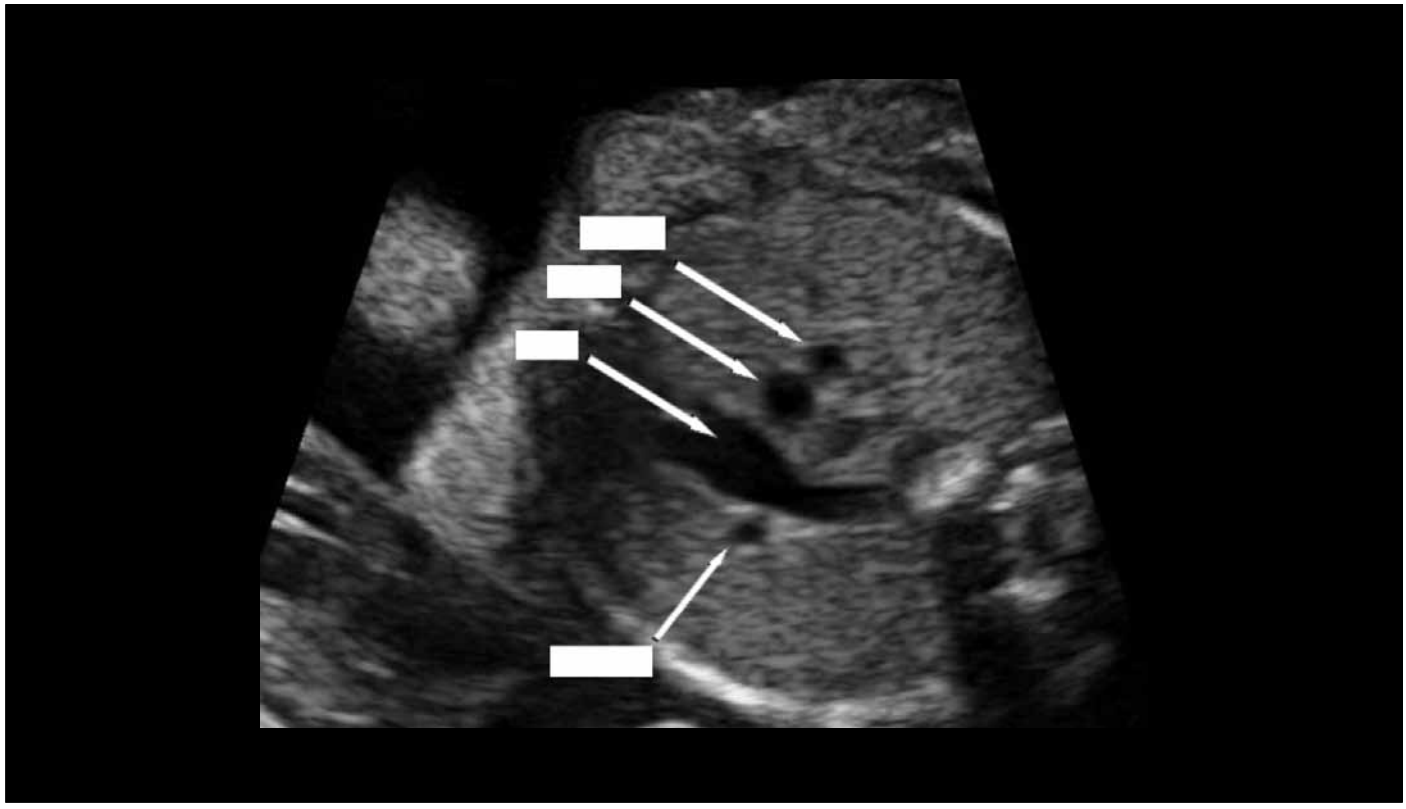

Figure 1. Fetal heart USG

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Answer

Detailed fetal ultrasonographic cardiac examination showed dilated coronary sinus and PLSVC was determined on the supernumerary vessel to the left of the pulmonary trunk (Figure 2).

Persistent left superior vena cava (PLSVC) represents the most common form of anomalous systemic venous return in adults. It has been observed in 0.3% of autopsies in the general population and in 4-8% of patients with congenital heart disease (CHD) (1).

PLSVC should be considered in case of detection of extra vessel on the left side and the coronary sinus dilatation at the pulmonary artery outflow cross-section (cross-section of three-vessel) during obstetric sonography (1).

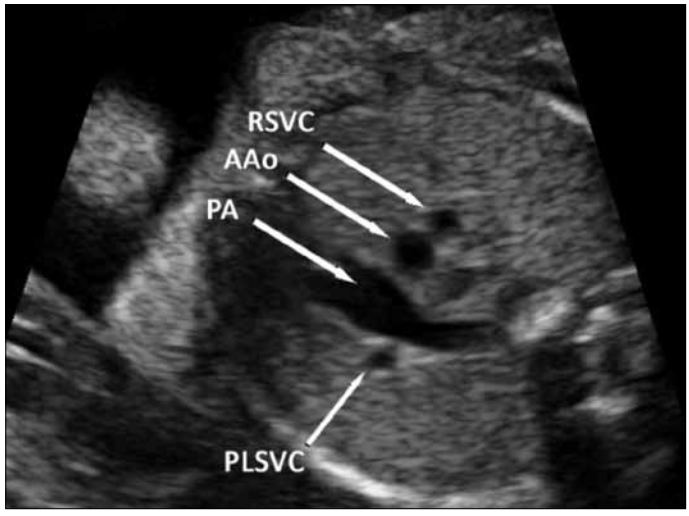

Figure 2. Abnormal three-vessel view. Persistent left superior vena cava (PLSVC) near right ventricule outflow tract at three vessels section. PA, pulmonary artery, AAo, ascending aorta, RSVC, right superior vena cava

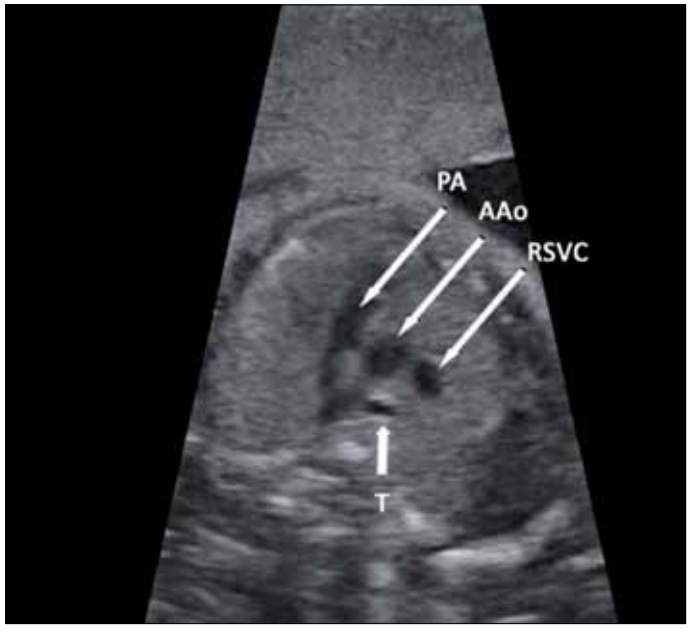

Figure 3. Normal three-vessel view. PA, pulmonary artery, AAo, ascending aorta, RSVC, right superior vena cava, T, trachea

After diagnosis of PLSVC; fetal echocardiography, karyotype analysis, and ultrasonographic assessment of fetal anatomy should be made.

The prevalence of PLSVC in the fetal population remains uncertain. Under normal conditions, the coronary has a diameter of 1 to 3 mm, courses perpendiculer to interatrial septum. In the presence of PLSVC, the coronary sinus is dilated and measures between 3 and 7 mm.

The three-vessel view is a transverse view of the fetal upper mediastinum is as simple to obtain as the four-chamber view. It demonstrates the main pulmonary artery, ascending aorta and superior vena cava in cross- or oblique sections (Figure 3).

PLSVC was diagnosed in the presence of an abnormal three-vessel view showing a supernumerary vessel to the left of the pulmonary trunk (2). The diagnosis was then confirmed in the long-axis view, demonstrating by color Doppler direct or indirect drainage via the coronary sinus into the left or right atrium.

The importance of a PLSVC lies in a greater prevalence of associated CHD. PLSVC occurs in up to 3-8% of patients with CHD, making PLSVC the most common venous anomaly associated with CHD (3). Additionally chromosomal anomalies were reported in 9% of PLSVC(4).

During the early development the cephalic portion of the embryo, fetal venous blood is drained by bilateral symmetrical right and left anterior cardinal veins. The development of the left innominate vein that bridges the anterior cardinal veins at 7-8 weeks gestation is followed by atrophy of the left anterior cardinal vein. A small portion remains as the left superior intercostal vein and the distal part gives rise to the coronary sinus (5).

To gether with a concomitant dilated coronary sinus, PLSVC can be detected at three vessels view of the right ventricule outflow tract (Figure 1). These findings must be examined for cardiac (heterotaxy, ventricular septal defect ve coarctation of aorta) and noncardiac abnormalities (4, 6, 7). In our case, there was no extra cardiac or noncardiac abnormalities. The chromosome analysis of the fetus revealed a normal caryotype.

With all these findings, our definitive diagnosis was isolated PLSVC. Isolated PLSVC cases have been reported to cause no adverse abnormalities either at early neonatal period or at adulthood (1).

All this information was given to family and the pregnancy was followed up.

Three-vessel cross-section is a crucial view for antenatal obstetric ultrasonography during cardiac examination.

At this section in the presence of an extra blood vessels next to the pulmonary trunk and dilated coronary sinus PLSVC should be considered.

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Questions on the article within the scope of CME/CPD

1. Choose the incorrect treatment modality for uterine fibroids.
   a) Gonadotropin-releasing hormone (GnRH) agonists
   b) Selective progesterone receptor modulators (SPRMs)
   c) Aromatase inhibitors
   d) Levonorgestrel-releasing intrauterine devices
   e) Beta-mimetics

2. Which choice does not contribute to uterine fibroid pathogenesis?
   a) Estrogen and progesteron
   b) Growth factors
   c) Profibrotic cytokines
   d) Proinflammatory mediators
   e) Angiotensin converting enzyme

3. In uterine fibroid pathogenesis progesterone can function through activating the…….. pathway.
   a) PI3K/Akt pathway
   b) Classical pathway
   c) Cysteine metabolism pathway
   d) Estrogen pathway
   e) Aldosterone pathway

4. Microtubule regulates the intracellular localization and the activities of many transcription factors except:
   a) ERα
   b) PR
   c) TGF-β
   d) Growth factors
   e) Insulin

5. Which of the following statement is incorrect?
   a) Uterine fibroids substantially increase the risk of pain, preterm labor, placental abruption, postpartum hemorrhage, and cesarean section.
   b) There are currently no effective therapies for uterine fibroids
   c) MT-targeting drugs have met with excellent clinical success in the treatment of many fibrotic diseases
   d) There are only few comparative studies about robotic-assisted hysterectomy for benign indications
   e) None

6. What are the advantages of the da Vinci Surgical System compared to conventional laparoscopic surgery?
   a) Three dimensional (3D) vision
   b) Wristed instrumentation
   c) İmproved dexterity
   d) Ergonomic positioning
   e) All

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4-8 May 2013	**61st Annual Clinical Meeting of ACOG** New Orleans, LA, USA http://classic.acog.org/acm/
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