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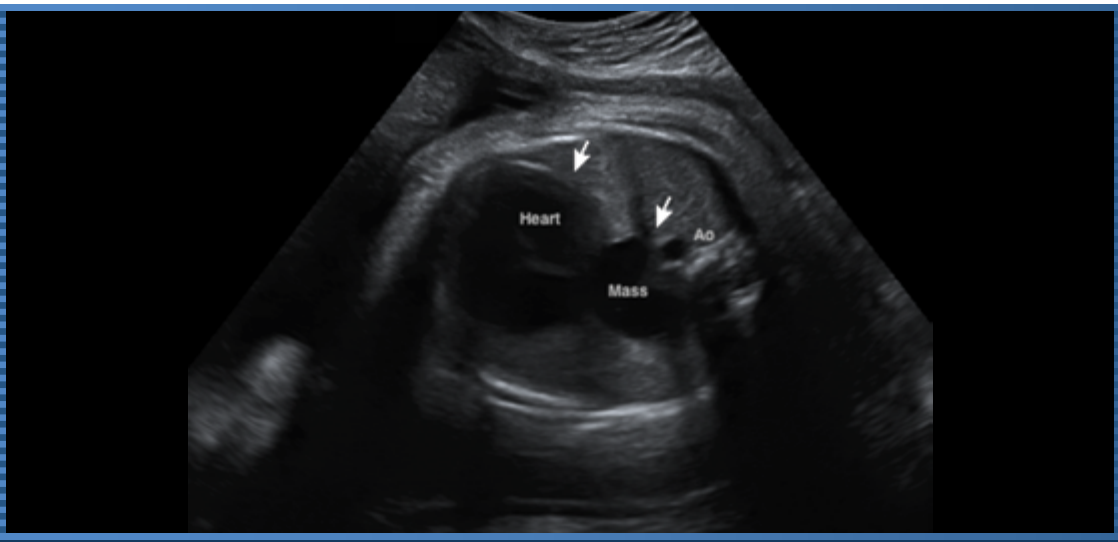
Journal of the Turkish-German Gynecological Association



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Cover Picture: Dolgun et al. A mass in the fetal thorax

Original Investigations

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Aims and Scope

Journal of the Turkish-German Gynecological Association is the official open access publication of the Turkish-German Gynecological Education and Research Foundation and Turkish-German Gynecological Association 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.

It is an independent peer-reviewed international journal printed in English language. Manuscripts are reviewed in accordance with "double-blind peer reviewev" process for both referees and authors.

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The "Journal of the Turkish German Gynecological Association" (ISSN 1309-0399; Abbreviated as "J Turk Ger Gynecol Assoc") is the official, open access publication of the Turkish-German Gynecological Education and Research Foundation and the Turkish-German Gynecological Association. Formerly named "ARTEMIS", the journal is published quarterly (March, June, September, December) in English and publishes original peer-reviewed articles, reviews, case reports and commentaries in the fields of Gynecology, Gynecologic Oncology, Endocrinology & Reproductive Medicine and Obstetrics. Reviews will be considered for publication only if they are prepared by authors who have at least three published manuscripts in 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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The main document and the tables, should be prepared with "Microsoft Office Word software". Times New Roman font (size 12) should be used throughout the main document with 1.5 line spacing. The side margins of the main document should be set at 25 mm from all sides.

The figures should be submitted separately through the submission system in .JPG of .TIFF format. Please do not embed the figures in the main document. Make sure that the minimum resolution of each submitted figure is 300DPI.

A cover letter and a title page should be provided with all submissions. It should be stated in the cover letter that the manuscript was not previously published in any other publication, that it is not accepted for publication in another publication and that it is not under review for possible publication elsewhere.

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CONSORT statement for randomized controlled trials (Moher D, Schultz KF, Altman D, for the CONSORT Group. The CONSORT statement revised recommendations for improving the quality of reports of parallel group randomized trials. JAMA 2001; 285: 1987-91) (http://www.consort-statement.org/),

PRISMA for preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.) (http://www.prisma-statement.org/),

STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al, for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4.) (http://www.stard-statement.org/),

STROBE statement—checklist of items that should be included in reports of observational studies (http://www.strobe-statement.org/),

MOOSE guidelines for meta-analysis and systemic reviews of observational studies (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting Meta-analysis of observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12).

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Manuscripts submitted for publication must contain a statement to the effect that all human studies have been reviewed by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards described in an appropriate version of the 1975 Declaration of Helsinki, as revised in 2000. It should also be stated clearly in the text that all persons gave their informed consent prior to their inclusion in the study. Details that might disclose the identity of the subjects under study should be omitted. Experimental animal studies should be presented with the disclosure of the appropriateness to the institutional/national/international ethical guides on care and use of laboratory animals.

Reports of animal experiments must state that the "Principles of laboratory animal care" (NIH publication No. 86-23, revised 1985) were followed, as well as specific national laws where applicable.

The editors reserve the right to reject manuscripts that do not comply with the abovementioned requirements. The author will be held responsible for false statements or for failure to fulfil the above mentioned requirements.

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ation site. The copyright transfer form should be signed by all contributing authors and a scanned version of the wet signed document should be submitted.

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Submissions should have the following parts.

Title Page
A separate title page should be submitted with all submissions and should include the title of the article, name(s), affiliations and major degree(s) of the author(s) and source(s) of the work or study, a short title (running head) of no more than 50 characters. The name, address, telephone (including the mobile phone number) and fax numbers and e-mail address of the corresponding author should be listed on the title page.

Abstract
All manuscripts should be accompanied by an abstract. A structured abstract is required with original articles and it should include the following subheadings: Objective, Material and Methods, Results and Conclusion. A structured abstract is not required with review articles and case reports. The abstract should be limited to 250 words for original articles and review articles and 150 words for case reports.

Key Words
Below the abstract provide 3 to 5 key words. Abbreviations should not be used as key words. Key words should be picked from the Medical Subject Headings (MeSH) list (www.nlm.nih.gov/mesh/MBrowser.html).

Original articles should have the following sections.

Introduction
State concisely the purpose and rationale for the study and cite only the most pertinent references as background.

Material and Methods
Describe the plan, the patients, experimental animals, material and controls, the methods and procedures utilized, and the statistical method(s) employed. In addition to the normal peer review procedure, all randomized controlled trials (RCTs) submitted to the journal are sent to members of a team of professional medical statisticians for reviewing.

Address "Institutional Review Board" issues as stated above. State the generic names of the drugs with the name and country of the manufactures. Provide information on informed consent and ethics committee approval.

Results
Present the detailed findings supported with statistical methods. Figures and tables should supplement, not duplicate the text; presentation of data in either one or the other will suffice. Emphasize only your important observations; do not compare your observations with those of others. Such comparisons and comments are reserved for the discussion section.

Discussion
State the importance and significance of your findings but do not repeat the details given in the Results section. Limit your opinions to those strictly indicated by the facts in your report. Compare your finding with those of others. Provide information on the limitations of the study. No new data are to be presented in this section.

The main text of case reports should be structured with the following subheadings: Introduction, Case Presentation, Discussion.

References
Number references in Arabic numerals consecutively in the order in which they are mentioned in the text starting with number "1". Use the form of the "Uniform Requirements for Manuscript Submitted to Biomedical Journals" (http://www.amaassn.org/public/peer/wame/uniform.htm). If number of authors exceeds seven, list first 6 authors followed by et al.

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Ertan AK, Tanriverdi HA, Schmidt W. Doppler Sonography in Obstetrics. In: Kurjak A, Chervenak FA, editors. Ian Donald School Textbook of Ultrasound in Obstetrics and Gynecology. New Delhi, India: Jaypee Brothers; 2003. p. 395-421.

Book;
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Contents

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Editorial

Dear colleagues,

It is my great pleasure to meet with our loyal readers again in the first issue of the **Journal of the Turkish - German Gynecological Association (JTGGA)** in the publishing year of 2014.

I would like to inform you that the **archive of our journal starting with September 2009 issue has been indexed in PubMed Central and now available for access.** The number and quality of the submitted manuscripts and citations to our articles have risen sharply. In this issue, you will find an opportunity to read many high quality manuscripts. There is no doubt that, **JTGGA** will increase its respectable status to a higher level in the international scientific community with our strict policy. Please do not hesitate to send your best works to our journal.

We are also proud to be announcing the **2nd International Research Awards on Obstetrics & Gynecology** in this issue. All manuscripts submitted in this period have been peer-reviewed in terms of their scientific contribution, originality and content by the evaluation committee and the awards will be presented to the winners at the Opening Ceremony of the X. Turkish German Gynecology Congress on April 30th, 2014. We would like to thank all contributing authors in this period for submitting their precious studies to our journal.

This coming spring, we will be celebrating the **X. Turkish German Gynecology Congress**, which will be held between the dates of April 30th and May 4th, 2014 in Antalya. Our foundation which has been organizing one of the biggest congresses of Turkey for the past twenty years has worked hard to organize a unique and memorable organization at its decennial anniversary. It is always our biggest pride that the interest of the gynecology and obstetrics community in our congress is increasing steadily. I am very proud to announce that **more than 500 abstracts** have already been submitted for presentation at our congress in poster, oral and video presentation categories. The best three of them will be financially awarded with a total of **5.000 TL**. The best abstract in Endoscopic Surgery category will also be awarded with **4.000 TL**. The aim of these awards is to appreciate the prolificacy of our colleagues in research projects and to encourage especially our young colleagues for the forthcoming years.

In addition to the pre-congress courses, hands-on training sessions, satellite symposiums and round table meetings taking place in our congresses regularly; we have enriched our scientific program with **live surgeries and innovative sessions**. As well as our previous congresses, we continue our tradition of collaborated sessions this year with the **AAGL - TAJEV Joint Session on Endoscopy** and **NOGGO - TAJEV Joint Session on Oncology**. Several leading scholars are invited in order to share their knowledge and experiences with the participants in special themes.

Please do not forget to mark **April 30th, 2014** on your calendars in order to not to miss this scientific festival.

Yours Faithfully,

Cihat Ünlü, M.D.
Editor in Chief of JTGGA
President of TAJEV

Journal of the
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2nd International Research Awards on Obstetrics & Gynecology

Dear Readers and Colleagues,

As you know, back in June 2013 we have announced that **Journal of Turkish-German Gynecological Association (JTGGA)** would accept submissions to compete in the **2nd International Research Awards on Obstetrics & Gynecology**.

Following the announcement, we were overjoyed by the interest we have received from international researchers. We have received many high quality submissions in this period. On behalf of the editorial, I would like to extend our sincere gratidute to the participants for submitting their valuable manuscripts for evaluation to win the award.

All participating manuscripts were peer-reviewed to evaluate their scientific contribution to the international literature, originality and content by external reviewers. We would also like to thank to all of our reviewers whose valuable opinions guided us to choose the best among many high quality manuscripts.

The evaluation committee, formed by the editorial board of the **Journal of Turkish-German Gynecological Association** has reviewed every single manuscript. Unfortunately the committee could not decide on a manuscript to win the 1st place among the submissions. The winners of the 2nd and 3rd places are listed below.

2nd Place

The effect of Silymarin on VEGF, VEGFR-1 and IL-1α levels in placental cultures of severe preeclamptic women

Mustafa Derda Kaya, Eralp Başer, Sibel Kay, Mustafa Kemal Takal, Feride Şahin, Esra Kuşçu, Filiz Yanık

Department of Obstetrics and Gynecology, Başkent University Faculty of Medicine, Ankara, Turkey

3rd Place

The role of TWIST, SERPINB5 and SERPIN1 genes for leiomyoma uteri

Mehmet Süha Bostancı, Merih Bayram, Murat Bakacak, Özge Kızılkale, Rukset Attar, Gazi Yıldırım, Ümit Emin Bağrıaçık, Baran Celtemen

Department of Obstetrics and Gynecology, Sakarya University Faculty of Medicine, Sakarya, Turkey
Department of Obstetrics and Gynecology, Gazi University Faculty of Medicine, Ankara, Turkey
Department of Obstetrics and Gynecology, Kahramanmaraş Sütçü İmam University Faculty of Medicine, Kahramanmaraş, Turkey
Department of Obstetrics and Gynecology, Yeditepe University Faculty of Medicine, İstanbul, Turkey

On behalf of the editorial board of the **Journal of Turkish-German Gynecological Association** and the **Turkish-German Gynecological Education and Research Foundation** I would like to congratulate the winners.

The awards of the winners will be presented to them during the opening ceremony of the X. Turkish German Gynecology Congress which will be held on **April 30th, 2014 in Antalya, Turkey.**

Yours Faithfully,

Cihat Ünlü, M.D.
Editor in Chief of JTGGA
President of TAJEV

Role of spiral artery Doppler to screen type 2 endometrial cancer cases

Soner Düzgüner[1], Mehmet Burak Özkan[1], Tuncay Küçüközkan[1], Enis Özkaya[1], Fadıl Kara[1], İpek Nur Balın[2], Vakkas Korkmaz[1], Mehmet Fatih Karslı[1], Burak Gültekin[1]

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[2]Department of Obstetrics and Gynecology, Etlik Zübeyde Hanım Gynaecological Diseases Training and Research Hospital, Ankara, Turkey

Abstract

Objective: The purpose of this study was to determine the value of endometrial blood flow assessment in predicting type 2 endometrial carcinoma.

Material and Methods: Sixty-five consecutive post-menopoausal women who had vaginal bleeding were enrolled in the study. All subjects were directed to transvaginal sonography to determine endometrial blood flow and underwent endometrial biopsy. Doppler findings were analysed to predict endometrial pathology. Subjects with unsatisfactory Doppler analyses were excluded from the study.

Results: Mean age of the study population was 50.1±6.9 years (42-73). Mean endometrial thickness was 10.1±2.9 mm (4-15 mm) and mean cancer antigen 125 (CA125) level was 20.1±17.4 U/mL (3-92). Histopathological evaluation revealed 14 cases of type 2 endometrial cancer and 18 cases of endometrial hyperplasia without atypia, while the other 33 cases had normal endometrial tissue. CA125 (Area under curve (AUC)=0.853, p=0.000), spiral artery resistance index (AUC=0.905, p=0.000), and spiral artery peak systolic velocity (AUC=0.822, p=0.000) were significant predictors for the type 2 endometrial cancer cases. Endometrial thickness did not significantly predict pathologic cases (p>0.05). Hyperplasia cases were not predicted by any of these diagnostic modalities (p>0.05).

Conclusion: In patients with postmenopausal bleeding, spiral artery Doppler ultrasound, could play a role in refining the diagnosis of type 2 endometrial carcinoma; however, its predictive value should be evaluated with further studies. (J Turk Ger Gynecol Assoc 2014; 15: 1-5)

Key words: Type 2 endometrial cancer, post-menopausal woman, spiral artery Doppler

Received: 03 November, 2013 **Accepted:** 25 December, 2013

Introduction

Endometrial carcinoma is predominantly a disease of postmenopausal women and the presenting sign is vaginal bleeding in more than 90%. Type II endometrial neoplasms account for 10 to 20 percent of endometrial carcinomas (1, 2). They have non-endometrioid histology (usually serous or clear cell) with an aggressive clinical course. These tumours are often high-grade, have a poor prognosis, and are not clearly associated with oestrogen stimulation. A precursor lesion is rarely identified. Type II neoplasms are generally associated with more aggressive clinical behaviour than type I tumours. An office endometrial biopsy is a sensitive test but the correct histology may not be identified in all cases (3). For these reasons, we focused this study on predicting type 2 endometrial cancer. In women with postmenopausal bleeding, an evaluation of endometrial morphology and vascularisation by using Doppler ultrasound imaging can be used to further refine the estimation of risk of pathology and, in particular, the risk of endometrial cancer (4-6).

Spiral artery is the end artery located just beneath the endometrial wall. To establish the fact in terms of endometrial histopathology, a Doppler study of the spiral arteries using resistance index (RI), pulsatility index (PI), peak systolic velocity (PSV) can be useful.

We hypothesised that vascular characteristics may correlate with the histopathology of the endometrium, knowledge that could be of value in assessment of the preoperative tumour and perhaps be used for risk evaluation. The aim of the study was to describe spiral artery Doppler sonographic features of the endometrium and relate the findings to predicting type 2 endometrial cancer.

Material and Methods

Patients

Between November 2009 and July 2013, 1523 postmenopausal women consulting for vaginal bleeding, underwent examination prospectively by two-dimensional grey-scale transvaginal sonography (TVS), colour and power Doppler.

Address for Correspondence: *Soner Düzgüner, Department of Obstetrics and Gynecology, Dr. Sami Ulus Maternity and Children Training and Research Hospital, Ankara, Turkey. Phone: +90 532 440 45 17 e.mail: sonerduzguner@yahoo.com*

DOI:10.5152/jtgga.2014.90197

Inclusion criteria were as follows: 1) Women with measurable spiral artery Doppler; 2) transvaginal sonography with a measurable endometrial thickness; 3) not taking hormone replacement therapy or tamoxifen; and 4) a definitive type 2 endometrial carcinoma histological diagnosis obtained at our centre. Of 1523 women with postmenopausal bleeding, 65 were eligible for inclusion, but 1458 were excluded (Figure 1).

After obtaining ethical approval and patient informed consent, a structured history was taken following a standardised research protocol regarding parity, age at menopause, history of polycystic ovarian syndrome (PCOS), diabetes, hypertension, height, weight, medicine usage and any genetic disease. None of these patients was receiving treatment with a hormone replacement regimen. Doppler characteristics of the endometrial spiral artery were recorded and all patients were scheduled for a diagnostic procedure by sampling endometrial tissue with the method of Dilatation & Curettage (D&C). The sonographic findings were compared with the histopathological diagnostics.

Sonography

Ultrasound examination of all patients was performed by same radiologist, transvaginally, before endometrial sampling, after completely emptied their bladders. The blood flow of endometrial spiral artery and endometrial thickness were performed by transvaginal 8 MHz ultrasonography (LOGIQ S6; General Electric, Milwaukee, USA). In order to describe the sonographic features of the endometrium, measurements were performed according to a consensus opinion from the International Endometrial Tumour Analysis (IETA) group (7). Endometrial blood flow was detected by intra-endometrial or the adjacent sub-endometrial regions within 10 mm of the echogenic endometrial borders. Double thickness of the endometrium was measured (maximum distance between each myometrial/endometrial interface). Thereafter, colour Doppler energy was superimposed on the 2-D Doppler studies that were performed on the selected area. The pulsatility index (PI), resistance index (RI) and peak systolic velocity (PSV, cm/s) of the endometrial spiral arteries were calculated when three similar, consecutive waveforms of good quality were obtained (pulse repetition frequency 0.8 kHz, wall filter 40 Hz, colour power Doppler gain was reduced until all colour artefacts disappeared) (7). The parameters were analysed for: (i) RI: the difference between maximal systolic blood flow and minimal diastolic flow divided by the peak systolic flow (S-D/S); (ii) PI: the difference between maximal systolic blood flow and minimal diastolic flow divided by the mean flow throughout the cycle (S-D/mean); and (iii) PSV.

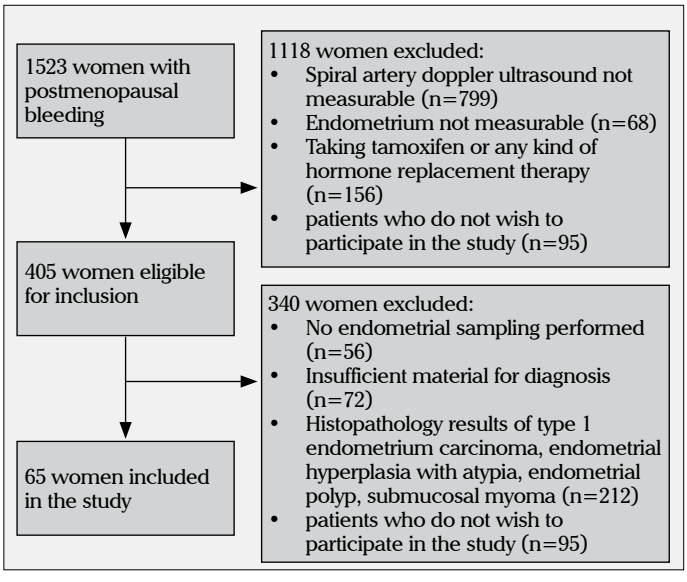

Figure 1. Algorithm showing the selection of the study population

Sample Size and Power

Sample size was calculated with 80% power and 95% confidence interval according to the previous study by Wang et al. (8).

Statistical Analysis

Data were entered to SPSS version 15; all data were presented as mean and standard deviation. The student t test was used to compare groups, correlation analyses were used to show association between variables and linear regression analyses were used to calculate adjusted associations. Receiver Operating Characteristic (ROC) analyses were used to assess the value of the test to predict abnormal cases. P value <0.05 was accepted to be statistically significant.

Results

One thousand five hundred and twenty three women with postmenopausal bleeding were screened from November 2009 to July 2013. The mean age of the study population was 50.1±6.9 years (42-73), and Body mass index (BMI) was 29.3±3.9 kg/m^2 (22.3-37.8). Mean CA125 level was found to be 20.1±17.4 U/mL (3-92). All women had postmenopausal bleeding. Mean endometrial thickness was 10.1±2.8 mm (4-15). Out of 65 postmenopausal women, 2 had diabetes mellitus, while 10 women had hypertension. Thirteen women were smokers in the study population. Endometrial tissue sample histopathological evaluation revealed 14 (21.5%) cases of type 2 endometrial cancer and 18 (27.7%) cases of endometrial hyperplasia without atypia. Another 33 women had proliferative, secretory or atrophic endometrium. In correlation analysis, age was found to be significantly correlated with endometrial biopsy histopathological results (r=0.513, p<0.001) and the spiral artery resistance index (r=0.284, p=0.029). Smoking was negatively correlated with spiral artery resistance index (r=-0.270, p=0.039), CA125 level (r=-0.274, p=0.027) and endometrial cancer (r=-0.270, p=0.039). Endometrial thickness was negatively correlated with the CA125 levels (r=-0.440, p<0.001). CA125 level was significantly correlated with endometrial cancer (r=0.516, p=0.001). Mean age, BMI, CA125, and spiral artery Doppler results of women with and without endometrial cancer are shown in Table 1. The predictive value of different variables to predict cancer cases are shown in Table 2. The optimal cut off value for PSV was 40.5 with 93% sensitivity and 60% specificity, and for RI was 0.73 with 86% sensitivity and 87% specificity; the cut-off value for CA125 was 19.5 with 86% sensitivity and 78% specificity (Figure 2).

Table 1. Clinical data and ultrasound results for patients with benign and malignant endometrium in the study

		N	Mean	Std. Deviation	*p* value
Patients Age (years)	N-H	51	47.7	3.8	<0.001
	EC	14	58.9	8.6	
BMI (kg/m^2)	N-H	51	29.2	4.3	NS
	EC	14	29.6	2.0	
Endometrial Thickness (mm)	N-H	51	10.4	2.4	NS
	EC	14	9.2	3.7	
CA125 Level	N-H	51	15.1	9.9	0.004
	EC	14	38.6	25.4	
Spiral Artery Doppler Resistance Index	N-H	51	0.68	0.12	<0.001
	EC	14	0.81	0.07	
Spiral Artery Doppler Pulsatility Index	N-H	51	0.99	0.20	NS
	EC	14	1.10	0.20	
Spiral Artery Doppler Peak Systolic Velocity	N-H	51	40.8	11.6	<0.001
	EC	14	52.6	7.2	

EC: Endometrial cancer; N-H: Normal endometrium and endometrial hyperplasia; NS: Not significant; BMI: Body mass index

Table 2. ROC curve statistics results of different variables to predict endometrial cancer cases

	Area	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
Spiral Artery Doppler Resistance Index	0.905	0.000	0.824	0.986
Spiral Artery Doppler Peak Systolic Velocity	0.822	0.000	0.717	0.928
CA125 Level	0.853	0.000	0.742	0.965
Patients Age (years)	0.859	0.000	0.730	0.987
Endometrial Thickness (mm)	0.431	0.438	0.219	0.642

[b]Null Hypothesis

In multivariate regression analyses, Age (R^2=0.82, beta=0.409, p=0.009), CA 125 (R^2=0.82, beta=0.256, p=0.01), spiral artery Doppler resistance index (R^2=0.82, beta=0.207, p=0.02) and the spiral artery peak systolic velocity values (R^2=0.82, beta=0.316, p<0.001) were significantly associated with the endometrial cancer cases.

Discussion

The best combination of clinical and cost-effective diagnostic methods are not yet defined in the evaluation of postmenopausal bleeding (9). There are a lot of studies that have constructed some sonographic methods and multivariate logistic regression models for the prediction and diagnosis of endometrial malignancy. Endometrial thickness, vascular patterns, fluid content of the endometrial cavity, and blood flow indices of the uterine artery are some of those that have been used in different models (4, 6, 10). Re-evaluating and adding further individual risk factors to the logistic regression model might improve its diagnostic performance. In this study, we focused on predicting type 2 endometrial cancer, a rare entity without well known risk factors, by means of spiral artery blood flow assessment.

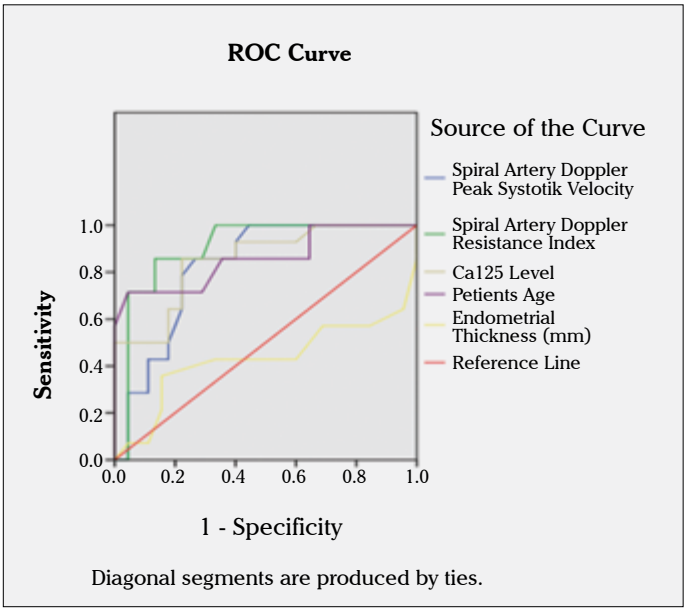

Figure 2. ROC curve of age, endometrial thickness, spiral artery RI and the PSV to predict endometrial cancer cases

Our study showed that endometrial spiral artery Doppler ultrasound examination can contribute to the correct prediction of type 2 endometrial malignancy, irrespective of endometrial thickness. We measured the resistance index in the spiral artery of 14 cases with type 2 endometrial carcinoma and found a significantly higher value for the spiral artery resistance index (RI=0.81±0.07) compared to that of normal and premalignant endometrium (RI=0.68±0.12). This is in contrast to a previous study in which velocimetric parameters (RI, PI, PSV) were not statistically different among different histopathologies (11). This may be explained by the high mean age of the study population with a wide range of distribution (47-83 years) and, in addition, the histopathological type of endometrial cancer was not mentioned in that study. Our study included a specific histopathological type of endometrial cancer (type 2) that may cause this kind of controversy. One study has shown that the median spiral artery RI (0.40) in 24 patients with endometrial carcinoma was significantly lower in comparison with the median spiral artery RI (0.61) of 82 patients with benign histopathologies (12). In that study, the authors found low vascular resistance in malignant cases; the reasons for this may be the variation in sonographic methods used to evaluate the endometrial lesions by transvaginal colour Doppler ultrasound and the assessment of both histopathological types of endometrial cancer. In our study, conversely, the mean value of PI was 1.10±0.20 in patients with type 2 endometrial cancer.

In the present data, there were only two postmenopausal women with an endometrial thickness of ≤5 mm. We saw that it was difficult to obtain data from the thin or indistinct endometrial stripe. In our series, no significant correlation was shown between the mean endometrial thickness and type 2 endometrium carcinoma (p=0.438). None of the spiral artery Doppler findings (RI, PI, PSV) were correlated with endometrial thickness (p>0.05).

In the beginning, we planned this study to evaluate Doppler measurements of type 2 endometrial cancer, which mainly originates from atrophic endometrium. Therefore, those cases with endometrial hyperplasia were grouped as the control. Thereafter, we showed that endometrial spiral artery Doppler ultrasound examination can contribute to a correct prediction of type 2 endometrial malignancy, irrespective of endometrial thickness. Additionally, our modalities (Doppler measurements) were not able to predict those cases with endometrial hyperplasia.

The results obtained by spectral Doppler procedures correlated with age and other measurements of BMI, such as CA125 levels. When regression analysis was performed by showing a causal relationship, high CA125 levels and advanced age were significantly associated with spiral artery RI and PSV; however, we did not find any significant association between spiral artery RI and BMI. The interpretation of CA125 levels has been based on a normal value of <35 U/mL (13). One study suggests that CA125 appears to be a significant independent predictor of the advanced stage of the disease (14). In our series, CA125 levels of patients with carcinoma were significantly higher (Mean value=38.6±25.4, p=0.004) than in patients with normal and premalignant histopathology. Ferrazi and co-workers found that the risk of endometrial cancer increased with increasing BMI (15). We did not find a positive correlation between BMI and type 2 endometrium carcinoma in this study (p>0.05). Also, there was no correlation between spiral artery RI and BMI (p>0.05).

Spiral artery Doppler analyses are satisfactory only in 30% of women within 1-5 years post-menopause (16). In our study, spiral artery Doppler analyses were optimal in a few number of women with normal and hyperplasic histopathological results; therefore, few women were left in the control group, while all analyses were satisfactory in the group with cancer. This result led us to conclude that satisfactory spiral artery Doppler assessment in late postmenopausal years necessitates further investigation for the higher risk for malignancy in postmenopausal women.

It is a strength that sonographic measurements (machine settings, qualitative assessment of the endometrium, colour and power Doppler assessment) were performed according to a consensus opinion from IETA (7). Since we used a standardised terminology, it would allow comparisons between future studies on the endometrium. The differences in results between studies can probably be explained by differences in the experience of the examiners and ultrasound equipment. Three-dimensional ultrasound imaging might also prove useful in the diagnosis of endometrial pathology, but in this study we limited ourselves to colour Doppler flow imaging and two dimensional grey-scale ultrasound.

In conclusion, although our series was relatively small, our data indicate that spiral artery Doppler ultrasound may play a role in refining the diagnosis of type 2 endometrium carcinoma in patients with post-menopausal bleeding. Further studies in larger series are needed to confirm or refute these preliminary data.

Ethics Committee Approval: *Ethics committee approval was received for this study.*

Informed Consent: *Written informed consent was obtained from patients who participated in this study.*

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USG guided FNAC of ovarian mass lesions: A cyto-histopathological correlation, with emphasis on its role in pre-operative management guidelines

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Abstract

Objective: Ultrasonography (USG)-guided fine-needle aspiration cytology (FNAC) of ovarian masses is an efficient diagnostic modality for accurately diagnosing ovarian tumours prior to surgery. The main aim of this study was to assess the sensitivity, specificity and accuracy of FNAC in diagnosing ovarian masses.

Material and Methods: Eighty-three patients with ovarian masses were recruited and correlation of USG-guided FNAC was made with histopathology in all but 6 cases, where surgery was not indicated.

Results: Cytological diagnosis was obtained in all 83 ovarian lesions: 56 cases were benign, 6 possibly benign, 3 suspicious of malignancy and 18 cases as malignant. Out of 77 cases where histology was available, the 12 non-neoplastic cysts were endometriotic cysts and follicular cysts. The majority of neoplastic lesions were surface epithelial tumours. Out of 12 non-neoplastic cysts and 43 benign tumours, all but two were diagnosed as benign or possibly benign on cytology; of the 22 histologically malignant or borderline tumours, 18 were malignant or suspicious of malignancy on cytology, while four were false negative (three of these were borderline tumours). Thus, the sensitivity of cytological diagnosis was 83%, specificity was 97% and accuracy was 93%.

Conclusion: USG-guided FNAC seems to be a relatively safe, simple, fast and cost-effective procedure where most ovarian malignancies either present late in their course or no screening method is available. In addition, cyto-radiological correlation through this procedure may be useful in deciding management guidelines prior to any surgical intervention.

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Key words: Ultrasound, fine-needle aspiration cytology, ovarian mass, image-guided, cytology

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Introduction

With the increased use of imaging techniques, the detection of asymptomatic ovarian masses has risen considerably. The nature of ovarian lesions less than 5-6 cm may be difficult to determine and cysts in premenopausal women may be functional. However, an ovarian mass in perimenopausal and menopausal women is a matter of concern, owing to the increased risk of malignancy in this age group (1). The incidence of malignant ovarian masses has steadily increased over the past two decades and is one of the leading causes of cancer-related deaths globally. The majority (>90%) of ovarian masses are benign but almost two-thirds of malignant ovarian tumours present at an advanced stage (stage III or IV) (2). Clinicians are aware of the difficulty in differentiating a unilocular cystadenoma and a follicular or corpus luteum cyst in the clinical setting (3). Unfortunately, no single test or combination of tests has been shown to accurately predict ovarian histologic findings. Limitations of our current techniques might be the cause of many unnecessary surgical interventions which could have been otherwise avoided (1). Fine-needle aspiration cytology (FNAC) of these ovarian cysts may offer the potential to decrease the need for surgical procedures in these women. Historically, gynaecologists have been hesitant to aspirate ovarian cysts in view of the possibility of seeding an early stage ovarian cancer. The magnitude of risk of such a procedure is unknown and not substantiated by convincing evidence. It is rather overestimated and has not been pathologically confirmed (4). Some researchers believe that ovarian cysts can be safely aspirated for diagnos-

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tic purposes, and that FNAC should be used in conditions like suspected benign ovarian cysts and recurrent and metastatic tumours, when the patient's condition is unsuitable for surgery (1, 5). Among the available imaging modalities, ultrasonography (USG) is economical, rapid and widely available, not only providing substantial information regarding the nature of the mass but also guiding the fine-needle aspiration (FNA) with adequate precision (6). Previous studies have attempted to estimate the efficacy of image-guided FNAC in the accurate preoperative diagnosis of ovarian lesions (1, 5-8). The main aim of this study was to assess the sensitivity, specificity and diagnostic accuracy of USG-guided FNAC in the distinction of neoplastic and non-neoplastic ovarian masses, considering histopathology as the gold standard.

Material and Methods

Patients presenting with ovarian masses diagnosed clinically (abdominal and per vaginal examination) and/or by USG during the period from September 2008 to March 2011 were included in this study. FNAC under USG guidance was performed through the abdominal or trans-vaginal route for incidentally detected localised mass lesions, benign cystic lesions or advanced malignant neoplasms. Informed consent was obtained from the patients, mentioning that the procedure was carried out for diagnostic purposes and to decide upon further management. Ethical committee approval was obtained before the study was commenced. The ovarian lesions were aspirated using a 20 ml syringe fitted with a 22-gauge long needle. Air-dried smears were prepared and stained with May-Grünwald-Giemsa (MGG) and wet-fixed smears were subjected to Papanicolaou and/or H&E (Haematoxylin & Eosin) stain. In cases where cyst fluid was aspirated, it was subjected to cytocentrifugation and the sediment was stained by similar methods. Patients suspected of harbouring malignant lesions based on menopausal status and suggestive USG findings were subjected to serum CA-125 estimation. In all but 6 cases, surgery was performed within 10 days of FNAC. The resected ovarian mass lesions were routinely processed and the tumours were histologically classified as per the guidelines established by the World Health Organisation (WHO) classification. Based on clinico-radiological correlation, the cytological findings were categorised as benign, possibly benign, suspicious of malignancy and malignant. Based on the cytological diagnosis, the cases were grouped into the following categories: 1 for malignant, 2 for 'suspicious of malignancy' and 3 for 'possibly benign' and benign lesions. Similarly, for histological diagnosis, 1 was designated for malignant SOLs, 2 for the borderline malignant category and 3 for benign lesions. Unilocular cysts less than 5 cm where only straw-coloured fluid was aspirated were classified as possibly benign. Specimens with cells with a mild increase in the nuclear/cytoplasmic ratio or mild nuclear atypia was assigned as suspicious of malignancy. In addition, background showing tumour diathesis and debris were also considered as features suspicious of malignancy. Cytological features indicating malignancy were high cellularity with cells in three-dimensional clusters and dissociation, nuclear pleomorphism, increase in nuclear-cytoplasmic ratio, prominent nucleoli, presence of mitotic figures and tumour diathesis. Specific categorisation of the lesions was also possible on cytology in cases with certain characteristic findings on smears.

Descriptive statistics were used to determine correlation between cytological and histological findings. Sensitivity and specificity for the cytological diagnoses were calculated using the histological confirmation as the gold standard. Analyses were performed using the SPSS software, version 16.0 (SPSS Inc., Chicago, IL, USA).

Results

During the 30 month period, 83 cases of ovarian mass lesions were evaluated on cytological smears; of these cases, histopathology was not available in 6 patients. The mean age of the women was 39.8 years (age range 15-70 years). The most common presenting feature was abdominal mass (68.83%) followed by lower abdominal pain (41.6%), menstrual disturbances (28.57%) and weight loss (11.68%). USG helped in the assessment of the type (cystic, solid, unilocular or multilocular), size, location and extent of the lesion. In case of malignant neoplasms diagnosed during laparotomy, all were beyond stage IIC, except in one patient who had stage IA disease. On image-guided aspiration cytology, 56 cases were diagnosed as benign, 6 as possibly benign, 3 as suspicious of malignancy and 18 cases as malignant.

Histological confirmation was available in 77 cases. Of the 12 non-neoplastic cysts and 43 benign neoplasms on histology, all but two were benign or possibly benign on cytology; of the 22 histologically malignant or borderline tumours, 18 were malignant or suspicious of malignancy on cytology while four were false negatives (three of these were borderline tumours) (Table 1, 2).

All but one of the non-neoplastic cystic lesions were diagnosed accurately by FNAC, which included 2 cases reported as possibly benign and 5 more cases where histopathology was not performed since the cyst dimension was less than or equal to 5 cm. These latter 5 cases of follicular cyst were diagnosed as 'benign cystic lesion' on cytology. One endometriotic cyst was erroneously diagnosed as a serous carcinoma, while the remaining 6 endometriotic cysts were diagnosed accurately. Another case where histology was not available was a serous cystadenocarcinoma with metastasis and peritoneal nodules. For all 83 cases, the sensitivity and specificity of FNAC considering final (histological) diagnosis as the gold standard (Table 3) were 83% and 97%, respectively, with a diagnostic accuracy of 93%. Chi square test was performed to correlate between cytological and final (histological) diagnosis, and was highly significant ($p<0.001$). The measure of agreement between the diagnoses, as obtained by 'Kappa' value, was 0.725, indicating substantial agreement between the cytological and histological diagnoses.

Table 1. Comparative analysis of confirmed benign ovarian lesions (on histology) and their corresponding cytological diagnoses

Histopathological Diagnoses	Cytopathological Diagnoses		
Non-neoplastic lesions	**Benign**	**Possibly Benign**	**False Positive**
Follicular cyst (n=4)	2+5*	2	
Corpus Luteal cyst (n=1)	1		
Endometriotic cyst (n=7)	6		Serous carcinoma - 1
Benign neoplasms			
Brenner tumour (n=1)			Mucinous carcinoma - 1
Serous cystadenoma (n=17)	17		
Mucinous cystadenoma (n=14)	14		
Benign cystic teratoma (n=9)	9		
Fibroma (n=2)	2		
Total (n=55)	51+5*	2	2

*In 5 cases, histopathology was not performed; hence, a total of 60 cases were evaluated on image-guided aspiration cytology

Table 2. Comparative analysis of confirmed benign ovarian lesions (on histology) and their corresponding cytological diagnoses

Histopathological Diagnoses	Cytopathological Diagnoses		
	Malignant	**Suspicious of malignancy**	**False negative**
Serous cystadenocarcinoma (n=7)	7+1*		
Mucinous cystadenocarcinoma (n=4)	3		Serous cystadenoma - 1
Serous borderline tumour (n=4)	1	2	Serous cystadenoma - 1
Mucinous borderline tumour (n=3)	0	1	Serous cystadenoma - 1
			Mucinous cystadenoma - 1
Dysgerminoma (n=1)	1		
Yolk sac tumour (n=1)	1		
Granulosa cell tumour (n=1)	1		
Squamous cell carcinoma (n=1)	1		
Total (n=22)	15+1*	3	4

*In 1 advanced case, histopathology was not performed; hence, 23 cases in total were evaluated on image-guided aspiration cytology

Table 3. Correlation of ovarian image guided FNAC and histological (confirmed) diagnoses (n=83)

Histological Diagnosis	FNAC Diagnosis		
	Malignant	**Benign**	**Total**
Malignant	19*	2	21
Benign	4	58#	62
Total	23	60	83

FNAC: Fine-needle aspiration cytology
*Includes one advanced case without histology
#Includes 5 cases <5 cm, which were not biopsied
- Confirmed diagnosis either on histology or clinico-radiological analysis, where histology was not available
- Malignant in FNAC also includes lesions suspicious of malignancy; benign also includes 'possibly benign' lesions

When characteristic cytomorphological findings were appreciated, the specific diagnosis (instead of merely 'benign', 'possibly benign' or 'malignant') could be offered on cytology. The diagnosis of endometriotic cysts was offered on cytology when sheets of epithelial cells and spindle (stromal) cells were seen against a haemorrhagic background containing haemosiderin-laden macrophages (Figure 1). Out of 77 cases where histology was available, the majority of cases were surface epithelial tumours of serous and mucinous variety (Table 1, 2). Serous cystadenomas on FNA yielded straw-coloured fluid. Smears prepared from the centrifuged deposit showed few papillary fragments with bland nuclei and cyst macrophages. Benign

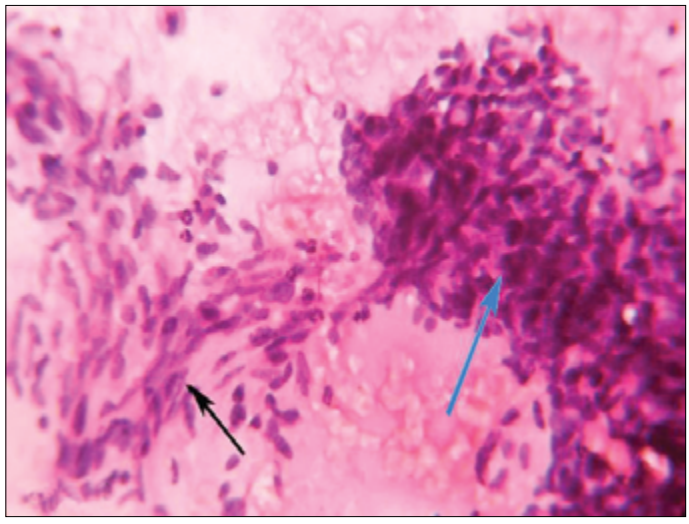

Figure 1. Stromal component (*black arrow*) & epithelial component (*blue arrow*), (Endometriotic cyst), H&E, 40 X

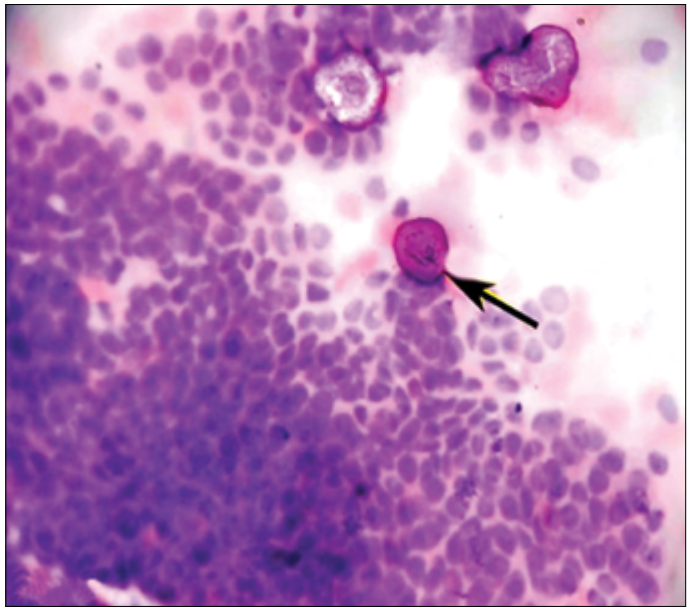

Figure 2. Papillary tissue fragments of malignant glandular cells, psammoma body (*black arrow*) (Papillary serous cystadenocarcinoma), H&E, 40 X

mucinous neoplasms showed small clusters and isolated columnar epithelial cells with basally placed nuclei against a mucinous background. In most of the cases of serous and mucinous cystadenomas, specific diagnosis could be rendered on cytology. However, 2 cases of borderline mucinous tumour, 1 case of borderline serous tumour and 1 mucinous cystadenocarcinoma were diagnosed erroneously (Table 2). Papillary serous cystadenocarcinoma showed papillary fragments comprised of tumour cells with hyperchromatic nuclei and a high nucleo-cytoplasmic ratio. Psammoma bodies were identified in 2 cases (Figure 2). Mucin-producing cells with malignant nuclear features against a background of mucin was seen in mucinous cystadenocarcinomas (Figure 3a, b). One case of Brenner

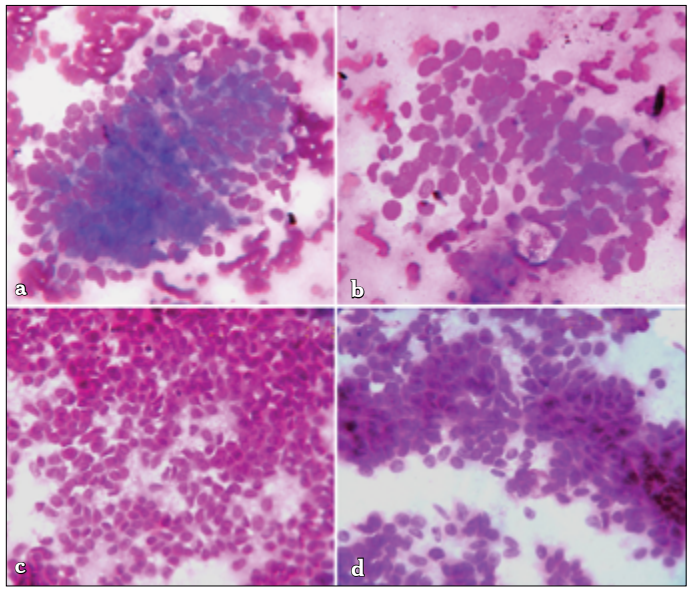

Figure 3. a-d. Mucinous cystadenocarcinoma. Mucin-producing cells in clusters, MGG, 40 X (a). Mucinous cystadenocarcinoma. Epithelial cells with prominent nucleoli, MGG, 40 X (b). Granulosa cell tumour. Uniform round to ovoid cells with microfollicle formation, H&E, 40 X (c). Granulosa cell tumour. Loose cluster of cells with uniform, ovoid nuclei, some with grooves, H&E, 40 X (d)

tumour was misdiagnosed as mucinous cystadenocarcinoma on cytology (Table 1). Aspirate from a benign cystic teratoma showed mature squamous cells and degenerated cells in a dirty background, whereas fibroma showed a few tight clusters of benign plump spindle cells. The only case of granulosa cell tumour showed uniformly small round nuclei with microfollicle formation and nuclear grooves, which were more prominent in alcohol-fixed smears (Figure 3c, d, 4). Dispersed cells with distinct nucleoli and pale fragile cytoplasm, along with scattered lymphocytes in the background, were found in dysgerminoma. Yolk sac tumours, on the other hand, showed papillary clusters of cells with cytoplasmic vacuolation and pink globules. We also had one case of squamous cell carcinoma, possibly arising from a teratoma, which showed squamous cells with dense refractile cytoplasm and irregular hyperchromatic nuclei. Smears from 3 lesions that were cytologically labelled as 'suspicious of malignancy' showed monolayered sheets of epithelial cells with an increased nucleo-cytoplasmic ratio against a dirty background. However, mitotic figures and nucleoli were not conspicuous in these cases (Figure 4). Two cases belonging to this category were serous borderline tumours, while one case was a mucinous borderline tumour.

Discussion

Patients with ovarian masses, particularly those having malignant lesions, usually present with advanced disease. There are conflicting data regarding the diagnostic accuracy and safety of FNA (9-11). Aspiration cytology has been widely used method for the diagnosis of solid and cystic masses of the ovary. The

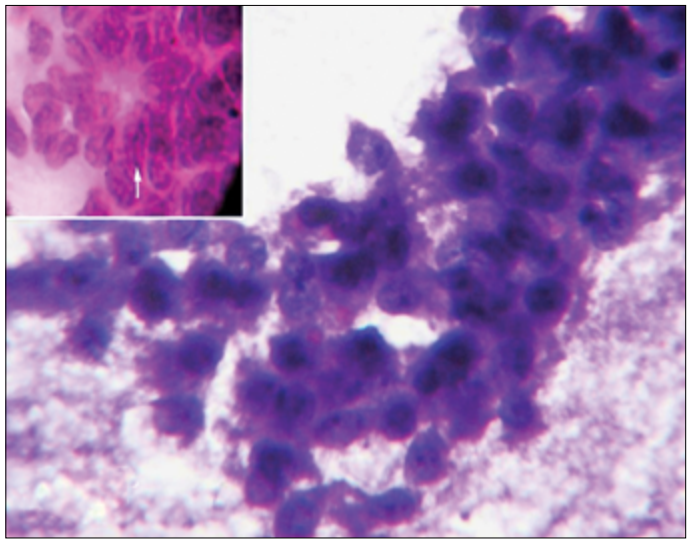

Figure 4. Monolayered sheets of epithelial cells with increased nucleo-cytoplasmic ratio and inconspicuous nucleoli suspicious of malignancy on cytology. Inset showing grooves (*white arrow*) in Granulosa cell tumour MGG, 40 X

procedure has been used for both the primary diagnosis of ovarian lesions and the follow-up of recurrent malignancies. Developing radiologic guidance techniques have also contributed to the higher accuracy of FNAC in recent years (2). This technique is used in other fields of medicine and of proven value in diseases of breast, thyroid and lung (12).

In gynaecologic oncology, FNAC has been used both for primary diagnosis and follow-up of recurrence in malignant ovarian lesions. The procedure is also accurate and safe for the diagnosis of disease that has metastasised to the lymph nodes, parametrium and vagina (13). Advancement of the radiologic guidance technique has contributed to the higher accuracy of FNAC in recent years (2). Gynaecologists are concerned about the safety of this procedure and the consequent upstaging of ovarian cancers. Zanetta et al. (14) reported fewer complications in a study of aspiration of 838 ovarian cysts. They concluded that FNAC can decrease the need for surgery in many women with ovarian cysts.

Owing to its complexity and the wide spectrum of diagnoses, cytological analysis of ovarian lesions is a difficult issue. However, differentiation into malignant and benign tumours is possible by the careful evaluation of the cytoarchitecture and background features (2). Pinpoint diagnosis can be made in a large number of cases. A critical issue of this procedure excluding its safety is regarding its accuracy. Information available in this regard projects some conflicting results. Ganjei & Dickinson correctly diagnosed 9 out of 12 ovarian malignancies by FNAC; cytological examination correctly predicted all benign lesions of the ovary in their study, and they observed a sensitivity of 75% (15). Wojcik & Selvaggi also reported that the majority of cystic ovarian lesions can be diagnosed accurately; however, they did not correlate FNAC with histology in 53% of their cases (16). Aysun & Canan compared the findings of FNAC and histology in ovarian masses and found a high sensitivity (95.1%) and a specificity of 90.4% (2). Gupta and Rajwanshi found a sensitivity of 85.7% and a specificity of 98.0% (7). Cole and co-workers found FNAC to be highly specific (100%) but conversely with a very low sensitivity of only 50% (8).

Our observations corroborate closely with those of other investigators, which indicates that FNAC can have appreciable sensitivity, specificity and accuracy in the diagnosis of ovarian masses. Higgins et al. (1) reported a specificity of 90% in the cytological evaluation of ovarian cysts, which is comparable to the present study, but showed a much lower sensitivity of 25%. This may have been due to the inclusion of cystic ovarian lesions only in their study and the aspiration of cysts in post-surgical specimens.

The differences in the reported accuracy of cytological evaluation of ovarian masses may reflect the differences in the technique used to aspirate the lesion (transvaginal, transabdominal, laparoscopic or during laparotomy, with or without image guidance) as well as differences in smear preparation. Correlations with clinical parameters of the patients undergoing FNAC may be important, including serum markers and USG, as some studies included only women with a lower risk (11). USG can provide necessary clues towards the nature of the lesion: anechoic to hypoechoic lesions suggest a benign cyst, while solid cystic lesions with heterogeneous echogenicity indicate malignancy. Our study population included women with both cytological and histopathological materials available. Consequently, this study may be biased towards cases that are more suspicious clinically and patients requiring subsequent surgery.

Several other factors may explain a poor cyto-histopathological correlation. FNAC of an ovary may yield cyst fluid, ovarian cortex, ovarian stroma, or a combination of these structures. Ovarian cyst fluid may have occasional cells only (in a background of fluid) to provide an accurate impression of the lesion. Malignant cells in the ovary may not be uniformly distributed in the organ, and it can often be seen that cytological examination of the peritoneal washings in patients with known ovarian malignancy fail to identify malignant cells (1). Clinicians may have an unrealistic impression that interpreting ovarian cytological evidence is similar to analysing cytological findings from other organs. Ovaries have an incidence of an extensively diverse spectrum of primary tumours; hence, the impression on image guided cytology may not always accurately corroborate with the histopathology. In addition, borderline epithelial tumours may be difficult to interpret on aspiration cytology. Careful observation of a few small clusters of atypical cells with tumour diathesis may prompt a diagnosis towards 'epithelial lesion, suspicious of malignancy' in such cases. Many pathologists might not have the training and experience in the diagnosis of aspiration smears as they have in histopathological sections (1).

Fine-needle aspiration cytology provides some advantages for evaluating ovarian diseases, including excellent patient compliance and an extremely low complication rate. However, precisely categorising borderline tumours and false negative

cytological analysis may be its limitations (2). Some studies indicate that the use of FNAC in ovarian cystic lesions can mislead the clinician about the nature of the cyst. If all types of ovarian lesions are analysed in sufficient numbers, it might improve the diagnostic accuracy (1).

Pelvic masses should be evaluated meticulously by laboratory, radiography and USG tests. Despite the lack of evidence, gynaecologists prefer exploratory laparotomy to FNAC due to the fear of peritoneal seeding from tumour cell spillage. FNAC of solid ovarian SOLs may play a useful role in determining tumour type and formulating management. Moreover, FNAC in patients with benign lesions like endometriosis or inflammatory masses may also lead to the patients being spared unnecessary surgery (15). Although the potential risk of seeding of an ovarian cancer during FNA has been mentioned in textbooks, only one reference was documented, 19 years ago (17-19). This was a series of 2 cases having a tumour which was believed to have spread due to the FNA performed during laparoscopy (20), while available recent literature remains silent in this regard.

Mulvany further reports in his study of 235 ovarian cyst aspirates than none of the 7 malignant cases in his series had an increased recurrence due to ovarian cyst aspiration (21). Hence, it seems reasonable to state that the potential threat of tumour spillage due to FNA has not been convincingly and adequately reported and the magnitude of such risk remains unknown (22). In addition, since more than two-thirds of malignant ovarian tumours present in an advanced stage, the concern for tumour dissemination seems much less important when weighed against the less invasive, effective and economical diagnostic tool available in the form of FNAC. In this clinical setting, neoadjuvant chemotherapy may be considered prior to cytoreductive surgery, and it is imperative that accurate diagnosis is required for such therapy. Although in this study the specificity of cytologic evaluation of ovarian cystic masses was comparable with other similar studies, a much higher sensitivity is desirable to identify women in whom subsequent surgical intervention may be unnecessary. FNA of ovarian cystic masses with 97% specificity and 83% sensitivity still surpasses other clinical parameters in the diagnosis of malignancy. Hence, the available clinical, radiological and laboratory findings may be combined with FNAC for an accurate preoperative diagnosis.

To conclude, image-guided FNAC is a quick, easy, fairly sensitive, specific and cost effective modality for the preoperative diagnosis of malignant as well as benign ovarian masses with minimal morbidity, pending histological confirmation. Dissemination and seeding of malignant cells during the procedure is not supported by adequate and conclusive literature. Targeted larger trials to address the issue of seeding of malignant cells during the procedure are needed to prove or disprove its debatable role in diagnosis. On the other hand, the procedure may help in avoiding unnecessary surgery or laparoscopy and making decisions regarding neoadjuvant chemotherapy; hence, it might be indispensible in this part of the world where most of the ovarian malignancies either present late in their course or as such no screening method is available. Accurately identifying borderline tumours and false negative cytological analysis due to low cellularity or secondary degenerative changes may be its limitations.

Ethics Committee Approval: *Ethics committee approval was received for this study.*

Informed Consent: *Written informed consent was obtained from patients who participated in this study.*

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Expression of P-cadherin (cadherin-3) and E-selectin in the villous trophoblast of first trimester human placenta

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Abstract

Objective: Although trophoblastic invasion has a critical role in human placental development, very little is known about them. The aim of the present study was to localise the expression of P-cadherin (cadherin-3) and E-selectin in first trimester placenta.

Material and Methods: This study was conducted on 140 patients who had applied to Gülhane Military Medical Academy, Haydarpaşa Education Hospital, Department of Obstetrics and Gynaecology between 2005 and 2006. The patients were divided into three groups: ectopic pregnancy group (Group 1), spontaneous abortion group (group 2) and curettage group (group 3 and/or control group). Patients with a history of systemic diseases (such as thrombophilia), a disease or anatomical diagnosis that may cause recurrent abortion or an aetiological factor for ectopic pregnancy were excluded from the study. Paraffin blocks were stained with E-selectin and P-cadherin in accordance with the procedure. Demographic characteristics of patients (patient age, gravida, parity, number of previous abortions, and last menstrual period) and staining intensities were compared using Analysis of Variance (ANOVA) among groups.

Results: According to the average scale score of P-cadherin staining of cells, the three groups were statistically different from each other ($p=0.0001$). This difference stems from statistically significantly lower scores in the spontaneous abortion group than in both the ectopic pregnancy group ($p<0.001$) and the control group ($p<0.001$). E-selectin immunostaining showed no positive staining in the groups.

Conclusion: In placental trophoblasts, decreased P-cadherin immunoreactivity plays a role in the aetiopathogenesis of spontaneous abortion.

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Key words: Adhesion molecules, E-selectin, human trophoblast, P-cadherin, placenta

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Introduction

For the initiation and continuation of a healthy pregnancy, implantation of blastocysts to the endometrium prepared with oestrogen and progesterone stimulations is required. The implantation is, in fact, a union that occurs between the two tissues which are genetically different from each other (1, 2). Following endometrial attachment and implantation of the blastocyst, interstitial and intravascular invasion of the maternal tissue by trophoblast occurs and a human haemochorial placenta with foetal origin composed of cytotrophoblast stem cells is formed (3). Inflammatory cells, extracellular matrix components and cell adhesion molecules (CAMs) play a major role in the entire complex chain of events where several reactions take place (1, 2, 4-8). A potential glitch in one of the stages, such as implantation, invasion and placentation may result in many adverse pregnancy outcomes including early pregnancy loss (EPL), foetal malformation, foetal growth retardation, and stillbirth (1, 2, 9-14).

Cell adhesion molecules are named according to their functions and structures. The role of cell adhesion molecules in the regulation of many events such as histological and embryological development, cell growth, cell differentiation, cancer and inflammation has been reported in previous studies (1-4, 9-12, 15-19). Selectin among CAMs is particularly involved in the implantation stage (10), whereas the majority of others play a role at every stage, ranging from implantation to placentation (3, 9-12, 15-18). The cadherin family constitutes the largest group of CAMS. To date, studies have defined almost one hundred cadherin molecules. Cadherin, a calcium-dependent transmembrane glycoprotein, is required for the expression of specific adhesion molecules in the embryo, cell migration, and coalescence of cells in early embryonic tissues (3, 9, 16-18). In particular, E-cadherin plays a key role in regulating trophoblastic invasion (19).

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In human reproduction, EPL is one of the most common complications and has an incidence ranging between 50 and 70% of all conceptions (14). Chromosomal abnormalities are important in the aetiopathogenesis. In recent years, studies at the molecular level have demonstrated the role of the inadequate secretion of CAMs in early pregnancy loss (13). During *in vitro* studies, the down-regulation of VE-cadherin and up-regulation of E-cadherin have been reported to cause EPL (14). In particular, the insufficient invasion and abnormal placentation by trophoblasts are known to play a role in EPL. However, the presence and role of CAMs and cadherins, in particular in human placenta, are not fully known. The presence of a very low rate of P-cadherin molecule (cadherin-3) has been shown in only the human placenta in previous reports (20).

The purpose of this study is to investigate whether E-selectin and P-cadherin (cadherin-3), among those cell adhesion molecules that have wide-ranging roles in implantation and placentation, have a role in early pregnancy complications by measuring their levels in human villous trophoblast cells of patients with an early pregnancy complication and healthy individuals.

Material and Methods

Study Design

The study was approved by the local ethics committee, and written informed consent was obtained from all participants. This retrospective immunohistochemical study was conducted on patients who applied to Gülhane Military Medical Academy, Haydarpaşa Training Hospital, Obstetrics and Gynaecology Department between February 2005 and June 2006, who were operated upon with a diagnosis of ectopic pregnancy and pathologically diagnosed with ectopic pregnancy, had spontaneous abortion with remaining abortion material, and had an elective pregnancy termination for family planning within legal limits or had their pregnancy terminated because of exposure to teratogenic agents. Accordingly, patients were divided into three groups: ectopic pregnancy group (group 1), spontaneous abortion group (group 2) and curettage group (group 3 or control group). Demographic characteristics of patients (patient age, gravida, parity, number of previous abortion and last menstrual period) were retrieved from the patients' follow-up cards and hospitalisation files held in the department. Patients with a history of systemic disease, thrombophilia, congenital uterine anomaly, sub-mucous and/or intramural myoma greater than 4 cm and with an aetiological factor for recurrent abortion or ectopic pregnancy in their past medical history were excluded from the study. In addition, those patients whose materials were subjected to coagulation necrosis and those showing no chorionic villus under light microscopy were excluded from the study. Materials of the three different groups in the study were evaluated by only one pathologist without specifying the group of the patients in order to minimise inter- and intra-observer variability. For immunohistochemical staining, we selected E-selectin and P-cadherin, which are particularly applicable to paraffin blocks and are known to be effective in both the implantation and placentation.

Procedures and Methods

We have used the paraffin blocks selected in accordance with predetermined cases from the archive between February 2005 and June 2006. Sections from each block were stained with haematoxylin-eosin and examined. Two sections with a thickness of 3 μm, including one for negative control and one for testing purposes, were taken on positively charged slides from selected blocks for E-selectin and P-cadherin applications. The sections were incubated for 18 hours at 56°C and rehydrated with distilled water following the standard deparaffinisation with two different xylene solutions and three different ethanol solutions. After the prepared sections underwent the antigen retrieval procedure with 10% Citrate for 35 min at 100°C, endogenous peroxidase was deactivated with 3% hydrogen peroxide. In accordance with the recommended procedures, after incubation with P-cadherin and E-selectin primary antibodies for 30 min and 18 hours, respectively, 3,3'Diaminobenzidine (DAB) chromogen and Mayer's haematoxylin stains were performed before immunohistochemical procedures were completed. In this study, the primary antibodies P-cadherin Ab-1 clone 56C1 (Thermo Fisher Scientific Anatomical Pathology, California, USA) and E-selectin P2H3 (Santa Cruz Biotechnology, Texas, USA) were used. Preparations were evaluated by light microscopy. The cells were defined as positively or negatively stained on the basis of the presence or absence of membranous staining and rated according to the staining status: 1 point, negative; 2 points, weak staining; 3 points, moderate staining; and 4 points, severe staining (Figure 1).

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences for Windows 13.0 software (SPSS Inc., Chicago, IL, USA). Descriptive statistics were given as mean, standard deviation, median, min-max. Analysis of variance (ANOVA) was used for independent group comparisons. If a significant p value was identified between groups, we used

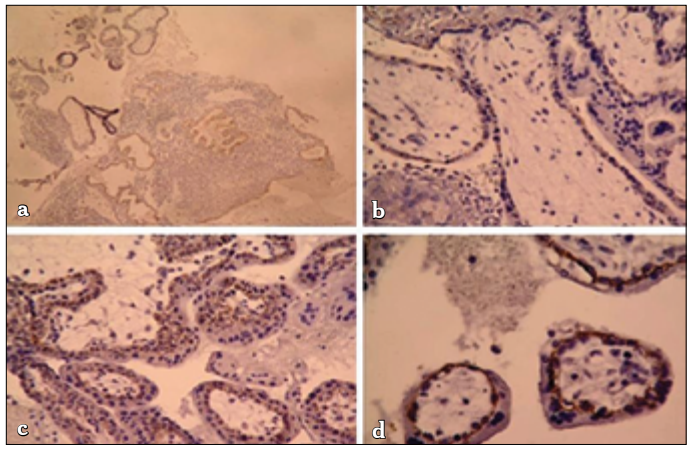

Figure 1. a-d. Immunohistochemical staining with E-selectin and P-cadherin for the villous trophoblast of first trimester human placenta. E-selectin was only positive in the endometrial glands and tubal epithelium lining (a). P-cadherin was positive for the samples of all placental villi (b=weak staining, c=moderate staining, d=severe staining) (b-d)

Tukey-Kramer Multiple Comparisons Test among Post hoc testing options for intergroup comparisons. We calculated a 95% confidence interval for the results and the statistical significance was defined as $p<0.05$. A two-sided p value was considered for all comparisons.

Results

The present study was performed on paraffin blocks of a total of 140 patients including 34 patients in the ectopic pregnancy group (Group 1), 60 patients in the spontaneous abortion group (Group 2) and 46 patients in the control group (Group 3). Patients' demographic characteristics that are shown in Table 1 showed no statistically significant difference between groups. The mean maternal age of all groups was 30.7 years and the mean gestational age was 6.8 weeks.

The average scale score for P-cadherin staining of the cells within groups is shown in Table 1. Accordingly, the average scale scores for P-cadherin staining were statistically significantly different among the three groups ($p=0.0001$), as shown in Table 2. Table 2 shows a statistically significant difference between the spontaneous abortion group and both the ectopic pregnancy ($p<0.001$) and control groups ($p<0.001$), but not between the ectopic pregnancy group and the control group. In addition, our study also demonstrated the presence of endometrial glandular cells and stromal P-cadherin (cadherin-3) antibodies.

Although E-selectin positivity was seen in endometrial glands and tubal epithelium lining, there was no immunoreactivity for the samples of placental villi on staining for this marker (Figure 1a). Therefore, no statistical analysis was performed for E-selectin staining.

Discussion

Implantation is a fusion between embryonic and maternal tissues which are genetically different (1, 2). In mammals, the embryo which has only reached the blastocyst stage can be implanted in the uterus (2). Although some of the events in implantation are similar to some of the events in tumour invasion or inflammation, implantation is different as it comprises a series of completely controlled events (3, 21). Especially, trophoblastic cells play very important roles in the attachment and invasion of blastocysts to the endometrium during the process of implantation (1, 2). Interaction between the outermost layer of the trophectoderm with a precursor of the placenta and the luminal epithelium lining of the uterus initiates implantation with a delicate equilibrium (1). Various structural, cellular and molecular changes occur in the endometrium during the preparatory period of endometrial receptivity, which is also referred to as the "window of implantation", although the uterus seems to have a limited role in the events (1). Oestrogen and progesterone hormones seem to be largely responsible for these changes (5, 6). Some adhesion molecules and proteins have been reported to be produced as a result of the progesterone-induced stimulation of the endometrium prepared by oestrogen and to have an important role at various stages in reproductive physiology (1, 2, 10-12). Following the implantation stage, the invasion of trophoblast cells in the form of a complex formation accompanied by CAMs and different proteins occurs, which eventuates in placentation. Human placenta consists of two distinct cell populations originating from cytotrophoblast stem cells, one of which is immotile villous trophoblast cells and the other is extravillous trophoblast cells that perform the invasion. Failure of the formation of uterine receptivity or abnormalities of placentation is regarded as a major aetiological factor in cases of preeclampsia, foetal growth retardation, unexplained infertility and early pregnancy loss (1, 2, 9-14, 22, 23).

Cell adhesion and migration are essential for embryonic development and tissue regeneration, but also for tumour development. CAMs are the protein molecules that are located on the cell surface and provide cell-to-cell and cell-to extracellular matrix connections (3, 9). They are investigated under four main groups according to their functions and structures: immuno-

Table 1. The features demographic and stain with P-cadherin of patients

Parameters	Group 1	Group 2	Group 3	p
Maternal age (y) (┼)	30.5±6.1	30.6±5.8	31.6±7.3	0.800
Gravidity (n) (┼)	3.5±1.4	3.4±1.3	3.9±1.7	0.510
Parity (n) (┼)	2.1±1.2	1.6±0.9	2.0±1.2	0.242
Prior abortion (n) (┼)	0.4±0.5	0.8±0.7	0.8±0.7	0.109
Week of gestation at diagnosis (w) (┼)	6.7±0.9	6.7±1.3	6.9±1.3	0.777
Stain with P-cadherin (┼)	2.9±0.8	2.0±0.8	2.8±0.8	0.0001*
Total (n)	34	60	46	140

One-way Analysis of Variance (ANOVA) test is performed. Data are presented as mean±standard deviation

*Statistically different was defined as $p<0.05$. y; years and w; week

Table 2. Comparison among groups

Comparison	Mean Difference	95% Confidence Interval		p
		From	To	
Group 2 - Group 1	-0.8490	-1.251	-0.4473	<0.001*
Group 2 - Group 3	-0.7493	-1.116	-0.3825	<0.001*
Group 1 - Group 3	0.09974	-0.3235	0.5230	>0.05

Tukey-Kramer Multiple Comparisons Test is performed
*Statistically different was defined as $p<0.05$

globulin family, integrin family, selectin family and cadherins. In addition, a group of molecules that are known to have a role in the adhesion function and cannot be included in one of the groups mentioned above are termed as the unclassified adhesion molecules. CAMs play a role in the specific orientation of the cells to the tissues, cell-to-cell recognition, and regulation of events such as embryogenesis, cell growth, cell differentiation and inflammation (1, 2, 4, 9-12, 15). In some studies, adhesion molecules are emphasised to have a function in the regulation of cellular changes, gene transfer, angiogenesis, apoptosis and cellular signalling as well (9, 23). Damsky et al. (24) have demonstrated that cell-to-cell adhesion and signalling play a crucial role in the early implantation and relationship between the embryo and the endometrium. Abnormal levels or the absence of CAMs impedes the formation and continuation of a healthy pregnancy. For instance, a limited trophoblast invasion of maternal vessels has been correlated to both preeclampsia and foetal growth restriction, whereas an excessive trophoblast invasion is associated with invasive mole, placenta accreta and choriocarcinoma (13, 21). While an increase in the secretion of proteins, including adhesion molecules such as cadherin and integrin, in invading extravillous trophoblast cells prevents foetal rejection, a decrease prevents invasion and foetal growth stops (14). In our study, we assigned three groups to evaluate the efficacy of adhesion molecules in the continuation of pregnancy. We investigated whether there is any difference between the ectopic pregnancy group representing early implantation, the spontaneous abortion group that cannot provide continuation of pregnancy and the control group, with ongoing healthy pregnancy in terms of E-selectin and P-cadherin (cadherin-3) immunoreactivity.

Cadherin, a calcium-dependent transmembrane glycoprotein, is required for the expression of specific adhesion molecules in the embryo, cell migration, coalescence of cells in early embryonic tissues, and tissue differentiation (3, 9, 16-18, 25). In particular, E-cadherin plays a key role in regulating trophoblastic invasion (19). They are cell surface glycoproteins responsible for the selective cell recognition in an adult organism and lifelong normal tissue architecture (3, 25). Cadherins are divided into several sub groups and have more than 100 different types. The cadherin family of adhesion molecules include E-, N-, P-, T-, and VE-cadherins, protocadherins, seven-transmembrane cadherin, and FAT-family cadherin. They are the main adhesion molecules that hold the cells together mostly in early embryonic tissues. They have been reported to play an important role in implantation in some reports (1, 15, 18). Certain studies have demonstrated the presence of cadherin molecules in glandular epithelium and stroma of human endometrium (3, 26). Fujimoto et al. (10) reported that cadherins and adhesion junctions are activated for the preparation for a possible nidation following ovulation. In contrast, Damjanov et al. (27) showed that cadherins are down-regulated in the human and rat trophoblast cells during early implantation, especially during trophoblast invasion. Mac Calman et al. (11) showed the localisation of cadherin in placental syncytial trophoblasts and extravillous cytotrophoblasts that intercourse with decidualised cells in the endometrium during implantation. Among the classical cadherin group, the presence of a very low rate of P-cadherin molecule only could be demonstrated in the human placenta in previous reports (20). The expression of P-cadherin is transient in many tissues, and its permanent expression is limited to certain tissues such as the epidermis, the mesothelium, and the corneal endothelium (3). In this study, we identified P-cadherin in placental villi. P-cadherin was co-expressed with E-cadherin in local regions of various tissues, and the onset or termination of expression of P-cadherin was closely associated with the connection or segregation of cell layers, as found with other cadherins (18). The present study has also demonstrated the presence of endometrial glandular cells and stromal P-cadherin (cadherin-3) antibodies. The rate of P-cadherin staining in placental villi was found to be statistically significantly lower, particularly in abortion materials than in both ectopic pregnancy and control groups (Table 2), which suggested a potential role in the aetiology of abortion.

Selectins are cell surface carbohydrate-binding proteins that mediate the diversity of transient calcium-dependent cell-to-cell adhesion interactions in blood flow (10). Selectins are a family of CAMs which bind to specific sugar determinants on the surface of adjacent cells which act as adhesion counter-receptors. The selectin family includes leukocyte-expressed L-selectin (CD62L), endothelial-expressed E-selectin (CD62E), and P-selectin (CD62P), which is expressed by both platelets and endothelial cells. Many researchers argued that pregnancy and labour are an inflammatory reaction in which cell adhesion molecules play an important role. In this regard, the E-selectin molecule is presented from cytokine-induced endothelial cells and mediates the activation of neutrophils, monocytes, and lymphocytes (10, 12, 28). They provide a loose association between leukocytes and endometrial endothelial cells and help leukocytes to roll on the endothelium. Following this activation, the integrin group of adhesion molecules is released and provides more potent intercellular binding. In our study, all paraffin blocks analysed for E-selectin immunoreactivity showed varying degrees of staining in endometrial glands in the field of view and tubal epithelium lining. However, the foetal placental villi showed no E-selectin immunoreactivity (Figure 1a). This result suggests that E-selectin adhesion molecules arise as a result of temporary and inflammatory reactions, thus playing a role in implantation, but does not take a role in placentation.

In conclusion, the lack of E-selectin immunoreactivity in foetal villi suggests that this molecule emerges as a result of temporary and inflammatory reaction in the early stage of implantation. Our results also suggest that the statistically significantly lower P-cadherin immunoreactivity in foetal placental villi found in the spontaneous abortion group compared to the ectopic pregnancy and control groups, plays an important role in the aetiopathogenesis of spontaneous abortion and that higher P-cadherin levels are needed for the continuation of pregnancy. Larger and more recent studies are needed for the association of adhesion molecules with the aetiopathogenesis of ectopic pregnancy.

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Antenatal diagnosis and outcome of agenesis of corpus callosum: A retrospective review of 33 cases

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Abstract

Objective: To present antenatal sonographic findings and postnatal outcome of a population of foetuses diagnosed with agenesis of corpus callosum.

Material and Methods: The database of our ultrasound laboratory was retrospectively searched for cases of agenesis of the corpus callosum suspected at antenatal sonography between 2002 and 2012. The following variables were assessed: maternal age, gestational age at diagnosis, gender, any additional cerebral and extra-cerebral malformations, results of karyotype analysis and pregnancy and foetal/neonatal outcomes.

Results: During the study period, 33 foetuses with agenesis of the corpus callosum were identified antenatally, with a male preponderance. The mean maternal age was 28.48 years. In all cases, pre/postnatal MRI and/or necropsy were performed in order to confirm the diagnosis. Among those, there were additional brain findings in 23 (69.7%) and additional extra-cerebral anomalies in 3 (9.1%) foetuses. Karyotype analysis was performed in 21 of 33 (63.6%) cases. As for pregnancy outcome, the pregnancy was terminated in 14 (42.4%) of the remaining 19 foetuses; eighteen (54.5%) were delivered near term and one (3.1%) who was delivered prematurely died during the neonatal period.

Conclusion: The diagnosis of congenital brain malformation is a challenging issue, since additional findings have a considerable effect on prognosis; detailed examination with genetic counselling should be performed.

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Key words: Agenesis of corpus callosum, foetal MRI, prenatal diagnosis, ultrasound

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Introduction

The corpus callosum (CC) is the main junction between the two cerebral hemispheres, comprised of approximately 180 million axons, extending from the frontal lobe anteriorly to above the quadrigeminal plate posteriorly (1). Functionally, CC permits not only the information transfer between cerebral hemispheres, but also inhibition of concurrent activity in the contralateral hemisphere (1). From anterior to posterior it has 4 parts, namely the rostrum, genu, body and splenium (1). The anterior portion of the genu forms at the same time as the posterior callosal body, after which the splenium forms, and the last part to develop is the rostrum (1). By the end of the 20th week of gestation, the CC is well established with a shape similar to that of the adult, but with less myelination, reaching adult size by the age of two (1). The prevalence of agenesis of corpus callosum (ACC) varies in different studies, depending on the population studied and the diagnostic criteria, between 0.3% and 0.7% in the general population and 2% and 3% in the developmentally disabled population (2). Sonographic findings of ACC were first described by Comstock et al. (3), divided into direct findings such as the complete or partial absence of CC in the midsagittal plane, and indirect findings, such as colpocephaly, obliteration of the cavum septum pellucidum, elevation and dilatation of the 3rd ventricle and abnormal course of the pericallosal artery (4). Congenital anomalies of CC are commonly associated with other cerebral and extra-cerebral malformations, aneuploidies, genetic syndromes or inborn errors of metabolism, but can also be found in asymptomatic individuals with normal intelligence (5).

By the help of advanced foetal imaging techniques, antenatal diagnosis of complete callosal agenesis is feasible with midtrimester sonography. Beside this, accurate diagnosis of ACC and differentiation between partial and complete forms is still a challenge. Due to the uncertainty of postnatal outcome, giving a prognosis is extremely difficult. Our aim in this study is to report the results of follow-up and perinatal outcomes of cases with ACC between 2002 and 2012.

Material and Methods

Data were collected from our Maternal-Fetal Medicine Unit database. A retrospective database search for ACC was performed and all of the cases with a diagnosis of ACC were selected between 2002 and 2012. The informed consent of

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each participant was taken. The statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) 17.0 (SPSS Inc., Chicago, IL, USA). For each case, the following variables were assessed: maternal age, gestational age at diagnosis time, foetal gender, additional cerebral and extra-cerebral malformations, karyotype analysis, pregnancy and foetal/neonatal outcome. The diagnoses were confirmed at follow-up by pathology or postnatal neuroimaging with ultrasonography and magnetic resonance imaging (MRI).
Ultrasound investigations were carried out using Siemens Sonoline Antares (Siemens AG, North Rhine-Westphalia, Germany) and Voluson 730 pro (GE Healthcare, Milwaukee, WI, USA).

Results

During the study period, 33 foetuses with ACC were identified antenatally; the general features are given in Table 1. The mean age of the pregnant women was 28.48±5.60 years. The mean gravida was 2.21±1.38 and 39.39% of the patients were primipara. The mean gestational age at initial diagnosis was 24.06±4.50 weeks. Twenty-four of the 33 foetuses (72.7%) were male and 9 (27.3%) were female.
Postnatal sonography and MRI were available in 14 cases (42.4%) and autopsy reports were available in ten of the fourteen cases in which a post-mortem examination had been performed (71.4%).
Among the 33 foetuses with ACC, seven (21.2%) showed isolated ACC. Additional findings were given in Table 1. Following sonographic diagnosis, foetal brain MRI was performed in four cases and confirmed the ultrasound findings in all of them. Additional cerebral findings were encountered in 23 foetuses (69.7%). Additional extra-cerebral anomalies were recognised in three foetuses (9.1%), including cerebro-oculo-fascio-skeletal syndrome, multicystic dysplastic kidney and single umbilical artery with a single kidney.
Eighteen of 33 foetuses had complete ACC (54.5%). Thirteen of these cases had additional cerebral findings (72.2%), 1 had multicystic dysplastic kidney (5.5%) and the remaining 4 were isolated cases of complete ACC (22.3%). Four out of 18 cases had chromosomal abnormalities (22.3%), including mosaic trisomy 8, ring chromosome 14, trisomy 18 and the partial duplication of 6p. All of these chromosomal abnormalities were found in complete ACC cases presenting with additional cerebral findings. Ten out of 18 cases were terminated (55.6%); the remaining 8 were alive in the neonatal period (44.4%).
Fifteen of 33 foetuses had partial ACC (45.5%). Ten of these cases had additional cerebral findings (66.7%), 2 presented with cerebro-oculo-fascio-skeletal syndrome and single umbilical artery with single kidney (13.3%) and the remaining 3 were isolated cases of partial ACC (20.0%). Two out of 15 cases had chromosomal abnormalities (13.3%), one case each of trisomy 21 and trisomy 18. Both of these chromosomal abnormalities were found in partial ACC cases presenting with additional cerebral findings. Four out of 15 cases were terminated (26.6%), 10 were alive in the neonatal period (66.7%) and one (6.7%) who was delivered prematurely at 32 weeks, died during the neonatal period because of necrotising enterocolitis. The details are given in Table 1.
Twelve out of 33 (36.4%) cases did not undergo karyotype analysis due to the late admission in 6 (50.0%), and patient preference in the other 6 (50.0%). Postnatal karyotype analysis was not performed on the basis of the initial postnatal evaluation. Three cases presenting with additional extra-cerebral findings, as mentioned before, had normal karyotype analysis results.

Discussion

Agenesis of corpus callosum is one of the most common central nervous system (CNS) abnormalities diagnosed in the antenatal period (4). ACC can present in different forms, complete or partial, isolated or associated with other cerebral and extra-cerebral abnormalities. In the literature, it has been recommended to evaluate the development of corpus callosum between the 20th and 24th gestational weeks since it is difficult to estimate the presence of callosal abnormalities before the 18th gestational week. In accordance with the literature, we diagnosed ACC with a mean gestational age of 24 weeks.
Vasudevan et al. (1) reported that isolated ACC accounts for approximately 50% of patients diagnosed with ACC. In the other half, various CNS abnormalities were described (1). In our study, we found that 7 out of 33 (21.2%) had isolated ACC. On the other hand, Mangione et al. (6) reported a large series of 175 patients in which CNS abnormalities were found in 50% of isolated ACC cases. It has also been shown that the presence of extra-cerebral abnormalities occurs in about 65% of antenatally diagnosed ACC patients (7). Consistent with the literature, we found that 3 out of 33 cases had extra-cerebral malformations. Since these cerebral and extra-cerebral malformations play a serious role in the prognosis, they should be mentioned during counselling.
It is difficult to estimate the exact prognosis because of the limited data due to the relatively low incidence of this disorder. In the literature, there is great variability among the studies evaluated. Some assessed ACC cases with additional cerebral malformations; while the others assessed ACC cases with extra-cerebral malformations. It is well known that associated cerebral and extra-cerebral abnormalities result in poor prognosis (1). The sonographic finding of ACC should be a guide for the clinician for further assessment of not only the subtle cerebral anomalies but also the additional extra-cerebral abnormalities. It is also known that 5-20% of patients who were thought to have isolated ACC in antenatal imaging were found to have associated anomalies postnatally (6). In this perspective, foetal MRI plays a critical role in detecting them (1). If available, magnetic resonance imaging should be performed since it allows direct visualisation of CC. It can reduce false-positive rates on ultrasound while confirming ACC, and it can assess whether this is complete or partial. Beside these advantages it can also help to detect coexisting brain abnormalities not seen on ultrasound (8). In our study, 5 out of 33 of patients had foetal MRI to confirm the sonographic diagnosis of ACC; overall, 4 out of 5 (80%) had additional cerebral malformations, including hydrocephalus and ventriculomegaly, while one had isolated ACC on foetal MRI.

Table 1. Patient characteristics

ACC Types	Week of diagnosis (week)	Week at birth	Pregnancy outcome	Birth weight	Sex	Karyotype analysis	Additional findings
Complete ACC with additional anomaly	21 w	37 w	Alive	3440 g	female	Normal	Ventriculomegaly
Complete ACC with additional anomaly	17 w	24 w	ToP	840 g	male	Normal	Ventriculomegaly
Complete ACC	18 w	34 w	Alive	2180 g	male	Normal	None
Partial ACC with additional anomaly	26 w	41 w	Alive	3900 g	male	Absent	Ventriculomegaly
Complete ACC with additional anomaly	19 w	20 w	ToP	160 g	female	Abnormal, trisomy 18	Hydrocephalus
Complete ACC with additional anomaly	29 w	37 w	Alive	3000 g	male	Absent	Ventriculomegaly
Complete ACC with additional anomaly	22 w	23 w	ToP	340 g	male	Normal	Multicystic dysplastic kidney
Partial ACC with additional anomaly	26 w	39 w	Alive	2990 g	male	Normal	Ventriculomegaly
Partial ACC with additional anomaly	28 w	38 w	Alive	3200 g	male	Absent	Ventriculomegaly
Partial ACC with additional anomaly	19 w	20 w	ToP	390 g	male	Abnormal, trisomy 21	Dandy-Walker syndrome
Partial ACC with additional anomaly	22 w	23 w	ToP	730 g	male	Abnormal, trisomy 18	Ventriculomegaly
Complete ACC with additional anomaly	32 w	35 w	Alive	2650 g	male	Absent	Hydrocephalus
Partial ACC	29 w	38 w	Alive	2960 g	female	Absent	None
Partial ACC with additional anomaly	26 w	26 w	ToP	780 g	male	Normal	Cerebro-oculo-fascio-skeletal syndrome
Partial ACC with additional anomaly	27 w	40 w	Alive	4140 g	male	Absent	Ventriculomegaly
Complete ACC with additional anomaly	24 w	24 w	ToP	950 g	male	Normal	Hydrocephalus
Complete ACC with additional anomaly	33 w	38 w	Alive	3530 g	male	Absent	Hydrocephalus
Complete ACC with additional anomaly	18 w	21 w	Top	350 g	male	Abnormal, mosaic trisomy 8	Hydrocephalus
Partial ACC	21 w	38 w	Alive	3370 g	male	Absent	None
Complete ACC with additional anomaly	15 w	23 w	ToP	850 g	female	Abnormal, partial duplication of 6 p	Hydrocephalus
Complete ACC with additional anomaly	29 w	29 w	ToP	1230 g	female	Normal	Dandy-Walker syndrome
Partial ACC with additional anomaly	23 w	39 w	Alive	2860 g	male	Normal	Dandy-Walker syndrome
Partial ACC with additional anomaly	22 w	38 w	Alive	3010 g	female	Normal	Ventriculomegaly
Partial ACC with additional anomaly	24 w	24 w	ToP	1100 g	male	Normal	Single umbilical artery with single kidney
Complete ACC with additional anomaly	28 w	34 w	Alive	2400 g	male	Absent	Hydrocephalus
Partial ACC with additional anomaly	23 w	38 w	Alive	3580 g	male	Absent	Absence of splenium
Partial ACC	26 w	37 w	Alive	2810 g	female	Normal	None
Partial ACC with additional anomaly	24 w	32 w	Neonatal Exitus	1840 g	male	Absent	Hydrocephalus
Complete ACC	31 w	37 w	Alive	3130 g	female	Absent	None
Complete ACC	19 w	20 w	ToP	450 g	male	Normal	None
Complete ACC	28 w	37 w	Alive	3070 g	female	Normal	None
Complete ACC with additional anomaly	24 w	26 w	ToP	1140 g	male	Abnormal, ring Ch 14	Inter-hemispheric porencephalic cyst
Complete ACC with additional anomaly	21 w	24 w	ToP	720 g	male	Normal	Porencephaly and schizencephaly

ACC: Agenesis of corpus callosum; w: Week; ToP: Termination of pregnancy; Ch: Chromosome

Moutard et al. (9) reported that during postnatal neuropsychological follow-up, the median intellectual quotient (IQ) was within the normal range, regardless of whether ACC is complete or partial. Since distinguishing these two by foetal ultrasonography is difficult, the clinician should pay more attention to associated cerebral and extra-cerebral anomalies.

In conclusion, the diagnosis of a congenital brain malformation creates great anxiety among the parents. In our clinical practice, since findings of additional cerebral and extra-cerebral abnormalities have a considerable effect on prognosis, we performed detailed examination with genetic counselling. Although a male preponderance was observed in our study, a gender-based research protocol is not advisable. In isolated cases of ACC, long-term neurodevelopmental outcome is expected to be normal in approximately 75% of cases, meaning that continuation of pregnancy can be preferred (5). On the other hand, if the case is not an isolated one, to the best of our knowledge, termination should be offered because of poor neurodevelopmental prognosis. For an exact diagnosis, the evaluation of CC should be postponed until after 20 weeks of gestation and foetal MRI should be offered in cases of uncertainty about termination versus continuation of pregnancy. In continuing pregnancies, delivery should be performed in multidisciplinary centres for the benefit of the infant.

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Incidence of gestational trophoblastic disease in Tokat province, Turkey

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Abstract

Objective: This study investigated the incidence of gestational trophoblastic disease (GTD) in Tokat province, Turkey.

Material and Methods: The medical records of patients who had been diagnosed and treated at one university hospital, six government hospitals, and one specialist hospital in Tokat province between January 2005 and December 2012 were evaluated retrospectively.

Results: During the study period, there were 59,754 births and GTD was diagnosed in 73 cases. The calculated GTD incidence was 1.22/1000. The mean age of the patients diagnosed with GTD was 28.6±7.3 (range 17-51) years. In GTD, complete moles occurred in 26%, partial moles in 74%, and no invasive moles, choriocarcinomas, or placental site trophoblastic tumours were found. Only two patients received chemotherapy (methotrexate). There was no mortality associated with the disease during follow-up.

Conclusion: The incidence of GTD in Tokat province was 1.2 per 1000 births. Early diagnosis, treatment, and follow-up play a critical role in preventing the morbidity and mortality associated with disease. The incidence of GTD, which has a high recovery rate with adequate treatment and follow-up, can be determined from regional and community-based research. (J Turk Ger Gynecol Assoc 2014; 15: 22-4)

Key words: Gestational trophoblastic disease, molar pregnancy, incidence

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Introduction

Gestational trophoblastic disease (GTD) is classified histopathologically as complete or partial mole, invasive mole, placental site trophoblastic tumour, and gestational choriocarcinoma (1). Menarche age, parity, first pregnancy age, mole pregnancy history, time interval between previous pregnancies, genetic factors, malnutrition, viral infections, and socioeconomic level all predispose to GTD (2). The aetiology is not clear, but the disease is characterised by abnormal gametogenesis, fertilisation, and malignant transformation of trophoblastic tissue.

The incidence of GTD differs across geographic regions. The reported GTD incidence was 0.3-16 per 1000 pregnancies in Turkey, 0.6-1.2 in Europe and North America, 0.2-4.6 in Latin America, and 3.2-5.8 in Middle East countries (3, 4). This study determined the incidence of GTD in Tokat province, Turkey.

Material and Methods

This study was performed between January 2005 and December 2012 and patients were collected from one university hospital, six government hospitals, and one private hospital in Tokat. The study protocol was approved by the Medical Ethics Committee and informed consent was taken. The patients diagnosed with GTD were confirmed histopathologically. Epidemiological data, laboratory and pathology results, and follow-up examination findings were obtained from the patients' records. Some information was obtained by telephoning patients when it was missing from the records. GTD was classified as complete and partial mole, invasive mole, placental site trophoblastic tumour, and gestational choriocarcinoma. Patients diagnosed with GTD were evaluated according to their age, pregnancy, birth, abortion number, and histopathology. All data were analysed using "PASW Statistics version 18.0" (PASW, Chicago, IL, USA). Data were given as mean±SD (standard deviation) and n (%).

Results

Between January 2005 and December 2012, there were 59,754 births in Tokat province. During this period, 73 cases were diagnosed as GTD histopathologically. The calculated GTD incidence was 1.22 per 1000 births. The mean age of the diagnosed patients was 28.6±7.3 (range 17-51) years. Many patients were aged 20-29 years (Figure 1). The mean numbers of pregnancies, births, and abortions were 3.5±2.9 (range 1-15), 1.3±1.4 (range 0-5), and 1.1±2.3 (range 0-13),

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respectively. There was no history of molar pregnancy in any case. Comparing blood types, 45.9% were type A, 21.3% were type B, 31.1% were type O, and 1.6% were type AB. Vacuum curettage was performed in all patients for diagnosis and treatment. Histopathologically, 26% were complete moles, 74% were partial moles, and there were no invasive moles, choriocarcinomas, or placental site trophoblastic tumours (Figure 2). Two patients were treated for non-metastatic disease with single-agent chemotherapy (methotrexate) (Emthexate; Med Ilac, İstanbul, Turkey) and were cured. No hysterectomy was performed in any patient and there was no disease-dependent mortality during the follow-up period.

Discussion

Gestational trophoblastic disease, which arises from the abnormal proliferation of trophoblasts, is seen in 0.6-11.5 per 1000 pregnancies; however, this ratio differs among communities (2, 5, 6). The suggested GTD incidence is 0.3-16 per 1000 gestations (4). The incidence of GTD also differs among regions in Turkey. The incidence is 12.1 per 1000 births in Şanlıurfa, 8.1 in Van, 1.78 in Ankara, 3.35 in Konya and 5.9 in Istanbul (7-11). The reason for the increased GTD incidence in these cities might be the fact that these studies were performed in referral centres (10). Özalp et al. (12) conducted a society-based study, and found an incidence of 0.8 per 1000 live births and 0.6 per 1000 pregnancies. Our study is the first conducted in Tokat and the GTD incidence was 1.22 per 1000 live births. It is apparent that the GTD incidence is lower when studies are based on large communities.

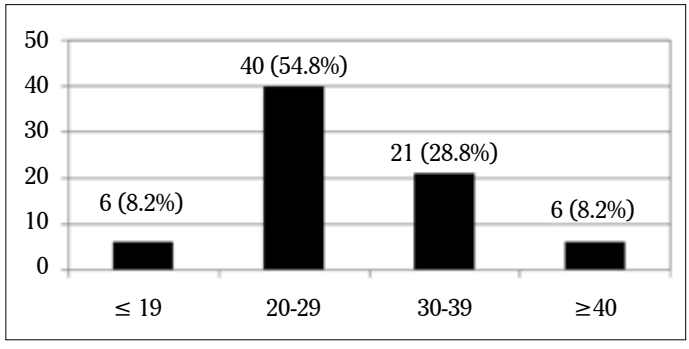

Figure 1. The distribution of patients according to age range

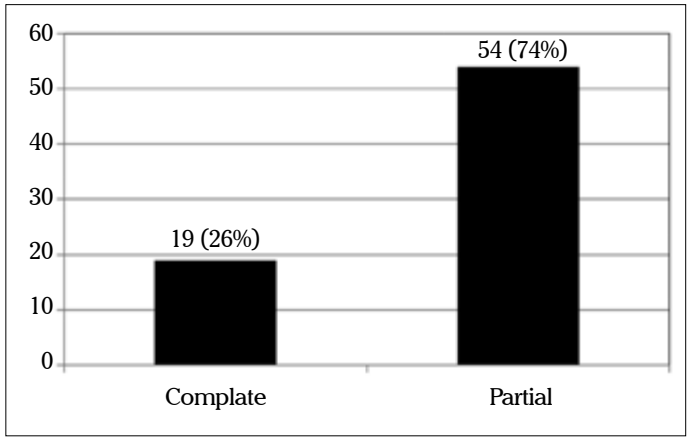

Figure 2. The distribution of patients according to histopathological diagnosis

Çetin et al. (13) found that the incidence of GTD was 6.60 per 1000 births in Sivas province, so the incidence differs among regions. This rate is approximately six-fold higher than in our study. In comparison, Malatyalıoğlu et al. (14) reported a GTD incidence of 0.3 per 1000 pregnancies in Samsun. Unlike other studies, however, they calculated the incidence using the number of pregnancies, not births. Given the differences among regions, the incidence can differ between two cities, possibly because the calculation can be based on the number of pregnancies or births.

In our study, GTD was most common in the third decade of life and the mean patient age was 28.6±7.3 (range 17-51) years. In the literature, the disease is usually seen during the early and late fertility periods, *i.e*. younger than 20 and older than 35 years (15, 16). GTD in Turkey usually occurs at ages from 19-35 years (11, 17). We found that blood type A (45.9%) was the most frequent, and this is the most common maternal blood type A in the literature (8, 11).

Vacuum curettage, hysterectomy, and chemotherapy are usually used to treat GTD. In our study, vacuum curettage was performed in all patients, while no hysterectomies were done. In the literature, hysterectomy is usually used to treat old grand multiparity patients because malignant degeneration increases with age and the risk decreases from 20% to 3-10% with hysterectomy (18, 19).

Chemotherapy is given if the β-hCG level plateaus or increases or stays high for more than 6 months, choriocarcinoma is diagnosed histologically, or metastatic disease is present (20). Chemotherapy is based on the anatomical staging of the International Federation of Gynecology and Obstetrics (FIGO) and a prognostic scoring system devised by the World Health Organisation and modified by FIGO. Methotrexate or actinomycin is usually used as a single agent, while methotrexate, actinomycin-D, and cyclophosphamide (MAC) or etoposide, methotrexate, actinomycin-D, cyclophosphamide, and vincristine (EMA-CO) combinations are used as multiple treatment modalities (21). Cures are obtained in 100% of the low-risk group and 80-90% of the high-risk group (20, 22, 23). In our study, only two patients were treated with methotrexate because of persistent β-hCG. No chemotherapy-dependent morbidity occurred.

In conclusion, the incidence of GTD in Tokat province was 1.22 per 1000 births. Early diagnosis, treatment, and follow-up are important to prevent morbidity and mortality. We believe that sufficient treatment and follow-up will facilitate the cure of GTD and the incidence can be calculated more accurately by performing broad community-based studies.

Ethics Committee Approval: *Ethics committee approval was received for this study from the Medical Ethics Committee.*

Informed Consent: *Written informed consent was obtained from patient who participated in this study.*

Peer-review: *Externally peer-reviewed.*

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A financial analysis of operating room charges for robot-assisted gynaecologic surgery: Efficiency strategies in the operating room for reducing the costs

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Abstract

Objective: To analyse the steps taking place in the operating room (OR) before the console time starts in robot-assisted gynaecologic surgery and to identify potential ways to decrease non-operative time in the OR.

Material and Methods: Thirteen consecutive robotic cases for benign gynaecologic disease at the Department of Obstetrics and Gynecology at University of Texas Medical Branch (UTMB) were retrospectively reviewed. The collected data included the specific terms 'Anaesthesia Done' (step 1), 'Drape Done' (step 2), and 'Trocar In' (step 3), all of which refer to the time before the actual surgery began and OR charges were evaluated as level 3, 4, and 5 for open abdominal/vaginal hysterectomy, laparoscopic hysterectomy, and robot-assisted hysterectomy, respectively.

Results: The cost of the OR for 0-30 minutes and each additional 30 minutes were $3,693 and $1,488, $4,961 and $2,426, $5,513 and $2,756 in level 3, 4, and 5 surgeries, respectively. The median time for step 1 was 12.1 min (5.25-23.3), for step 2 was 19 (4.59-44) min, and for step 3 was 25.3 (16.45-45) min. The total median time until the actual operation began was 54.58 min (40-100). The total cost was $6948.7 when the charge was calculated according to level 4 and $7771.1 when the charge was calculated according to level 5.

Conclusion: Robot-assisted surgery is already 'cost-expensive' in the preparation stage of a surgical procedure during anaesthesia induction and draping of the patient because of charging levels. Every effort should be made to shorten the time and reduce the number of instruments used without compromising care. (J Turk Ger Gynecol Assoc 2014; 15: 25-9)

Key words: Cost analysis, fees, gynaecology operating rooms, robot-assisted surgery

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Introduction

The da Vinci Surgical System (Intuitive Surgical, Sunnyvale, CA, USA) has been the subject of debate with regard to high costs since its first approval by the U.S. Food and Drug Administration in 2001 for general surgery. This system is the only approved robotic surgical unit and has fixed costs, with prices for each unit ranging from $1 million to $2.5 million, as well as annual maintenance costs and the costs of additional consumables (1). To date, although procedure-based analyses have demonstrated higher costs for robotic surgery compared with conventional laparoscopic surgery and abdominal/vaginal surgery, robotic surgery has still been increasingly used, and more than 1,900 robotic surgical systems have been installed worldwide (2-5). Moreover, robot-assisted surgery in gynaecology have become an important area in residency training programmes (6).

Minimally invasive surgery (MIS) is rapidly gaining popularity in the field of gynaecology and there has been a shift towards MIS in the last 10 years in US (7). This shift was dramatically increased after the approval of robotic-assisted surgery in 2005 and is still being used for a variety of applications including hysterectomy, sacrocolpopexy, tubal reanastomosis, and radical oncological operations (2-4, 8). Initially, the number of opponents of robotic surgery was much higher than the number of supporters, and there was a clear trend towards not using the robot because of its high costs and similar clinical benefits compared with laparoscopy. However, the clear advantages over traditional laparoscopy, including three-dimensional imaging, tremor filtration, augmented dexterity, and surgeon comfort, have led physicians to investigate approaches to reduce costs without compromising care (9).
The absolute costs of procedures in the American health care system are calculated according to operative time, surgical

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complications, length of stay, and other probable cost drivers compared to hospital estimates and individually negotiated reimbursement agreements. Operating room (OR) charges are one of the most important factors affecting the total cost of procedures, and the two main factors that affect the OR cost are the time spent in the OR and the OR charging levels. Currently, medical data focuses on the actual surgery time, console time, and total operating-room time (4, 7, 10). Less emphasis is placed on the time frame before the console time starts.
In this study, we analysed the steps taking place in the operating room before the console time starts and discuss potential ways to decrease non-operative time in the OR.

Material and Methods

Thirteen consecutive robotic cases for benign gynaecologic disease at the Department of Obstetrics and Gynecology at University of Texas Medical Branch (UTMB) were retrospectively reviewed. Institutional Review Committee approval was obtained. Patient data were arranged in chronological order. The collected data included the specific terms 'Anaesthesia Done', 'Drape Done', and 'Trocars Placed In', all of which refer to the time before the actual surgery began. In the presence of faculty members from the anaesthesia and gynaecology departments as well as the circulating nurse, the patient is physically wheeled into the operating room. Safety checks were completed before the induction of anaesthesia was initiated. A second intravenous line (IV) opened after intubation was securely completed. 'Anaesthesia Done' was defined as the time period that started from the patient being wheeled into the operating room and ran until the second IV line was opened; this included time out, intubation, and secondary intravenous access. 'Drape Done' was defined as the time period that included patient positioning, preparation, and draping. 'Trocars Placed In' was defined as the placement of the uterine manipulator and when all trocars had been introduced into the abdominal cavity. The docking time and the operating time were not included in the study. This also helped to translate the data obtained from this study to laparoscopic cases. The time during 'Anaesthesia Done' was defined as 'step 1', that during 'Drape Done' was defined as 'step 2' and 'Trocars Placed In' was defined as 'step 3'. Because the amount of time lapsed until the actual operation begins is identical in both robotic and conventional laparoscopic surgery, we did not create a study group for patients who underwent laparoscopic surgery.

Surgery Levels

According to UTMB Charge Description Master (CDM) standardisation, a formula was devised for an organisation-wide standard for the number of surgery levels and the criteria for categorising surgical procedures into a specific surgery level based on five drivers (Table 1). These drivers are elements in a surgical procedure that allow for differentiation based on the complexity of the procedure.
The following information presents the drivers that guided the surgical team in determining the number of surgery levels in the protocol along with the characteristics of each level:

A. Equipment: Degree of specialised equipment required
B. Instruments: Number of trays/kits
C. Setup time: Required preparation and teardown of room
D. Staff: Number of staff (defined as hospital employees)
E. Supplies: Routine in nature (non-billable)

Charges for OR services generally depend on the complexity of the particular operation. There is an initial charge, followed by an additional charge for every 30 minutes (Table 2). Robotic surgery charges are based on level 5, whereas laparoscopic surgery charges are based on level 4, and open abdominal hysterectomy and vaginal hysterectomy charges are based on level 3. These financial data were obtained from the Hospital Financial Management and Physician Billing Departments. The cost of the OR for 0-30 minutes and each additional 30 minutes was evaluated.
The da Vinci Surgical System (Intuitive Surgical, Sunnyvale, CA, USA) was used for the robotic surgical procedures, whereas traditional laparoscopic instruments were utilised for laparoscopic surgery.

Statistical Analysis

Descriptive statistics were calculated, and the median and range were examined. Statistical analyses were performed using the Statistical Package for Social Science for Windows Version 20.0 (SPSS Inc., Chicago, IL, USA).

Results

The results are presented as median and ranges. The median time for step 1 was 12.1 min (5.25-23.3), for step 2 was 19 (4.59-44) min, and for step 3 was 25.3 (16.45-45) min (Figure 1). The total median time until the actual operation began was 54.58 min (40-100). The cost of OR for 0-30 minutes and each additional 30 minutes were $3,693 and $1,488, $4,961 and $2,426, and $5,513 and $2,756 in level 3, 4, and 5 surgeries, respectively (Table 2).
If the charge was calculated according to level 4, then the costs of step 1, step 2 and step 3 were $2000.9, $3049 and $2045.9, respectively. If the charge was calculated according to level 5, then the costs of step 1, step 2 and step 3 were $2223.6, $3390.5 and $2296.6, respectively.
In a total median time of 54.58 minutes, the total costs were $6948.7 and $7771.1 when the charge was calculated according to level 4 and level 5, respectively (Table 3). The absolute difference between the robotic and laparoscopic cases was $822.

Discussion

To the best of our knowledge, this study is the first report focusing primarily on performing a thorough evaluation of the time period prior to the actual beginning of the operation. This time period is identical for both laparoscopic and robotic techniques. Developing new approaches to decrease the time frame before the actual surgery started would be cost effective for both robotic and laparoscopic techniques.
Efficiency, in dictionaries, describes the extent to which time, effort or cost is well used for the intended task or purpose, and

Table 1. UTMB CDM standardised surgery levels

A. Equipment - Degree of specialised equipment required		
Criteria Points	**Equipment Level**	**Equipment - Level Criteria**
1	Room Standard ($5,000)	Suction, bovie, bair hugger, head light
2	Basic ($5,000-$10,000)	Basic microscope, Fluoroscan, Power equipment (drills, reamers, saws, shavers), Tourniquet, Berkley evacuator, C-arm, Ultrasound, Video system
3	Complex ($10,000-$250,000)	Cell saver, Laser, Ultra drive, Harmonic scalpel, Argon beam, Anspach, Thermochoice, Versapoint, Surex, Fluid management system, Tables, (Chix, FX, Jackson), MIS Suite, NeoProbe
4	Specialty ($25,000-$75,000)	CUSA, Heart/Lung, Stealth, Retinal equipment, Lesion generator, NIM, Specialty tables, Specialty microscopes, Phaco equipment, Holmium laser, Cryo machine
5	Advanced specialty ($75,000+)	Robotics, CT scanner, Brain Lab, Bypass pump
B. Instruments - Number of trays/kits		
Criteria Points	**Criteria**	
1	0-1 Tray	
2	2-5 Trays	
3	6-10 Trays	
4	11+ Trays	
C. Setup Time - Preparation & teardown of room		
Criteria Points	**Criteria**	
1	Up to 10 minutes	
2	11-20 minutes	
3	21-40 minutes	
4	40+ minutes	
D. Staff - Number of staff needed		
Criteria Points	**Criteria**	
1	1 person	
2	2 persons	
3	3 persons	
4	4 persons	
E. Supplies - Routine (non-billable)		
Criteria Points	**Supply-level name**	**Supply-level criteria**
1	Basic (Minimally invasive/ Minimum supply as breast biopsy)	Towels, drapes (half sheet), prep set, gloves, suction, bovie pad, gown, masks, shields, minimal dressings, raytecs
2	Complex (Cases with moderate supplies such as exploratory laparoscopy)	All the basic supply pus: Packs (covers, drapes, gowns, basins, sponges)
3	Advanced (Cases with extensive supplies, such as Whipples)	All the basic supply pus: Packs (covers, drapes, gowns, basins, sponges)
Point system summary		
Surgery level	**Total points assigned**	
1	0-6 points	
2	7-8 points	
3	9-11 points	
4	12-13 points	
5	14+ points	

UTMB: University of Texas Medical Branch; CDM: Charge Description Master

Table 2. Operating room charges of abdominal/vaginal, laparoscopic and robotic

Complexity level	Initial 30 min ($)	Each additional per 30 min ($)
3	3.693	1.488
4	4.961	2.426
5	5.513	2.756

Level 3: Abdominal/Vaginal
Level 4: Laparoscopy
Level 5: Robot

Table 3. Costs of each step according to complexity levels of the procedures before the surgery begins

Cost ($)	Level 3 (Abdominal/ Vaginal)	Level 4 (Laparoscopy)	Level 5 (Robot)
Step 1	1489.5	2000.9	2223.6
Step 2	2258	3049	3390.5
Step 3	1254.9	2045.9	2296.6
Total	4912.2	6948.7	7771.1

efficiency could be implemented in the OR to eliminate wasteful activities. To maintain efficiency in the OR, first, a dedicated room for robotic surgery is needed. The OR should be large (approximately 60 m^2) and should include back-up materials in case of potential equipment malfunctions (9). Once the physical plant of the OR is setup appropriately, it is of vital importance to create a cooperative team for the efficiency of the program. Fagin published a model for the efficient utilisation of the OR and argued that a team including five dedicated people (two scrub techs, one circulator, one first assistant, one operating room attendant) is sufficient to perform parallel tasking (task overlap) in the robotic OR and described 'task overlap' as performing tasks in parallel rather than in a consecutive series (11). To succeed in this efficiency model, individual team member roles must be defined, standardised and the task overlap should be carried out effectively. In general, the circulator is responsible for the overall flow of the room, scrub techs should be proficient in organising procedure-based surgical instruments and the first assistant (or resident/fellow), who is the bedside colleague of the surgeon, should be proficient in manipulating tissue and managing instruments. Teaching and training the team are very important because any inefficient behaviour increases the amount of time required to perform the steps, leading to higher costs for the procedures. However, all of the people involved in the robotic program have their own learning curve; therefore, no more than one person should be trained at a time, as increasing the number of trainees will also increase the length of the operation. Additionally, each team member, including the surgeon, must be actively involved in the parallel tasking. For example, when the patient enters the room, the surgeon (or resident/fellow) and the circulator should position and prep the patient while the scrub tech is focused on preparing the table and draping the robot.

Our study shows that in a median time of 55 minutes before the actual operation begins, the use of the robotic system results in an additional $2858.9 in charges when compared with open abdominal hysterectomy or vaginal hysterectomy, indicating that robotic surgery has already become dramatically more expensive at the beginning of the procedure. If evaluated step-by-step, there was an additional cost of $734 with regard to step 1, $1132 with regard to step 2, and $1042 with regard to step 3. Although step 3 was the longest, its costs were lower than those of step 2 because the OR charges differ after the first 30 minutes. To shorten the time period and decrease the cost for step 1 in an efficient way, time-out can be finished before the patient enters the room or after the patient has been intubated and intravenous lines can be accessed before the patient enters the OR. The key point for shortening the time for step 2, which is the most expensive step, is that 'parallel tasking' must be carried out very effectively in this period. The circulator should focus on positioning the patient, the scrub tech should make the table ready, and the resident/fellow should prep and drape the patient all at the same time. Once the patient is draped, the surgeon should be ready with abdominal access to make the initial incision, insufflate the abdomen and finally place the trocars. At this stage, the team should know the order of the surgeon's tasks very well, as the circulator can connect the gas prior to insufflation and the scrub tech can make the instruments ready according to the task order. This anticipation will contribute to shortening the time period and decreasing the cost for step 3.
All of these methods can be applied to both laparoscopic and robotic procedures, thus leading to more comparable costs with abdominal/vaginal procedures. One other reason causing these high costs is likely related to the increased equipment levels and an increased number of instruments that need to be prepared for robotic surgery, leading to high charge levels, although some instruments are unnecessary. Moreover, the term 'robot' also adds to the complexity of the name of the surgery, thereby contributing to the high charge levels.
Our study also has certain limitations. The study is limited by its retrospective nature with inherent selection bias, and the data collection itself is subject to measurement bias as a result of errors in data gathering.
In conclusion, robotic surgery is already 'cost-expensive' in the preparation stage of a surgical procedure during anaesthesia induction and draping of the patient because of the charging levels. Every effort should be made to shorten the time and reduce the number of instruments without compromising care.

Ethics Committee Approval: *Ethics committee approval was received for this study (IRB11-340).*

Informed Consent: *Written informed consent was not taken because this study was not involved direct patient contact.*

Peer-review: *Externally peer-reviewed.*

Author contributions: *Concept - G.S.K., B.Z.; Design - C.H.K., T.Ö.; Supervision - G.S.K.; Resource - G.S.K.; Materials - C.H.K., B.Z.; Data Collection&/or Processing - G.S.K., M.A.B.; Analysis&/ or Interpretation - C.H.K.; Literature Search - T.Ö.; Writing - G.S.K.; Critical Reviews - G.S.K., M.A.B.*

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The effect of Silymarin on VEGF, VEGFR-1 and IL-1α levels in placental cultures of severe preeclamptic women

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Abstract

Objective: The purpose of this study was to evaluate the effects of Silymarin on vascular endothelial growth factor (VEGF), soluble VEGF Receptor-1 (sVEGFR-1) and Interleukin-1 alpha (IL-1α) levels in placental tissue samples of severely preeclamptic women.

Material and Methods: We conducted an in vitro study in Başkent University Faculty of Medicine, Ankara, Turkey between September 2008 and May 2009. A total of 16 placental tissue samples (8 from severe preeclamptic, and 8 from controls) were analysed. Placental samples were incubated, and VEGF, sVEGFR-1, and IL1- α were measured in culture media using an ELISA kit. The effect of Silymarin on these levels was investigated. Descriptive statistics were initially performed, followed by Mann Whitney U-test and Kruskal-Wallis test to compare means between groups. P values less than 0.05 were considered statistically significant.

Results: Eight patients were included in the severe preeclampsia (SP) group, whereas the remaining 8 patients were included in the control group. There were no significant correlations between gestational age and placental VEGF, sVEGFR-1 and IL-1α after 48 or 72 hours of incubation. Basal VEGF levels were lower in the SP group; however, it did not reach statistical significance. sVEGFR-1 and IL-1α levels were also similar between the SP and control groups ($p>0.05$). After 48 and 72 hours of incubation, sVEGFR-1 levels in Silymarin-added SP and control placental cultures were lower than in the samples without Silymarin addition; however, this difference also did not reach significance.

Conclusion: Although we could not demonstrate a significant effect on placental cytokines, considering the role of vasospasm, inflammation, angiogenesis, endothelial cell activation, and oxidative stress in preeclampsia, the potential benefits of Silymarin should be evaluated in future trials with a larger sample size. (J Turk Ger Gynecol Assoc 2014; 15: 30-5)

Key words: Severe preeclampsia, placenta, vascular endothelial growth factor, Silymarin

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Introduction

Preeclampsia is a syndrome that is specific to pregnancy, and is mainly characterised by decreased organ perfusion secondary to vasospasm and endothelial activation. The pathophysiological changes observed in preeclampsia develop with the influence of genetic, immunological and inflammatory factors (1-3). In healthy pregnancies, spiral arterioles within the uteroplacental bed are invaded endovascularly by the trophoblasts; thus, they are converted to vessels with low resistance, low pressure and high blood flow (4). Vascular endothelial growth factor (VEGF) is thought to play an important role in placental evolution, particularly in angiogenesis and microvascular permeability (5). VEGF production was previously reported to be decreased in preeclampsia (6). VEGF acts by binding to the tyrosine kinase receptors VEGFR-1(Flt-1) and VEGFR-2 (7-12). However, free VEGFR-1 in the circulation (sVEGFR-1 - soluble VEGFR-1) has a strong antagonistic effect on VEGF and placental growth factor (PlGF). High sVEGFR-1 levels are detected in preeclamptic pregnant women compared with normal pregnant women, and these high levels are thought to have negative effects on angiogenesis (13). Studies on preeclamptic pregnancies have also shown that placental interleukin-1 (IL-1) has a key role in maternal inflammatory response and endothelial activation (14-16).

Silymarin is a flavonoid, which is extracted from the plant *Silybum marianum*. Its major bioactive component is Silybinin. It has anti-proliferative, pro-apoptotic, anti-angiogenic, anti-inflammatory and anti-fibrotic effects (17-24). This study was designed to evaluate the effects of Silymarin on VEGF, VEGF Receptor-1 (VEGFR-1) and IL-1 alpha (IL-1α) levels in placental tissue samples of severely preeclamptic women.

Material and Methods

Patient Selection

We conducted an *in vitro* study in Başkent University Faculty of Medicine, Ankara, Turkey between September 2008 and

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May 2009, following scientific and ethical approval from Başkent University Institutional Review Board (BUTF IRB Approval No:08/59, 02.04.2008). A total of 16 placental tissue samples (8 preeclamptic, and 8 controls) were analysed.

After obtaining informed consent, severe preeclamptic women who underwent caesarean section above 30 weeks of gestation were prospectively included in the study. Severe preeclampsia (SP) was defined as new-onset hypertension and proteinuria in a >20 week pregnant woman with one or more of the following features: 1) severely elevated blood pressure (systolic ≥160 mmHg and/or diastolic ≥110 mmHg) measured at least twice with a 6 hour interval; 2) proteinuria ≥5 gr in 24-hour collected urine or ≥2+ in dipstick test; 3) serum creatinine ≥1.2 mg/dL; 4) oliguria (<400 cc in 24 hours); 5) thrombocytopenia (<100,000/mm^3); 6) microangiopathic haemolysis (Lactate dehydrogenase (LDH) ≥600 U/L or uncongugated bilirubin ≥1.2 mg/dL); 7) impaired liver function tests (Aspartate serum transaminase ≥ twice normal); 8) foetal growth restriction (FGR); 9) symptoms of central nervous system dysfunction (severe headache, blurred vision); 10) symptoms of liver capsule distention (epigastric or right upper quadrant pain); and 11) symptoms suggesting pulmonary oedema (dyspnoea) or cyanosis.

Patients with pre-existing hypertension, diabetes, renal disease, and patients in whom steroids were used for foetal pulmonary maturation were excluded from the study. A control group comprising 8 women with a normal pregnancy follow-up, who underwent caesarean section (C/S) due to a previous C/S and gave informed consent, was constituted for comparison with the SP group.

Preparation of Placental Samples

During caesarean section, a 1x1cm sample of placental tissue sample involving foetal membranes and decidua was obtained using a sterile technique. Placental samples were placed in a transport medium RPMI-1640 (PAA Cell Culture Company, NJ, USA) and was transferred to the laboratory in +4°C containers within 12 hours of delivery. Samples were further separated into chorionic villi under laminar airflow. Culture medium was composed of 5% foetal bovine serum, 1% Penicillin-Streptomycin, and 2% L-Glutamine (Biochrom KG, Berlin, Germany).

A total of six wells were processed for each placental sample. Each well contained 0.5 mL of culture medium and 20 mg placental tissue. The 1st and 4th wells were processed without Silymarin. Silymarin concentrations in wells were based on the study by Wang et al. (25). Concentrations of 6.25 mg/L were achieved in the 2nd and 5th wells. In the 3rd and 6th wells, 25 mg/ml Silymarin concentrations were achieved (Table 1).

Placental samples were incubated in a CO_2 incubator (Heraeus, Thermo Scientific Corp., Asheville, NC, USA) in a 5% CO_2 environment. Incubation durations were 48 hours for the 1st, 2nd and 3rd wells, and 72 hours for the 4th, 5th and 6th wells. Upon completion of the incubation period, incubated cultures were transferred into sterile Eppendorf tubes (1.5 ml) and were transferred at +4°C to the laboratory for biochemical analysis.

Measurement of Placental Cytokines

Samples transferred for biochemical analysis were initially stored at -80°C until reaching the kit sample size. Samples were then defrosted, and Vascular Endothelial Growth Factor (VEGF), soluble VEGF receptor-1 (sVEGFR-1) and Interleukin (IL)-1α were measured in culture media using an ELISA kit (Bender MedSystems, Austria).

Statistical Analysis

Statistical analysis of the study data was performed with SPSS 16.0 (SPSS Inc., IL, USA) software. Descriptive statistics were initially performed, followed by Mann Whitney U-test and Kruskal-Wallis test to compare means between the groups. Correlations between variables were assessed with Spearman's correlation analysis. P values less than 0.05 were considered statistically significant.

Results

A total of 16 patients were included in the study. Eight patients were included in the severe preeclampsia (SP) group, whereas

Table 1. Processing order of the placental samples

Well Number	Silymarin concentration	Incubation time prior to Silymarin addition	Incubation time after Silymarin addition	Total incubation time
1	None	-	-	48 hrs
2	6.25 mg/L	24 hrs	24 hrs	48 hrs
3	25 mg/L	24 hrs	24 hrs	48 hrs
4	None			72 hrs
5	6.25 mg/L	24 hrs	48 hrs	72 hrs
6	25 mg/L	24 hrs	48 hrs	72 hrs

Table 2. Demographic and clinical characteristics of severe preeclampsia and control groups

	Severe preeclampsia group (n=8) mean±SD (range)	Control group (n=8) mean±SD (range)	p
Maternal age (years)	29.6±9.5 (17-42)	31.6±5.1 (24-39)	>0.05
Parity	1.9±2.7 (0-8)	0.4±0.5 (0-1)	>0.05
Gestational age (weeks)	33.1±2.8 (30-39)	38.5±1.6 (35-40)	0.002
Systolic blood pressure (mmHg)	155.0±9.3 (140-170)	111.3±8.3 (100-120)	0.01
Diastolic blood pressure (mmHg)	105.0±9.3 (90-120)	68.8±6.4 (60-80)	0.02
Platelet count (/mm^3)	170250±72013.4 (82,000-272,000)	278250±127928.3 (161000-550000)	>0.05
Newborn weight (gr)	1870.0±600.9 (1130-3010)	3361.3±390.8 (2840-3810)	0.03

the remaining 8 patients were included in the control group. Demographic and clinical characteristics of the SP and control groups are presented in Table 2. In the SP group, 4 patients had systolic blood pressures >160 mmHg, 4 had diastolic blood pressures >110 mmHg, 6 had >5 gr/ 24hrs proteinuria, and 2 had platelet counts less than 100,000/mm^3. None of the women had oliguria, impaired renal or hepatic function tests, or laboratory findings suggesting haemolysis. Four foetuses in the SP group had foetal growth restriction.

Basal (no Silymarin) VEGF, sVEGF-R and IL-1α levels in placental cultures of SP and control groups (wells 1 and 4) are presented in Tables 3 and 4. When all cases (n=16) were included in the analysis, there were no significant correlations between gestational age and placental VEGF, sVEGFR-1 and IL-1α after 48 or 72 hours of incubation (p>0.05). On the other hand, basal VEGF levels after 72 hours of incubation had a significant correlation with newborn weight (r=0.615, p=0.001). VEGF, sVEGFR-1 and IL-1α levels after the administration of 6.25 mg/L and 25 mg/L Silymarin after 48 and 72 hours of incubation in the SP and control groups are presented in Table 5.

Discussion

Preeclampsia is a clinical condition that is specific to pregnancy, of which the underlying aetiopathological factors remain to be discovered. Recent investigations have focused on pro-inflammatory processes that cause disturbances in placental angiogenesis as an aetiological factor. In this study, we investigated VEGF, sVEGFR-1 and IL-1α levels in placental cultures of pregnant women with severe preeclampsia compared to the control group with healthy pregnancies. In addition, the impact of low (6.25 mg/L) and high (25 mg/L) concentrations of Silymarin, a drug with anti-angiogenic and anti-inflammatory properties, on these cytokine levels were assessed.

Vascular endothelial growth factor (VEGF) plays an important role in angiogenesis, induces nitrous oxide and prostacycline secretion from endothelial cells, and has a critical function in controlling the vascular tonus (6, 26, 27). It also promotes the migration and adhesion of leukocytes to the inflammation site and increases vascular permeability, thereby acting as a cytokine with proinflammatory properties (28, 29). Previous studies have demonstrated that in cases with preeclampsia, inadequate invasion of spiral arterioles by trophoblasts commonly exists (5, 30). There are also studies that have reported lower local concentrations of angiogenic factors such as VEGF and PlGF in preeclamptic subjects (1, 8, 9, 31, 32). On the other hand, some publications have claimed that defects in placental invasion of trophoblasts might result in increased VEGF levels (33).

In this study, we found that basal VEGF levels were lower in the SP group; however, it did not reach statistical significance. In addition, basal VEGF levels after 72 hours of incubation cor-

Table 3. Basal levels of VEGF, sVEGFR-1 and IL-1α after 48 hours of incubation

	Severe preeclampsia group (n=8) mean±SD (range)	Control group (n=8) mean±SD (range)	p
VEGF (pg/mL)	12.75±7.59 (7.230-29.401)	23.64±32.06 (5.429-95.910)	>0.05
sVEGFR-1 (pg/mL)	8.29±4.93 (1.096-14.933)	5.43±3.34 (1.332-11.257)	>0.05
IL-1α (pg/mL)	1.05±0.46 (0.643-2.051)	1.07±0.16 (0.792-1.274)	>0.05
VEGF: Vascular endothelial growth factor; sVEGFR-1: Soluble VEGF receptor-1; IL1α: Interleukin1 alpha			

Table 4. Basal levels of VEGF, sVEGFR-1 and IL-1α after 72 hours of incubation (Well 4)

	Severe preeclampsia group (n=8) mean±SD (range)	Control group (n=8) mean±SD (range)	p
VEGF (pg/mL)	12.19±3.37 (8.269-19.327)	32.95±24.85 (8.542-73.141)	>0.05
sVEGFR-1 (pg/mL)	8.12±2.81 (4.652-12.169)	6.08±3.51 (1.474-13.258)	>0.05
IL-1 α (pg/mL)	1.03±0.53 (0.739-2.315)	1.05±0.36 (0.668-1.892)	>0.05
VEGF: Vascular endothelial growth factor; sVEGFR-1: Soluble VEGF receptor-1; IL1α: Interleukin1			

Table 5. VEGF, sVEGFR-1 and IL-1α levels after administration of Silymarin

		Basal 48h (pg/mL)	Silymarin 6.25 mg/L 48h (pg/mL)	Silymarin 25 mg/L 48h (pg/mL)	p	Basal 72h (pg/mL)	Silymarin 6.25 mg/L 72h (pg/mL)	Silymarin 25 mg/L 72h (pg/mL)	p
Control Group	VEGF	23.6 ±32	28.8±28.5	27.4±28.2	>0.05	32.9±24.9	38.5±48.8	48.9±54.2	>0.05
	VEGFR-1	5.4±3.3	5.0±2.5	5.8±2.4	>0.05	6.0±3.5	4.8±1.5	4.2±0.6	>0.05
	IL-1α	1.0±0.16	1.0±0.16	1.0±0.18	>0.05	1.0±0.36	1.3±0.6	1.1±0.47	>0.05
Severe Preeclampsia	VEGF	12.7±7.6	17.6±10.7	13.2±5.5	>0.05	12.2±3.3	14.3±5.9	18.5±11.4	>0.05
	VEGFR-1	8.2±4.9	6.4±3.7	5.5±4.3	>0.05	8.1±2.8	6.0±3.5	4.8±3.4	>0.05
	IL-1α	1.0±0.46	1.4±0.86	1.5±1.6	>0.05	1.0±0.5	1.8±1.3	1.7±1.6	>0.05
VEGF: Vascular endothelial growth factor; sVEGFR-1: Soluble VEGF receptor-1; IL1α: Interleukin1									

related significantly with newborn weight. Not surprisingly, our findings of decreased VEGF levels in FGR support the claim that inadequate placentation might be an important aetiological factor in these cases (34).

Previous studies have reported increased VEGFR-1 levels in cases with preeclampsia (1, 13, 35-38). It has also been suggested that high levels of sVEGFR-1 inhibits angiogenesis by antagonising the effects of VEGF and PlGF (39, 40). It has also been shown that sVEGFR-1 levels positively correlate with the severity of preeclampsia (1, 9). In this study, we could not demonstrate significantly different VEGFR-1 levels in placental cultures of women with SP compared to controls ($p>0.05$).

IL-1α and IL-1β are secreted from monocytes and tissue macrophages, therefore playing a role in acute and chronic inflammation (15, 41). It has also been previously reported that IL-1 has a role in maternal inflammatory response and endothelial dysfunction in preeclamptic women (42). In several studies, it has been shown that IL-1α secretion from placental villous tissue is increased in accordance with tissue hypoxia (43-45). From this point of view, in this study, we compared IL-1α levels in placental samples between severely preeclamptic women and controls. However, IL-1α levels were similar between the two groups after 48 and 72 hours of incubation.

Silymarin is a flavonoid with anti-proliferative, anti-inflammatory, anti-oxidant, pro-apoptotic, anti-angiogenic and anti-fibrotic properties that is derived from the plant *Silybum marianum* (46). It has been previously investigated as a drug against cancer, diabetes, chemotherapeutic resistance, and biliary disturbances in pregnant women. In this study, we investigated the effects of low (6.25 mg/L) and high (25 mg/L) concentrations of Silymarin on placental VEGF, sVEGFR-1 and IL-1α levels in severely preeclamptic and control (healthy pregnant) subjects. Compared to basal VEGF levels, we observed a Silymarin dose-dependent rise in VEGF levels in the SP and control groups after 72 hours of incubation ($p=0.01$).

After 42 and 72 hours of incubation, sVEGFR-1 levels in Silymarin added SP and control placental cultures were lower than the samples without the addition of Silymarin; however, this difference did not reach significance. Interestingly, we also observed that this decline was positively correlated with Silymarin dose and incubation duration. These results suggest that Silymarin may have favourable effects in SP cases.

IL-1α levels after incubation periods in Silymarin added SP and control groups were similar to levels in the samples without the addition of Silymarin. The mean gestational age was higher in the control group when compared with the SP group. As basal VEGF, sVEGFR-1 and IL-1α levels in the SP and control groups were similar after 48 and 72 hours of incubation, an analysis including all study subjects ($n=16$) was conducted to determine the associations between gestational age and VEGF, sVEGFR-1 and IL-1α levels after 48 and 72 hours of incubation. However, no significant correlations were noted between these groups. Thus, we assumed that the difference between gestational ages of study groups did not have any effect on our findings.

In currently ongoing studies, the role of secretion and the effects of placental cytokines in preeclampsia pathogenesis are being investigated. Considering the role of vasospasm, inflammation, angiogenesis, endothelial cell activation, and oxidative stress in preeclampsia, the potential benefits of Silymarin should be evaluated in future trials.

Ethics Committee Approval: *Ethics committee approval was received for this study from Başkent University Scientific and Ethical Committee (KA 08/57).*

Informed Consent: *Written informed consent was obtained from patients who participated in this study.*

Peer-review: *Externally peer-reviewed.*

Author contributions: *Concept - M.D.K., F.Y.; Design - M.D.K.; Supervision - F.Y., E.K. Resource - M.D.K, S.K., E.B.; Materials - F.Ş., S.K.; Data Collection&/or Processing - M.D.K., E.B.,; Analysis&/or Interpretation - M.D.K., F.Y., E.K.; Literature Search - E.B., M.K.T., S.K.; Writing - M.D.K., E.B., M.K.T.; Critical Reviews - F.Y., E.K.*

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Can maternal serum C-reactive protein levels predict successful labour induction with intravenous oxytocin in term pregnancies complicated with premature rupture of the membranes? A cross-sectional study

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Abstract

Objective: High sensitive C-reactive protein (hs-CRP) is a serum marker for acute inflammation and/ or infection. The diagnostic value of serum levels of this protein has been investigated among patients with preterm delivery, premature rupture of the membranes (PROM) and preeclampsia. In this study, the predictive value of hs-CRP for successful labour induction in patients with PROM has been evaluated.

Material and Methods: Eighty-six term pregnant patients who experienced pre-labour amniotic membrane rupture from 37-41 weeks of gestation were selected for the study. Maternal serum hs-CRP levels were determined upon admission to the delivery unit and low dose intravenous oxytocin infusion was started to induce labour. The mode of delivery and time interval from labour induction to delivery were the primary endpoints of the study.

Results: Twenty-five (29%) out of 86 patients had delivered by caesarean section, while the remaining 61 (71%) had delivered vaginally. The receiver operator characteristic (ROC) curve for testing the significance of higher hs-CRP values and lower probability of vaginal delivery revealed that higher hs-CRP values were found to be insignificant for predicting the need for caesarean section. No statistically significant correlation between high serum hs-CRP levels and the probability of caesarean delivery has been established (Spearman rho:-.126; p=0.24). The mean maternal serum hs-CRP levels during PROM were found to be similar between vaginal and abdominal deliveries.

Conclusion: Hs-CRP, as an inflammatory marker, was found to be neither specific nor sensitive for the prediction of successful labour induction in term pregnancies with pre-labour rupture of the membranes. (J Turk Ger Gynecol Assoc 2014; 15: 36-40)

Key words: C-reactive protein, premature rupture of the membranes, labour induction

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Introduction

High sensitive C-reactive protein (hs-CRP) is an acute phase reactant protein that is secreted to the circulation from the liver as a reaction to the onset of inflammation and/or acute tissue injury. Maternal serum hs-CRP measurement was assumed to be a clinical indicator for women with preterm labour or preterm rupture of membranes related to the possible preceding subclinical maternal infection. Watts et al. (1) determined hs-CRP levels serially from 22 weeks' gestation until delivery in healthy pregnant women without antepartum complications; the median hs-CRP values ranged from 0.7-0.9 mg/dL for women who were not in labour and showed no significant change in serum levels of hs-CRP according to the gestational age. Kashanian et al. (2) evaluated the diagnostic value of maternal serum hs-CRP measurement during the first trimester of pregnancy for predicting pre-eclampsia. A systematic review conducted by Rebelo et al. (3) also suggested that women with higher levels of hs-CRP may have an increased risk of developing preeclampsia. Measurement of the first trimester maternal serum hs-CRP levels for the prediction of subsequent preterm delivery was found to be use-

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less (4). Unexpectedly, Moghaddam et al. (5) found a significant relationship between elevated maternal serum hs-CRP levels in the first 20 weeks of pregnancy and the later occurrence of preterm premature rupture of membranes (PPROM) and preterm birth, with a cut-off level of hs-CRP level >4 mg/L demonstrating statistically significant relationships with PPROM and preterm birth. Although the hs-CRP values seem to be higher than expected for non-pregnant women, hs-CRP values physiologically increased during labour (6). However, hs-CRP levels increased following both vaginal and caesarean deliveries; the exact interval between the elevation of hs-CRP and the onset of labour at term is not known. A possible association between high hs-CRP levels in maternal serum early in pregnancy have also been described as a marker of preterm delivery, intrauterine infection and PPROM (7). The relationship between maternal serum hs-CRP levels during admission to the delivery unit and successful labour induction with i.v. oxytocin in patients with pre-labour PROM has not been hugely studied before. In this study, we tried to evaluate the relationship between serum hs-CRP levels of term pregnant women who have experienced pre-labour amniotic membrane rupture and successful labour induction with a low dose oxytocin infusion. Our aim was to determine a cut-off value for hs-CRP levels that predicts the low probability of achieving vaginal delivery.

Material and Methods

This cross-sectional study was conducted at the delivery ward of a tertiary education and research hospital with a delivery rate of approximately 20,000/year between January 2011 and June 2011. This study was approved by the Ethical Committee of the hospital and informed consent was taken from the patients before the study began. During this time period, 572 term pregnant patients who experienced pre-labour amniotic membrane rupture from 37-41 weeks of gestation were evaluated and 86 eligible women were selected for the study. Patients with a Bishop score ≥5, a non-vertex presentation, cephalopelvic disproportion, macrosomia, uterine contractions on non-stress test, active labour with cervical dilatation more than 3 centimetres upon admission, systemic illness, gestational hypertension, gestational diabetes and patients who had not undergone labour for other obstetric indications were excluded from the study. All patients received prophylactic antibiotics (1 g of i.v. cephazoline 12 hours apart) from admission to delivery. Hs-CRP was measured with a high sensitivity immunoturbidimetric assay (Roche Diagnostics, Indianapolis, IN, USA) using an automated clinical chemistry analyser. The hs-CRP assay coefficients of variation were 2.7% at 0.12 mg/L, 3.45% at 0.41 mg/L, and 5.7% at 0.03 mg/L. The assay had a detection limit of 0.03 mg/L and a calibration range of up to 300 mg/L. The normal range reference interval of hs-CRP for adults was accepted as <5 mg/L. Blood samples for the determination of hs-CRP levels of patients were drawn only once immediately upon admission to the ward.

Then, low dose intravenous oxytocin infusion, prepared as a 500 mL isotonic fluid including 5 IU oxytocin, was started with different time intervals following the membrane rupture to induce labour. Dose increments were made every 15 minutes starting with 12 mL/hour until satisfactory uterine contractions (3 contractions/10 minutes) were achieved. The progression of labour of the 86 recruited patients was followed until delivery by physicians who were blinded about the study. The primary endpoints of the study were the mode of delivery and time interval from labour induction to vaginal delivery. All statistical analyses were performed using IBM SPSS Statistics Software (19.0, SPSS Inc., Chicago, IL, USA). Data were assessed for normality using the Kolmogorov-Smirnov test. The continuous variables were presented by means± standard deviation (SD) and compared using the independent samples t test. The non-parametric variables and data without normality were tested using the Mann Whitney U test. The comparison of categorical values was accomplished by using Fisher's exact test or the chi-square test. P values <0.05 were considered statistically significant. The Receiver Operating Characteristic (ROC) analysis was used to estimate an optimal threshold score of hs-CRP to predict successful labour progress. The spearman correlation test was used for evaluation of the correlation between variables of which variances were not equally assumed.

Results

The clinical characteristics of the total study group are presented in Table 1 (N=86). The majority of the participants were nullipar (72.1%) and 60.5% of them had a low socioeconomic status. Twenty-five (29%) out of the 86 patients had delivered by caesarean section, while the remaining 61 (71%) delivered vaginally. The caesarean section indications were unsuccessful labour induction (60%), cephalopelvic disproportion (24%) and foetal distress (16%) (N=25). Among all patients, 15 (17%) underwent caesarean section due to unsuccessful labour induction. When the cases were categorised according to the delivery mode, no significant differences were found between the vaginally and abdominally delivered patients regarding the mean levels of age, gestational age at admission, body mass index, hs-CRP, lactate dehydrogenase (LDH), neutrophil count percent, white blood cells count, birth-weight and the time interval between PROM and the induction of labour (p>0.05) (Table 2). The mean cervical length measurement (millimetres) of the vaginally delivered patients at admission was significantly lower than abdominally delivered patients (26±7 versus 32±4 respectively; p=0.01). The mean time intervals between labour induction and delivery (hours) of the vaginally and abdominally delivered patients were 8.2±6.9 and 12±6.7 hours, respectively (p=0.016). The receiver operator characteristic (ROC) curve for testing the significance of higher hs-CRP values and higher probability of caesarean delivery revealed that higher hs-CRP values had at least one insignificant relation with a higher caesarean section rate (Area under curve (AUC):0.57; p=0.22) (Figure 1). A significant relationship between higher cervical length at admission and lower probability of vaginal delivery was established (AUC=0.71; p=0.001, 95% CI=0.61-0.82) (80% sensitivity and 58% specificity for a cut-off value 27.5 mm) (Figure 2). The ROC curve analysis of the increasing time interval elapsed from premature membrane rupture to

Table 1. The clinical characteristics of the study group (N=86)*

	N	Minimum	Maximum	Mean	Std. Deviation
Age (years)	86	18	40	26	5
Gestational week at admission to the ward	86	37	41	38	1
BMI (kg/m^2)	86	22	38	28	3
CRP (mg/dL)	86	0.4	44	9.5	11.1
LDH (IU)	86	206	576	341	75
Haemoglobin (mg/dL)	86	9.1	14.7	11.8	1.2
WBC (number/mm^3)	86	5840	21000	11497	2814
Neutrophil count (percent)	86	58	90	74	7
Cervical length (mm)	86	6	41	28	7
Birth-weight (grams)	86	2530	4280	3142	391

*: Whole study group
BMI: Body mass index; CRP: C-reactive protein; LDH: Lactate dehydrogenase; WBC: White blood cell

Table 2. The clinical characteristics of the study group (N=86)*

Parameter	Vaginal Delivery (N=61)	Abdominal Delivery (N=25)	p value
Age (years)	25.7±5.2	27.8±5.8	0.08**
Gestational week at admission to the ward	38±1	39±1	0.28**
BMI (kg/m^2)	27.7±3.2	29.1±3.5	0.06**
CRP (mg/dL)	8.1±9.2	11.6±13.2	0.22*
LDH (IU)	352±78	325±70	0.10**
Neutrophil count (percent)	75±8	73±5	0.21*
WBC (number/mm^3)	11690±3334	11215±1818	0.63*
Cervical length (mm)	26±7	32±4	0.01*
Birth-weight (grams)	3150±160	3191±156	0.16**
Time interval between premature membrane rupture and labour induction (hours)	7.6±4.5	9.3±5.3	0.10**
Time interval between labour induction and delivery (hours)	8.2±6.9	12±6.7	0.016**

*=p value (Mann-Whitney U test)
**=p value (Independent Samples t test)
BMI: Body mass index; CRP: C-reactive protein; LDH: Lactate dehydrogenase; WBC: White blood cell

labour induction (hours) and delivery revealed a positive but insignificant relationship with higher abdominal delivery rate (AUC=0.59; p=0.14). When we tested the possible correlation between high serum hs-CRP levels and the probability of caesarean delivery, we could not establish any significant correlation (Spearman rho: -.126; p=0.24).

Discussion

In this study, we evaluated the relationship between serum hs-CRP levels and the mode of delivery among patients with PROM who received labour induction with low dose i.v. oxytocin. Although hs-CRP levels increase during active labour, the clinical value of this acute phase reactant had not been previously studied in detail for patients with membrane rupture preceding uterine contractions. Whether an increased hs-CRP level represents a subclinical intrauterine infection without any microbiological confirmative test that precludes efficient uterine contractions to proceed labour or not has been evaluated. Previous studies demonstrated a relationship between high serum hs-CRP levels and PROM (8). Before encountering the clinical scene of the preterm labour caused by certain intrauterine infections, hs-CRP levels can be found to be high in the serum earlier during the course of the preterm labour pathophysiology. In two systematic reviews, conducted by Van de Laar et al. (9) and Trochez-Martinez et al. (10), the predictive value of maternal serum hs-CRP for clinical chorioamnionitis and/or neonatal sepsis in women with PPROM was evaluated.

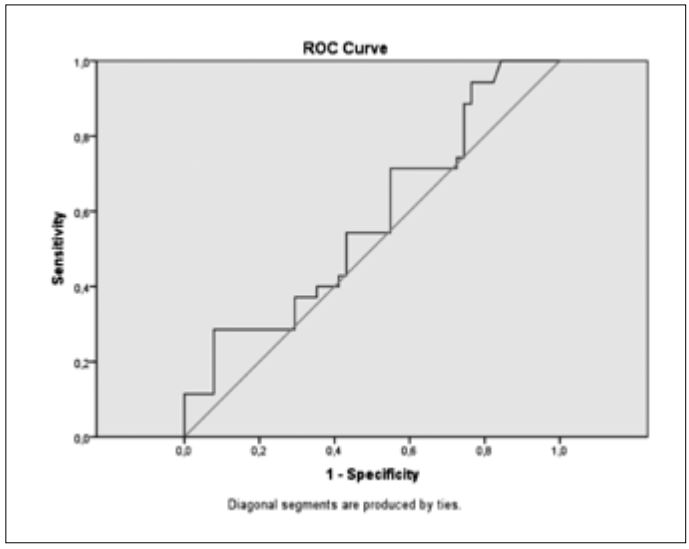

Figure 1. The ROC curve demonstrating the direct proportional relationship between the higher CRP values and the higher probability of caesarean section (AUC=0.57; p=0.22, 95% CI=0.45-0.70) (N=86)

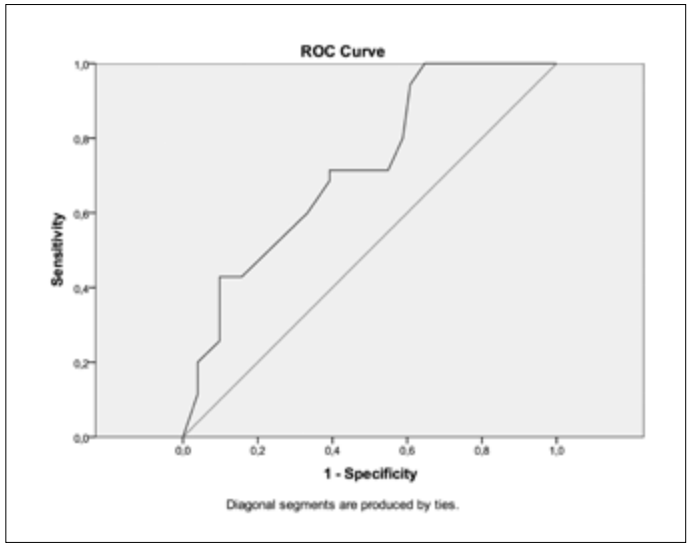

Figure 2. The ROC curve demonstrating the direct proportional relationship between the higher cervical length and lower probability of vaginal delivery (AUC=0.71; p=0.001, 95% CI=0.61-0.82) (N=86)

The current data were not sufficient to suggest the use of hs-CRP in women with PPROM. The foetal immune system also has the ability to produce hs-CRP into the amniotic fluid as a response to subclinical intrauterine infection. In a prospective study, amniotic fluid hs-CRP measurements were studied during mid-trimester amniocentesis for genetic indications and levels >0.65 mg/L were found to be related to increased preterm delivery risk (11). Ghezzi et al. (12) evaluated pre-existing intrauterine inflammation by measuring amniotic fluid hs-CRP levels in the first half of gestation as a possible condition that leads to preterm delivery; they found that an amniotic fluid hs-CRP concentration of >110 ng/mL had a sensitivity of 80.8% and a specificity of 69.5% in the prediction of spontaneous preterm delivery at <34 weeks, revealing that subclinical intrauterine/foetal inflammatory processes early in gestation may be a cause of preterm delivery in the second half of gestation. Oh et al. (13) evaluated the predictive value of intra-amniotic matrix metalloproteinase 9 (MMP-9), interleukin 6 (IL-6) levels and maternal serum hs-CRP for histologic chorioamnionitis and intra-amniotic infection among patients with preterm labour or preterm PROM (21-35 weeks of gestation) who delivered within 72 hours of transabdominal amniocentesis. The amniotic fluid (AF) MMP-9 was found to be a better diagnostic marker than AF IL-6 and maternal serum hs-CRP in predicting intra-amniotic infection. Interestingly, in the same study, the serum hs-CRP levels obtained up to 72 hours before delivery were found to be valuable for the early identification of histologic chorioamnionitis in women without an intra-amniotic infection.

In this study, a significant relationship between higher cervical length at admission and lower probability of vaginal delivery was established for patients with PROM. Greater cervical length of the patients with PROM at admission seemed to preclude successful labour induction with oxytocin. We could not establish any relationship between the serum hs-CRP levels and the mode of delivery. Hs-CRP levels of patients with PROM did not have any predictive value for successful labour induction following the rupture of the membranes. It is possible that subclinical intrauterine infection with high serum hs-CRP levels exerts little effect on the uterine contractility, which precludes any significant change in the mode of the delivery. Before the initiation of uterine contractions following the PROM event, the mechanism that increases the hs-CRP values to the levels that are consistent with active labour might already have been established. The rapid initiation of prophylactic antibiotics to the patients also might have lowered the negative effects of the subclinical intrauterine infection to the uterine contractility. Randomised controlled studies conducted among patients with PROM are needed to evaluate the predictive value of serum hs-CRP and/or other systemic inflammatory markers for successful labour induction. However, the higher serum hs-CRP levels have been detected among postdate (>40 gestational weeks) women whose labour will start with PROM than in women whose labour starts otherwise; the clinical utilisation of this fact is lacking (8). When a PROM patient is admitted to the delivery unit, it is wise to evaluate a possible subclinical intrauterine infection with confirmative microbiological tests of the amniotic fluid rather than serum hs-CRP levels. Administration of prophylactic antibiotics immediately upon admission to the ward is another realistic option for these patients because the microbiological culture results will probably not be available as quickly. The prediction of successful labour induction among patients with PROM using serum hs-CRP levels does not have promising results for the routine recommendation of this test to all patients with PROM.

Ethics Committee Approval: *Ethics committee approval was received for this study.*

Informed Consent: *Written informed consent was obtained from patients who participated in this study.*

Peer-review: *Externally peer-reviewed.*

Author contributions: *Concept - S.K.; Design - S.K.; Supervision - Y.E.Ü.; Resource - S.K.; Materials - İ.K.; Data Collection&/or Processing - H.T., R.E., E.G.Y.E.; Analysis&/or Interpretation - S.K.; Literature Search - S.K.; Writing - S.K.; Critical Reviews - Y.E.Ü.*

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Prediction of staging with preoperative parameters and frozen/section in patients with a preoperative diagnosis of grade 1 endometrioid tumor in endometrial cancer

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Abstract

Objective: To investigate the likelihood of the detection of the necessity of staging preoperatively with the use of clinical parameters and frozen/section (FS).

Material and Methods: 219 patients were included who were operated on between 1996 and 2010 with a diagnosis of grade 1 endometrioid adenocarcinoma in probe curettage.

Results: Among the clinical characteristics, only age and body mass index (BMI) predicted staging preoperatively. The probability of staging increased as age increased and BMI decreased. The concordance between preoperative diagnosis and FS was 89.5%. The diagnosis was upgraded at postoperative evaluation for 13 patients (5.9%), and downgraded for 2 patients (0.9%) compared with FS. The wrong diagnosis regarding grade, the depth of myometrial invasion DMI, tumour type and cervical invasion in FS was clinically significant and affected the decision of staging in 10 patients. In conclusion, only 7 patients (3.2%) who acquired staging surgery were missed in FS.

Conclusion: It was shown that preoperative clinical parameters could not effectively predict the patients who should be staged. FS predicted the lymphatic involvement with high accuracy. The patient with a preoperative diagnosis of grade 1 endometrium cancer should be operated upon in centres where FS is utilised and oncologic staging surgery can be performed. (J Turk Ger Gynecol Assoc 2014; 15: 41-8)

Key words: Endometrial cancer, body mass index, age, frozen/section, staging

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Introduction

Endometrium cancer is usually diagnosed at an early stage (1). It is still controversial whether routine lymphadenectomy should be involved in surgical staging of this tumour that has been staged surgically in accordance with the guidelines of FIGO (International Federation of Gynecology and Obstetrics) since 1988. Some authors suggested routine lymphadenectomy in order to define lymphatic spread and to improve survival (2, 3). Nevertheless, it was shown that lymphadenectomy in addition to total abdominal hysterectomy and bilateral salpingo-oophorectomy in patients with early stage endometrium cancer did not improve survival (4, 5). Additionally, pelvic and para-aortic lymphadenectomy increases surgical morbidity (6, 7). Therefore, it is clear that performing lymphadenectomy for all of the patients with endometrium cancer will cause overtreatment and an increase in morbidity.

Determination of the risk factors that may indicate lymphatic spread in endometrium cancer and performing lymphadenectomy for patients with these risk factors will be an appropriate option. These risk factors are tumour type, cervical involvement, grade and depth of myometrial invasion (DMI) (8-12). These factors could be defined intraoperatively with frozen/section (FS). Preoperatively, age, body mass index (BMI), serum Ca-125, haemoglobin and platelet levels could be utilised as risk factors for lymphatic metastasis.

Age is associated with advanced disease and lymphatic metastasis (13, 14). An increase in BMI is associated with lower grades. However, it is difficult to say that greater BMI is associated with lower nodal metastasis rates (15). Preoperative high Ca-125 level is an independent risk factor nodal spread (16-18). In addition, preoperative lower haemoglobin level is associated with nodal metastasis and therefore with advanced disease and worse survival (19, 20). Preoperative thrombocytosis is observed in patients with

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advanced stages; however, there are studies stating the opposite (16, 21, 22).

The accuracy rate of grade that is detected with probe curettage in accordance with the results of paraffin blocks ranges between 36%-96% (2, 23-25). Intraoperatively, grade could be defined with an accuracy of 58%-98%; with FS, according to postoperative pathology, these rates for DMI and cervical invasion are 54%-95% and 95%, respectively (26-34). In contrast, others argue that FS could not predict lymphatic spread well, meaning that all patients with endometrium cancer should be staged systematically (27).

In this study, the surgical results of patients with grade 1 endometrioid endometrium cancer were evaluated. The likelihood of the detection of the necessity of staging preoperatively with the use of clinical parameters and FS were investigated.

Material and Methods

In this study, 219 patients were included who were operated on between 1996 and 2010 with a diagnosis of grade 1 endometrioid adenocarcinoma in probe curettage. The pathological specimens of the patients coming from other hospitals with a diagnosis of endometrial cancer or complex hyperplasia with atypia were evaluated again in our hospital.

Since FS was utilised in the study, the presence of myometrial invasion and the type of cervical invasion, glandular or stromal, were important factors. Therefore, patients were staged according to the 1988 FIGO criteria. Nevertheless, stages of the patients in the study group were also defined according to the 2009 FIGO criteria.

Staging surgery is performed in our clinic for patients whose frozen-section analysis reveals a tumour type other than endometrioid adenocarcinoma, grade 2 or grade 3 disease, myometrial invasion ≥1/2, cervical invasion and tumour size greater than 2 cm. Staging surgery involves total abdominal hysterectomy, bilateral salpingo-oophorectomy, systematic pelvic and paraaortic lymphadenectomy, cytology and omentectomy as a standard. Cytoreductive surgery was performed in addition to staging surgery in case there was macroscopic disease intraoperatively. The patients who had not been staged according to the result of FS analysis, but who were upgraded with postoperative pathology result were restaged and given adjuvant therapy (chemotherapy and/or radiotherapy), or directly given adjuvant therapy without reoperation depending on the collective decision of both the surgeon and the patient.

Bilateral pelvic lymphadenectomy was performed. This involved complete skeletonisation of all lymphatic tissue of the common, external and internal iliac vessels and obturator fossa after visualisation of the obturator nerve. The superior surgical margin of dissection for the pelvic nodes was aortic bifurcation and the anterior distal surgical margin was the circumflex iliac vein. The lymphatic tissue of the presacral region was also harvested separately. The para-aortic lymphadenectomy was performed by mobilising the paracolic peritoneum along the lateral border of the ascending and descending colon, permitting identification of the proximal ureters and high division of the ovarian vessels. This allowed visualisation of the whole retroperitoneum up to the superior borders of the renal veins. All lymphatic tissue was then harvested from the lateral, anterior, and medial aspects of the vena cava and aorta up to the renal veins in all patients.

In evaluation of FS, the uterus was opened and the cavity was inspected for irregularities of counter and colour. The 2-5 full-thickness slices were made through the wall of the uterus. The area of deepest myometrial invasion was selected for FS examination. If no tumour was apparent on gross examination, at least 5 random sections were performed. All of the samples were frozen at -25˚C, were cut to 8μ in thickness and stained with haematoxylin and eosin manually. They were evaluated in terms of grade, the depth of myometrial invasion, lymphovascular space invasion and the size of the tumour.

Descriptive statistics were calculated using the Statistical Package for Social Sciences (SPSS) 17.0 package program (SPSS Inc., Chicago IL, USA). The nominal values and the differences between the ratios were evaluated with Chi-Square and ANOVA Table Test. Univariant analysis was performed using a log rank test. The cut-off for statistical significance was set at $p<0.05$.

Results

The mean age of the patients was 60.1 years and ranged between 35 and 84 years. The ratio of probe curettages performed in other hospitals was 54.8% and all of these were re-evaluated in our hospital preoperatively. According to the FIGO 1988 system, 90% of the patients had stage 1 disease. Lymph node metastasis was observed in 5% of the patients. Preoperative Ca-125 level was 9 IU/mL (range: 2-1834 IU/mL), platelet level was 261.940/mL (range: 100.000-596.000/mL), haemoglobin was 12.3 (range: 4.4-16.1 mg/dL) and the mean value of BMI was 34.6 kg/m^2 (range: 18.3-57.3 kg/m^2). The BMI was below 25 kg/m^2 in only 7 patients. Preoperative clinical characteristics, stages and lymph node status of the patients in the study group are listed in Table 1.

Sixty-nine (31.5%) patients were staged intraoperatively according to the criteria used in our clinic. The mean number of the pelvic and para-aortic lymph nodes removed was 39 (range: 10-81) and 10 (range: 1-24), respectively. In 11 (16%) patients who were staged, lymph node metastasis was observed. Lymph node involvement was only in the pelvic region in 5 patients, in the para-aortic region in 2 patients and in both regions in 4 patients (Table 1). The number of lymph nodes removed in patients who had nodal involvement and those who did not were similar (48.2 vs. 53, respectively, $p=0.694$). In the patient group who had staging surgery, 22% had advanced disease (stage III-IV). However, only 1 (0.7%) patient in the group of 150 patients who did not have staging surgery had advanced disease (stage IIIA) (Table 2).

Among the clinical characteristics, only age and BMI predicted staging preoperatively (Table 3). The probability of staging increased as age increased and BMI decreased. Staging surgery was performed for 24% of the patients whose ages were under 60 years and for 39% of the patients whose ages were above 60 years ($p=0.016$). When 34 kg/m^2 was accepted as

the median BMI, 35% and 20% of the patients below and above this value were staged, respectively (p=0.044). When 25 kg/m^2 was accepted as the boundary, these numbers were 57% and 26%, respectively. Nevertheless, this difference was insignificant (p=0.074), even though the difference was 30%. The reason for this was the disproportionate distribution between the groups, since only 7 patients had a BMI below 25 kg/m^2. When age and BMI were evaluated together, the prediction of staging preoperatively was improved. Forty-five percent of the patients with these criteria and 15% of the patients without these criteria were staged (p=0.009) (Table 3). By utilising these criteria, 73% of the patients requiring staging and 62% of the patients who did not were defined, meaning that the sensitivity and specificity of these factors for staging were 73% and 62%, respectively. The false positive ratio and false negative ratio were 38% and 15%, respectively. Preoperative Ca-125 and haemoglobin level, platelet value and the place of the probe curettage did not predict the probability of staging.

In the FS evaluation of patients with a preoperative diagnosis of grade 1 endometrioid adenocarcinoma, 13 patients did not have a tumour and 10 patients had a grade 2 tumour (Table 2). The concordance between preoperative diagnosis and FS was 89.5%. Similarly, the concordance of grade between preoperative and postoperative diagnosis and FS and postoperative diag-

Table 1. Characteristic features

Parameter		n / Mean	% / Median (Range)
Age (years)		60.1	60 (35-84)
1988 FIGO Stage	IA	40	18.3
	IB	141	64.4
	IC	16	7.3
	IIA	4	1.8
	IIB	2	0.9
	IIIA	5	2.3
	IIIC	10	4.6
	IVB	1	0.5
2009 FIGO Stage	IA	183	83.6
	IB	19	8.7
	II	2	0.9
	IIIA	4	1.8
	IIIC1	5	2.3
	IIIC2	5	2.3
	IVB	1	0.5
Staging Surgery	Performed	69	31.5
	Not performed	150	68.5
Number of removed pelvic lymph nodes	Pelvic	39	38.5 (10-81)
	Paraaortic	10	10 (1-24)
	Total	49	49 (12-98)
Lymph node metastasis	Negative	58	84
	Positive	11	16
Region of metastatic lymph nodes	Only pelvic region	5	2.3
	Only paraaortic region	2	0.9
	Both regions	4	1.8
Preoperative platelet level (n/mL)		261.940	261.000 (100.000-596.000)
Preoperative haemoglobin level (mg/dL)		12.3	12.7 (4.4-16.1)
Preoperative body mass index (kg/m^2)		34.6	34 (18.3-57.3)
Preoperative Ca-125 level (IU/mL)		55.6	9 (2-1834)
Place of probe curettage	Our centre	99	45.2
	Other centre	120	54.8

FIGO: International Federation of Gynecology and Obstetrics

nosis was 92.7% and 93.2%, respectively (Table 4). The diagnosis was upgraded at postoperative evaluation for 13 patients (5.9%), and was downgraded for 2 patients (0.9%) compared with FS. This change was clinically significant for only 3 of the 13 upgraded patients. These 3 patients were stated to have a grade 1 tumour intraoperatively and reported to have grade 2 disease in the final pathology report.

Thirty-nine patients (17.8%) were defined to have DMI ≥1/2 in FS and 41 patients (18.7) had DMI ≥1/2 at postoperative examination. DMI defined postoperatively was similar to FS in 188 (85.8%) patients (Table 5). However, DMI was underestimated in 21 patients (9.6%) and overestimated in 10 patients (4.6%). Nevertheless, this discordance was clinically significant only in 5 patients who had a DMI<1/2 in FS and DMI≥1/2 at postoperative evaluation. The concordance of DMI between the FS and postoperative pathology was not affected by the preoperative clinical parameters (Table 5).

In the study population, any tumour other than endometrioid-type was not defined in the intraoperative examination, while clear cell tumour in 1 patient and mixed-type tumour in one patient were diagnosed at postoperative evaluation (Table 6). These 2 patients were stated to have endometrioid tumour intraoperatively and were not staged.

Cervical invasion could not be defined in FS in 4 patients. Invasion was glandular in 2 patients who did not have high risk surgical factors. These 2 patients were reported to have stage IB disease according to the FIGO 2009 criteria. The other 2 patients had stromal invasion, which was clinically significant.

The wrong diagnoses regarding grade, DMI, tumour type and cervical invasion in FS were clinically significant and affected the decision of staging in 10 patients. In 2 patients, more than one parameter was wrongly defined. Three of these 10 patients were staged because of the existence of other high risk factors. The first patient who was staged had grade 1 disease and DMI ≥1/2.

Table 2. Stages of the patients

	1988 FIGO Stage							
Staging Surgery	**IA**	**IB**	**IC**	**IIA**	**IIB**	**IIIA**	**IIIC**	**IVB**
Performed, n (%)	-	37 (53.6)	14 (20.3)	2 (2.9)	1 (1.4)	4 (5.8)	10 (14.5)	1 (1.4)
Not performed, n (%)	40 (26.7)	104 (69.3)	2 (1.3)	2 (1.3)	1 (0.7)	1 (0.7)	-	-

FIGO: International Federation of Gynecology and Obstetrics

Table 3. Clinical parameters determining the probability of staging preoperatively

Parameter		**Staging Surgery (%)**		**p**
		Performed	**Not Performed**	
Age [1]	<60	24	76	0.016
	≥60	39	61	
Preoperative platelet level (n/mL)	≤400.000	33	67	0.269
	>400.000	50	50	
Preoperative platelet level (n/mL)[1]	<261.000	33	67	0.690
	≥261.000	36	64	
Preoperative haemoglobin level (mg/dL)[1]	≤12	40	60	0.247
	>12	31	69	
Body mass index (kg/m^2)	<25	57	43	0.073
	≥25	26	74	
Body mass index (kg/m^2)[1]	<34	35	65	0.044
	≥34	20	80	
Age and body mass index	<60 and ≥34	15	85	0.009
	≥60 and <34	45	55	
Preoperative Ca-125 level (IU/mL)	<35	28	72	0.178
	≥35	50	50	
Preoperative Ca-125 level (IU/mL)[1]	<9	36	64	0.616
	≥9	29	71	
Place of probe curettage	Our centre	32	68	0.794
	Other centre	31	69	

[1]Median values

Table 4. Concordance of grade and depth of myometrial invasion between intraoperative and postoperative pathologies

Intraoperative	Postoperative		
	Grade		
Grade	**No malignancy**	**Grade 1**	**Grade 2**
No malignancy, n (%)	3 (23.1%)	10 (76.9%)	-
Grade 1, n (%)	1 (0.5%)	192 (98%)	3 (1.5%)
Grade 2, n (%)	-	1 (10%)	9 (90%)
	Depth of myometrial invasion		
Depth of myometrial invasion	No malignancy and invasion	<1/2	≥1/2
No malignancy and invasion, n (%)	30 (76.9%)	9 (23.1%)	-
<1/2, n (%)	7 (5%)	129 (91.5%)	5 (3.5%)
≥1/2, n (%)	1 (2.6%)	2 (5.1%)	36 (92.3%)

Table 5. Factors determining discordance of depth of myometrial invasion between intraoperative and postoperative pathologies

Parameter		Depth of myometrial invasion		p
		Concordance	Discordance	
Age[1]	<60	82	18	0.108
	≥60	90	10	
Preoperative platelet level (n/mL)	≤400.000	88	12	0.452
	>400.000	80	20	
Preoperative platelet level (n/mL)[1]	<261.000	91	9	0.209
	≥261.000	84	16	
Preoperative haemoglobin level (mg/dL)[1]	≤12	85	15	0.364
	>12	90	10	
Body mass index (kg/m^2)	<25	100	-	0.239
	≥25	83	17	
Body mass index (kg/m^2)[1]	<34	85	15	0.905
	≥34	84	16	
Preoperative Ca-125 level (IU/mL)	<35	91	9	0.309
	≥35	84	16	
Preoperative Ca-125 level (IU/mL)[1]	<9	89	11	0.576
	≥9	85	15	

[1]Median values

In the other 2 patients who had DMI <1/2, the reason for staging surgery was tumour size. These 2 patients were reported to have grade 1 disease intraoperatively. There was no lymph node involvement in these 3 patients. In conclusion, only 7 patients (3.2%) who acquired staging surgery were missed by FS.

The 7 missed patients who were not staged intraoperatively according to the FS results are defined in Table 7. In 1 of the 2 patients who were missed due to wrong tumour type in FS, the postoperative tumour type was mixed-type (Patient #1). The tumour had both endometrioid and mucinous components and adjuvant therapy was not considered. The postoperative tumour type was clear cell in the second patient and staging surgery was chosen for this patient (Patient #2). However, the patient rejected surgery and she was lost to follow-up. For the patient who had a wrong diagnosis with regard to DMI and grade, staging was not considered and she had adjuvant pelvic radiotherapy (Patient #3). She died of a cause other than her tumour at the end of 60 months of follow-up without recurrence. The patient with an underestimated DMI in FS was recommended to have adjuvant pelvic radiotherapy. Nevertheless, she rejected this treatment and was lost to follow-up (Patient #4). Another patient with underestimated DMI was defined to have stromal cervical invasion postoperatively (Patient #5). This patient underwent staging surgery and did not have lymph node involvement. She had adjuvant pelvic radiotherapy and did not report recurrence in 46 months of follow-up. The other patient with underestimated DMI in FS had adjuvant pelvic radiotherapy and was lost to follow-up after 7 months (Patient #6). There was no recurrence during follow-up. The last patient who was not staged due to underestimation in FS, resulting in clinically significant fault, had stage IIIA disease according to FIGO 1988 (Patient #7). This patient had ovarian involvement. Cervical stromal metastasis was also missed, in addition to microscopic ovarian involvement in FS. This patient was not restaged and took 6 cycles of paclitaxel (175 mg/m^2) +carboplatin (AUC=6) chemotherapy and pelvic radiotherapy following chemotherapy. There was no recurrence during 120 months of follow-up.

Discussion

An increase in BMI is associated with endometrioid histology, lower grade and lower stages, since advanced age is associated with non-endometrioid histology and advanced stages of endometrial cancer (14, 35). In the present study, 35% of the patients with a BMI under 34 kg/m^2, 20% of the patients with a BMI above it, 24% of the patients whose ages were under 60 years old and 39% of the patients whose ages were above 60 were staged (p=0.044, p=0.016, respectively). When both of these parameters were evaluated together, 45% of the patients who were 60 years old or older with a BMI <34 kg/m^2 were staged, while 15% of the patients who were below 60 years old with a BMI ≥34 kg/m^2 were staged (p=0.009). The sensitivity of these factors when used together was 73%, meaning that more than 25% of the patients with high risk factors who should be staged could not be detected when preoperative clinical parameters were used. Therefore, which patients with a preoperative diagnosis of grade 1 endometrioid type tumour should be staged could not be detected by using these clinical parameters.

A high level of preoperative Ca-125 was shown to be associated with high tumour grade, advanced stages and DMI (17, 18, 21, 36). Additionally, lower levels of preoperative haemoglobin levels and thrombocytosis were associated with advanced stages and worse prognosis (19, 20, 21, 22). In the presented study, preoperative Ca-125, platelet and haemoglobin levels could not define the probability of staging.

Table 6. Intraoperative and postoperative results of grade, depth of myometrial invasion and histopathology

Parameter	Grade			
Grade	No malignancy		1	2
Intraoperative	13 (5.9%)		196 (89.5%)	10 (4.6%)
Postoperative	4 (1.8%)		203 (92.7)	12 (5.5)
	Depth of myometrial invasion			
Depth of myometrial invasion	No malignancy or invasion		<1/2	≥1/2
Intraoperative	39 (17.8%)		141 (64.4%)	39 (17.8%)
Postoperative	38 (17.4%)		140 (63.9)	41 (18.7%)
	Histopathology			
Histopathology	No malignancy	CAH	Endometrioid type	Other
Intraoperative	7 (3.2%)	6 (2.7%)	206 (94.1%)	-
Postoperative	3 (1.4%)	1 (0.5%)	213 (97.2%)	2 (0.9%)

CAH: Complex Atypical Hyperplasia; Other: Clear cell in one patient, mixed-type tumour in one patient

Table 7. Patients who were not staged due to faulty Frozen/Section

			Frozen/Section			Postoperative histopathology				Additional or	Last
Pt	Stg1	Age	Gr	DMI	Tumour type	Gr	DMI	Tumour type	Cx in	adjuvant therapy	Status
1	IB	65	1	<1/2	Endometrioid	1	<1/2	Mix	-	No therapy	AWOD
2	IA	66	1	No invasion	Endometrioid	1	No invasion	Clear cell	-	Re-operation	Lost to f-up
3	IC	75	1	<1/2	Endometrioid	2	≥1/2	Endometrioid	-	Pelvic RT	DOOD
4	IB	84	1	<1/2	Endometrioid	2	<1/2	Endometrioid	-	Pelvic RT	Lost to f-up
5	IIB	43	1	<1/2	Endometrioid	1	≥1/2	Endometrioid	+	Re-operation followed by pelvic RT	AWOD
6	IC	62	1	<1/2	Endometrioid	1	≥1/2	Endometrioid	-	Pelvic RT	Lost to f-up
7	IIIA	59	1	<1/2	Endometrioid	1	≥1/2	Endometrioid	+	CT followed by pelvic RT	AWOD

Pt: Patient; Stg: Stage; 1: FIGO 1988; Gr: Grade; DMI: Depth of myometrial invasion; Cx in: Cervical invasion; f-up: Follow-up; CT: Chemotherapy; RT: Radiotherapy; AWOD: Alive without disease; DOOD: Death of other disease

As the grade of the tumour increases, the probability of lymph node involvement rises (37). Higher or lower tumour grade may be detected in the intraoperative FS according to the preoperative pathology result. There may be discordance between preoperative and postoperative pathologies. Nevertheless, intraoperative FS had a high accuracy rate (88-89%) in determining grade (32, 38). In the present study, grade detected in FS was upgraded in postoperative pathology for 5.9% of patients and was downgraded for 0.9% of patients. Concordance of grade between preoperative diagnosis and FS was 89.5% and it was 92.7% between preoperative and postoperative diagnoses. In the study of Sanjuan et al. (38), concordance of grade of patients with a preoperative diagnosis of grade 1 or 2 disease with postoperative pathology was 89%. However, in the study of Neubauer et al. (39), 22.5% of the patients with a preoperative diagnosis of grade 1 endometrial cancer had a final pathology result showing a grade higher than 1. In the study by Ben-Shacher et al. (40), when similar factors were used for staging (grade 1 or 2 disease in addition to DMI ≥1/2, cervical invasion, grade 3 and non-endometrioid histology), 82% of 182 patients with grade 1 disease acquired staging surgery. Additionally, the grades of 19% of these patients were upgraded in postoperative pathology, and none of them were downgraded (40).

As DMI increases, the rate of lymphatic involvement increases. DMI could be defined accurately in FS with a rate of 88-95% compared to postoperative pathology (32, 41-43). In the present study, patients with a preoperative diagnosis of grade 1 endometrioid tumour were evaluated and DMI was defined accurately in 85.8% of the patients according to the postoperative pathology.

In this study, when patients with a preoperative diagnosis of grade 1 endometrioid tumour were managed with FS, only 3.2% of the patients were not staged, although they should be. Additionally, FS was shown to have a high accuracy rate in detecting risk factors for lymph node metastasis. When risk factors determined in FS were used, 30% of this group of patients were staged and 5% (n: 11/219) were found to have lymph node involvement. When Qinlivan et al. (32) used similar criteria (grade 1 or 2 disease in addition to DMI ≥1/2, cervical invasion, grade 3 and non-endometrioid histology) for staging, 2.3% of

patients were found to undergo suboptimal surgery according to the postoperative pathology.

Who should operate on patients with a diagnosis of endometrial cancer is controversial and has not been discussed as much as ovarian cancer. There are limited numbers of studies in the literature. It was stated that, when patients with a preoperative diagnosis of endometrial cancer were operated upon by gynaecologic oncologists, they were found to acquire postoperative adjuvant radiotherapy less often and were found to have less morbidity secondary to radiotherapy (44). In the present study, it was shown that preoperative parameters did not predict patients requiring staging accurately and that FS predicted the lymphatic involvement with high accuracy. Therefore, in all of the patients with a diagnosis of grade 1 endometrial cancer, FS should be performed and their surgery should be performed in centres with gynaecologic oncology expertise.

The retrospective nature of the study is the main limitation of this paper. However, this study was performed in a homogeneous group containing only patients with grade 1 endometrial cancer. In addition, the higher number of patients involved compared with the previous studies and the higher number of lymph nodes removed were the advantages of the present study.

In the presented study, among the selected preoperative clinical parameters, only age and BMI were found to be associated with risk factors for lymph node metastasis. However, even when both of these were evaluated together, only 45% of the patients with at least one of the risk factors determined in FS could be defined. More than 25% of the patients with high risk factors who should be staged could not be detected when preoperative clinical parameters were used. Therefore, which patients with a preoperative diagnosis of grade 1 endometrioid type tumour should be staged could not be detected by using these clinical parameters. Patients with a preoperative diagnosis of grade 1 endometrium cancer should be operated upon in centres where FS is utilised and oncologic staging surgery could be performed.

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What do we know about metabolic syndrome in adolescents with PCOS?

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Abstract

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy of reproductive-aged women that manifests itself with a variety of features. For this reason, three different diagnostic criteria have been introduced. For adults, the National Institutes of Health Conference (NIH) criteria, which consists of hyperandrogenism and oligo-anovulation, is the most widely used. Symptoms of PCOS usually start with puberty and may overlap with normal pubertal development. Hormonal fluctuations during this period make the diagnosis of PCOS more difficult. Until now, there is no validated diagnostic criteria for PCOS in adolescents. Although menstrual disorders and cosmetic problems are the most common complaints of adolescents with PCOS, patients should also be evaluated for the potential risk for insulin resistance, obesity, subclinical atherosclerosis, diabetes, metabolic syndrome and cardiovascular disease. Obesity is the most prominent predictor of metabolic syndrome. As the incidence of obesity is increasing both in childhood and adolescence, governments will be faced with a social and economic burden in the future. Adolescents with PCOS are more obese than normal adolescents and have an increased risk of metabolic syndrome. It is suggested that abdominal adiposity increases the risk of metabolic syndrome by inducing various cytokine secretions. Although there is no consensus on metabolic syndrome criteria in the adolescent period, International Diabetes Federation (IDF) criteria may be used for children older than 10 years. Various clinical and metabolic markers are investigated for the prediction of metabolic syndrome in the literature. Waist circumference, serum triglycerides and androgens are the suspected predictors of metabolic syndrome. The prevention of abdominal adiposity and the early diagnosis of PCOS in adolescence should be the main target for the prevention of metabolic syndrome. Clinicians should investigate adolescents with PCOS for metabolic and cardiovascular risks and take preventive action. A Mediterranean diet, low in fat and high in fruits and vegetables, along with moderate-intensity exercise and smoking cessation are the recommended interventions for especially obese adolescents with PCOS. Metformin may be the treatment of choice when lifestyle modifications are ineffective.

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Definition of Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) was first described by Stein and Leventhal in 1935 (1). The combination of polycystic ovaries and amenorrhoea, with variable hirsutism, were the clinical features of the syndrome. PCOS is a heterogeneous disease that manifests itself with a variety of features; therefore, various definitions are proposed by different working groups. Nowadays, three different diagnostic criteria are currently used for PCOS diagnosis; these are listed in Table 1. According to the Rotterdam Criteria, four phenotypes of PCOS are defined and the groups showed different metabolic characteristics (2). Polycystic ovary was accepted to be an alternative to ovarian dysfunction with the presence of hyperandrogenism, according to the Androgen excess society (AES) criteria; however, a combination of anovulation and polycystic ovaries without hyperandrogenism was not accepted as PCOS (3).

Until now, there is no validated diagnostic criteria for PCOS in adolescents. The Endocrine Society suggested that the diagnosis of PCOS can be made with the presence of persistent oligomenorrhoea and hyperandrogenism (clinical or biochemical) after excluding other pathologies in adolescents (4). Although the National Institutes of Health (NIH) criteria for diagnosis of PCOS is frequently preferred, unexplained hyperandrogenism accompanied by the presence of ovulatory dysfunction is the diagnostic criteria for adolescent PCOS in most cases. However, there is some debate on merely using the Rotterdam-AES criteria (5). The presence of polycystic ovaries in normally ovulating women is a common finding. PCOS can be over-diagnosed in adolescents as the AES criteria accepts the polycystic appearance of the ovaries as evidence of ovulatory dysfunction.

The diagnostic challenge in adolescents may result from many reasons like the higher rate of physiologic anovulatory cycles, irregular menses during the first 2 years following menarche, and the presence of acne at this age group and

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Table 1. Definitions of PCOS

Working Group	Date	Definition
NIH (56)	1990	Chronic anovulation & clinical or biochemical hyperandrogenism & exclusion of other diseases
ESHRE-ASRM / Rotterdam (57)	2003	Presence of at least two of the three criteria: Clinical or biochemical hyperandrogenism, Oligo-anovulation, Polycystic ovaries
AES (3)	2009	Hyperandrogenism (hyperandrogenaemia and/or hirsutism) & ovarian dysfunction (oligo-anovulation & polycystic ovaries) & exclusion of other diseases

PCOS: Polycystic ovary syndrome; NIH: National Institutes of Health Conference; ESHRE: European Society of Human Reproduction and Embryology; ASRM: America Society of Reproductive Medicine; AES: Androgen Excess Society

even in "normal" adolescents. Hyperandrogenaemia is thought to be a more reliable diagnostic criteria for the diagnosis of adolescent PCOS after ruling out other causes of hyperandrogenaemia such as late-onset adrenal hyperplasia and Cushing's Syndrome. Moreover, the clinical heterogeneity of the patients who often present with hirsutism without anovulation or anovulation without hirsutism, and the disagreement over whether the polycystic ovarian morphology without hyperandrogenism represents a subgroup of PCOS, leading to a lack of consensus on the diagnostic criteria, especially for adolescents.

Prevalence of PCOS in the Adolescent Population

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy of reproductive-aged women. While the prevalence of PCOS is given as approximately 7% by the NIH (6), it is not easy to estimate the prevalence in adolescents due to the diversity among the experts in this field about the diagnostic criteria and the fact that many symptoms and signs of PCOS may overlap with normal puberty (7, 8). Under-diagnosis of PCOS may lead to more serious clinical presentations; for example, women with a diagnosis of PCOS were found to have a 2-fold increased risk of metabolic syndrome in a cross-sectional study from Turkey that reported the prevalence of PCOS under NIH and Androgen Excess Society criteria as 6.1% and 15.3%, respectively (9).

Onset of Clinical Manifestation in PCOS

Although clinical manifestations of PCOS usually occur during puberty with the onset of maturation of the hypothalamic-pituitary-ovarian axis, the female foetus might be programmed to develop PCOS in adult life due to exposure to an excess of androgen in foetal life because of the genetic or environmental factors or a combination of them (10, 11).

Genetically-determined hypersecretion of the androgens from the ovary is proposed to be the primary event that leads to the development of PCOS by favouring excess luteinising hormone (LH) secretion and insulin resistance (12). However, insulin resistance with or without a genetic mutation may be the initiator, followed by hyperandrogenism, as is seen in hyperandrogenism-insulin resistance-acanthosis nigricans (HAIR-AN) syndrome (13, 14). Insulin resistance is an important contributing factor to abnormal steroidogenesis in PCOS. Insulin acts with LH to increase androgen production and promotes LH binding to the receptors. Hyperinsulinaemia stimulates insulin like growth factor-I (IGF-I) pathway in theca cells of the ovary by cross-reacting with the receptors for IGF. This state blocks the down-regulation of androgens by LH surge and leads to the hyperandrogenic environment in the ovary. Treatments include weight loss, which lowers insulin levels, restores ovulation and lowers the ovarian androgen levels (15).

Genetic Factors Related to PCOS

No consistent abnormality was detected in the chromosomal studies of the patients with PCOS but genetic studies of the families of the affected women showed a high incidence of affected relatives, indicating both X-linked and autosomal dominant inheritance (16). Moreover, there are data implying the linkage of adolescent PCOS with paternal metabolic syndrome (17).

In order to identify the genetic factors resulting in the hereditary nature of PCOS, genes encoding enzymes involved in androgen synthesis (serine hyperphosphorylation of P450c17, 21hydroxylase (CYP21) mutation), or protein transducers of insulin signals (excessive phosphorylation of IR-beta, insulin receptor substrate (IRS) proteins, IRS-1 (Gly(972)Arg) and IRS-2 (Gly(1057) Asp) have been analysed (18, 19). However, the role of genetic polymorphisms or mutations in the pathogenesis of PCOS is still under investigation and further research is required.

Metabolic Manifestations of PCOS

In the past, PCOS was considered only a hyperandrogenic disorder which can lead to infertility. Current data show that the diagnosis of PCOS is related to an increased risk of metabolic disturbances like insulin resistance (IR), hyperinsulinism (HI), impaired glucose intolerance, increased risk of type 2 diabetes in later life due to HI and IR, obesity, subclinical atherosclerosis, vascular dysfunction, metabolic syndrome and cardiovascular disease. Because central obesity is associated with hyperandrogenism and cardiovascular diseases, the Endocrine Society also recommends screening adolescents with PCOS for central obesity by body mass index (BMI) and waist circumference measurements (4).

For this reason, primary care for metabolic and cardiovascular risks and defining preventive methods in women with PCOS are the definite goals of the treatment of PCOS (20).

The American Heart Association categorised the cardiovascular risks of women with PCOS. Patients with obesity, especially

abdominal adiposity, hypertension, dyslipidaemia, subclinical vasculopathy, impaired glucose tolerance, a family history of familial cardiovascular disease (<55 years of age in a male relative and <65 years of age in a female relative) and cigarette smoking were categorised as at risk for PCOS-related cardiovascular disease. Those who had metabolic syndrome, type 2 diabetes, and overt renal and vascular disease were categorised as the high-risk population according to American Heart Association criteria (21).

Metabolic Markers of Metabolic Syndrome in PCOS

In a recent study, the relationship of activins and follistatins with metabolic markers in PCOS was investigated (22). Serum follistatin levels were found to be elevated in PCOS patients, independent of age and BMI. Activin levels were found to be similar in both groups with and without PCOS. In this study, follistatin was related to markers of adiposity and lipids in both women with and without PCOS. Activins A and B have various reproductive and metabolic actions in females. They stimulate follicular growth and also inhibit androgen production in the theca cells of the ovary (23). On the other hand, follistatin neutralises activin activity, and inhibits follicle stimulating hormone (FSH) secretion and folliculogenesis. Follistatin is also a promoter in the inflammation process, which has been shown to initiate insulin resistance and diabetes (24). For this reason, the increased levels of follistatin might inhibit folliculogenesis by increasing ovarian androgen production. In order to understand the possible role of follistatin in the pathogenesis of PCOS, further research is necessary.

Women with PCOS usually have abdominal adiposity and an increased risk of metabolic syndrome. Central obesity leads to the secretion of various adipocyte-derived peptide hormones, named adipocytokines. Adiponectin is the major adipocytokine that is secreted from the visceral fat cells. The presence of adiponectin impairs glucose tolerance and is an important predictor of metabolic syndrome (25). Ghrelin is also another peptide hormone which has a role in energy metabolism and low levels were reported to be associated with insulin resistance and diabetes (26). Adiponectin and ghrelin levels were negatively correlated with androgen levels in some trials, thus supporting the relationship between the hyperandrogenaemic state of PCOS and metabolic risk factors (27). In this study, obese hirsute women with PCOS were found to have lower adiponectin levels than obese controls and women with PCOS also had lower ghrelin levels than weight-matched controls. Panidis et al. (28) reported an inverse correlation between ghrelin levels and androgen levels. They found ghrelin levels to be lower in women with PCOS and also lower still in patients with hyperandrogenaemia.

Ersan et al. (29) investigated the relationship between adipocytokines and metabolic syndrome in pre-menopausal women with PCOS; adiponectin was found to be significantly lower and leptin was significantly higher in patients with PCOS and metabolic syndrome.

However, in a recent study, the levels of metabolic risk markers like adiponectin, leptin and ghrelin were measured in obese adolescents with and without PCOS; all were found to be similar in both groups (30). The investigators concluded that the presence of PCOS alone does not result in a higher risk of metabolic syndrome in adolescents. As expected, adiponectin levels were negatively correlated and leptin positively correlated with BMI.

Prevalence of Metabolic Syndrome in Adolescents with PCOS

After the first description of metabolic syndrome by Reaven in 1988, many organisations like the National Cholesterol Education Program (NCEP), the International Disease Federation (IDF), the World Health Organisation (WHO), and the European Group for the Study of Insulin Resistance published the diagnostic criteria for syndrome (31). Among these, the 2001 Third Report of NCEP's Adult Treatment Panel is the most widely accepted definition as all risk factors can be easily and routinely measured using diagnostic criteria. However, the WHO and European Group for the Study of Insulin Resistance definition includes routinely unmeasured criteria like insulin resistance and microalbuminaemia. According to the NCEP criteria, the presence of any three criteria defines metabolic syndrome. Those criteria are denoted as follows: Central obesity (waist circumference ≥88 cm in women), serum triglycerides ≥150 mg/dL, serum HDL concentration <50 mg/dL in women, systemic hypertension ≥130/85 mmHg, and fasting plasma glucose level ≥100 mg/dL (32).

In Turkey, Çalışkan et al. (33) investigated the frequency of metabolic syndrome according to different diagnostic criteria in women with PCOS. All criteria used identified higher metabolic syndrome in patients with PCOS than in controls. However, the highest prevalence (26%) was demonstrated by using IDF criteria due to the lower cut-off values for waist circumference and fasting glucose levels in these definitions.

In a U.S. population survey, the overall presence of metabolic syndrome was identified as 22% and gradually increased with age. The prevalence of metabolic syndrome in the US population was determined as 6.7% in the twenties, increasing to 43.5% in the sixties (34). Aging increases the visceral fat deposition, which worsens the glucose and lipid metabolism. Contrary to US data, the prevalence of metabolic syndrome in Italy was determined as 2.4% in general population in the 20s and this was found to increase to nearly 5% in the 40s. This is probably due to the lower incidence of obesity in Italy. However, the prevalence was 3-fold higher in young women with PCOS (35).

There is an ongoing debate regarding the definition of metabolic syndrome in adolescents in the literature. Hormonal fluctuations which lead to metabolic changes during transition to adolescence may mimic the features of metabolic syndrome. In one study of 1098 adolescents, nearly half of the adolescents initially diagnosed as metabolic syndrome lost this diagnosis during the three years observation period (36). The reason for this change might be due to the lack of objective and consistent criteria for identifying metabolic syndrome in adolescents. In 2007, Jolliffe et al. (37) reported the age-specific metabolic syndrome criteria for adolescents by linking them to the NCEP and

ITP adult criteria with growth chart modelling. Similar to the growth charts used to monitor height and weight in children, the growth curve method is used to easily identify metabolic syndrome. Growth curves for waist circumference, blood pressure, serum high-density lipoprotein (HDL) and triglyceride (TG) concentrations were defined, but no growth curve was set for fasting glucose level due to the constant level (100 mg/dL) from 12 to 20 years of age in this study.

The International Diabetes Federation put forward a new definition to identify children and adolescents with metabolic syndrome in 2007. The definition is easily applicable in clinical practice and categorised according to the age group (32). The IDF suggests that the diagnosis of metabolic syndrome should not be used for children younger than 10 years of age. If the waist circumference is ≥90 percentile in the children younger than 10 years of age, weight reduction is recommended. For children aged between 10 and 16, the presence of abdominal obesity according to waist circumference percentiles with any two clinical features (elevated TG, low levels of HDL, elevated blood pressure, elevated fasting glucose) is sufficient for the diagnosis of metabolic syndrome. For children aged 16 years and older, it is recommended to use the adult criteria.

In a study conducted on Iranian adolescents with PCOS, the presence of metabolic syndrome was nearly three-fold higher than the control group (33.3% and 11.2%, respectively) (38). The frequency of metabolic syndrome components like hypercholesterolemia, hypertriglyceridemia and elevated blood pressure was significantly higher in obese adolescents with PCOS. However, there was no significant difference among metabolic parameters between the non-obese adolescents with or without PCOS.

The National Heart, Lung, and Blood Institute Growth and Health Study (NGHS) identified predisposing factors for developing metabolic syndrome in childhood. After 10 years follow-up, waist circumference and serum triglycerides were identified as predictive factors of metabolic syndrome in girls aged 9 and 10 years. For every 1 cm increase in waist circumference at year 2, the metabolic syndrome risk increased by 7.4% and for every increase of 1 mg/dl in triglycerides level, the metabolic syndrome risk increased by 1.3% (39). In one cohort study with a 25 year follow-up, it was found that self-reported cardiovascular disease was observed more often (19.4%) in adults who had clinical features of metabolic syndrome as children than in those who did not (1.5%) (40).

Pathogenesis of Metabolic Syndrome in Adolescent PCOS Women

Obesity is an important predictor of metabolic syndrome. Even normal weight females with PCOS are found to have a 50% greater body fat level than normal weight females (41). In a study of 205 adolescents (≤20 years), the presence of metabolic risk factors and metabolic syndrome was investigated. The prevalence of being overweight or obese was significantly higher in adolescents with PCOS compared with those without (60% vs. 18%) (42).

The relationship between features of PCOS and features of metabolic syndrome were investigated in a cohort study of adolescent Australian girls; neither menstrual disturbances nor PCO morphology were found to be related to insulin resistance. BMI is the most prominent factor for the presence of IR. When it is estimated independent of obesity, an elevated free testosterone level is the most prominent indicator for the presence of the insulin resistance. Nearly one third of the adolescents with PCOS (35.3%) were found to be at risk of metabolic syndrome, whereas only 15.5% of adolescents without PCOS had this risk (43).

In a study of 469 South Asian women with PCOS, the relationship between different phenotypes of PCOS and metabolic syndrome was investigated. Although normal cycling hyperandrogenic women (Hyperandrogenism and PCO morphology) had a significantly lower incidence of obesity than the other phenotypes, the prevalence of metabolic syndrome was similar in all phenotypes. In contrast to a large USA study, the data of which reported a two-fold increased risk of metabolic syndrome in hyperandrogenic women, this study did not reveal any link between plasma testosterone and the occurrence of metabolic syndrome (44).

In a recent study, we analysed the endocrine and cardiovascular risk profile differences between 139 women with main PCOS phenotypes in Turkey. Among 4 PCOS phenotypes, patients with hyperandrogenism and PCOS (HA&PCOS) had the lowest carotid intima thickness; low-density lipoprotein cholesterol (LDL-C), total cholesterol and BMI were also found to be lower in this group. For this reason, this phenotype is said to have the lowest cardiovascular risk compared to other phenotypes (2).

Amato et al. (45) conducted a study in order to verify a method for distinguishing the metabolic health of women of reproductive age with PCOS. The visceral adiposity index is suggested as an easy and successful method for the assessment of metabolically unhealthy women and the detection of cardiometabolic risk factors. The visceral adiposity index (VAI) is calculated by a formula using waist circumference (WC), BMI, TG and HDL levels.

BMI is the most important variables which precludes the presence of metabolic syndrome. In a cross-sectional study of overweight and obese adolescents, the presence of PCOS did not add any weight to the presence of the features of metabolic syndrome. In this study, 53% of PCOS and 55% of the control group obese adolescents met the diagnostic criteria of metabolic syndrome (46).

Management of PCOS in Adolescents

In an internet survey that questioned specialists about their clinical approaches to PCOS in North America, the percentage of the respondent's patients with PCOS who were <18 years was found to be 53% and the percentage of respondent's PCOS patients who were obese was found to be 65% (7). The percentage of specific tests used for the initial diagnosis was highly variable; nearly 80% of the specialists evaluated thyroid stimulating hormone (TSH) and prolactin (PRL), whereas 17% of them evaluated sex hormone binding globulin (SHBG). For the evaluation of metabolic syndrome features, nearly 60% of specialists searched lipid profile and fasting glucose level, 41%

investigated fasting insulin levels and 25% assessed haemoglobin A1C. In a large cohort of normal weight women with PCOS in Austria, the efficiency of diabetes screening tests like HbA1c and fasting glucose level were evaluated. The true incidence of diabetes was 12.8%, which was determined by using oral glucose tolerance testing (OGTT); in contrast, when using only HbA1C and fasting glucose levels, only 3.2% and 5.2% of patients, respectively, had a diagnosis of pre-diabetes. In conclusion, the authors stated that although the OGTT is time consuming, neither fasting glucose nor HbA1c can be used as an alternative screening test for pre-diabetes in PCOS (47).

Weight loss with a low-fat and low-carbohydrate diet has improved menstrual function in obese adolescents with PCOS in a recent study (48). Marsh et al. (49) compared the low glycaemic index diet and conventional healthy diet in patients with polycystic ovary syndrome; after similar weight losses, women who consumed the low glycaemic diet showed more regular menstrual cycles. In a cohort study, the presence of insulin resistance in lean women with PCOS is investigated; none of the lean PCOS women were found to have insulin resistance and, as a conclusion, the routine performance of OGTT in lean women with PCOS is not recommended (50). The most recent guideline of the Endocrine Society also recommends exercise therapy in overweight and obese adolescents in order to reduce the cardiovascular risk. However, in normal weight women with PCOS, exercise therapy alone is not sufficient for treatment (4).

In our recent study, obesity was found to be negatively correlated to health-related quality of life in patients with PCOS. We analysed the health quality profiles of infertile women according to different PCOS phenotypes in this study (51). PCOS phenotype 1 patients (Hyperandrogenism and anovulation) had significantly higher BMI and hirsutism scores in comparison to other phenotypes and also showed significantly lower health-related quality of life scores.

Studies have demonstrated higher rates of many psychiatric disorders like anxiety, depression and eating disorders in adults and adolescents with PCOS (4, 52). The impact of hirsutism on the development of psychiatric problems are debatable (53). Given the high prevalence of anxiety and depression in women with PCOS, adolescents with PCOS should also be screened for these in their history and should be referred to psychiatrists for treatment.

Sleep disturbances like obstructive sleep apnoea appear to be a common complaint in women with PCOS. Sleep disordered breathing and daytime sleepiness were also more common in women with PCOS than in controls (54). In particular, the presence of hyperandrogenism and obesity are the suspected contributing factors for sleep disorders. Given the high prevalence of obstructive sleep apnoea in women with PCOS, especially overweight and obese adolescents should be evaluated for possible obstructive sleep apnoea symptoms and referred for polysomnography when suspected (4).

Management of Metabolic Syndrome in Adolescents

The prevention of adiposity, especially abdominal adiposity, is the primary target for the prevention of metabolic syndrome. For weight loss, lifestyle modifications like a restricted calorie diet and exercise are recommended as the first-line treatment by the recently published Endocrine Society guideline. There is no evidence that supports the superiority of one type of diet (4). The Mediterranean low fat diet that is high in fruit and vegetables has been found to improve glucose intolerance, insulin resistance, vascular endothelial function and lipid metabolism (55). The current recommended exercise program is a daily minimum of 30 minutes of moderate-intensity physical activity. Weight loss of about 5 to 10% of baseline weight is recommended in order to correct the abnormal glucose metabolism, but a cut-off level of fasting glucose has not yet been determined in patients with metabolic syndrome without diabetes.

Currently, studies in the literature investigating metabolic syndrome in children and adolescents with PCOS are quite limited; for this reason, it is difficult to define the long-term risk of cardiovascular disease and diabetes. Two randomised controlled studies demonstrated that the use of metformin improves the ovulation, hyperandrogenisim and abnormal lipid profile in adolescents with PCOS. Based on these data, the Endocrine Society recommended the use of metformin for the treatment of metabolic syndrome (4). However, early intervention with lifestyle changes such as increased physical activity, diet and smoking cessation may ameliorate these features in especially overweight and obese adolescents with PCOS. Metformin may be a choice of treatment when lifestyle modification is ineffective in obese adolescents.

Conclusion

The diagnosis of PCOS in adolescents is not easy due to a variety of diagnostic criteria and overlapping symptoms of pubertal development. However, the early diagnosis of PCOS is also important for identifying potential metabolic and cardiovascular risks during this period. Sleep disorders and psychiatric disease may also be diagnosed and treated earlier during the adolescence period. We know that especially obese adolescents with PCOS have an increased risk of metabolic syndrome. Although there is debate on the diagnostic criteria of metabolic syndrome during adolescence, abdominal obesity is the most prominent predictor of metabolic syndrome during childhood and adolescence. Therefore, early interventions with a Mediterranean diet, increased physical activity and smoking cessation are recommended in order to prevent metabolic syndrome, especially in obese adolescents with PCOS.

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Integration of three-dimensional ultrasonography in the prenatal diagnosis of amniotic band syndrome: A case report

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Abstract

Amniotic band syndrome is a rare disorder which is thought to be caused by early rupture of the amniotic membrane. The extent of the disease may vary from minor digital amputations to severe lethal anomalies. For many years in routine clinical practice, this syndrome has been diagnosed with two-dimensional ultrasonography. Evolving imaging techniques by means of three-dimensional ultrasonography gives the chance of early and accurate diagnosis of this devastating anomaly. By integrating three-dimensional ultrasonography to the suspected findings diagnosed in the two-dimensional ultrasonography allows us to predict possible outcomes and provides convenience in counselling. Herein we present a case of amniotic band syndrome diagnosed at 19 weeks of gestation with three-dimensional ultrasonography and pregnancy was terminated in the 20th week. Using three-dimensional ultrasonography in certain suspected foetal anomalies may provide the early diagnosis and more accurate knowledge about extent of the disease.(J Turk Ger Gynecol Assoc 2014; 15: 56-9)

Key words: Amniotic band, constriction band, three-dimensional ultrasonography, prenatal diagnosis

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Introduction

Amniotic band syndrome is a rare disorder with an incidence ranging from 1 in 1300 to 1 in 15,000 (1). The cause is thought to be amniotic bands resulting from the early rupture of amniotic membranes and wrapping of the free amniotic bands around various foetal parts (2). Abnormal growth and, in severe cases, amputation of extremities may be observed. The disease has a very wide spectrum of anomalies from minor to lethal depending on involvement of the foetal parts, degree of constriction of the band and timing of the rupture of the amniotic membrane. Thus, the prognosis of the disease may vary from isolated digital amputation to severe lethal anomalies of the central nervous system, face and viscera (1).

Amniotic band syndrome may be detected by ultrasonography with the observation of asymmetrical limb deformities or defects and visualisation of the amniotic membranes wrapping around foetal portions (1). The most common defect is constriction bands around foetal extremities. Management of the disease may change from expectant management to the termination of pregnancy according to the severity of disease (1). Spontaneous resolution of amniotic bands was also described (3).

Here, we represent an amniotic band syndrome case with the involvement of all extremities, in which the diagnosis was confirmed with three-dimensional (3D) ultrasonography.

Case Presentation

A 29 year old woman, gravida 1 para 0, was referred to our unit with the suspicion of foetal limb malformations. Her past medical and obstetric history was unremarkable. On the ultrasonographic examination of the foetus at the 19th week of gestation, both lower extremities were observed to be swollen and oedematous. With a detailed examination of the amniotic cavity, multiple amniotic bands were observed to be wrapping around both foetal lower extremities above the ankles and the involvement of one hand (Figure 1). The other hand was observed to be free. Accompanying organ anomalies were not seen. In 3D ultrasonographic examination, constriction rings around the foetal limbs and distal to ring malformations of the foetal feet were observed (Figure 2). In colour Doppler evaluation of the foetal lower limbs, decreased blood flow was observed. The final diagnosis of foetal amniotic band syndrome was considered and the possible outcomes were discussed with the patient; termination of the pregnancy was decided upon.

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At the 20th week, the pregnancy was terminated. In the postpartum evaluation of the foetus, constriction rings were observed around both lower limbs above the ankles and distal to this, the extremities were swollen and oedematous. It was also observed that all of the digits of the right hand and only two digits of the left hand were amputated (Figure 3). Further pathological examination could not be performed since the family did not consent to an autopsy due to their religious beliefs.

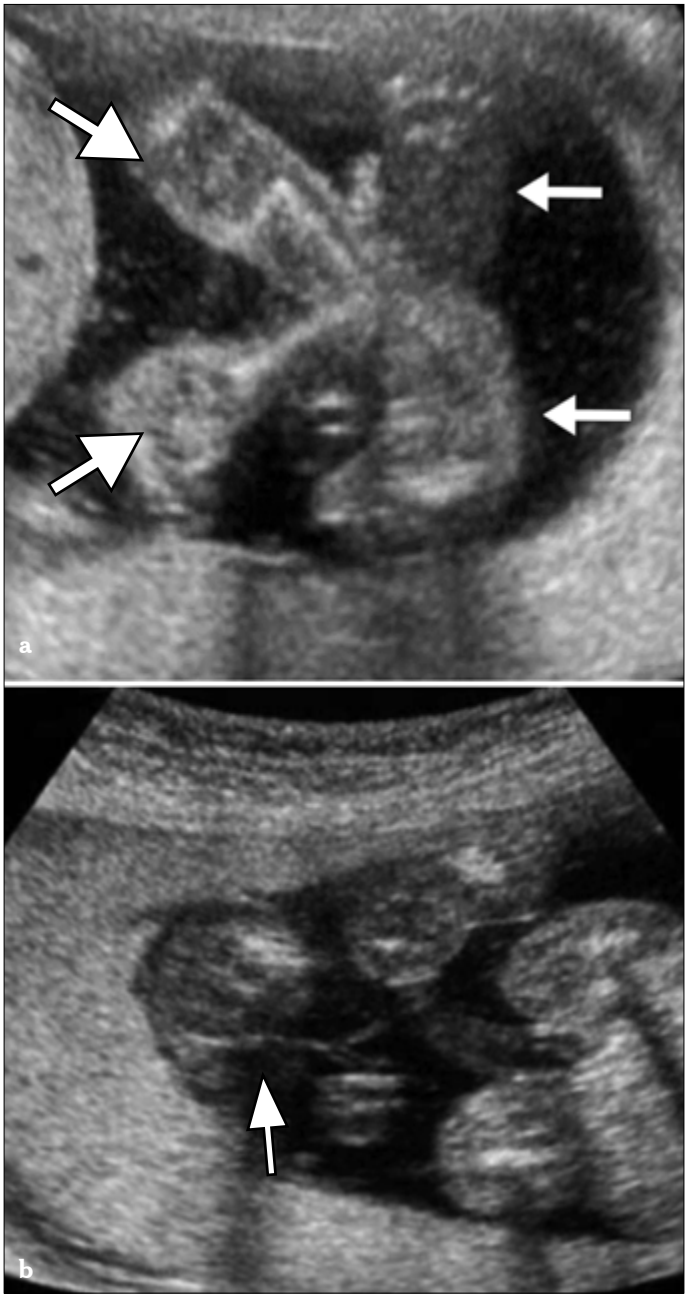

Figure 1. a, b. Ultrasonographic examination of the foetus. Thin white arrows show the deformed foetal feet. Thick white arrows identify the foetal lower limbs (a). White arrow indicates the amniotic band (b)

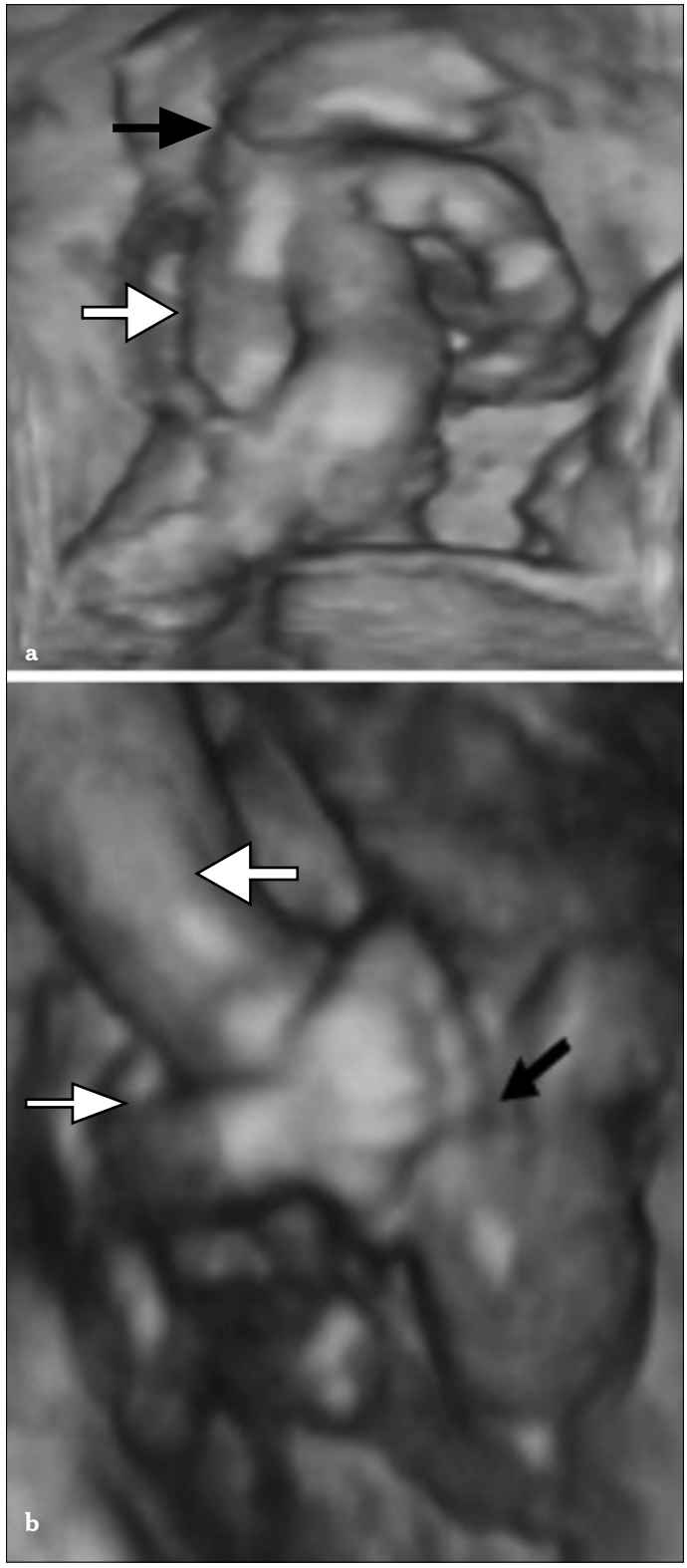

Figure 2. a, b. Three-dimensional examination of the foetus. Black arrow pointing to the constriction ring in the foetal foot. White arrow highlighting the foetal lower limb (a). Black arrow identifies the relationship of the foetal hand with the hand-foot-band complex. Thick white arrow points to the foetal hand and thin white arrow points to the oedematous foetal foot (b)

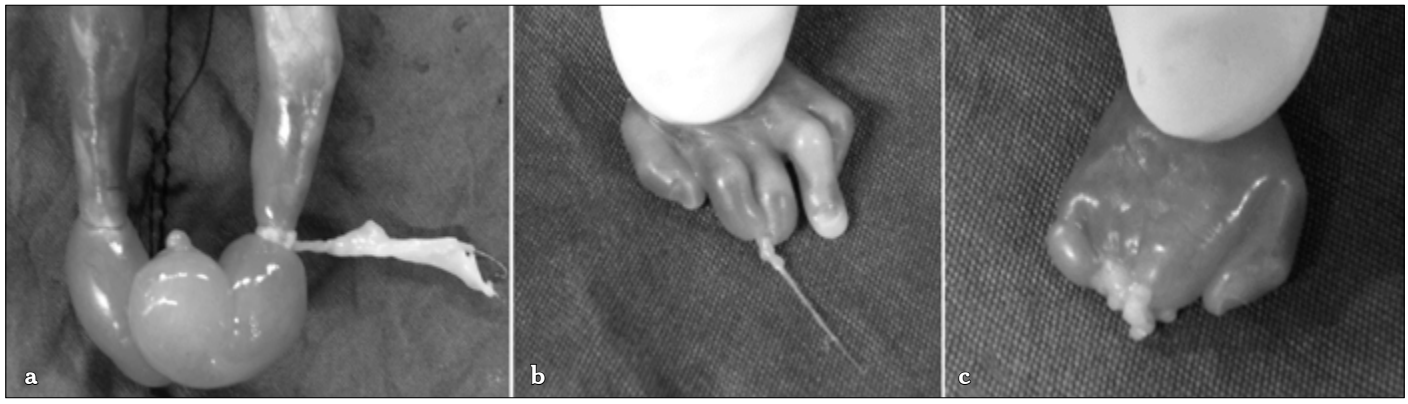

Figure 3. a-c. Examination of the foetus after delivery. Appearance of foetal feet (a). The left hand (b). Note that the 2nd and 3rd fingers were amputated from the distal phalanx. The right hand (c). Note that all of the fingers except the thumb were amputate

Table 1. Prenatal diagnosis of amniotic band syndrome with 3D (three-dimensional) ultrasound and postnatal outcome

Authors	Year	Gestational age at diagnosis	Ultrasonographic features	Postnatal features	Outcome
Paladini et al. (7)	2004	28	• Amniotic band at supracondylar level of left arm	• Band detached spontaneously from neonatal left arm	No injury of left arm
Inubashiri et al. (9)	2008	14	• Multiple amniotic bands • Acrania • Kyphoscoliosis • Gastroschisis • Club-foot	• Multiple amniotic bands • Acrania • Kyphoscoliosis • Gastroschisis • Club-foot	Termination of pregnancy
Hata et al. (10)	2011	13	• Multiple amniotic bands • Acrania • Absence of fingers • Amputation of bilateral toes	• Multiple amniotic bands • Acrania • Absence of right fingers • Partial absence of left fingers • Amputation of bilateral toes • Amputation of bilateral toes	Termination of pregnancy
Hata et al. (10)	2011	15	• Multiple amniotic bands • Acrania • Cleft lip • Right hand syndactyly	• Multiple amniotic bands • Acrania • Cleft lip • Right hand syndactyly	Termination of pregnancy
Nardozza et al. (8)	2012	34	• Two amniotic bands at right forearm	• Bands detached surgical procedure from neonatal right forearm	No injury of right arm
Turgal et al. (Current study)	2012	19	• Multiple amniotic bands • Bilateral constriction rings above ankles • Amniotic band at right forearm	• Multiple amniotic bands • Bilateral swollen and oedematous lower limbs above the ankles • 2nd and 3rd fingers of left hand amputated from distal phalanx • All the fingers of right hand amputated	Termination of pregnancy

Discussion

The occurrence of amniotic band syndrome is rare. The most commonly accepted theory to describe the pathogenesis is the early rupture of the amniotic membrane (2). With rupture, the amniotic membrane detaches from the chorion and fluid moves through the tear between the amnion and chorion. Meanwhile, some portions of the foetus may also exit through this tear. Then, the remaining free ends of the amniotic membranes entangle various body portions, causing constriction. As the foetus grows, the constriction ring tightens and the decreased venous return from the affected site causes oedema and swelling of the distal part. As a result, in severe cases, the clinical presentation is characterised by asymmetrical limb involvement accompanied by a short umbilical cord (4). Thus, the degree of involvement determines clinical presentation. However, some authors have challenged this theory, stating that it did not explain the involvement of some internal organs of the foetus (5). In the management of the amniotic band syndrome, foetoscopic laser surgery was also reported for the release of amniotic bands, but it is unclear whether release of the band also causes relaxation of the constriction ring. This approach may be beneficial in cases with isolated involvement when severe circulatory alterations had not occurred (6). Therefore, invasive procedures in treatment are still experimental.

The prenatal ultrasound detection of amniotic constriction bands around extremities has been described many times. This can be performed both by two-dimensional and three-dimensional ultrasonography. When giving information to the family about the prognosis and discussing the possible outcomes, a more accurate description of the extent of the disease is essential. The surface rendering mode of three-dimensional ultrasonongraphy allows spatial analysis of the foetus and amniotic bands, which provides superiority over two-dimensional ultrasonography. This helps families to have a better understanding of the severity of the syndrome and clinicians to provide more detailed counselling. In our case, the ultrasonographic examination revealed involvement of only three extremities, but after delivery, it was observed that all of the extremities were involved. We consider the fact that the fourth affected limb was not detected was the unsatisfactory aspect of our clinical practice.

In the literature, there have been five reported cases of amniotic band syndrome diagnosed by prenatal 3D/4D (four-dimensional) ultrasound, except for this report. The first case was reported by Paladini et al. (7), in which a 3D ultrasound was employed to characterise the anomaly at 28 weeks of gestation. Similarly, the last case was reported by Nardozza et al. (8), who diagnosed the case at 34 weeks gestation. Isolated arm injuries were diagnosed in these two case reports. Pregnancies were followed with serial ultrasonographic assessments and foetuses were born at term. Both neonates were discharged in good condition. Two other case reports have described three foetuses with amniotic band syndrome in the first trimester and early second trimester (9, 10). These three foetuses had multiple severe anomalies, such as acrania, kyphoscoliosis and gastroschisis, from constriction rings and all of the pregnancies were terminated due to these lethal anomalies. Details of the current and other reports are given in Table 1. Evolving imaging techniques are improving the prenatal diagnosis of foetal anomalies and providing us with a more accurate diagnosis of the extent of the anomaly. The 4D examination of the movement of extremities and relationship with the amniotic band provides us with a more precise extent of disease which is very important in determining prognosis. As a conclusion, we describe a case of amniotic band syndrome with involvement in all extremities. This case is one of the rare reports in the literature in which 3D ultrasound was used in the diagnosis of amniotic band syndrome as early as the 19th week of pregnancy.

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Peer-review: *Externally peer-reviewed.*

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A diagnostic dilemma of acute abdomen in pregnancy: Leiomyoma of the small intestine

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Abstract

Small intestinal tumours are rare and difficult to diagnose. This neoplasms may be responsible for haemorrhage, occlusion, perforation and subsequent emergent surgeries. A 28 year old G2P1 woman in her 22nd week of pregnancy was referred to our emergency department with a complaint of left lower abdominal pain that had begun the day before. She underwent an emergent laparotomy with the general surgeons. Histopathological examination defined the diagnosis of leiomyoma of the small intestine. Gastrointestinal pathologies should always be taken into consideration in the differential diagnosis of acute abdomen in pregnancy. (J Turk Ger Gynecol Assoc 2014; 15: 60-2)

Key words: Acute abdomen, pregnancy, small intestinal tumour

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Introduction

Small intestinal tumours are rare and difficult to diagnose. These neoplasms may cause haemorrhage, occlusion, and perforation, and therefore, subsequent emergent surgeries may have to be performed (1). We report a case of a pregnant woman who underwent surgery for suspected ovarian torsion during the second trimester of pregnancy and was subsequently diagnosed as having leiomyoma of the small intestine. To the best of our knowledge, this is the first reported case of leiomyoma of the small intestine causing acute abdomen during pregnancy in the English literature.

Case Presentation

A 28-year-old woman (gravida 2 para 1) who was 22 weeks pregnant was referred to our emergency department with a complaint of left lower abdominal pain that she had been experiencing since the previous day. She presented with severe nausea and vomiting but did not report vaginal discharge, constipation, or rectal bleeding. Physical examination showed that she had a gravid abdomen corresponding to 20-22 weeks of pregnancy and tenderness, with guarding in her left lower abdomen. Abdominopelvic colour Doppler sonography revealed a solid mass, measuring 8×10 cm, with no vascularisation in the left pelvic region and a living foetus of 22 weeks gestation. The patient experienced progressively worsening pain and vomiting. She underwent emergent laparotomy because of the possibility of torsion due to adnexal pathology. During abdominal exploration, the ovaries and tubes appeared normal and the uterus appeared enlarged because of pregnancy. A semi-solid, dark brownish-red, infarcted mass, measuring 8×10 cm, was observed originating from the jejunum (Figure 1). The mass was resected with a 10 cm segment of the jejunum, and end-to-end anastomosis was performed in the usual manner by general surgeons. The final histopathological diagnosis was leiomyoma of the small intestine (Figure 2). The postoperative course of the patient was uneventful, and she was discharged home on the seventh postoperative day. Thereafter, she had an uncomplicated pregnancy and delivered a full-term baby.

Discussion

The incidence of adnexal masses during pregnancy has been reported to be 1-2%. These pelvic masses are usually defined as functionally or hormonally active cysts that resolve by the 16th gestational week. The masses that have been reported are mature cystic teratomas and cystadenomas (2). The major concern regarding these masses is the possibility of complications such as torsion, rupture, and malignancy (3).
On the other hand, pelvic masses could be attributed to extragonadal causes as well. Small bowel neoplasms such as leiomyoma, lipoma, hamartoma, or desmoid tumours are benign and usually asymptomatic (4). Leiomyomas are the most common type of small intestinal tumours, with an incidence of 20-30%. The tumour is most com-

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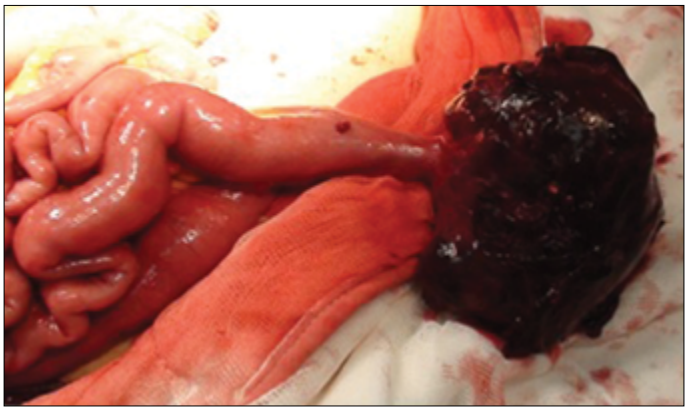

Figure 1. A semi-solid dark brownish-red mass originating from the small intestine

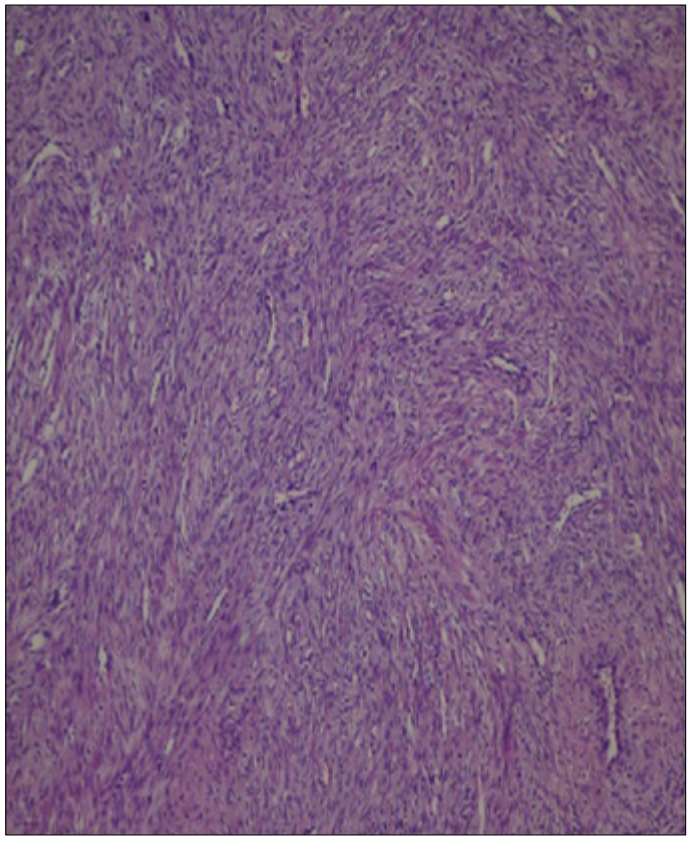

Figure 2. Histopathological appearance of leiomyoma with fusiform-shaped, interlacing bundles of smooth-muscle cells with no necrosis or mitotic activity

monly located in the stomach, but rarely in the jejunum, ileum, or duodenum. Leiomyomas present with 4 different growth patterns: intraluminal, intramural, extraluminal, and dumbbell-shaped (5). The presenting symptoms depend on the location of the tumours. The most common presenting symptoms are intermittent gastrointestinal bleeding, obstruction, and intestinal invagination (5). Although most leiomyomas remain asymptomatic and are diagnosed incidentally during laparotomy, iron deficiency anaemia and obstructive symptoms are important in alerting one to the presence of leiomyomas (5). However, the diagnosis of small intestinal neoplasms is often delayed because the small intestine is relatively difficult to access during routine endoscopy. Magnetic resonance imaging (MRI) is generally considered safe during pregnancy (6). Moreover, it can also be used to determine the extent of possible malignancy and aid in the diagnosis of acute bowel conditions such as appendicitis and inflammatory bowel disease (7). In the case of our patient, MRI could have been useful in the differential diagnosis; however, this imaging modality is not available in emergency conditions.

The most significant problem in the diagnosis of the present case was the ongoing pregnancy and the absence of a history suggestive of intestinal pathologies. In the present case, the surgeons examined the patient preoperatively but were unable to make a diagnosis. However, we operated on the patient together with general surgeons. The tumour was resected, and end-to-end anastomosis was performed. General surgeons should participate in surgeries where the diagnosis is challenging and the patient is pregnant.

In the literature, there are reports on cases of intestinal pathologies such as gastrointestinal stromal tumours (GISTs) presenting during pregnancy (8). Leiomyomas usually mimic GISTs and GISTs mostly mimic ovarian malignancies and uterine leiomyomas on ultrasonography (9). However, histopathologically, leiomyomas are benign tumours that are negative for CD117 and CD34 and positive for smooth muscle actin and desmin. Furthermore, mitosis is the most important criterion for discrimination of these tumours (10). Distinction of the 2 tumours is important because leiomyomas, but not GISTs, can be treated with a simple enucleation.

To the best of our knowledge, this is the first case report describing a leiomyoma of the proximal jejunum that mimicked other gynaecologic masses in a pregnant woman who presented with acute abdomen due to infarction of the mass. The diagnosis was complicated because the symptoms were nonspecific and were obscured by the ongoing pregnancy. Moreover, it is difficult to take a decision regarding surgery in such cases considering the high rates of maternal complications, foetal loss, and premature births.

Ethics Committee Approval: *N/A.*

Informed Consent: *Written informed consent was obtained from patient who participated in this case.*

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Two cases of successful pregnancies after hysteroscopic removal of endometrioid adenocarcinoma grade I, stage IA, in young women with Lynch syndrome

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Abstract

We present two cases of endometrioid adenocarcinoma grade I, FIGO IA (staging according to the International Federation of Gynecology and Obstetrics) in young women, diagnosed within endometrial polyps. Both patients underwent repeated hysteroscopies and multiple biopsies after initial treatment to medroxyprogesterone one 400 mg daily or the insertion of IUD-LND (intrauterine device-levonorgestrel) for three months. In both of them, all histological samples were negative. Both of them decided that they would try to conceive. The first patient conceived spontaneously and the second patient after IVF (in vitro fertilisation) treatment. They both gave birth to full-term infants. Hysterectomy was recommended to both of our patients, and was carried out. Both of the patients fulfilled both Amsterdam II and revised Bethesda criteria for hereditary non-polyposis colorectal cancer (HNPCC). (J Turk Ger Gynecol Assoc 2014; 15: 63-6)

Key words: Endometrial cancer, Lynch syndrome, hysteroscopy, reproduction

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Introduction

Endometrial cancer is the most common invasive cancer of the female genital tract in developing countries, representing approximately 7% of all invasive malignancies in women. Primarily, it is a malignancy that occurs in postmenopausal women, with the peak of incidence between 55 and 60 years of age. According to the literature, only 3-14% of cases occur among young women <40 years of age (1). Lynch syndrome, also known as hereditary non-polyposis colorectal cancer (HNPCC), is associated with cancer diagnosis at an early age and the development of multiple cancer types, particularly colon and endometrial cancer (2). Women with HNPCC have a 27 to 71% risk of endometrial cancer, which equals or exceeds their risk of colorectal cancer. In addition, they have a 3 to 14% risk of ovarian cancer (3). HNPCC is an autosomal dominant inherited cancer syndrome caused by germline mutations in one of the DNA mismatch repair genes: MSH2 (also known as MutS protein homolog 2), MLH1 (MutS homolog 1), MSH6 (MutS homolog 6) and PMS2 (mismatch repair endonuclease). The risk of endometrial and ovarian cancer varies with the genotype; MSH6 mutations are associated with higher risk of endometrial cancer in comparison with MLH1 and MSH2 mutations (4). Loss of mismatch repair occurs in sporadic cancers (5). Approximately 20% of endometrial cancers are positive for microsatellite instability, but fewer than 5% are thought to be attributable to HNPCC (6). Within the manuscript, we present two cases of endometrial cancer which occurred in young women with Lynch syndrome, both of whom had achieved full term pregnancies and delivered live infants.

The aim of this case report is to show that fertility-sparing surgery (endometrial ablation in one case) is an alternative treatment for these patients, and that pregnancy after this kind of treatment is possible, even in a spontaneous cycle.

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Case Presentation

We report two cases of endometrial endometrioid cancer grade I, FIGO IA (staging according to the International Federation of Gynecology and Obstetrics). The first reported case was a woman aged 30 (nulligravida) whose family history was positive for HNPCC. Two of her uncles had been diagnosed with colon cancer at the ages of 45 and 48, and her grandmother was diagnosed with endometrial cancer. At the time of admittance, her cousin had also been admitted to the urology department due to the suspicion of a ureter malignancy.

Two years prior to admission, a uterine polyp was first diagnosed by ultrasound and followed up (Figure 1). Occasionally, she had complained of spotting. Three months before the surgery, a left ovarian cyst 4 cm in diameter was identified, which was suspicious of endometriosis; Doppler revealed pericystic vascularisation, RI (resistance index) 0.40. CA-125 (cancer antigen, or carbohydrate antigen) was measured and its value was 39 IU/mL. Due to the family history, colonoscopy was performed, without abnormalities, and all random biopsies were negative. Laparoscopy and hysteroscopy were performed; a cyst and polyp were removed (Figure 2). Pathological review revealed endometrioid adenocarcinoma grade I and left endometriotic cyst. A month later, at repeated hysteroscopy, there was apparently no evidence of disease. Endometrial ablation was performed and all of the samples were negative. Distension media for hysteroscopy was purisol (mannitol/sorbitol mixture) and intrauterine pressure was limited to around 100 mmHg in order to lower the risk of tumour cell spread into the peritoneal cavity. Although there might be an increased risk of peritoneal contamination by cancer cells, there is currently no evidence that these patients have a worse prognosis or propagation of the disease (7, 8).

Hysterectomy as a definitive treatment was discussed with the patient, but she chose a conservative approach with high dose progesterone treatment for 3 months (400 mg medroxyprogesterone per day) and to attempt to conceive. A month after completing her hormonal treatment, a third diagnostic hysteroscopic biopsy was performed and histopathology was negative. The patient was under the constant surveillance of her gynaecological endocrinologist due to the relatively thin endometrium; and therefore received oestrogen supplementation during her menstrual cycle. Three months after the procedure, she conceived spontaneously and vaginally delivered a full term infant. Three months after the delivery, an operative procedure was performed. 3DPD (3D power Doppler) and MRI (magnetic resonance imaging) of the abdomen and pelvis were performed prior to surgery. There was no sign of myometrial invasion. During the operation, peritoneal washing for cytological sampling was performed (negative), and a frozen section was taken. Due to the result of the frozen section (locus of the hyperplasia complex atypica), there was no indication for pelvic lymphadenectomy. Hysterectomy was performed, but the patient refused the suggested adnexectomy, although she was presented with the risk of ovarian malignancy and the necessity of further follow-ups. Postoperative pathology revealed hyperplasia complex atypical and EIN (endometrial intraepithelial neoplasia).

The second reported case was a 39 year old woman (nullipara, secundigravida) who had already been operated upon for primary colon carcinoma 9 years prior to admittance. Her family history was positive for HNPCC according to the Amsterdam II criteria. Both her father and grandfather died

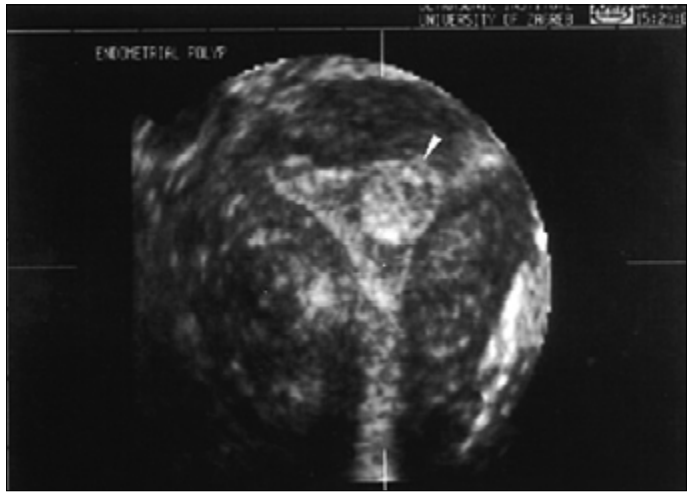

Figure 1. An endometrial polyp diagnosed by 3D ultrasound

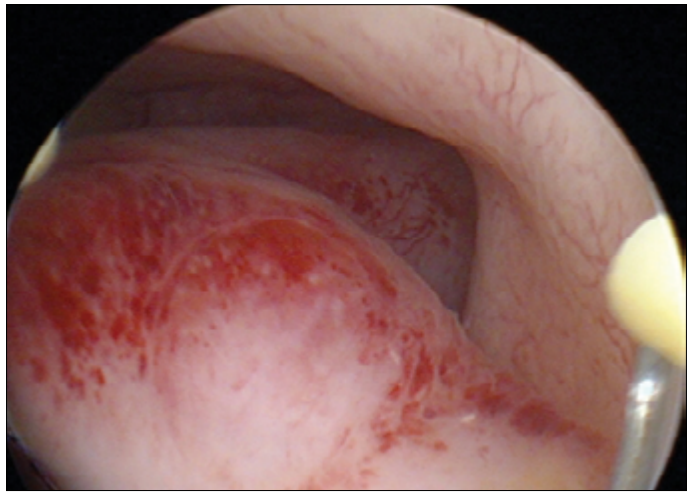

Figure 2. An endometrial polyp shown by hysteroscopy

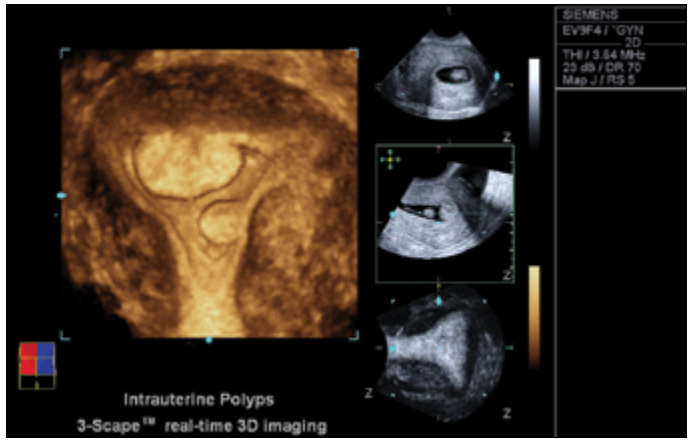

Figure 3. Coronal and transversal plains of uterus. Endometrial polyp within the uterine cavity

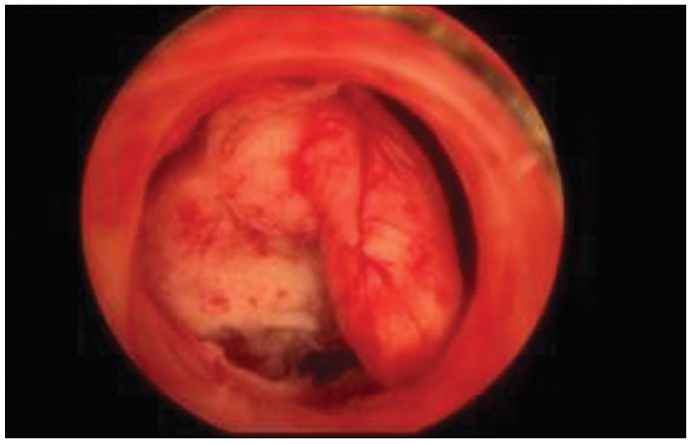

Figure 4. Clear visualisation of uterine polyp, shown by minimally invasive operative procedure

due to colorectal carcinoma, and a second degree relative had been diagnosed with small intestine cancer. She was admitted to our clinic because of the suspicion of an endometrial polyp, taking into the consideration her anamnesis (Figure 3). At the time of admittance, she had no complaints. Hysteroscopy was performed, and several polyps were removed (Figure 4). Pathological examination revealed endometrioid adenocarcinoma grade I on one of the polyps and hyperplasia glandularis complex atypica on the other sample. After the counselling, hysteroscopy was repeated in a month. One out of ten samples was positive for hyperplasia atypica. The patient refused suggested hysterectomy. We agreed to continue her treatment with IUD-LNG for a period of three months. Hysteroscopic biopsies of the endometrium were performed again, and all samples were negative. The patient tried to conceive spontaneously, but suffered a miscarriage. After unsuccessful trials of spontaneous conception, she was immediately referred for an IVF procedure; approximately 10 months after the initial procedure, she gave birth to a term infant. Three months after the delivery she underwent an operative procedure: including peritoneal washing for cytological sampling and hysterectomy. Frozen sections revealed endometrioid cancer grade I without myometrial invasion, and therefore without any further need for pelvic lymphadenectomy, but adnexectomy was performed. Peritoneal washing was negative. Postoperative pathology confirmed intraoperative diagnosis.

Both patients were operated on three months after the delivery because both of them insisted on completing puerperium and preparing physically and emotionally for the operation; also, according to the literature, there were no strict disadvantages to this delay.

Both of our patients fulfilled both Amsterdam criteria II and revised Bethesda criteria for HNPCC. In the first case, as the size of the polypoid tumour extracted from her uterine cavity was too small for microsatellite instability (MSI) testing, and as we could not obtain a colon cancer tumour sample from her affected relative, we proceeded with DNA blood analysis at the commercial facility of Myriad Genetic Laboratories, Seattle, WA. Gene sequencing and MSI testing was performed.

Complete sequencing of the MLH1 and MSH2 genes was performed in the first case, but the results were negative. MSH6 analysis identified a mutation. In the second case, the polypoid tumour showed a high-frequency (MSI-H) phenotype, as in the colon cancer samples.

According to our results, we have not observed worsening of the pathohistological findings, probably due to the surgical and hormonal therapy, and normal placental endocrine activity, which is considered to have a therapeutic effect due to natural, extremely high-dose progestin.

Discussion

The diagnosis of endometrial cancer in young women may be delayed due to the presenting symptoms of vaginal bleeding, which is often considered dysfunctional. Whenever there is a positive family history, HNPCC should be suspected. Hysteroscopy is considered to be a gold standard for the evaluation of endometrial pathologies. Transvaginal ultrasound is still considered a first-line diagnostic procedure in detecting endometrial cancer in postmenopausal women without abnormal uterine bleeding, because it is not invasive and it has high sensitivity for detecting endometrial cancer; however, outpatient hysteroscopy with biopsy is absolutely mandatory in all postmenopausal women with abnormal uterine bleeding (9). According to the data from the literature, it is possible that hysteroscopy in patients with endometrial cancer poses a risk for cancer cell dissemination within the peritoneal cavity (10), but other data suggest that hysteroscopy has no adverse effect on the incidence of positive peritoneal washings or on prognosis in stage I endometrial cancer patients (7). Myometrial invasion is the most important prognostic factor for endometrial cancer and could be suspected either by transvaginal sonography and/or magnetic resonance imaging. They share similar specificity and sensitivity of approximately 90%. Women with low grade (grade 1 or 2) endometrioid cancers confined to the endometrium (stage IA) are classified as having low-risk disease. The overall probability of recurrence in this group is very low following surgical treatment alone (11). Standard therapy in endometrioid cancer FIGO IA cases consists of hysterectomy, which could be performed either by conventional laparoscopy, robotic surgery, vaginally or by open surgery. Systematic lymphadenectomy for this stage is not indicated. Both cases were endometrioid adenocarcinoma grade I, FIGO IA. Both of the patients have fulfilled the Amsterdam II and revised Bethesda criteria for HNPCC. Criteria known as Amsterdam and Bethesda are sets of diagnostic criteria used to identify families and individuals who are likely to have Lynch syndrome or HNPCC (12). Because both of the patients had not completed their reproduction at the time of diagnosis, we had to consider conservative treatments prior to hysterectomy. The first case reports regarding conservative treatment of endometrial cancer were published in the early 1960s. Since then, the safety and efficacy of hormonal therapy as a primary treatment of endometrial cancer in reproductive age have been reported in several articles (13, 14). Lately, papers have been published about hysteroscopic resection of the endometrium in order to preserve fertility (15), and

hysteroscopic endomyometrial resection as an alternative treatment to hysterectomy for an early stage endometrial cancer in both pre- and postmenopausal women (16).

In conclusion, conservative treatment in young women who have not completed their reproduction and desire the preservation of fertility may be considered an option. All treatment options should be discussed in detail with a patient. Strict selection criteria are of the highest importance, such as age, FIGO classification, histological type and grade of the tumour, reproduction. Careful follow-up is mandatory.

Ethics Committee Approval: *N/A*

Informed Consent: *Informed consent was received from the participants of this study.*

Peer-review: *Externally peer-reviewed.*

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What is your diagnosis?

A 27 year-old pregnant woman was referred to our perinatology clinic for an abnormal fetal ultrasound finding. She was a nulliparous lady with three gestations of one ectopic pregnancy, one miscarriage and this ongoing pregnancy at its 37th week. In her gestational history she was followed carefully by the same obstetrician with low-risk double and triple test results and second-level prenatal ultrasonography.

We detected a hypoechogenic, regular bordered, sausage-like cystic mass behind the heart, between the thoracic aorta and right atrium (Figure 1, 2). The fetus had compatible measurements with its gestational age except that its head circumference was 100 mm (41 weeks). There was no other ultrasonographic abnormality detected. Amniotic fluid index was within the normal range (9 cm). The heart was left sided and had normal 4 chambers with normal three vessels and trachea view. What is your diagnosis?

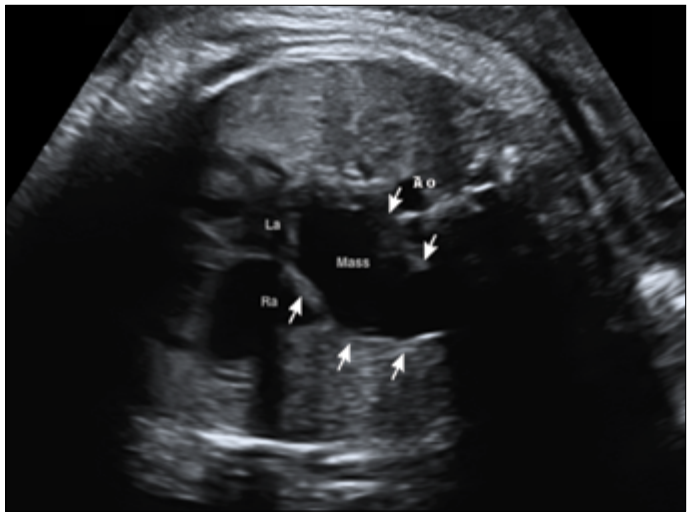

Figure 1. The arrows show the borders of the mass. Ao indicates the thoracic aorta , La indicates the left atrium and Ra the right atrium

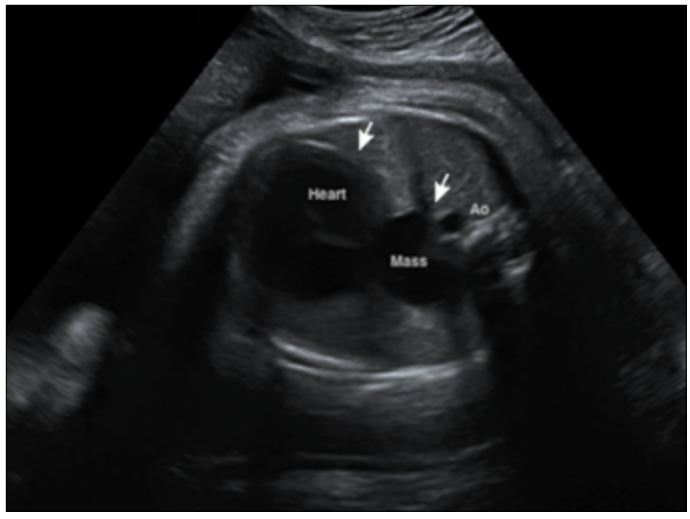

Figure 2. The relation of the heart, mass and aorta

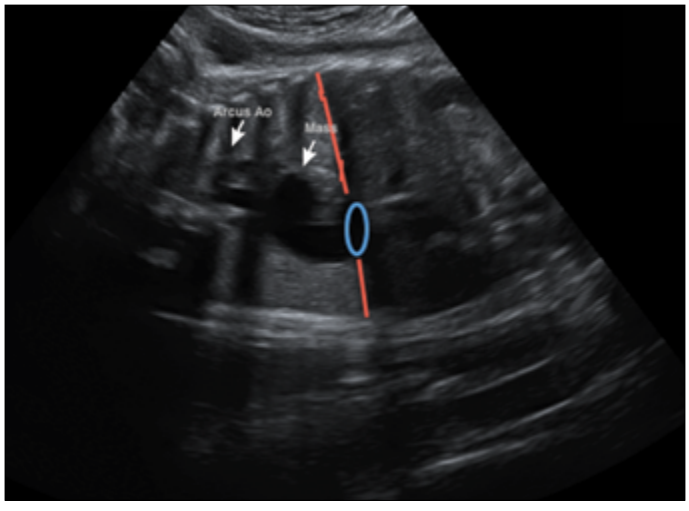

Figure 3. In this longitudinal view the red line shows the diaphragm and the blue circle shows the diaphragmatic hole

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Answer

Detailed examination of the internal organs revealed an absent stomach. With attention directed to this, although the diaphragm seemed intact and the lungs were normal in shape and volume, a stomach sliding to the thorax through diaphragm defect was detected (Figure 3).

Congenital diaphragmatic hernia (CDH) has an incidence of approximately 1/3,000 live births (1, 2). The primary embryological events leading to hernia remain largely unknown (3). Identification of the causes is challenging because of its heterogeneous and multifactorial character (4). It occurs as an isolated malformation in around 60% of cases, usually being sporadic.

Congenital diaphragmatic hernia can generally be classified into two types depending on its position: posterolateral and nonposterolateral. It is often located on the left side (85%) and least frequently located bilaterally (2%). The posterolateral defect- generally named as a Bochdalek hernia- is seen in 70-75% of cases (1). Nonposterolateral defects can be sub-divided into anterior and central types. The anterior type occurs in approximately 23-28% of cases. As in our patient, central hernias account for the remaining 2-7% of cases.

In our case, the fetus had a small, central defect of the diaphragm. Despite the expected, the fetus had no other abnormalities. These small defects may not be visible at the time of second level ultrasonography and may become prominent with advancing gestation.

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JTGGA CME/CPD CREDITING

Questions on the article within the scope of CME/CPD

1. Which of the following is not defined by the American Heart Association as a cardiovascular risk for women with PCOS?
   a) Abdominal obesity
   b) Hypertension
   c) Impaired glucose intolerance
   d) Cigarette smoking
   e) Family history of cardiovascular disease <65 years of age in male relative

2. Which one of the following is not a defined National Cholesterol Education Program (NCEP) criteria, for the diagnosis of metabolic syndrome?
   a) waist circumference ≥88 cm in women
   b) serum triglycerides ≥150 mg/dL
   c) serum low density lipoprotein concentration >130 mg/dL in women
   d) serum high density lipoprotein concentration <50 mg/dL in women
   e) systemic hypertension ≥130/85 mmHg

3. What is the most predictive factor for developing metabolic syndrome in girls aged 9-10 years?
   a) Waist circumference
   b) Serum high density lipoprotein levels
   c) Menstrual irregularity
   d) Acne
   e) Hirsutism

4. Based on the recent Endocrine Society recommendations, which drug can be used for treatment of metabolic syndrome?
   a) Statins
   b) Asetilsalisilicacid
   c) Vitamin D
   d) Metformin
   e) Glyburide

5. What is the average relative risk of metabolic syndrome in adolescents with PCOS in comparison to normal adolescents without PCOS?
   a) 1.5
   b) 3
   c) 4.5
   d) 6
   e) 9

6. Which of the following is not used in the formula of visceral adiposity index?
   a) waist circumference
   b) body mass index
   c) serum triglyceride level
   d) serum high density lipoprotein level
   e) fasting glucose level

JTGGA CME/CPD CREDITING

Answer form for the articles within the scope of CME/CPD

1st Question				
A	B	C	D	E

2nd Question				
A	B	C	D	E

3rd Question				
A	B	C	D	E

4th Question				
A	B	C	D	E

5th Question				
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6th Question				
A	B	C	D	E

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CONGRESS CALENDAR

INTERNATIONAL MEETINGS

23-26 April 2014	**Annual Meeting of the Middle East Society (The MESGE) and the International Society for Gynecological Endoscopy (The ISGE)** Dubai, United Arab Emirates http://www.mesgeisge2014.com
24-26 April 2014	**12th Annual Meeting of the Mediterranean Society for Reproductive Medicine 2014 (MSRM 2014)** Barcelona, Spain http://www.medical.theconferencewebsite.com/conference-info/MSRM-2014
29 June - 2 July 2014	**30th Annual Meeting of the European Society for Human Reproduction and Embryology (ESHRE)** Munich, Germany http://www.eshre.eu/Annual-meeting
18-22 October 2014	**American Society for Reproductive Medicine Annual Meeting** Honolulu, Hawaii http://www.asrm.org/ASRM2014
17-21 November 2014	**43rd AAGL Global Congress on Minimally Invasive Gynecology** Vancouver, BC Canada https://www.aagl.org/annual-meeting

NATIONAL MEETINGS

5-8 March 2014	**Palandöken Winter Congress on Obstetrics & Gynecology** Erzurum, Turkey http://www.pkd2014.org
20-22 March 2014	**6th Aegean Gynaecological Endoscopy Symposium** İzmir, Turkey http://egelaparoskopi2014.org
30 April - 3 May 2014	**10th Turkish - German Gynecology Congress** Antalya, Turkey www.tajev2014.org www.tajev.org
15-19 May 2014	**12th National Gynecology and Obstetrics Congress** Antalya, Turkey http://www.tjod2014.org
6-9 November 2014	**6th Biannual Meeting of the Turkish Society of Reproductive Medicine** Antalya, Turkey http://www.tsrm.org.tr/tsrm-kongre/tsrm-2014

Türkçe Özler – Mart 2014

Özgün Araştırma

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Tip 2 endometrial kanseri olgularında spiral arter dopplerin rolü

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ÖZ

Amaç: Tip 2 endometrial karsinomu belirlemede endometrial kan akımı ölçümünün prediktif değeri.

Gereç ve Yöntemler: Postmenapozal vajinal kanaması olan 65 hasta çalışmamızda yer aldı. Tüm olgulara transvajinal ultrason ile endometrial kan akımı ölçümü ve endometrial biyopsi örneklemesi uygulandı. Endometrial Doppler bulguları, patoloji sonuçları ile karşılaştırıldı. Doppler ölçümleri yetersiz olan hastalar çalışma dışı bırakıldı.

Bulgular: Hastaların yaş ortalaması 50.1±6.9 yıldı (42-73). Endometrial kalınlık ortalaması 10.1±2.9 mm (4-15 mm) ve CA125 düzeyi 20.1±17.4 U/mL (3-92) idi. Doppler bulgularının incelendiği olguların histopatolojik değerlendirmesinde 14 olgu tip 2 endometrial karsinom, 18 olgu atipisiz endometrial hiperplazi ve 33 olguda normal endometrial dokudan oluşmaktaydı. CA125 düzeyi (EAA=0.853, p=0.000), spiral arter rezistans indeksi (EAA=0.905, p=0.000) ve spiral arter pik sistolik hızının (EAA=0.822, p=0.000) tip 2 endometrial kanserin varlığını belirlemede prediktif değerleri istatistiksel düzeyde anlamlı bulundu. Endometrial kalınlık, tip 2 endometrial kanseri predikte etmede anlamlı değildi (p>0.05). Hiperplazi olguları kullandığımız modalitelerle predikte edilemedi (p>0.05)

Sonuç: Postmenapozal kanaması olan kadınlarda spiral arter Doppler ultrason bulguları tip 2 endometrial karsinomun tanısına yaklaşılması amacıyla değerli bir prediktif yöntem olmakla birlikte bu tetkikin etkinliği ileri çalışmalarla değerlendirilmelidir.

Anahtar kelimeler: Tip 2 endometrial kanser, postmenapozal kadın, spiral arter Doppler

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Özgün Araştırma

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Over kitle lezyonlarında USG kılavuzluğunda İİAS: Bir sito-histopatolojik korelasyon, pre-operatif yönetim kılavuzlarındaki rolü vurgulanarak

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ÖZ

Amaç: Ultrasonografi (USG) kılavuzluğunda over kitlelerinin ince iğne aspirasyon sitolojisi (İİAS) over tümörlerinin cerrahi öncesi doğru şekilde tanısı için etkili bir tanı yöntemidir. Bu çalışmanın başlıca amacı over kitlelerinin tanısında İİAS›nin duyarlılık, özgüllük ve doğruluğunu değerlendirmekti.

Gereç ve Yöntemler: Over kitlesi olan 83 hasta çalışmaya alındı ve cerrahi endikasyonu olmayan 6 hasta hariç tümünde USG kılavuzluğunda İİAS›nin histopatoloji ile korelasyonuna bakıldı.

Bulgular: Sitolojik tanı 83 over lezyonunun tümünde elde edildi: 56 olgu benign, 6 olasılıkla benign, 3 malignite şüpheli ve 18 olgu malign idi. Histolojisi mevcut olan 77 olgudan non-neoplastik kist olan 12'si endometriotik kistler ve foliküler kistlerdi. Neoplastik lezyonların büyük bir kısmı yüzey epitelyal tümördü. 12 non-neoplastik kist ve 43 benign tümörden, ikisi hariç tümü sitolojide benign veya muhtemelen benign olarak tanı aldı; 22 histolojik olarak malign veya borderline tümörden 18'i sitolojide malign veya malignite şüpheli idi, ancak dördü yalancı negatifti (bunlardan üçü borderline tümör idi). Böylece, sitolojik tanı duyarlılığı %83, özgüllüğü %97 ve doğruluğu%93 idi.

Sonuç: USG kılavuzluğunda İİAS çoğu over malignitesinin ya seyri içinde geç geldiği ya da herhangi bir tarama yönteminin olmadığı durumlarda nispeten güvenli, basit, hızlı ve maliyet-etkin bir prosedür gibi görünmektedir. Ek olarak, bu prosedür ile sito-radyolojik korelasyon herhangi bir cerrahi müdahaleden önce tedavi kılavuz ilkelerine karar vermede yararlı olabilir.

Anahtar kelimeler: Ultrason, ince iğne aspirasyon sitolojisi, overde kitle, görüntü kılavuzluğunda, sitoloji

Özgün Araştırma

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Birinci trimester insan plasentasındaki villöz trofoblastlarda P-kaderin (kaderin-3) ve E-selektin ekspresyonu

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ÖZ

Amaç: İnsan plasentasının gelişiminde kritik role sahip olmasına rağmen trofoblastik invazyon az bilinmektedir. Bu çalışmanın amacı ilk trimester plasentasında P-kaderin (kaderin-3) ve E-selektinin araştırılmasıdır.

Gereç ve Yöntemler: Çalışma 2005-2006 yılları arasında Gülhane Askeri Tıp Akademisi Haydarpaşa Eğitim Hastanesi Kadın Hastalıkları ve Doğum Servisine müracaat etmiş 140 hasta üzerinden yapıldı. Hastalar ektopik gebelik (Grup 1), spontan abortus grubu (grup 2) ve küretaj grubu (grup 3 veya kontrol grubu) olarak üç gruba ayrıldı. Sistemik hastalık öyküsü olan (trombofili gibi), rekürren aborta neden olabilecek bir hastalık ya da anotomik tanısı olan veya ektopik gebelik için etyolojik faktör öyküsü bulunan olgular çalışmaya dahil edilmedi. Hastaların parafin blokları, E-selektin ve P-cadherin ile usulüne uygun olarak boyandı. Hastaların demografik özellikleri (hasta yaşı, gravide, parite, önceki abort sayısı ve son adet tarihi) ve boyanma şiddetleri gruplar arasında ANOVA istatistiksel yöntemiyle karşılaştırıldı.

Bulgular: Hücrelerin P-cadherin ile ortalama boyanma puan skala sonuçlarına göre, 3 grup istatistiksel olarak birbirinden farklıdır ($p=0.0001$). Bu farklılık spontan abortus grubunun hem ektopik gebelik grubundan ($p<0.001$) hem de kontrol gebelik grubundan ($p<0.001$) istatistiksel olarak anlamlı şekilde daha düşük olmasından kaynaklanmaktadır. E-selektin ile yapılan immun boyamada ise hiçbir grupta boyanma pozitifliği görülmedi.

Sonuç: Plasental trofoblastlarda, P-cadherin immünreaktivite düşüklüğü spontan abort etiyopatogenezinde rol oynamaktadır.

Anahtar kelimeler: Adezyon molekülleri, e-selektin, insan trofoblastı, p-kaderin, plasenta

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Özgün Araştırma

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Korpus kallozum agenezisinin antenatal dönemde tanisi ve gebelik sonuçlari: 33 olgunun retrospektif değerlendirmesi

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ÖZ

Amaç: Korpus kallozum agenezisi tanısı alan bir grup fetusun antenatal ultrason bulgularını ve postnatal sonuçlarını sunmak amaçlanmıştır.

Gereç ve Yöntemler: Ultrason laboratuarımızın veri tabanı 2002 ile 2012 yılları arasında korpus kallozum agenezisi açısından şüpheli antenatal ultrasonu olan olgular için retrospektif olarak taranmıştır. Şu değişkenler değerlendirilmiştir: anne yaşı, tanı sırasındaki gebelik haftası, cinsiyet, eşlik eden serebral ve ekstra-serebral malformasyonlar, karyotip analiz sonuçları ve gebelik ve fetal/yenidoğan sonuçları.

Bulgular: Çalışma sürecinde korpus kallozum agenezisi olan, erkek daha fazla olmak üzere 33 fetus antenatal olarak tespit edilmiştir. Ortalama anne yaşı 28.48 idi. Tanıyı doğrulamak için tüm olgulara pre/postnatal MRG ve/veya otopsi yapılmıştır. Bunlar arasında, 23'ünde (%69.7) eşlik eden beyin bulguları ve 3'ünde (%9.1) eşlik eden ekstra-serebral anomaliler vardı. Otuz üç olgunun 21'ine (%63.6) karyotip analizi yapıldı. Gebelik sonuçlarına baktığımızda; 14 olguda (%42.4) gebeliğin sonlandırıldığı, kalan 19 fetusun 18'inin (%54.5) terme yakın doğurtulduğu, prematüre doğan birinin (%3.1) ise yenidoğan döneminde öldüğü görüldü.

Sonuç: Ek bulguların varlığı prognoz üzerinde önemli bir etkiye sahip olduğu için konjenital beyin malformasyonlarının tanısı mühim bir konudur; genetik danışmanlığın yanında detaylı değerlendirme gerçekleştirilmelidir.

Anahtar kelimeler: Korpus kallozum agenezisi, fetal MRG, prenatal tanı, ultrason

Özgün Araştırma

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Türkiye'de Tokat ilinde gestasyonel trofoblastik hastalık insidansı

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ÖZ

Amaç: Bu çalışmanın amacı Tokat ilinde gestasyonel trofoblastik hastalık (GTH) insidansının araştırılmasıdır.

Gereç ve Yöntemler: Ocak 2005 - Aralık 2012 tarihleri arasında Tokat ilinde bir üniversite, altı devlet hastanesi ve bir özel hastanenin kadın hastalıkları ve doğum kliniklerinde tanısı konulup tedavi edilmiş GTH hastaların medikal kayıtları retrospektif olarak değerlendirildi.

Bulgular: Bu tarihler arasında il genelinde toplam 59754 doğum gerçekleştiği ve 73 GTH tanısı konulduğu saptandı. GTH insidansı 1.22/1000 doğum olarak hesaplandı. Tanı alan hastaların yaş ortalaması 28.6±7.3 [17-51] olarak tespit edildi. Bu olgular içerisinde komplet mol %26 ve parsiyel mol %74 oranında saptanırken invaziv mol, koryokarsinom veya plasental site trofoblastik tümör saptanmadı. İki hastaya tek ajan kemoterapi (Metotreksat) uygulandığı tespit edildi. Takipler sırasında hastalığa bağlı mortalite bildirimi saptanmadı.

Sonuç: Gestasyonel trofoblastik hastalık insidansı Tokat ilinde 1000 doğumda 1.22 olarak saptanmıştır. Erken tanı, tedavi ve takip bu hastalığa bağlı morbidite ve mortalite gelişmesini önlemede kritik rol oynamaktadır. Gestasyonel trofoblastik hastalıkların ülke genelinde insidansının saptanmasında bölgesel ve geniş toplum temelli araştırmaların yararlı olacağını düşünmekteyiz.

Anahtar kelimeler: Gestasyonel trofoblastik hastalık, mol gebelik, insidans

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Özgün Araştırma

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Robotik jinekolojik cerrahide operasyon odası masrafları finansal analizi: Operasyon odasındaki masrafları azaltmak için verimlilik yöntemleri

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ÖZ

Amaç: Robotik asiste cerrahide konsol zamanı başlamadan önce ameliyat odasında geçen basamakları analiz etmek ve ameliyat odasında operasyon yapılmayan zamanı azaltmaya yönelik noktaları belirlemek.

Gereç ve Yöntemler: Teksas Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum Anabilim Dalı'nda benign jinekolojik hastalıklar nedeniyle robotik cerrahi yapılan 13 ard arda vaka retrospektif olarak değerlendirildi. Aktif cerrahinin başlamasından önceki zamanı değerlendiren bilgiler 'anestezi tamamlandı' (1. basamak), 'örtüler tamamlandı' (2. basamak) ve 'trokarlar içeride' (3. basamak) şeklinde özel terimlerle ve ameliyat odası masrafları ise düzey 3, 4 ve 5 olmak üzere sırasıyla açık abdominal/vajinal histerektomi, laparoskopik histerektomi ve robot assiste histerektomi şeklinde değerlendirildi.

Bulgular: Operasyon odası masrafları ilk 30 dakika ve sonrasındaki her 30 dakika için düzey 3, 4 ve 5 cerrahilerde sırasıyla 3693$ ve1488$; 4961$ ve 2426$; 5513$ ve 2756$ olarak belirlendi. Birinci basamak için median zaman 12.1 dakika (5.25-23.3) iken 2. basamakta 19 dakika (4.59-44) ve 3. basamakta 25.3 dakika (16.45-45) idi. Aktif operasyonun başlamsından önceki toplam median zaman 54.58 dakika (40-100) idi. Toplam masraf ise düzey 4'e göre hesaplandığında 6948,7$ düzey 5'e göre hesaplandığında 7771,1$ idi.

Sonuç: Robotik cerrahi, anestezi indüksiyonu ve hastanın örtülmesi süresinde cerrahi prosedürün hazırlık safhasında masraf düzeyi açısından şu anda pahalıdır. Bakımdan ödün vermeden zamanı kısaltmak ve kullanılan alet sayısını azaltmak için her türlü efor sarf edilmelidir.

Anahtar kelimeler: Maliyet analizi, ücretler, jinekoloji operasyon odaları, robotik assiste cerrahi

Özgün Araştırma

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Şiddetli preeklamptik kadınlarda Silymarin'in plasental kültürlerdeki VEGF, VEGFR-1 ve IL-1 α düzeyleri üzerine etkisi

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ÖZ

Amaç: Bu çalışmanın amacı, Silymarin'in şiddetli preeklampsili olguların plasentalarındaki vaskuler endotelyal büyüme faktörü (VEGF), VEGF Reseptoru-1 (VEGFR-1) ve İnterlökin-1 alfa (IL-1α) düzeylerine etkilerini araştırmaktır.

Gereç ve Yöntemler: Bu in-vitro çalışma Başkent Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum Bölümü'nde Eylül 2008 ile Mayıs 2009 arasında gerçekleştirilmiştir. Toplam 16 plasental doku örneği (8 ciddi preeklampsili, 8 kontrol) incelenmiştir. Plasental örnekler inkübe edildikten sonra kültür vasatında VEGF, VEGFR-1, ve IL1- α düzeylerine bakılmıştır. Silymarin uygulamasının bu düzeyler üzerine olan etkisi araştırılmıştır. Tanımlayıcı istatistikleri takiben, gruplar arası ortalamaların karşılaştırılmasında Mann-Whitney U testi ve Kruskal-Wallis testleri kullanılmıştır. P değerlerinin 0.05'ten düşük olduğu durumlar istatistiksel olarak anlamlı kabul edilmiştir.

Bulgular: Sekiz hasta şiddetli preeklampsi (SP) grubuna, diğer 8 hasta da kontrol grubuna alınmıştır. Gestasyonel yaş ile 48 veya 72 saat inkübasyondan sonra VEGF, sVEGFR-1 ve IL-1α düzeyleri arasında anlamlı korelasyon tespit edilmemiştir. Bazal VEGF düzeyleri SP grubunda daha düşük olmakla birlikte, bu fark istatistiksel olarak anlamlı düzeye ulaşmamıştır. sVEGFR-1 ve IL-1α düzeyleri de gruplar arasında benzer olarak saptanmıştır. 48 ve 72 saatlik inkübasyonu takiben kültür ortamına Silymarin eklenmesi, VEGFR-1 düzeylerini düşürmüş olsa da, bu sonuç da istatistiksel olarak anlamlı düzeye erişememiştir.

Sonuç: Çalışmamızda anlamlı etkisi gösterilememiş olsa da, preeklampside vazospazm, inflamasyon, anjiyogenez ve endotelyal hücre aktivasyonunun yeri düşünüldüğünde, daha geniş örneklem büyüklüğüne sahip gelecek çalışmalarda Silymarin'in yeri değerlendirilmelidir.

Anahtar kelimeler: Şiddetli preeklampsi, plasenta, vasküler endotelyal büyüme faktörü, Silymarin

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Özgün Araştırma

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Maternal serum C-reaktif protein seviyeleri erken membran ruptürü ile komplike olan term gebeliklerde intravenöz oksitosinle doğum indüksiyonunun başarısını öngörebilir mi? Kesitsel bir çalışma

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ÖZ

Amaç: Yüksek sensitiviteli C-reaktif protein (ys-CRP) akut enflamasyon ve/veya enfeksiyonun serumdaki bir belirteçidir. Bu proteinin serumdaki seviyelerinin tanısal değeri preterm doğum, erken membran ruptürü (EMR) ve preeklampsi hastalarında araştırılmıştır. Bu çalışmada, EMR olan hastalarda ys-CRP'nin doğum eyleminin indüklenmesinin başarısını öngörmedeki değeri değerlendirilmiştir.

Gereç ve Yöntemler: Çalışma için 37-41 gebelik haftası arasında eylem başlamadan önce amniotik membran ruptürü olan 86 term gebe seçilmiştir. Doğum ünitesine kabul edildiği anda maternal serum ys-CRP seviyeleri tespit edilmiş ve doğum eylemini indüklemek için düşük doz intravenöz oksitosin infüzyonu başlanmıştır. Doğum şekli ve doğum indüksiyonu ile doğum zamanı arasındaki zaman aralığı çalışmanın primer sonuçlarıdır.

Bulgular: Seksenaltı hastadan 25 (%29) tanesi sezaryan ile doğum yaparken geri kalan 61 (%71) hasta vajinal yolla doğurmuştur. Ys-CRP seviyelerinin yüksekliği ile vajinal doğum olasılığının azalması arasındaki ilişkinin anlamlılığı ROC eğrisi ile test edildiğinde yüksek ys-CRP değerlerinin sezaryan gerekliliğini öngörmede anlamlı bir belirteç olmadığı tespit edildi. Yüksek ys-CRP seviyeleri ile sezaryan ile doğum olasılığı arasında istatistiksel anlamlı bir korelasyon tespit edilemedi (Spearman rho:-.126; p=0.24). EMR esnasında maternal serumdaki ortalama ys-CRP seviyeleri sezaryan ile normal doğum arasında benzer olarak bulunmuştur.

Sonuç: Ys-CRP enflamatuar bir belirteç olarak eylem başlamadan önce membranları ruptüre olan term gebeliklerde doğum indüksiyonunun başarını öngörmede sensitif veya spesifik değildir.

Anahtar kelimeler: C-reaktif protein, erken membran ruptürü, doğum indüksiyonu

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Özgün Araştırma

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Preoperatif tanısı grade 1 endometrioid tümör olan endometrium kanseri olgularında evrelemenin preoperatif parametreler ve frozen/section ile prediksiyonu

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ÖZ

Amaç: Klinik parametreleri kullanarak preoperatif olarak evreleme gereksiniminin preoperatif parametreler ve frozen/section (FS) ile prediksiyonun araştırılması.

Gereç ve Yöntemler: Probe küretaj sonucu grade 1 endometrioid adenokanser olan ve 1996-2010 tarihleri arasında opere olan 219 hasta çalışmaya dahil edildi.

Bulgular: Klinik parametreler içinde sadece yaş ve vücut kitle indeksi preoperatif olarak evrelemeyi öngörebildi. Vücut kitle indeksi azaldıkça ve yaş arttıkça evleme olasılığı artı. Preoperatif tanı ve FS arasındaki uyumluluk %89,5 idi. Postoperatif grade derecesi FS' ye göre 13 hastada (%5.9) daha yüksek, 2 hastada (%0.9) daha düşük bulundu. FS'da grade'i, DMI, tümör tipini ve servikal invazyonu belirlemekle ilgili klinik açıdan önemli olan ve evreleme kararını etkileyecek toplam 10 hastada hata yapıldığı görüldü. Sonuçta FS'da, postoperatif patolojiye göre evrelendirilmesi gereken sadece yedi hastanın (%3.2) atlandığı görüldü.

Sonuç: Bu çalışmada preoperatif klinik parametrelerin evrelenmesi gereken hastaları iyi bir şekilde öngöremediği gösterildi. FS lenfatik tutulumu yüksek oranda öngörebildi. Bu yüzden, preoperatif tanısı grade 1 endometrioid tümör olan hastalar mutlaka FS'nın kullanıldığı jinekolojik onkoloji merkezlerinde opere edilmelidirler.

Anahtar kelimeler: Endometrial kanser, vücut kitle indeksi, yaş, frozen/section, evreleme

Derleme

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Adolesan PCOS'ta metabolik sendrom hakkında ne biliyoruz?

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ÖZ

Farklı klinik özellikler gösteren polikistik over sendromu üreme çağındaki kadınların en sık görülen endokrinopatisidir. Bu nedenle bugüne kadar değişik tanı kriterleri ortaya sürülmüştür. Genel olarak en çok kabul gören hiperandrojenizm ve oligo-anovulasyonun birlikteliğinin gerektiği Amerikan Ulusal Sağlık Enstitüleri (NIH) kriterleridir. Bu hastaların semptomları adolesan dönemde başladığı, bu dönemdeki hormonal dalgalanma nedeniyle de bazen normal pubertal gelişmeden ayırt edilemediği için adolesan dönemde polikistik over sendromu (PCOS) tanısını koymak oldukça güçtür. Adolesan PCOS için literatürde henüz konsensus sağlanmış bir kriter yoktur. Adolesan dönemde hastalar için daha çok menstruel bozukluklar ve kozmetik kaygılar öne çıksa da artmış insülin resistansı, obesite, subklinik atheroskleroz, diabet (DM), metabolik sendrom ve kardiovasküler hastalıklarda göz önünde bulundurulmalı ve hastalar bu yönden de değerlendirilmelidir. Metabolik sendrom için belirleyici faktörlerden en önemlisi obesitedir. Günümüzde çocukluk ve adolesan dönemden itibaren obesite insidansı artmaktadır ve bunun sonucunda ülkeleri artmış bir sosyal ve ekonomik yük beklemektedir. PCOS'lu adolesanlar ise diğer adolesanlara göre daha obezdir ve metabolik sendrom riski de daha yüksektir. Özellikle abdominal yağlanmanın çeşitli sitokinlerin salınımına yol açarak metabolik sendrom riskine katkıda bulunduğu öne sürülmektedir. Adolesan dönemde metabolik sendrom tanısı ile ilgili fikir birliği olmasa da özellikle 10 yaşın üzerinde Uluslararası Diabet Federasyonu'nun (IDF) belirlediği kriterler kullanılabilir. Literatürde çesitli klinik ve metabolik markerlarla metabolik sendrom riski öngörülmeye çalışılmıştır. Bel cevresi ölçümü, trigliserid seviyeleri ve androjen seviyelerinin belirleyici olabileceği iddia edilmektedir. Çocukluktan itibaren özellikle abdominal yağlanmanın önlenmesi metabolik sendromu önlemek için temel hedef olmalıdır. Adolesan dönemde PCOS'lu hastalarda ise metabolik ve kardiovaskuler riskler değerlendirilmeli ve önleyici tedbirlerin alınmalıdır. Özellikle obese PCOS'lu adolesanlar için düşük yağ, yüksek meyve ve sebze tüketimin öneren Akdeniz tipi beslenme, orta şiddette fiziksel aktivite ve sigara alışkanlığının bırakılması önleyici tedbirler arasında sayılabilir. Hayat tarzı modifikasyonlarının etkili olmadığı hastalarda metformin kullanımı da bir tedavi seçeneği olabilir.

Anahtar kelimeler: Polikistik over sendromu, adolesan, metabolik sendrom

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Olgu Sunumu

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Amniyotik band sendromunun prenatal tanısına üç-boyutlu ultrasonografinin entegrasyonu: Bir olgu sunumu

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ÖZ

Amniyotik band sendromu amniyotik membranın erken rüptürü sonucu oluştuğu düşünülen nadir bir bozukluktur. Hastalığın yaygınlığı minör parmak amputasyonlarından ağır ölümcül anomalilere kadar değişkenlik gösterebilir. Uzun yıllardır rutin klinik uygulamada, bu sendromun iki boyutlu ultrasonografi ile tespit edilebildiği bilinmektedir. Gelişmekte olan görüntüleme tekniklerinden üç boyutlu ultrasonografi bu yıkıcı anomalinin erken ve kesin tanısına olanak sağlar. İki boyutlu ultrasonografi ile tespit edilen şüpheli bulgulara üç boyutlu ultrasonografinin entegre edilmesi olası sonuçları öngörmemize izin verir ve danışmanlıkta kolaylık sağlar. Burada 19. gebelik haftasında üç boyutlu ultrasonografi ile amniyotik band sendromu tanısı konulmuş ve 20. gebelik haftasında gebeliğin sonlandırıldığı bir olguyu sunuyoruz. Üç boyutlu ultrasonografinin bazı şüpheli fetal anomalilerde kullanımı erken tanı ve hastalığın yaygınlığı hakkında daha kesin bilgi elde edilmesini sağlayabilir.

Anahtar kelimeler: Amniyotik band, konstriksiyon bandı, üç boyutlu ultrasonografi, prenatal tanı

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Gebelikte akut karın tanısal ikilemi: İnce bağirsak leiomyomasi

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ÖZ

İnce barsak tümörleri nadir görülmekle beraber, tanısı zor konulan tümörlerdir. Hemoraji, oklüzyon, perforasyon ve bunları takiben acil ameliyatlara sebep olabilmektedirler. Yirmi sekiz yaşında G2P1, 22. gebelik haftasında olgu, bir günlük sol alt kadran ağrısı şikayetiyle acil kliniğimize başvurdu. Hastaya genel cerrahlarla birlikte acil laparotomi yapıldı. Histopatolojik incelemede olguya, ince barsak leiomyomu teşhisi konuldu. Gastrointestinal patolojiler gebelikte akut karının ayırıcı tanısı açısından göz önünde bulundurulmalıdır.

Anahtar kelimeler: Akut karın, gebelik, ince barsak tümörü

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Lynch sendromlu genç kadınlarda grade I, evre IA, endometrioid adenokarsinomun histeroskopik çıkarılmasından sonra başarılı gebeliği olan iki vaka

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ÖZ

Endometrial polip içinde tanı konan, genç kadınlarda Grade I, FIGO IA (Uluslararası Jinekoloji ve Obstetrik Federasyonuna göre evrelendirme) endometrioid adenokarsinomlu iki olgu sunmaktayız. Her iki hastaya üç ay boyunca ilk günde 400 mg medroksiprogesteron başlangıç tedavisi veya RİA-LND (rahim içi araç-levonorgestrel) yerleştirilmesinden sonra tekrarlanan histeroskopiler ve çoklu biyopsiler yapıldı. İkisinde de, tüm histolojik örnekler negatifti. İkisi de gebelik denemeye karar verdi. İlk hastada spontan ve ikinci hasta IVF (in vitro fertilizasyon) tedavisi sonrası gebelik oldu. Her ikisi de miadında bebek doğurdu. Hastalarımızın ikisine de histerektomi önerildi ve yapıldı. Her iki hastada da Amsterdam II ve kalıtsal non-polipozis kolorektal kanser (HNPCC) için revize Bethesda kriterleri karşılanıyordu.

Anahtar kelimeler: Endometrium kanseri, Lynch sendromu, histeroskopi, üreme