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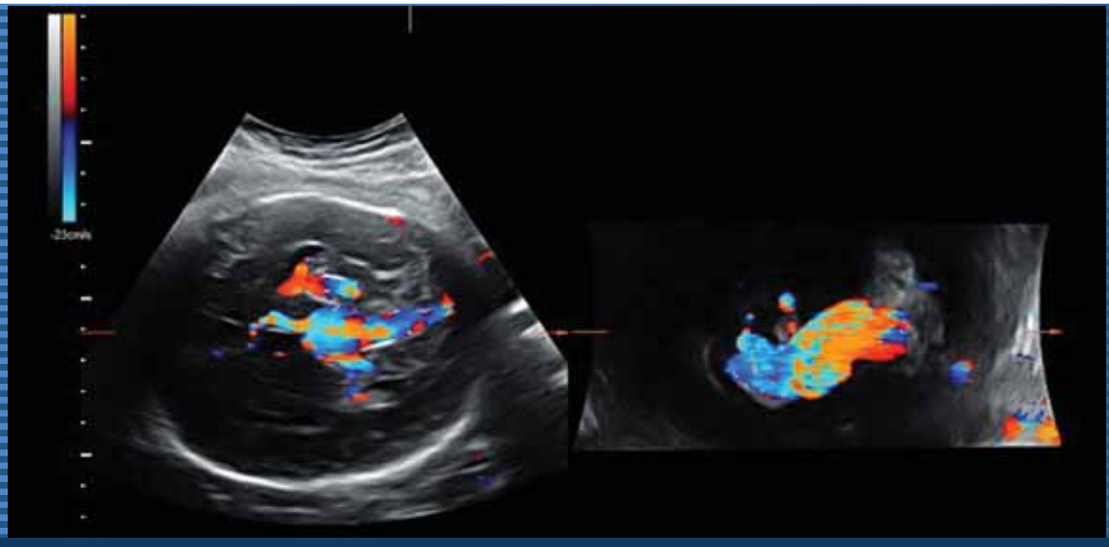

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Aims and Scope

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

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 refereed in accordance with "double-blind peer reviewed" process for both referees and authors.

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

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

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Contents

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Editorial

Dear Colleagues,

Here presented the second issue of the thirteenth volume of our journal - JTGGA (Journal of the Turkish - German Gynecological Association).

In this issue, you will find very interesting and scientifically satisfying articles. One of them is a review about urinary dysfunctions after tight midurethral sling operations. Another interesting article is a research finding out that urogynecology related urodynamy is not very useful in the preliminary period for the women with overactive bladder symptoms. Besides, an article about the increase of total and lipid-bound sialic acid levels with cardiovascular risk factor in the women with PCOS will draw your attention. Other interesting articles are about "The effect of serum and follicular leptin levels in In Vitro Fertilization", "The conflict on pre-post operative endometrial cancer diagnosis" and "The relation of preterm labor with angiogenesis and VEGF".

I would like ro remind my young colleagues that our journal is indexed by many internationally accepted databases such as SIIC, Tübitak/Ulakbim Turkish Medical Index, Turkish Citation Index, EBSCO host, SCOPUS, Excerpta Medica (EMBASE), DOAJ database, Gale/Cengage Learning, ProQuest, CINAHL and Index Copernicus. It will be our great pleasure to receive your qualified research studies to be published in a peer-reviewed and internationally indexed journal which will be very important in the many exams you will face. You can also contact our editorial team directly if you would like to be a reviewer and be actively involved in the evaluation process of our journal.

Dear young colleagues and assistants,

One of the products of the scientific research is the publication. A scientific experimentation is not complete unless published, even if it is very brilliant. As Gerard Piel says, "*Without Publication, Science is Dead*". Scientific researcher shall not only make science but also shall write it. Most of the scientists is unfortunately not also a good "*author*". My suggestion for you is to have a glance at the spelling rules of our journal and the printed or published sources about your topic before writing a good article. Please also do not hesitate to ask for assistance to more experienced instructiors or teachers. Besides, the editors of our journal Assoc. Prof. Eray Çalışkan and Assoc. Prof. Gazi Yıldırım will be pleased to assist you about these issues. I look forward to seeing your qualified research studies and articles in our journal.

Except the attractive articles and case studies, you will find a **quiz** in this issue at the tear-away pages. Please read our journal carefully, fill and send us your answers in order to take advantage of the **Turkish Medical Association Accreditation Points.**

I would also like to inform you about the fourth Social Responsibility Project of our foundation - Turkish German Gynecological Education and Research Foundation (TAJEV) which will be held on June 7-8, 2012, in Rize. The project is organized in four steps traditionally; public awareness meeting with participation of the locals, the scientific meeting with participation of health professionals, performing of the advanced operations and medical examination / screening to local women, and finally a medical device donation to the local hospital. Sessions directed to raise the public awareness of the people will include topics such as the pathway to be followed through pregnancy, the health of the baby and mother, family planning and reproductive health, prevention methods from genital and breast cancers and treatment of infertility. We believe our project will succeed even if we help only one woman to become more conscious about herself and her baby.

I sincerely wish the second issue of this year will contibute the valuable medical society and Turkish Gynecology and Obstetrics Science.

Best regards,

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

Total and lipid bound sialic acid levels in patients with polycystic ovary syndrome

Polikistik over sendromlu hastalarda total ve lipid bağlı sialik asit seviyeleri

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Abstract

Objective: To evaluate serum total and lipid bound sialic acid (TSA&LBSA) levels in patients with polycystic ovary syndrome (PCOS).

Material and Methods: Forty women with PCOS and 35 healthy controls were enrolled in the study. Serum TSA, LBSA, follicle stimulating hormone, lutenizing hormone, estradiol, thyroid stimulating hormone, prolactin, dehydroepiandrosterone sulphate, androstenedione, free testosterone, total testosterone, 17-OH progesterone, sex hormone binding globulin, cortisol, total cholesterol, triglyceride, high density lipoprotein and low density lipoprotein were measured in each subject. Insulin resistance was estimated by fasting insulin level, fasting glucose: insulin ratio and 75-g glucose tolerance test for 2 hours.

Results: Serum TSA levels were not significantly different between the groups. Serum LBSA levels were higher in patients with PCOS compared to the control group. TSA was correlated with androstenedione and HOMA-IR in the PCOS group. Positive correlations were found between LBSA and dehydroepiandrosterone sulphate in patients with PCOS. After correction for BMI, the only existing significant correlation was between LBSA and follicle stimulating hormone.

Conclusion: Serum LBSA levels, which has previously been found to be higher in cardiovascular diseases and diabetes mellitus, are elevated in PCOS. (J Turkish-German Gynecol Assoc 2012; 13: 79-84)

Key words: Polycystic ovary syndrome, total sialic acid, lipid bound sialic acid, risk

Received: 08 February, 2012 **Accepted:** 06 March, 2012

Özet

Amaç: Polikistik over sendromlu hastalarda (PKOS) serum total ve lipid bağlı sialik asit (TSA&LBSA) düzeylerinin değerlendirilmesi.

Gereç ve Yöntemler: Çalışmaya kırk PKOS'lu hasta ve 35 sağlıklı kontrol dahil edildi. Her olguda serumda TSA, LBSA, folikül stimülan hormon, luteinizan hormon, östradiol, tiroid stimülan hormon, prolaktin, dehidroepiandrosteron sülfat, androstenedion, serbest testosteron, total testosteron, 17-OH progesteron, seks hormon bağlayıcı globulin, kortizol, total kolesterol, trigliserid, yüksek densiteli lipoprotein ve düşük densiteli lipoprotein ölçüldü. Açlık insülin seviyesi, açlık glükozu/insülin oranı ve 2 saatlik 75-g glükoz tolerans testi ile insülin rezistansı değerlendirildi.

Bulgular: Serum TSA seviyeleri açısından gruplar arasında anlamlı fark yoktu. Kontrol grubuna göre karşılaştırıldığında PKOS'lu hastalarda serum LBSA seviyeleri yüksekti. PKOS grubunda TSA, androstenedione ve HOMA-IR ile korele bulundu. PKOS'lu hastalarda LBSA ile dehidroepiandrosteron sulfat arasında pozitif korelasyon bulundu. BMI'ya göre düzeltme sonrası, kalan tek anlamlı korelasyon LBSA ile folikül stimülan hormon arasında idi.

Sonuç: Kardiyovasküler hastalıklarda ve diabette arttığı bilinen LBSA'nın serum seviyeleri PKOS'da yükselir.

(J Turkish-German Gynecol Assoc 2012; 13: 79-84)

Anahtar kelimeler: Polikistik over sendromu, total sialik asit, lipid bağlı sialik asit, risk

Geliş Tarihi: 08 Şubat 2012 **Kabul Tarihi:** 06 Mart 2012

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disease in women during the reproductive ages (l). Patients with PCOS are in the high risk group for coronary heart disease because of their abnormal lipid profile, insulin resistance and obesity (2). Additionally, it was shown that PCOS causes significant risks for diabetes mellitus (DM) in patients early in their life. All these findings show that there is an increase in prevelance of cardiovascular disease (CVD) and DM in PCOS with time (3).

Sialic acids (SA) are acillated neuraminic acids found in glycoproteins and glycolipids of cell membrane and in other parts of the cell (4). SA has many biological functions: it provides additional electronegativity to the cell, is a main compound of many receptors on cell surface and affects the macromolecular structure of glucoconjugates and prevents their degradation (5).

The elevation in serum SA concentrations was demonstrated in coronary heart disease and myocardial infarction (6). Despite the observed relationship between SA and cardiovascular disease, the reasons for this are not clear. Additionally, serum total and lipid bound SA were found to be elevated in DM and total sialic acid levels were shown to be related with some diabetic complications (7). Sialic acids in the human body are mainly found in the terminal oligosaccharide of glycoprotein structured acute phase reactants which are

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fibrinogen, C-reactive protein, haptoglobulin, α-1 antitripsin, ceruloplasmin, transferrin and complement. Because some of these sializated glycoproteins are acute phase reactants, their concentrations increase rapidly at the beginning of inflammatory reactions (8, 9).
Since PCOS is related to DM and cardiovascular diseases and TSA and LBSA were found to be elevated in these two common disorders, we planned to evaluate the serum TSA and LBSA levels in patients with PCOS and healthy controls.

Material and Methods

Forty women between the ages of 18 to 35 years with PCOS, and 35 healthy women as the control group, were included in the study. Study participants were enrolled from patients who attended the outpatient clinics of the gynecology and obstetrics department in our institution. A full Institutional Review Board approval was obtained from Kirikkale University School of Medicine Ethical Committee (approval no. 2005/150). All subjects were informed, and written and signed consents were taken.
PCOS was diagnosed according to the 2003 Rotterdam criteria (10) after the exclusion of related disorders, by two of the following three features: i) oligo- or anovulation, ii) clinical and/or biochemical signs of hyperandrogenism, or iii) polycystic ovaries. Detailed medical history and physical examination were performed in all subjects.
Inclusion criteria for the study were:
1. Women at ages ranging from 18 to 35 years with the diagnosis of PCOS
2. Women at ages ranging from 18 to 35 years with regular menstrual cycles and without systemic and hormonal pathologies, who attended for vaginal discharge or for information about contraceptive methods were included in the study as the control group.

Exclusion criteria for PCOS and control groups were as follows:
1. Patients with previously diagnosed endocrinological diseases such as diabetes mellitus, hyper or hypothyroidism or Cushing syndrome,
2. History of malignancy,
3. Pneumonia, Rheumatoid arthritis, Behçet's and Crohn disease,
4. Patients on drugs such as oral contraceptives, steroids, GnRH agonists or antagonists or progesterone,
5. Patients with collagen tissue diseases, impaired renal functions or impaired liver functions,
6. Patients using drugs that alter sex hormone metabolism,
7. Patients with atherosclerosis and hypertension,
8. History of previous thromboembolism.

Age, weight, height and waist/hip ratio (WHR) of the subjects were noted and body mass indices (BMI) were calculated according to the body weight (kg) / height (m^2) formula. Pelvic transabdominal or transvaginal ultrasonography was performed for each subject.

Laboratory Measurements

Blood samples were taken from all subjects between 08:00-09:00 A.M. after 12 hours of fasting on the third day of the menstrual cycle for sialic acid and routine hormonal measurements Follicle stimulating hormone (FSH), lutenizing hormone (LH), estradiol (E_2), thyroid stimulating hormone (TSH), prolactin (PRL), dehydroepiandrosterone sulphate (DHEAS), androstenedione, free testosterone (free T), testosterone (T), 17-OH progesterone, sex hormone binding globulin (SHBG), cortisol, total cholesterol, triglyceride, high density lipoprotein (HDL) and low density lipoprotein (LDL) levels were measured for each subject. Blood samples for TSA and LBSA were centrifuged at 4°C and 1.600 r/m for 15 minutes. Serum obtained after this procedure was kept at -20°C for the analysis of total and lipid bound sialic acid levels. TSA and LBSA levels were measured by using methods previously defined by Katopodis et al. (11) and Plucinsky et al. (12).
After 12 hours fasting, 75 gr OGTT was performed for all subjects. Fasting blood glucose and insulin levels were measured, and then blood glucose level was measured again at the second hour after ingestion of 75 g of glucose solution. Additionally, fasting glucose/fasting insulin ratio was calculated. Insulin resistance was calculated according to the HOMA (Homeostasis Model Assessment) method (Formula=Fasting blood glucose level (mg/dl)XFasting insulin level (μIU/ml)/405).
FSH, LH, E_2, TSH, PRL, DHEAS, total T and insulin levels were measured with the electrochemilluminescence immunoassay method in the Roche Hitachi E 170 Modular device (Roche Diagnostic, Germany) by using Elecsys 1010/1020 kits.
SHBG, free T, androstenedione, 17 OH progesterone levels were measured with the ELISA method in μQuant trade mark Spectrophotometric device (Biotek Instruments Inc., USA) using EIA kits (DSL, Diagnostic System Laboratories Inc., USA).
Triglyceride, HDL, LDL, total cholesterol and glucose levels were measured with the colorimetric method in the Roche Hitachi Modular P800 autoanalyzer device by using Roche mark kits (Roche Diagnostic, Germany).

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Science (SPSS) 11.5 (Inc., Chicago, Illinois, USA) programme. The Shapiro-Wilk statistics was used to test variables for normal distribution. Differences between the means were analyzed by Student's t-test and Mann-Whitney U-test according to the distribution of data. Data were represented as mean±standard deviation (SD). Pearson correlation coefficients were calculated for continuous variables with normal distribution, and Spearman rank correlation coefficients were calculated for non-normally distributed continuous variables. Partial correlation coefficients were calculated for the above-mentioned parameters, using BMI as a covariate. Power calculation in TSA and LBSA parameters were performed using the Number Cruncher Statistical System-Power Analysis and Sample Size (NCSS-PASS 2005) (Inc., Kaysville, Utah, USA).
In all examinations, a p-value of <0.05 was considered statistically significant.

Results

Demographic characteristics and mean serum hormone, insulin, glucose and lipid measurements of the groups are shown

in Table 1. There were no statistically significant differences between patients with PCOS and the control group in respect to age, FSH, TSH, PRL, androstenedione, total T, 17 OH progesterone, cortisol, fasting glucose, second hour glucose and total cholesterol levels.

BMI, WHR, LH, E_2, free T, fasting insulin, HOMA-IR, tryglyceride and LDL levels were significantly higher in patients with PCOS, whereas SHBG, DHEAS, fasting glucose/ fasting insulin ratio and HDL levels were significantly lower (Table 1).

Power rate was 53% for TSA and 88% for LBSA.

Mean TSA levels were 61.02±7.89 mg/dl in patients with PCOS and 57.94±5.53 mg/dl in the control group (p=0.052). LBSA levels were significantly higher in patients with PCOS (25.23±7.65mg /dl) compared to controls (20.41±5.25 mg /dl) (p=0.003) (Figure 1).

In the PCOS group, serum TSA was found to be positively correlated with androstenodione (r=0.338, p=0.032) (Table 2) and HOMA- IR (r=0.558, p=0.001) (Table 3). There was also a significant correlation between serum LBSA and DHEAS (r=0.508, p=0.001) in patients with PCOS (Table 3).

After adjusting for BMI, no correlations appeared between serum TSA and LBSA levels and the other parameters, except for the significant positive correlation between serum LBSA and FSH (r=0.335, p=0.037).

Discussion

Polycystic ovary syndrome is a common endocrine disease in women in the reproductive ages, and many studies about its etiology, metabolic effects and future risks are still underway.

We found that serum LBSA levels were higher in patients with PCOS, while serum TSA levels did not differ. Serum TSA levels have been reported to be a risk factor for cardiovascular and cerebrovascular disease (13). Higher serum SA levels have also been detected in diabetes mellitus, in either type (14). Recent reports in the literature regarding TSA and LBSA levels

Table 1. Demographic characteristics and mean serum hormone, insulin, glucose and lipid measurements of the groups

	PCOS	Control	p
Patient number (n)	40	35	
Age (years)	22.80±2.70	23.82±1.79	N.S.
BMI (kg/m^2)	27.94±6.78	21.59±2.68	p=0.001
Waist/Hip Ratio	0.82±0.09	0.75±0.05	p=0.001
FSH (mIU/ml)	5.94±2.23	5.50±2.27	N.S.
LH (mIU/ml)	9.60±4.45	6.30±2.86	p=0.005
LH/FSH	1.78±0.93	1.24±0.65	p=0.005
Estradiol (pg/ml)	102.13±88.58	53.99±50.86 (41.66)[a]	p=0.001
TSH (mIU/ml)	2.20±1.01	2.13±0.88	N.S.
PRL (ng/ml)	15.52±5.07	15.95±4.25	N.S
DHEAS (μg/ml)	260.64±104.83	324.68±111.32	p=0.011
Androstenedione (ng/ml)	4.56±2.17	3.85±1.50	N.S.
Free testosterone (pg/ml)	4.42±2.61	2.68±1.47	p=0.002
Total testosterone (ng/ml)	0.59±0.23	0.56±0.24	N.S.
SHBG (nmol/L)	37.09±37.02 (20.55)[a]	56.67±32.55	p=0.001
17 OH Prog. (ng/ml)	1.00±0.51	0.99±0.57	N.S.
Cortisol (nmol/L)	381.57±146.57	321.01±150.79	N.S.
Fasting insulin (μIU/ml)	17.87±10.97	12.34±10.09	p=0.001
Fasting glucose (mg/dl)	86.25±7.13	87.40±6.78	N.S.
Fasting glucose/insulin	7.00±7.30 (5.65)[a]	10.60±6.41	p=0.001
Second hour glucose (mg/dl)	90.77±12.32	91.60±10.89	N.S.
HOMA-IR	3.85±2.58	2.69±2.25	p=0.001
Triglyceride (mg/dl)	106.58±56.99	87.77±49.40	p=0.02
HDL (mg/dl)	52.02±10.79	63.29±14.51	p=0.001
LDL (mg/dl)	106.67±30.43	86.58±19.33	p=0.001
T. cholesterol (mg/dl)	160.82±30.15	161.37±25.02	N.S.

N.S.: Not significant, Mean Data±Standard Deviation, [a]: Median Value

Table 2. Pearson correlation coefficients (r) between TSA, LBSA and normally distributed variables in patients with PCOS

	TSA (r)	p	LBSA (r)	p
Age (years)	0.007	0.964	-0.066	0.686
LH (mIU/ml)	-0.215	0.182	0.083	0.609
LH/FSH	-0.174	0.281	-0.185	0.251
PRL (ng/ml)	0.057	0.726	0.141	0.384
Androstenedione (ng/ml)	0.338	0.032*	0.302	0.057
Total Testosterone (ng/ml)	0.116	0.473	0.178	0.269
Cortisol (nmol/L)	0.081	0.617	0.214	0.183
Fasting glucose (mg/dl)	0.005	0.972	-0.084	0.672
Second hour glucose (mg/dl)	-0.214	0.182	-0.272	0.088
HDL (mg/dl)	-0.165	0.306	-0.056	0.727
LDL (mg/dl)	0.081	0.615	0.264	0.098
T. Cholesterol (mg/dl)	0.088	0.586	0.123	0.449
p*:<0.05				

Table 3. Spearman correlation coefficients (r) between TSA, LBSA and non-normally distributed variables in patients with PCOS

	TSA (r)	p	LBSA (r)	p
BMI (kg/m^2)	0.293	0.067	0.142	0.383
Waist/Hip ratio	0.196	0.227	0.227	0.158
FSH (mIU/ml)	0.060	0.711	0.080	0.625
Estradiol (pg/ml)	-0.148	0.361	-0.106	0.517
TSH (mIU/ml)	0.227	0.160	0.117	0.470
DHEAS (μg/ml)	0.125	0.441	0.508	0.001*
Free Testosterone (pg/ml)	0.083	0.609	0.047	0.775
SHBG (nmol/L)	-0.090	0.581	-0.140	0.388
17OH Prog. (ng/ml)	-0.066	0.686	-0.047	0.772
Insulin (μIU/ml)	0.147	0.367	0.023	0.888
Fasting glucose/insulin	0.240	0.136	0.146	0.368
HOMA-IR	0.558	0.001*	0.217	0.178
Triglyceride (mg/dl)	0.014	0.933	0.148	0.363
p*:<0.05				

in patients with PCOS do not provide sufficiently clear data. Bickerton et al. (15) have previously evaluated a number of biochemical and biophysical markers indicating cardiovascular risk in patients with PCOS. Eleven women with PCOS and 12 controls were included and it was found that total sialic acid levels were similar between the groups (705±149 mg/l vs 713±112 mg/l, p=0.88). LBSA levels were not studied and correlations between TSA levels and other parameters were not investigated. Since data is limited concerning TSA and LBSA levels in PCOS, we also reviewed studies with sialic acid research in the general population and in other clinical situations.

Hag et al. (16) and Hangloo et al. (17) demonstrated that TSA levels did not change with varying age and sex. In contrast, Lindberg et al. reported in a study including approximately ten thousand subjects that TSA levels were similar between ages 25 and 44 years but afterwards progressively increased up to 74 years of age (13). Similarly, Crook et al. (14) stated that, in healthy cases, TSA levels in the elderly population were higher than those in the younger subjects, and this was explained by atherosclerosis which increased with age and thus TSA was a risk factor for cardiovascular disease.

Pönniö et al., (18) showed that serum TSA levels did not increase with age in men, but in women levels increased with age, especially during the menopausal years. In this study it was also shown that serum TSA levels increased in correlation with BMI, systolic and diastolic pressure in healthy male and female subjects. Additionally, after adjustment for age and BMI, the correlation with blood pressure remained. In a small healthy popu-

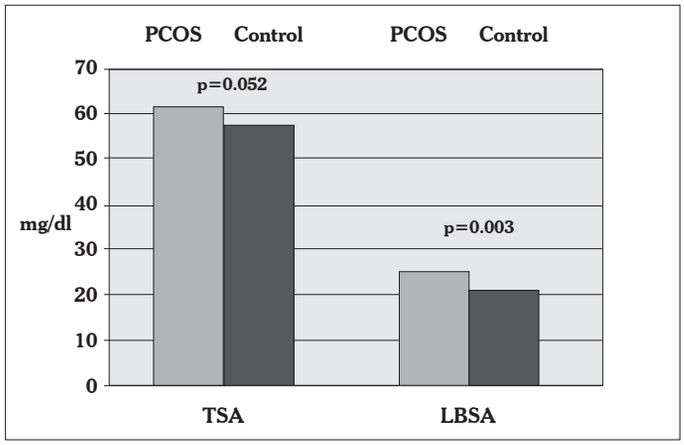

Figure 1. Serum total sialic acid and lipid bound sialic acid levels in patients with PCOS and the controls

lation, Crook et al. (19) found, that the correlation between serum TSA and blood presure was only present in women. High blood pressure is an important cardiovascular risk factor. As the correlation between blood pressure and serum TSA was shown, the role of TSA in predicting cardiovascular mortality could be explained (13, 20). Additionally, serum TSA levels also represented other cardiovascular risk factors such as acute phase reactants which contain sialic acid (21). Thus, serum TSA levels and the risk of coronary artery disease were found to be elevated during the menopause (22).

Diabetic patients, whether type I or II, have been reported to have elevated serum TSA levels in previous studies (23). Many studies have also revealed a direct correlation between serum TSA levels and coronary heart disease in type II DM (24). The coexistence of type II DM and cardiovascular disease may propose a possible insulin resistance or hiperinsulinemia association. Flynn et al. (25) reported that insulin resistance increased serum TSA levels. While we did not find any difference in TSA levels between patients with PCOS and the controls, a significant positive correlation was found between TSA and HOMA-IR in our study. This correlation disappeared after controlling for BMI.

Total SA was found to be elevated in atherosclerotic vascular inflammation (13, 26, 27). Although Crook et al. (19) have demonstrated that there was a significant relation between serum TSA and fasting plasma insulin and glucose in healthy population, especially in women. The associations between TSA levels and other cardiovascular disease risk factors such as fasting insulin level, fasting blood glucose level and insulin resistance are not clear. Bickerton et al. (28) evaluated cardiovascular risk in 11 PCOS and 12 healthy control subjects and reported similar sialic acid levels.

Power analysis for TSA revealed a power rate of 53% in our study. This power rate was lower than expected and, when studies with a larger number of patients and higher power values are performed, the significance of TSA levels in PCOS may be better understood.

Power analysis for LBSA revealed a power rate of 88% in our study and this was a sufficient rate. We found that LBSA levels were significantly elevated in the PCOS group compared to the controls. It was found in many studies that acute phase reactants increased in patients with PCOS (29). The increase in lipid bound SA in patients with PCOS in our study may correlate with the increase in acute phase reactants in PCOS, but we did not study these parameters.

After adjustment for BMI, no correlation was observed between serum LBSA and DHEAS in the PCOS group, whereas a significant correlation appeared between LBSA and FSH. We could not compare our results because we could not find similar data in the literature. Correlations in the PCOS group may be incidental and we think that this can be explained in further detailed studies, including a larger number of subjects.

The weakness in our study is the statistical difference between PCOS and normoovulatory controls. Higher BMI levels in PCOS patients may have affected their results. Further studies between BMI matched groups may clarify the correlations.

In conclusion, we found that serum LBSA levels were higher in patients with PCOS, but more detailed studies are necessary to investigate serum TSA and LBSA levels as risk factors for CVD and DM, and their relations with other hormonal and biochemical parameters in patients with PCOS.

Conflict of interest

No conflict of interest was declared by the authors.

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Trends in fetal indications for termination of pregnancy between 2002 and 2010 at a tertiary referral centre

Üçüncü basamak referans merkezinde 2002-2010 yılları arasında gebelik terminasyonuna yol açan fetal endikasyonların değişimi

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Abstract

Objective: We reviewed the data of the termination of pregnancy (TOP) cases between 2002 and 2010 to evaluate the changes in fetal indications for both early and late TOPs in this period.

Material and Methods: The data of 962 TOP cases were analysed in two groups according to the periods as in 2002-2006 and 2007-2010. The women were also subdivided into two categories according to their gestational age; <23 weeks' gestation (early termination) and ≥23 weeks' gestation (late termination).

Results: Four hundred and fifty-eight (47.6%) of TOPs were performed between 2002 and 2006 (Group 1) and 504 (52.3%) were performed between 2007 and 2010 (Group 2). The number of early (<23 weeks) and late (≥23 weeks) terminations were 583 (60.6%) and 379 (39.3%), respectively. The vast majority of anomalies were central nervous system malformations (51.8%). They were followed by multiple anomalies (10.2%) and chromosomal anomalies (9.4%). Chromosomal and cardiovascular system anomalies were significantly higher in 2007-2010 in comparison to 2002-2006 ($p<0.0001$ and $p=0.002$, respectively). There was no statistically significant difference between the fetal indications that led to early termination compared to those that led to late termination.

Conclusion: The distribution of indications for TOP was influenced by the development in prenatal screening policy, resulting in a significant increase in terminations due to chromosomal and cardiovascular system anomalies. Cultural, educational, religious and legal factors cause differences in the indications for TOP as well as the gestational age that TOPS are performed.

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Key words: Termination of pregnancy, fetal anomaly, chromosomal anomaly, ultrasound, prenatal screening

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Özet

Amaç: 2002-2010 yılları arasında gerçekleşmiş olan gebelik terminasyonlarına ait verilerin geriye dönük incelenmesi ile bu dönemdeki erken ve geç terminasyonların fetal endikasyonlarında görülen değişimi değerlendirmek.

Gereç ve Yöntemler: Dokuzyüz altmış iki terminasyon olgusuna ait veriler 2002-2006 ve 2007-2010 olmak üzere iki ayrı dönemde incelendi. Olgular ayrıca gebelik haftalarına göre iki alt gruba ayrıldı; <23 hafta (erken terminasyon) ve ≥23 hafta (geç terminasyon).

Bulgular: Terminasyonların 458'i (%47.6) 2002 ve 2006 yılları arasında (Grup 1) ve 504'ü (%52.3) 2007 ve 2010 yılları arasında (Grup 2) yapıldı. Erken (<23 hafta) ve geç (≥23 hafta) terminasyonların sayısı sırasıyla 585 (%60.6) ve 379 (%39.3) idi. Anomalilerin büyük çoğunluğunu santral sinir sistemi malformasyonları oluşturuyordu (%51.8). Bunu çoklu anomaliler (%10.2) ve kromozom anomalileri (%9.4) izliyordu. Kromozom ve kardiyovaskuler sistem anomalileri 2007-2010 yıllarında 2002-2006 yıllarına kıyasla anlamlı şekilde artış gösterdi (sırasıyla $p<0.0001$ and $p=0.002$). Erken terminasyon ve geç terminasyona neden olan fetal endikasyonlar arasında istatistiksel olarak anlamlı bir fark saptanmadı.

Sonuç: Terminasyon endikasyonlarının dağılımı prenatal tarama politikalarındaki gelişimden etkilenmiş, buna bağlı olarak kromozom ve kardiyovaskuler sistem anomalileri nedeniyle yapılan terminasyonların sayısı önemli ölçüde artmıştır. Kültürel, eğitimsel, dini ve yasal faktörler terminasyon yapıldığı gebelik haftasının yanı sıra terminasyon endikasyonlarında da değişikliklere yol açmaktadır.

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Anahtar kelimeler: Gebelik terminasyonu, fetal anomali, koromozom anomalisi, ultrason, prenatal tarama

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Introduction

As a consequence of advances in medical technology and the development of universal prenatal screening policies, increasingly more anomalies are being detected at an early stage of pregnancy, and this results in an increased rate of the termination of pregnancy (TOP). In the case of severe or lethal anomalies, some future parents prefer to interrupt the pregnancy. Several factors such as gestational age, involvement of the central nervous system, severity of anomaly, and presence of chromosomal abnormalities affect the decision of TOP (1).

The laws on performing TOP vary between countries, and may specify: 1) no upper gestational age limit for any TOP, 2)

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no upper gestational age limit for lethal anomalies, 3) an upper gestational age limit for any TOP, 4) no TOP at any gestational age (2). Since 1983, Turkish law has permitted the TOP at any period of gestation if the ongoing pregnancy is hazardous for a woman's health and/or fetus has a high risk of severe disability or incurable fatal disease (3). Approval for the TOP can be given by two specialists when there is a maternal or fetal reason justifying the TOP.

In the present paper, we aimed to review the TOP cases between 2002 and 2010 in our clinic, in order to seek the alterations in fetal indications of both early and late terminations within the last nine years.

Material and Method

We analysed the data of TOP cases in the Department of Maternal Fetal Medicine between January 2002 and December 2010. Our hospital serves as a tertiary referral center and there were 162,000 deliveries during the study period. A total of 962 women underwent TOP because of fetal anomalies. Ultrasonographic examinations were carried out by four specialists using a Voluson 730 Expert (GE Healthcare). First trimester Down syndrome screening test or triple test (if patient came to our clinic after 14th weeks) were offered to all women.

When the diagnostic work-up was completed, the couple was counseled by a multidisciplinary medical team that consisted of obstetricians, neonatologists, pediatriac surgeons and the other pediatric specialists, where the prognosis and treatment options were discussed. In the presence of lethal or severely disabling anomalies, if future parents required the TOP, induction of labor with misoprostol was started. For the pregnancies before 24th week, 200 μg misoprostol was administered vaginally every four hours for 48 hours. For those who had a uterine scar or pregnancies beyond 24 weeks, the dose wes reduced by half. Misoprostol administration was discontinued and oxytocin infusion was started whenever the Bishop's Score was ≥6 regardless of when the last dose of misoprostol was administered. We started the infusion with 5 U of oxytocin in 500 ml Ringer's Lactate or saline at 8 drops per minute with an increment of 4 drops every 15 minutes up to a maximal dose of 32 drops per minute. If cervical dilatation was not obtained within 48 hours, %0.1 Rivanol solution (20 ml per gestational week) was instilled extra-amniotically using a transcervical Foley catheter which was introduced under sterile conditions. Hysterotomy was performed on the patients with a uterine scar in the third trimester or in whom extra-amniotic Rivanol instillation was not sufficient for inducing labor. Additionally, from 24 weeks onward, fetocide was performed by injecting potassium chloride to the fetal heart. All patients were offered autopsy after the termination.

Medical and demographic characteristics of all cases were recorded. The data was analysed in two groups according to the period, as in 2002-2006 and 2007-2010. Also, the women were subdivided into two categories according to their gestational age; <23 weeks gestation (early termination) and ≥23 weeks gestation (late termination). This study was approved by the Institutional Ethics Committee.

Calculations were performed using SPSS software (Version 11, Chicago, IL, USA). Descriptive parameters are expressed as mean±SD. In order to compare the variables, x^2, Fisher exact test and student's t test were applied. P values of <0.05 were considered as statistifically significant.

Results

A total of 962 TOPs due to fetal anomalies in single pregnancies were locally performed over the nine-year period. In 891 cases, misoprostol succesfully induced labor. In 20 cases, oxytocin infusion was started without misoprostol administration, as the cervix was already 2 cm dilated. Extra-amniotic rivanol instillation was performed on 45 cases due to the failure of induction using misoprostol. Of these cases, 20 were before 23 weeks of gestation and 25 were beyond 23 weeks. Six patients at the third trimester of gestation underwent hysterotomy due to a previous cesarean scar of uterus. Fetocide was performed on 344 cases with no major complications.

The demographic and obstetric characteristics of the women are summarized in Table 1. 458 (47.6%) of TOPs were performed between 2002 and 2006 (Group 1) and 504 (52.3%) of them were performed between 2007 and 2010 (Group 2). The number of early (<23 weeks) and late (≥23 weeks) terminations were 583 (60.6%) and 379 (39.3%), respectively. The mean maternal age was 26.7±5.5 years in Group 1 and 27.7±6 years in Group 2. The interruptions of pregnancy were performed at a mean gestational age of 22.4±5.4 and 22.2±5.4 weeks in

Table 1. Demographic and obstetric characteristics of the women studied by period

	Group 1 (2002-2006)	Group 2 (2007-2010)	p
The number of TOP	458 (47.6)	504 (52.3)	-
Maternal age, year	26.7±5.5	27.7±6	0.01
Parity, median (range)	1 (0-10)	1 (0-9)	>0.05
Gestational age at TOP, weeks	22.4±5.4	22.2±5.4	>0.05
Prenatal karyotype, n (%)	73 (15.9)	161 (31.9)	<0.0001
TOP < 23 weeks, n (%)	277 (60.4)	306 (60.7)	0.23
TOP ≥ 23 weeks, n (%)	181 (39.5)	198 (39.2)	0.38

TOP: Termination of pregnancy

Group 1 and 2, respectively. Prenatal karyotype analysis were performed more frequently in Group 2 with a rate of 31.9% (161), while only 73 (15.9%) cases underwent karyotype analysis between 2002 and 2006 ($p<0.0001$). None of the parameters were statistically significantly different between the two groups except for the prenatal karyotype analysis.

All of the anomalies which led to the TOP were subdivided according to the affected system and they are listed in Table 2. The vast majority of anomalies were central nervous sytem malformations (51.8%). They were followed by multiple anomalies (10.2%) and chromosomal anomalies (9.4%). Chromosomal and cardiovascular system anomalies were significantly higher in 2007-2010 in comparison to 2002-2006 ($p<0.0001$ and $p=0.002$, respectively). There were no significant differences between the other system anomalies when they were compared according to the period of time.

The distribution of fetal anomalies according to the gestational age during TOP is demonstrated in Table 3. Central nervous system anomalies, especially spina bifida and anencephaly, were the leading causes of both early and late terminations during the nine-year period. Among the TOPs between 2002 and 2006, multiple anomalies came second both in the early and late termination groups with 9.3% and 9.9%, respectively. Chromosomal anomalies were the second most common cause of the TOP at all gestational ages between 2007 and 2010 (13.6% in early, 13.2% in late termination). Among the chromosomal anomalies, trisomy 21 was the most common type. There was no statistically significant difference between the fetal indications that led to early termination compared to those that led to late termination in the total cohort.

In 143 (14.6%) cases, a postmortem examination was performed. When we compared the prenatal and postmortem findings, we found complete agreement in 114 cases (79.7%), and major agreement with additional findings in 29 cases (20.3%). There was no significant disagreement in any of the cases.

Discussion

The prenatal diagnosis may result from routine screening by ultrasound and biochemical markers or from a specific parental request, for instance owing to a family history leading to genetic testing (4). The prevalence of chromosomally abnormal fetuses is reported to be 0.31% and that of chromosomally normal fetuses with major and minor malformations are 1.8% and 1.32%, respectively (5). In countries with a routine ultrasound screening policy, more than half of all congenital anomalies are diagnosed prenatally, including 74% major and 46% minor abnormalities (6). Romosan et al. (5), found that the detection rate of major malformations in chromosomally normal fetuses were 68% with a detection rate of 37% at <22 weeks, and the corresponding detection rates of chromosomally abnormal fetuses were 46% and 33%. These rates change according to the nature of the anomaly, as it is highest for malformations in the central nervous and genito-urinary systems, and lowest for malformations of skeletal and circulatory systems (5, 6).

In the present study, we analysed the alterations in fetal indications for TOP during the period between 2002 and 2010. For this, we divided the cohort into two groups according to years. Although the number of terminations in our clinic increased progressively, the number of TOPs due to central nervous system anomalies, especially anencephaly, were lower during the period between 2007 and 2010 (270/458 vs. 228/504). This might be a result of the increased use of pregestational and early gestational folic acid. Also, we found a significant rise in the cardiovascular system anomalies leading to the TOP within the last four years, which reflects the rise in the diagnosis of these anomalies in the pregnant population. The reason for this rise may be the growing use of echocardiogram as a complementary scan, as well as the increasing experience of fetal heart screening among the obstetricians in Turkey.

In our series, the most common chromosomal anomaly was trisomy 21, which was consistent with the other studies (4, 7, 8). The proportion of chromosomal anomalies leading to TOP has

Table 2. Fetal indications for termination of pregnancy by period

	Group 1 (2002-2006)	Group 2 (2007-2010)	Total	p
Central nervous system, n (%)	270 (59)	228 (45.2)	498 (51.8)	0.06
Multiple anomalies, n (%)	44 (9.6)	54 (10.7)	98 (10.2)	0.3
Chromosomal anomalies, n (%)	26 (5.7)	64 (12.7)	90 (9.4)	<0.0001
Genitourinary system n (%)	40 (8.7)	43 (8.5)	83 (8.6)	0.7
Musculosekeletal system, n (%)	30 (6.6)	39 (7.7)	69 (7.2)	0.3
Cardiovascular system, n (%)	8 (1.7)	26 (5.2)	34 (3.5)	0.002
Pulmonary system, n (%)	3 (0.7)	10 (2)	13 (1.4)	0.052
Gastrointestinal system, n (%)	7 (1.5)	6 (1.2)	13 (1.4)	0.8
Genetic diseases, n (%)	11 (2.4)	4 (0.8)	15 (1.6)	0.07
Face and neck, n (%)	7 (1.5)	7 (1.4)	14 (1.5)	1
Other, n (%)	12 (2.6)	23 (4.6)	35 (3.6)	0.06
Total, n (%)	458 (100)	504 (100)	962 (100)	-

Table 3. Fetal indications for termination of pregnancy by gestational age

		Group 1 (2002-2006) n (%)		Group 2 (2007-2010) n (%)		Total n (%)		
		<23 wk	≥23 wk	<23 wk	≥23 wk	<23 wk	≥23 wk	p
Central nervous system	Spina bifida	49	50	63	40	99	103	
	Anencephalus	77	20	33	13	97	46	
	Hydrocephalus	4	7	12	10	11	23	
	DWM	3	5	2	8	8	10	
	ACC	2	4	1	0	6	1	
	Holoprosencephalus	5	6	5	1	11	6	
	Encephalocele	11	6	18	4	17	22	
	Iniencephaly	6	1	2	0	7	2	
	Other	6	8	8	7	14	15	
	Total	163 (58.8)	107 (59.1)	145 (47.3)	83 (41.9)	270 (58.9)	228 (45.2)	0.46
Chromosomal anomalies	Trisomy 21	13	7	23	13	20	29	
	Trisomy 18	0	0	3	5	0	8	
	Trisomy 13	0	0	0	0	0	1	
	Turner	2	1	8	2	3	10	
	Triploidy	1	0	0	1	1	1	
	Other	0	2	3	6	2	9	
	Total	16 (5.9)	10 (5.5)	37 (13.6)	27 (13.2)	26 (5.6)	64 (12.6)	0.74
Genitourinary system	Renal agenesis	10	6	10	6	16	16	
	MCDK	7	2	10	3	9	14	
	PCKD	4	6	2	2	10	4	
	Hyronephrosis	1	1	1	1	2	2	
	Cloaca anomaly	0	0	1	1	0	2	
	Other	3	0	5	0	3	5	
	Total	25 (9)	15 (8.2)	30 (9.8)	13 (6.5)	40 (8.7)	43 (8.5)	0.48
Musculoskeletal system	Lethal skeletal dysplasia	9	8	15	11	17	26	
	Osteogenesis imperfecta	3	0	0	1	3	1	
	Hypophosphatasia	1	1	1	0	2	1	
	Kyphoscolisosis	2	1	1	0	3	1	
	FAS	0	1	1	2	1	3	
	Other	0	4	3	4	4	7	
	Total	15 (5.4)	15 (8.2)	21 (6.8)	18 (9)	30 (6.5)	39 (7.7)	0.75
Cardiovascular system	HLHS	0	3	0	7	3	7	
	Ectopia cordis	1	0	0	0	1	0	
	TOF	1	0	2	1	1	3	
	DORV	0	0	1	0	0	1	
	Complex anomalies	0	0	1	4	0	5	
	Other	1	2	4	6	3	10	
	Total	3 (1)	5 (2.6)	8 (2.6)	18 (8.3)	8 (1.7)	26 (4.9)	0.52

Pulmonary system	CCAM	1	0	2	1	1	3	
	Laryngeal atresia	1	0	1	0	1	1	
	Diaphragmatic hernia	0	0	1	1	0	2	
	Hydrothorax	0	1	1	2	1	3	
	Other	0	0	1	0	0	1	
	Total	2 (0.7)	1 (0.5)	6 (1.9)	4 (1.9)	3 (0.6)	10 (1.9)	0.69
Gastrointestinal system	Omphalocele	3	1	2	1	4	3	
	Gastrochisis	0	0	1	0	0	1	
	Duedonal atresia	0	1	0	1	1	1	
	Esophageal atresia	0	1	0	1	1	1	
	Other	0	1	0	0	1	0	
	Total	3 (1)	4 (2.2)	3 (0.9)	3 (1.5)	7 (1.5)	6 (1.1)	0.62
Genetic diseases	SMA	5	0	2	0	5	2	
	Cystic fibrosis	0	0	1	0	0	0	
	Thalassemia major	1	2	1	0	1	1	
	Other	3	2	0	0	5	1	
	Total	9 (3.2)	2 (1.1)	4 (1.3)	0 (0)	11 (2.4)	4 (0.7)	0.52
Face and neck	Cystic higroma	6	0	7	0	6	7	
	Severe cleft lip and palate	1	0	0	0	1	0	
	Total	7 (2.5)	0 (0)	7 (2.2)	0 (0)	7 (1.5)	7 (1.3)	-
Multiple anomalies		26 (9.3)	18 (9.9)	33 (10.7)	21 (10.6)	44 (9.6)	54 (10.7)	0.84
Other	Hydrops	8	4	10	10	12	20	
	Amniotic band	0	0	2	1	0	3	
	Total	8 (2.8)	4 (2.2)	12 (3.9)	11 (5.5)	12 (2.6)	23 (4.5)	0.41
Total		277 (100)	181 (100)	306 (100)	198 (100)	458 (100)	504 (100)	

Wk: weeks, DWM: Dandy-Walker mlformation, ACC: agenesis of corpus callosum, MCDK: multicystic dysplastic kidney, PCKD: policystic kidney disease, FAS: fetal-akinesia sequence, HLHS: hypoplastic left heart syndrome, TOF: tetralogy of Fallot, DORV: double outlet right ventricle, CCAM: congenital cystic adenomatoid malformation, SMA: spinal muscular atrophy

increased dramatically from 5.7% to 12.7% within the last four years. This might be a consequence of the increased number of women that undergo chromosomal screening tests in Turkey. Furthermore, more people accept karyotype analysis and the termination of the pregnancy with a chromosomal anomaly. In spite of the improvement in screening and detection of chromosomal anomalies in Turkey, the overall proportion of TOP due to chromosomal anomalies in our study (9.4%) was still lower than that in the previous studies (30-39%) (4, 7, 8). The reason for this low rate might be the religious and cultural factors which lead fewer couples to accept karyotype analysis or termination in comparison to the couples in Western countries. Moreover, Turkish people are more prone to terminate pregnancies because of the malformations that affect the external appearance (for instance the defects in face or extremities) rather than isolated chromosomal anomalies.

Wyldes et al. (9), in their study within the period between 1995 and 2004, showed that a significantly increasing proportion of cases occurred before 16 weeks (12.2% in 1995 vs 27.9% 2004, $p<0.00001$). Nuchal translucency (NT) measurement for the screening of Down syndrome increases the possibility to detect certain types of fetal malformations, such as acrania, at the end of the first trimester. The detection rate of structural abnormalities at 11-14 gestational weeks varies between 18% and 65% in the literature (10). Early detection of anomalies is very important, since it allows the termination process to be at an earlier stage of gestation when the psychological burden and physical morbidity due to the TOP is less severe. In our series, there was no significant difference in the mean of the gestational age between 2002-2006 and 2007-2010. Although the rate of TOP beyond 24 weeks gestation is 8.4% in UK and 6.6% in Europe, the rate of late termination was as high as 39.3% in our population (2, 9). The main reason for this high rate is that the laws permit the TOP at any gestational age in Turkey. Termination after fetocide is legally performed even in the last months of pregnancy in the presence of severe fetal malformation, leading pregnant women to act slowly and waste time making the decision regarding TOP. Women who are hesitant regarding the TOP, especially,

make a decision many weeks after the diagnosis. Moreover, ultrasonography is performed routinely in the third trimester in Turkey, enabling the detection of late-onset malformations at later stages of gestation. Finally, our unit is a tertiary center where patients are referred after several steps of examination in other hospitals. This might be another reason for the delay in the termination process.

In a study which compares the indications of terminations before and after 20 weeks, it was found that, while TOPs for karyotype anomalies were more common in early gestation, those for cardiac anomalies were more frequent after 20 weeeks gestation (11). As prenatal screening strategies are designed to detect fetal karyotype anomalies in the first and early second trimester, they are more frequently diagnosed prior to 20 weeks' gestation. Likewise, Garne et al. (2) reported that late TOP was more often performed for a nonchromosomal isolated major structural anomaly and less often for a fetus with a chromosomal syndrome or multiple anomalies. In our study, there were no statistically significant differences between early and late terminations for the indications of TOP. Central nervous system anomalies accounted for more than half of the indications for both early and late terminations. This finding is consistent with the studies which showed that central nervous system malformations are the most common structural malformations leading to the TOP (4, 7, 8, 12, 13).

Fetal autopsy has a particularly valuable role in the counseling of families after the TOP (14). Especially when prenatal diagnosis is based on the results of ultrasound scan only, autopsy may provide important information that changes the estimated risk of recurrence (13). Boyd et al. (13) reported that, in 27% of cases, information from the autopsy examination led to a refinement of the risk of recurrence, and in 8% this was increased to a one in four risk. Several studies have reported a progressive decline in the autopsy rates (15). The reason for this decrease has been speculated to be the physician and parental belief in the diagnostic capability of ultrasound and adjunctive testing modalities, as well as the obligation to obtain an autopsy consent (15). In our series, only 14.6% of the parents accepted a postmortem examination. We believe that this is mostly because of the religious and cultural considerations in the Turkish population, as well as the inadequate comprehension of the need and benefits of autopsy.

In conclusion, the distribution of indications for the TOP was influenced by the development in prenatal screening policy resulting in a significant increase in terminations due to chromosomal and cardiovascular system anomalies. Cultural, educational, religious and legal factors cause differences in the indications for TOP as well as the gestational age that TOPS are performed.

Conflict of interest

No conflict of interest was declared by the authors.

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The effects of GnRH analogs on serum and follicular fluid leptin levels and pregnancy outcomes in short protocols of assisted reproductive technology

Yardımcı üreme tekniklerinde kısa protokol uygulamalarında GnRH analoglarının serum ve foliküler leptin seviyeleri ve gebelik sonuçları üzerine etkileri

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Abstract

Objective: To determine serum and follicular leptin levels in patients using gonadotropin releasing hormone agonist and antagonist in Assisted Reproductive Technology short protocol cycles and to evaluate pregnancy outcomes.

Material and Methods: Patients randomly selected to join assisted reproductive technology cycles during February 2004-July 2004 were enrolled in this study. Group 1 consisted of 21 patients receiving r FSH+ GnRH agonists, whereas Group 2 consisted of 34 patients who received r FSH +GnRH antagonists. During the ovulation induction period 5 serum samples were collected (induction day 1, day 3 or antagonist starting day, human chorionic hormone day, oocyte pickup day, and twelfth day of embryo transfer). Follicular fluid samples were collected to be evaluated for leptin, estradiol, prolactin and luteinizing hormone.

Results: There was no difference in age, basal FSH, basal LH, and basal E2 between groups. Serum leptin levels were similar in both groups. Also, when each group's serum leptin levels were evaluated according to the presence of pregnancy, there was no significant difference in both groups. When follicle leptin levels were evaluated according to the existence of pregnancy, in both groups the follicle leptin levels were lower in pregnant participants but this difference was not statistically significant. When obesity is defined as body mass index over 26.5, there is a correlation between obesity and leptin levels in Group 2.

Conclusion: Our results have shown that both agonists and antagonists have similar efficacy and effect in poor responder women. Leptin levels in either groups, whether pregnant or non-pregnant were not statistically different. This result shows the need for more studies on leptin in infertility.

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Key words: GnRH agonist, GnRH antagonist, ART, leptin, prolactin

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Özet

Amaç: Yardımcı Üreme Teknikleri (YÜT) ile kısa protokol uygulanan sikluslarda gonadotropin salgılatıcı hormon (GnRH) agonist ve antagonist uygulanan olgularda serum ve foliküler leptin seviyelerinin belirlenmesi ve gebelik sonuçlarının değerlendirilmesidir.

Gereç ve Yöntemler: Çalışmaya dahil edilen hastalar random olarak Şubat 2004-Temmuz 2004 tarihleri arasında yardımcı üreme teknik siklusları uygulanan olgular arasından seçildi. Grup 1 rekombinant FSH+ GnRH agonist uygulanan 21 hastayı içerirken Grup 2 rekombinant FSH +GnRH antagonist uygulanan 34 hastayı içermekte idi. Ovulasyon indüksiyonu sürecinde 5 serum örneği alındı (indüksiyonun 1. günü, 3. günü veya antagonist başlandığı gün, insan koryonik hormon uygulama günü, oosit aspirasyon günü ve embryo transferi sonrası 12. gün). Foliküler sıvı örnekleri leptin, östradiol, prolaktin and luteinize edici hormon değerlendirilmesi amacı ile alındı.

Bulgular: Gruplar arasında yaş, bazal FSH, bazal LH ve bazal E2 açısından fark izlenmedi. Serum leptin düzeyleri her iki grupta benzer idi. Ayrıca her grupta gebelik varlığına göre serum leptin seviyeleri değerlendirildiğinde gruplar arasında fark izlenmedi. Folikül leptin seviyeleri gebelik mevcudiyetine göre değerlendirildiğinde her iki grupta da folikül leptin seviyeleri gebe olgularda daha düşük olmasına rağmen bu fark istatistiksel olarak anlamlı değildi. Obesite vücut kitle indeks değerinin 26.5 üzerinde olması olarak tanımlandığında Grup 2'de leptin seviyeleri ile obesite arasında korelasyon mevcut idi.

Sonuç: Sonuçlarımız düşük cevaplı olgularda hem agonistlerin hem de antagonistlerin benzer etkinlik ve etkiye sahip olduğunu göstermiştir. Her iki grupta da leptin seviyeleri gebe olanlarda veya olmayanlarda istatistiksel olarak farklı izlenmedi. Bu sonuçlar leptinin infetilitedeki yeri ile ilgili daha fazla çalışmaya ihtiyaç olduğunu göstermektedir.

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Anahtar kelimeler: GnRH agonisti, GnRH antagonisti, YÜT, leptin, prolaktin

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Introduction

Leptin, a 167-amino-acid product of the human leptin gene, is primarily expressed in adipose tissue, but it is also found in many other tissues, including the placenta, mammary gland, testes, ovary, endometrium, stomach, hypothalamus, pituitary, and others (1). It was first found through positional cloning of ob./ob. mice at the Jackson Laboratories (2). These mice had a homozygous mutation of the leptin gene. This mutation results in clinical hyperphagia, extreme obesity, dia-

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betes, neuroendocrine abnormalities, and infertility because of the incomplete leptin deficiency.

Leptin mainly plays a role in the regulation of body weight and energy homeostasis by signaling the amount of energy stores. In addition, leptin also plays a key role in human reproduction especially the hypothalamic leptin receptors that modulate the secretion of gonadotropin-releasing hormone (GnRH). Moreover some researchers suggested that leptin also has a direct role in the ovary and endometrium as well as the central actions. Leptin and its receptors were also shown to be synthesized by the granulosa cells in the ovary. The same leptin may inhibit FSH induced estradiol synthesis in granulosa cells (3-5).

The effects of leptin are mediated by receptors which are encoded by the LEPR gene found in 1q31 chromosome and belong to the gp130 family of receptors. Five leptin receptors have been described (Ob-Ra, Ob-Rb, Ob-Rc, Ob-Rd, Ob-Re). Ob-Rb is considered to be the main functional receptor expressed in the hypothalamus and in other sites as well (6). Leptin is secreted in a pulsatile fashion and has a significant diurnal variation, with higher levels in the evening and early morning hours. With higher levels during the luteal phase, it shows a considerable variation throughout the human menstrual cycle (7, 8).

Overall, leptin may have both direct and indirect effects on follicular growth and oocyte development as well as implantation. Although serum or follicular fluid (FF) leptin levels and its effects on pregnancy outcome has been studied by many authors, there are few studies that have compared pregnancy results of both agonist and antagonist treatment protocols through leptin levels. In this study we aimed to investigate the association between both serum and follicular fluid leptin levels and pregnancy outcomes in patients who were treated by a short protocol with GnRH agonist and antagonist in ARTcycles.

Methods

The study was carried out in the University Family Planning and Infertility Research and Treatment Center. The study protocol was approved by the Local Ethics Committee. Fifty-five women aged 20-40 years were enrolled in the study after giving their informed consent. Duration of infertility ranged between 6 months to 20 years. Inclusion criteria of infertility were male factor, tubal factor and idiopathic factor. Exclusion criteria were diagnosis of polycystic ovarian syndrome, any other medical illness and patients' desire to resign Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. For all patients, transvaginal sonography was performed in order to exclude ovarian and uterine pathologies.

Ovulation induction protocols

Group 1 (n=21) consisted of patients who were treated by GnRH agonists and gonadotropins as a short protocol. Ovarian stimulation was initiated on the 2nd menstrual day by administration of recombinant FSH (Gonal F, Serono International SA, Geneva, Switzerland- Puregon, Organon International, U.S.A.) and 0.1 mg GnRH analog (Decapeptyl, Ferring GmbhH Kiel, Germany). The dosage of recombinant FSH was adjusted according to the patients' individual requirements (age, basal FSH) and serum estradiol levels at day 3 of induction. Ovarian stimulation was monitored by sequential transvaginal ultrasonography and serum estradiol measurements in order to assess follicular development. Finally, human chorionic gonadotropin (hCG) 10.000 IU (Profasi HP 10000 Serono International S.p.A. Italy) was given subcutaneously when a consistent rise in serum estradiol concentrations was associated with the presence of two or more follicles of more than 18 mm diameter. Oocyte aspiration was performed by transvaginal ultrasonography 35-36 h after hCG injection.

Group 2 (n=34) consisted of participants who were treated with GnRH antagonist and gonadotropins. In group 2, ovulation inductions began on the second menstrual day by recombinant FSH (Gonal F, Serono International SA, Geneva, Switzerland-Puregon, Organon International, U.S.A.). The dosage of recombinant FSH was adjusted according to the patients' individual requirements (age, basal FSH) and serum estradiol levels on day 3 of induction. Ovarian stimulation was monitored by sequential transvaginal ultrasonography and when a 14 mm sized follicle was detected, daily administration of 0.25 μg GnRH antagonist (Cetrotide, Serano International SA, Geneva, Switzerland) was added to the treatment until the subcutaneous hCG injection. Criteria of hCG injection were the same as in Group 1.

Fertilization was achieved by intracytoplasmic sperm injection (ICSI) in both groups. Fertilization checks were performed 16-20 hours after ICSI. High quality embryos were transferred on the second or third day of ICSI after endometrial thickness measurements. For luteal phase support, 800 mg micronized transvaginal progesterone (Crinone gel, Serono International SA,Geneva, Switzerland) was administered once a day. Additionally, 2000 IU HCG was injected on transfer +1,+ 4, +7, and + 9. days.

Ovarian hyperstimulation was defined as the presence of simultaneous multifollicular development and estradiol levels over 2500 pg/ml.

Diagnosis of pregnancy was confirmed on embryo transfer (ET)+14 days, with hCG levels over 50 IU/l.

In both groups whole gonadotropin doses, duration of induction, number of aspirated oocytes, MI, PI, MII, fertilized oocytes and transferred embryos were recorded.

Serum Samples

Throughout the induction period, 5 separate blood and one FF sample were withdrawn in each group in the morning hours. In group 1 samples were taken: 1- first day of induction (FSH, LH, E2, prolactin, leptin) 2- third day of induction (E2, prolactin, leptin) 3- day of hCG administration (E2, LH, prolactin, leptin) 4- day of oocyte aspiration [serum (E2, prolactin, leptin), and FF (prolactin, leptin)] 5-12th day of embryo transfer (E2, HCG, prolactin, progesterone, leptin). In group 2, samples were taken as group 1 apart from the second sample. The second sample was withdrawn at the beginning of antagonist administration. All blood samples were centrifuged at 2000 xg for 10 minutes at room temperature and thesupernatant was stored at -80°C until examination. Analyses of estradiol, FSH, LH, prolactin, progester-

one and HCG were performed by ACS: 180® (Bayer HealthCare) automated chemiluminescence systems. Leptin was examined by immunoenzymometric assays (Biosource Europe S.A., Ninelles Belgium) in both serum and FF. Sensivity for leptin was 0.1 ng/ml and intraassay CV was 3.6% of 14.8 ng/ml.

Statistical analyses

Statistical package for social sciences (SPSS) 10.0 was used for evaluation of the statistical analysis. Data was presented as means±SD. ANOVA was used for continuous variables and Bonferroni as a post-hoc test where applicable. If data was not distributed normally the Mann Whitney U test was used. The Chi-square test was used for classified variables and Fisher exact test where needed. $p<0.05$ was considered as significant.

Results

There was no significant difference between group 1 (n=21) and group 2 (n=34) for age, weight, length, BMI, length of infertility, gonadotropin dosage, length of induction period, number of fertilized oocyte, transferred embryo and endometrial thickness (Table 1). Etiological classification of both groups was similar (Table 2). The number of aspirated oocytes was significantly greater in group 1 ($p<0.02$), but the pregnancy rate of each group was similar. When pregnants were compared with nonpregnants in both groups, the number of transferred embryos was significantly higher in pregnants (Table 3).

Basal hormonal parameters had similar values in both groups but in the hCG injection period LH values were significantly lower in group 2. Similar serum leptin levels were detected in both groups. When each group's serum leptin levels were evaluated according to the presence of pregnancy, there was also no significant difference in both groups (Figure 1a, b). In each group, leptin levels were different for each sample. In the period of hCG injection, levels of leptin in FF were significantly higher than serum in both groups. When FF leptin levels were evaluated according to the existence of pregnancy, in both groups FF leptin levels were lower in pregnant participants, but this difference was not statistically significant. Serum leptin levels also did not show correlation between serum estradiol and prolactin levels in both groups. Howev, when obesity was defined as BMI over 26.5, there was a correlation between obesity and leptin levels in Group 2.

Estradiol levels were significantly lower in the period of hCG injection and oocyte aspiration in group 2 compared to group 1. When estradiol levels were compared among pregnant women,

Table 1. Demographic data and treatment details of groups are listed

	Group	Mean values	Standart deviation	p value
Age	1	32.9	3,6	0.158
	2	34.3	3,1	
Weight (kg)	1	62.8	9,9	0.315
	2	66.2	11,5	
Height (cm)	1	161.4	5,7	0.992
	2	161.4	5,1	
BMI	1	24.0	3,5	0.382
	2	25.2	4,3	
Infertility duration	1	7.3	5,3	0.646
	2	8.2	5.6	
Gonadotrophin dose (U)	1	3178.5	956.6	0.573
	2	3327.9	928.6	
Gonadotrophin duration	1	8.7	1.4	0.056
	2	8.0	0.9	
Aspirated oocyte	1	11.2	6.5	0.020*
	2	7.4	5.7	
Fertilization	1	4.9	2.8	0.259
	2	4.3	3.4	
Transferred embryo	1	2.6	0.7	0.278
	2	2.3	0.9	
Endometrial thickness	1	11.1	2.3	0.391
	2	10.8	1.8	

BMI: Body mass index, *: $p<0.05$ (Mann Whitney U-test)

there was a significant difference and levels began to rise after oocyte aspiration in the pregnant participants in both groups (Figure 2a, b).

Prolactin levels in FF were detected significantly lower in group 2 than group 1 (28.9 ng/ml versus 45.5 ng/ml, $p<0.05$). When prolactin levels were evaluated through pregnancy, pregnant participants had lower levels than non pregnants in both groups, but this difference was not significant (Table 4).

When each group was evaluated for pregnancy outcomes there was no significant difference between the groups (Table 1).

Table 2. Distribution of infertility etiologies between groups

Etiology	Group 1 (n=21)		Group 2 (n=34)	
	%	n	%	n
Male factor	52.4	11	58.8	20
Tubal factor	33.3	7	20.6	7
Undefined	14.3	3	20.6	7

Table 3. Pregnancy number and rate of each group

	Pregnant	Non pregnant	Total
Group 1	7 (33%)	14 (66%)	21 (38.1%)
Group 2	17 (50%)	17 (50%)	34 (61.9%)
Total	24 (43.6%)	31 (56.4%)	55 (100%)

Discussion

In our study, we evaluated the effects of GnRH analogs to serum and FF leptin levels and pregnancy outcomes in short protocols of ART. The aim of treatment with GnRH analogs is mainly to prevent early LH increase. At the same time, it has beneficial effects in follicle synchronization (9, 10). Antagonists are generally part of short protocols, whereas agonists are generally combined with long protocols of controlled ovarian stimulation. When antagonists with short protocols are compared to an agonist with long protocols, antagonists express the advantage of low dose gonadotropin use, more precise and simple stimulation and lower incidence of hyperstimulation (11). Agonist supplementation to the short protocols provides ovarian stimulation in low responder patients without suppression effects,

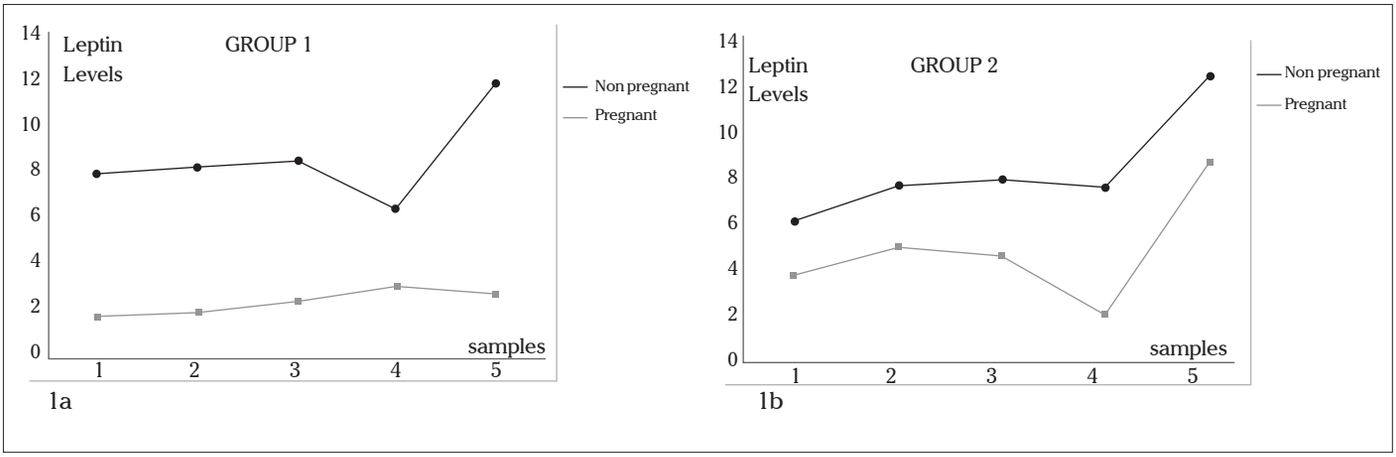

Figure 1a, b. When serum leptin levels of each group were evaluated according to the presence of pregnancy, there was no significant difference in both groups

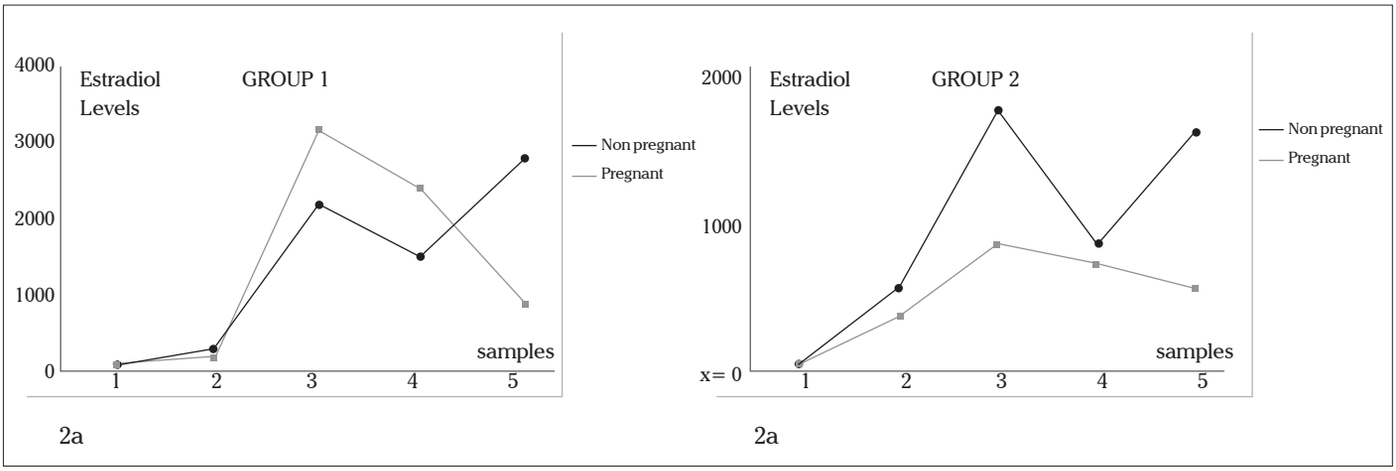

Figure 2a, b. When estradiol levels were compared among pregnant women, there was a significant difference and levels began to rise after oocyte aspiration in the pregnant participants in both groups

Table 4. The relationship of pregnancy and number of transferred embryo and FF prolactin levels

	Pregnancy	Mean number of transfered embryo	p value	Follicular fluid prolactin	p value
Group 1	Negative	2.3±0.7	0.016*	48.3±20.8	0.537
	Positive	3.1± 0.3		42.6±15.6	
Group 2	Negative	1.9 ±0.8	0.011*	30.0±10.3	0.546
	Positive	2.7± 0.9		27.9±10.5	
*: p<0.05 Mann Whitney U-test					

as in long protocols. As a result this provides a shorter time for ovarian stimulation and lower doses of gonadotropins (12-14).

All participants in both groups had similar demographic data. Throughout the ART cycles, five separate samples were withdrawn as blood and FF. When biochemical assays were compared between the two groups, the antagonist group had significantly lower estradiol levels in hCG injection and oocyte aspiration period and lower levels of LH in hCG injection time. These results were related to the effects of antagonists and consistent with the study of Albano et al. (15) that had compared both GnRH analogs. In addition, pregnants had significantly higher levels of estradiol in both groups. We suggest that lower levels of estradiol in non pregnants were related to the low responses in the induction period.

We detected lower FF prolactin levels in the antagonist group than the agonist group in the period of hCG administration in contrast to Noyes et al. (16) data. We also evaluated the relationship between prolactin levels and pregnancy outcomes. Mendoza et al. (17) suggested that there was a significant relationship between higher FF prolactin levels and pregnancy in their study of FF fluid hormones and pregnancy outcomes. However our results revealed that, although it was not statistically significant, pregnant participants had lower levels of FF prolactin in both groups. When pregnants were compared within the two groups, the antagonist group had significantly lower levels than the agonists. These inconsistent results indicate that we need to perform more detailed researches.

There was prominent difference among aspirated oocytes between groups in favor of the agonist treatment and similar data were reported for the agonist group in long protocol by Ludwig et al. (18). It was suggested that the short induction period of the antagonist group causes these low numbers of oocytes and Wikland et al. (19) reported that increasing doses of gonadotropins in antagonist cycles may provide significantly higher numbers of oocytes. However, in our study, although both groups had similar stimulation periods and gonadotropin doses, the antagonist group had significantly lower numbers of oocyte. These results suggest that there may be other related factors about lower responses. In the antagonist treatments, lower levels of estradiol and number of oocytes reveal fewer ovarian hyperstimulation syndromes associated with a negative effect on pregnancy. It was proven that higher levels of estradiol have adverse effects on the luteal phase. Additionally, higher numbers of oocytes do not always mean that all these oocytes have a capacity of fertilization. Chen et al. (20) reported in their study that, although the number of oocytes in both groups were significantly different, they had similar fertilization rates, number of embryos, as in our study.

In the present study, leptin levels did not differ in the two groups. Noyes et al. (16) examined both serum and FF leptin levels at the beginning of induction and day of oocyte aspiration in agonist and antagonist groups. Results were similar for serum leptin levels in both groups, but FF leptin levels differ in favor of the antagonist group (15.3±1.4 versus 24±3.9 p=0.03).

Leptin has negative effects on various growth factors (IGF-1, TGF-beta) and hormones (insulin, glucocorticoids) that affect gonadotropin stimulated sex steroid hormones when utilized over 10 ng/ml (21-24). In addition, higher doses of leptin decrease ovarian estradiol synthesis and block the dominant follicle development and oocyte maturation. Serum and FF leptin levels in successful pregnancies were significantly lower than in women with failed conception (25-27). On the other hand, De Placido et al. (28) reported that FF leptin concentration of 20.25 ng/ml was the most reliable cut-off in predicting fertilization of oocytes. Hadrie at al. (21) reported that leptin values increased significantly from the first to the second trimester, decreased slightly in the third trimester and declined markedly 4-6 weeks after delivery. Abnormally low serum leptin levels were observed in women suffering spontaneous abortion in the first trimester of pregnancy (29). In our study, serum leptin levels were similar in both groups. Also we could not establish a relationship between serum leptin levels and pregnancy outcomes, similar to Gürbüz et al. (30) but contrary to Yang and Huang (26). In both groups, FF leptin levels were lower in pregnants than non pregnants, but this difference was not statistically significant. On the other hand, FF leptin levels were significantly higher than simultaneous serum leptin levels.

There is a controversy about the relationship between leptin and estradiol. Some authors suggest that high serum leptin levels might inhibit estradiol production through direct or indirect mechanisms (30-32). Others suggest that there was no correlation between these hormones (33, 34). We also could not find any correlation between leptin and both estradiol and prolactin. Moreover, we evaluated the same relationship between pregnancy outcomes and prolactin levels of FF. There is a controversy about the value of FF prolactin levels in predicting pregnancy. Some researchers suggested that PRL concentration of FF might be an additional parameter of oocyte maturation and fertilizability (35, 36). However, others suggested that higher levels of prolactin has adverse effects or no impact on pregnancy outcome (37, 38). In our research, pregnant women in both

groups had lower follicular fluid prolactin levels than non pregnants but this was not statistically significant. When pregnants were compared within the two groups, the antagonist group had significantly lower levels than agonists.

All researchers do agree on the impact of BMI on leptin levels (2, 39, 40, 41). We also observed a statistically significant correlation between leptin levels and BMI in group 2 in contrast to Group 1.

Successful outcomes of assisted reproductive technology rely on many factors such as the patients' age, number of transferred embryo, and quality of both embryo and implantation sites. It was suggested that levels of estradiol alterations might have influence over implantation through leptin. So, whether leptin has an impact on fertility or not should be clearly introduced. The leptin level alterations during ovulation induction which is different from natural cycles, may be related induction protocols.

As a result, both GnRH agonists and antagonists in short protocols had the same efficacy over pregnancy outcomes as suggested in literature. Although leptin is thought to be an important predictor of ovulation induction cycles, we could not introduce this relationship significantly both in serum and FF samples. There is a need for more randomized controlled researches in order to determine the physiopathologic mechanisms of leptin over ART.

Conflict of interest

No conflict of interest was declared by the authors.

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How frequent are overactive bladder symptoms in women with urodynamic verification of an overactive bladder?

Ürodinami ile aşırı aktif mesane tanısı konmuş kadınlarda aşırı aktif mesane semptomları hangi sıklıkta bulunmaktadır?

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Abstract

Objective: To determine the relationship between overactive bladder symptoms and urodynamic verification of overactive bladder.

Material and Methods: Between June 2011 and November 2011, 159 patients underwent urodynamics (UDS) at our urogynecology unit in the Ege University Hospital. Of these, 95 patients who complained of urgency, did not have any overt neurological diseases, bladder outlet obstruction and did not take any medication affecting the lower urinary tract function were evaluated. SPSS (ver. 15.0) was used to evaluate the data and the chi-square test and t test for independent samples were used for analysis.

Results: The mean age was found to be 54.5±12. Frequency was the most frequent symptom in women with overactive bladder (OAB) (82.1%), nocturia (57.8%) and (57.8%) urgency urinary incontinence followed in frequency. Detrusor over activity incidence was found to be 38.9%. There was no significant relationship between the presence of detrusor over activity (DOA) and OAB symptoms. Leak at urodynamics was found in 46.3% and there is no significant association with detrusor overactivity. Total bladder capacity was found to be significantly lower in women who had DOA (p=0.000).

Conclusion: It appears that overactive bladder symptoms do not predict detrusor over activity. Urodynamic investigation is not mandatory in the initial management of women with only OAB symptoms.

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Key words: Overactive bladder, urodyamics, urgency urinary incontinence, detrussor over activity

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Özet

Amaç: Aşırı aktif mesane semptomları ile tanısı ürodinamik olarak doğrulanmış aşırı aktif mesane arasındaki ilişkinin belirlenmesi.

Gereç ve Yöntemler: Ege Üniversitesi Ürojinekoloji ünitesinde, Haziran 2011 ve Kasım 2011 tarihleri arasında ürodinami ile değerlendirilen 159 hasta sunulan çalışmaya dahil edilmiştir. Bu olguların 95'inde urgency yakınması bulunuyordu ve bu olgular da belirgin nörolojik hastalık, mesane çıkış obstrüksiyonu yada alt üriner sistemi etkileyebilecek ilaç kullanım öyküsü yoktu. İstatistiksel analizlerde ki-kare ve t-test SPSS (ver 15.0) ile kullanıldı.

Bulgular: Olguların ortalama yaşı 54.5±12 bulundu. Aşırı aktif mesaneli kadınlarda idrara sık çıkma şikayeti (%82.1) en sık saptanan yakınma iken noktüri (%57.8) ve urgency üriner inkontinans (%57.8) bunu takip eden yakınmalardır. Detrüsör aşırı aktivitesi (DAA) %38.9 bulundu. Detrusor aşırı aktivitesi (DAA) ile aşırı aktif mesane (AAM) arasında anlamlı ilişki bulunmadı. Ürodinamik inkontinans %46.3 bulundu ve DAA ile anlamlı ilişki saptanmadı. Total mesane kapasitesi DAA'lı olgularda anlamlı olarak daha düşük saptandı (p=0.000).

Sonuç: Aşırı aktif mesane semptomlarının detrusor aşırı aktivitesini öngörmüyor gibi gözükmektedir. Ürodinamik inceleme yanlızca aşırı aktif mesane semptomu olan kadınların başlangıç değerlendirmesinde gerekli değildir. (J Turkish-German Gynecol Assoc 2012; 13: 98-101)

Anahtar kelimeler: Aşırı aktif mesane, ürodinamik değerlendirme, urgency, üriner inkontinans, detrosor aşırı aktivitesi

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Introduction

Overactive bladder (OAB) is defined as the storage symptoms of urgency with or without urgency incontinence, usually with frequency and nocturia. Urgency Urinary Incontinence (UUI) is defined as the complaint of involuntary leakage accompanied by or immediately preceded by urgency. Urodynamic diagnosis of OAB is defined as involuntary detrusor contractions during the filling phase, which may be spontaneous or provoked (1).These involuntary contractions are termed detrusor over activity (DOA) and are mediated by acetylcholine-induced stimulation of bladder muscarinic receptors (2). It has been reported that the rate of DOA in women who have OAB symptoms is 22-58.4% (3-5). Some studies reported that there is a significant relationship between DOA and frequency, nocturia and urgency urinary incontinence (5, 6). However, the association between the symptoms of OAB and DOA are still unclear in women with OAB. There is no consensus about symptomatic diagnosis of OAB and DOA in women (3, 4, 7, 8). The aim of this study was to evaluate the relationship between OAB symptoms and an urodynamic diagnosis of detrusor over activity.

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Material and Method

Sample Population

Between June 2011 and November 2011, 159 patients underwent UDS at our urogynecology clinic in the Ege University Hospital. Of these, 95 patients who complained of urgency did not have any overt neurological, bladder outlet obstruction and did not take any medication affecting the lower urinary tract function were evaluated. We retrospectively scanned urogynecologic evaluation reports which have included urinary diary, patient socio-demographic characteristics, and urodynamics. The study obtained approval from the local ethics committees.

Urogynecologic evaluation

The routine urogynecological protocol was performed before urodynamic testing. This included a comprehensive urogynecologic history, pelvic examination, a 3-day urinary diary, and no urinary infection.

Urogynecologic history

It was included in the data on socio-demographic characteristics such as age, weight, height, smoking, parity, gravida, menopausal status, previous medication or surgery. Body mass index was calculated by weight (kg)/height (m^2). Obesity was defined as 30 or more BMI value.

Pelvic examination

It consists of a cough stress test, residual volume measuring, Q-tip test, and POP-Q staging (9, 10).

Urinary diary

Frequency (eight voids per day), nocturia (two voids per night), and symptomatic incontinence (OAB wet; at least once a day or OAB dry, respectively) were determined.

Urodynamics

Urodynamics were performed in accordance with the criteria established by the International Continence Society (ICS) (11). The presence or absence of DOA and leakage during UDS were determined.

Statistical Analysis

SPSS vers 15.0 was used for evaluation of the data. Continuous variables were presented as means±SD and analyzed via the t test for independent samples. Classified variables were presented as n-% tables and compared via the Yates corrected Chi-square test. $p<0.05$ was considered as significant.

Result

Table 1 shows the demographic characteristics of women who were included in the present study. One hundred fifty

Table 1. Participants' demographic characteristics

	All participants (n=95)		Detrusor Over Activity				*p
			Absent (n=58)		Present (n=37)		
	Mean	SD	Mean	SD	Mean	SD	
Age	54.5	12.1	53.3	11.98	56.5	12.2	NS
Parity	3.1	1.7	2.9	1.65	3.5	1.6	NS
Gravida	4.3	2.2	4.0	2.19	4.7	2.3	NS
BMI	29.2	4.3	29.0	4.52	29.7	3.9	NS
	n	%	n	%	n	%	**p
Menopause							NS
yes	33	34.7	38	61.3	24	38.7	
no	62	65.3	20	60.6	13	39.4	
Prolapse							NS
yes	25	26.3	28	75.7	9	24.3	
no	70	73.7	42	72.4	16	27.6	
Obesity							NS
yes	37	38.9	21	56.8	16	43.2	
no	58	61.1	37	63.8	21	36.2	
Smoking							NS
yes	21	22.1	15	71.4	6	28.6	
no	74	77.9	43	58.1	31	41.9	

NS: Non significant, BMI: Body mass index *t test for independent samples, ** X^2 Yates

nine women who had attended our urogynecology unit were evaluated. 95 of these women (59.7%) had urgency. These participants were described as an overactive bladder. In addition frequency, nocturia, urgency incontinence might be accompanying the urgency. DOA was found to be present in 38.9%. There is no significant relationship between the presence of DOA and OAB symptoms. Table 2 shows the relationship between OAB symptoms and DOA. Table 3 shows the urodynamics findings. Leak at urodynamics was found in 46.3%. Total bladder capacity was found significantly lower in women who had DOA.

Discussion

Epidemiological studies have reported the prevalence of OAB as 16-17%, and this percentage increased to 21% for women older than 70 years (12, 13).

Symptoms of urinary frequency, nocturia, and urgency are common among adult women. Frequency, urgency, and urge incontinence alone or in combination form the basic group of symptoms of OAB (14, 15). OAB is a common and distressing problem known to adversely affect the quality of life because of these symptoms (16).

Our study demonstrates that OAB symptoms do not overlap urodynamic verification of OAB. In the present study, total bladder capacity was found significantly lower in women with DOA as in a previous study (7). Although DOA was reported as a main factor for OAB, it appears different underlying pathophysiologic factors play a role in women with OAB. Urgency is a pivot symptom, according to the OAB definition (1). Some studies reported a significant association between urgency and DOA (6-17).

However, Brummen et al. (5) reported a main association between frequency and DOA, while urgency was associated poorly with DOA. Hashim and Abrahams reported that urgency coexisting with urgency incontinence and frequency is a better predictor than frequency alone for DOA. On the other hand, 10 or more daytime micturition episodes in women with OAB was found to be associated with DOA (4, 8). According to studies which reported an association between OAB symptoms and DOA, urodynamic evaluation might be a part of the assessment in the management of women who had OAB symptoms. However, there is controversy about the association between OAB symptoms and urodynamic verification of DOA. Digesu et al. reported that there is no significant correlation between OAB symptoms and DOA. On the other hand, they detected that 72.4% women who had DOA did not have OAB symptoms and 20.8% of women with OAB symptoms had an urodynamic diagnosis of genuine stress incontinence (3). In conclusion, it appears that overactive bladder symptoms do not predict detrusor over activity. Although there is no sufficient medical data based on urodynamic investigations in women with OAB, in the light of available data we suggested that urodynamic investigation is not mandatory in the initial management of women with only OAB symptoms.

Table 2. The relationship between OAB symptoms and DOA

	Detrusor Over Activity				***p**
	Absent		**Present**		
	n	**%**	**n**	**%**	
Frequency	51	87.9	29	78.4	NS
Nocturia	33	56.9	22	59.5	NS
Urge incontinence	32	55.2	23	62.2	NS
Frequency+Nocturia	31	56.3	20	54	NS
Frequency+Urge incontinence	30	51.7	19	51.4	NS
Nocturia+Urge incontinence	18	31	12	32.4	NS
Frequency+Nocturia+Urge incontinence	18	31	12	32.4	NS

NS: Non significant *X^2 Yates

Table 3. Urodynamics findings

	Detrusor Over Activity				***p**
	Absent		**Present**		
	Mean	**SD**	**Mean**	**SD**	
FD	161.12	62.76	147.89	84.45	NS
TBC	449.55	138.56	348.49	119.88	0.000
	n	**%**	**n**	**%**	****p**
Leak at UDS	25	43.1	19	51.4	NS

FD: First desire, NS: Non significant *t test for independent samples, **X^2 Yates; Bold indicates significant difference, TBC: Total bladder capacity, UDS: Urodynamics

Conflict of interest

No conflict of interest was declared by the authors.

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Factors influencing the contraceptive method choice: a university hospital experience

Kontraseptif yöntem seçimini etkileyen faktörler: Bir üniversite hastanesi deneyimi

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Abstract

Objective: To analyze the factors influencing behavior of women in choosing contraceptive methods.

Material and Methods: A total of 4022 women who were admitted to our clinic in a year, were the subjects in this current study for contraception choices. Relationship between the current contraceptive choice and the age, marital status, educational level, gravidity and induced abortions were evaluated.

Results: Current users of any contraceptive methods were found to make up thirty-three percent of the entire study population. The most preferred method of contraception was an intrauterine device (46.4%), followed by, condom (19.2%), coitus interruptus (16.4%), tubal sterilization (11%), oral contraceptives (5.7%) and lastly the "other methods" that consisted of depot injectables and implants (1.2%). Among other contraceptive methods, the condom was found to be used mostly by the younger age group (OR:0.956, 95% CI:0.936-0.976, p<0.001), while tubal sterilization was preferred mainly by the elderly population (p<0.001, OR:1.091, 95% CI:1.062-1.122). Women that have a higher educational level, were found to use OC (76.3%, OR:5.970, 95% CI:3.233-11.022), tubal sterilization (59.6%, OR:4.110, 95% CI:2.694-6.271) and other methods (62.5%, OR:3.279, 95% CI:1.033-10.402) more commonly than the low educational group (p<0.001).

Conclusion: These results demonstrated that the rates of both contraception utilization and the usage of more effective methods of contraception need to be increased by providing better family planning systems and counselling opportunities.

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Key words: Contraceptives, method choice, demographic factors, intrauterine device

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Özet

Amaç: Kontraseptif yöntem seçimini etkileyen faktörlerin analizi.

Gereç ve Yöntemler: Bir yıllık süre içerisinde kliniğimize başvuran 4022 olgunun, kontraseptif yöntem seçimleri incelendi. Mevcut kontraseptif seçimleri ve yaş, medeni hal, eğitim seviyesi, gebelik, kürtaj durumları arasındaki ilişki değerlendirildi.

Bulgular: Kontraseptif yöntem kullanan olgular, çalışma popülasyonunun %33'ünü oluşturmaktadır. En çok tercih edilen yöntem rahim içi araç (%46.4) iken, diğer yöntemler sırasıyla; kondom %19.2, geri çekme %16.4, tubal sterilizasyon %11, oral kontraseptifler %5.7, depo enjeksiyonlar ve implantlar %1.2 oranında kullanılmaktadırlar. Kondom diğer metotlara göre daha genç yaş grubunda tercih edilmekte iken (OR:0.956, %95 CI:0.936-0.976, p<0.001), tubal sterilizasyonun daha ileri yaş olgular tarafından tercih edildiği saptandı (p<0.001, OR:1.091, %95 CI:1.062-1.122). Eğitim seviyeleri, oral kontraseptif (%76.3, OR:5.970, %95 CI:3.233-11.022), tubal sterilizasyon (%59.6, OR:4.110, %95 CI:2.694-6.271), depo enjeksiyon ve implant (%62.5, OR:3.279, %95 CI:1.033-10.402) kullanıcılarında diğer gruplara göre anlamlı oranda yüksek saptandı (p<0.001).

Sonuçlar: Bu sonuçlar daha iyi bir aile planlaması sistemi ve danışmanlığı ile hem kontrasepsiyon oranının artırılması hem de daha etkin yöntemlerin kullanımının yaygınlaştırılması gerektiğini göstermektedir. (J Turkish-German Gynecol Assoc 2012; 13: 102-5)

Anahtar kelimeler: Kontraseptifler, metot seçimi, demografik faktörler, rahim içi araç

Geliş Tarihi: 24 Ekim 2011 **Kabul Tarihi:** 19 Ocak 2012

Introduction

Aproximately half a million women die around the world each year, as a result of pregnancy and associated complications. Most of these deaths could be prevented, not only by providing immediate and appropriate medical care, but also by offering family planning counseling and services, which could prevent many future unintended high-risk pregnancies and unsafe induced abortions (1). Contraception methods can prevent at least 25% of all maternal deaths by allowing women to prevent unintended pregnancies and unsafe abortions, and to protect themselves from sexually transmitted diseases including HIV (2). Demographic characteristics, cultural and religious beliefs, and economic and education levels of the female pop-

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ulation can also affect the selection of a contraceptive method (3). In this population-based study, we aimed to compare the factors that influence the choice of contraception.

Material and Method

A total of 4022 women admitted to the University hospital in the period of a year (March 2010-May 2011), were evaluated for contraceptive method preference. All of the sexually active women aged between 15-49 were included in this cross-sectional study. Relationship between the current contraceptive choice and the age, marital status, educational level, gravidity and induced abortions were evaluated. Major contraceptive methods in this study were oral contraceptives (OCs), intrauterine devices (IUDs), coitus interruptus (CI), male condom, tubal sterilization (TS). Depot injection agents and implants were grouped as other (miscellaneous). The results were evaluated with Kruskal Wallis, Chi-square and multinomial logistic regression statistical methods in SPSS 15 and p value <0.05 was accepted as statistically significant.

Results

Thirty-three percent of the patients (1327/4022) were currently using contraceptive methods. The mean age of women using contraception was 32.3 years (range 15-49). Demographic characteristics, marital status, educational level and the rate of contraception utilization of subjects were demonstrated in Table 1. The most preferred method of contraception was intrauterine device (46.4%), followed by other preferred methods, condom (19.2%), coitus interruptus (16.4%), tubal sterilization (11%), oral contraceptives (5.7%) and lastly the

Table 1. Demographic characteristics and percentage distribution of women using contraceptive methods (n=1327)

Sociodemographic characteristics	IUD (%)	Condom (%)	CI (%)	TS (%)	OCD (%)	Other (%)	Non-use (%)
Age (yrs)							
<20	13 (2.1)	13 (5.1)	5 (2.3)	-	3 (4)	-	123 (4.5)
20-29	18 (30.0)	97 (3.0)	67 (30.7)	20 (13.8)	24 (31.6)	5 (31.3)	348 (12.9)
30-39	227(36.9)	85 (33.3)	73 (33.5)	64 (43.8)	30 (39.5)	8 (50.0)	1304 (48.4)
>40	191 (31.0)	60 (23.6)	73 (33.5)	62 (42.4)	19 (25.0)	3 (18.7)	920 (34.2)
Gravida							
0	56 (9.1)	76 (29.8)	30 (13.8)	-	16 (21.1)	1 (6.2)	1211 (44.9)
1	130 (21.1)	42 (16.5)	42 (19.3)	10 (6.7)	14 (18.4)	4 (25.0)	867 (32.2)
2	150 (24.4)	52 (20.3)	51 (23.4)	27 (18.7)	19 (25.0)	3 (18.8)	427 (15.9)
≥3	280 (45.5)	85 (33.3)	95 (43.6)	109 (74.6)	27 (35.5)	8 (50.0)	190 (7.0)
Parity							
0	66 (10.7)	81 (31.8)	31 (14.2)	-	18 (23.7)	1 (6.4)	1582 (58.7)
1	172 (27.9)	53 (20.8)	53 (24.3)	15 (10.3)	21 (27.6)	5 (31.2)	919 (34.1)
2	245 (39.8)	85 (33.3)	92 (42.2)	59 (40.4)	27 (35.5)	5 (31.2)	118 (4.4)
≥3	133 (21.6)	36 (14.1)	42 (19.3)	72 (49.3)	10 (13.2)	5 (31.2)	76 (2.8)
Curettage							
0	431 (70.0)	199 (78.0)	162 (74.3)	79 (54.1)	53 (69.7)	10 (62.5)	814 (30.2)
1	105 (17.1)	34 (13.4)	31 (14.3)	34 (23.3)	12 (15.8)	4 (25.0)	1154 (42.8)
2	50 (8.0)	14 (5.5)	16 (7.3)	20 (13.6)	10 (13.2)	1 (6.2)	432 (16.0)
≥3	30 (4.9)	8 (3.1)	9 (4.1)	13 (9.0)	1 (1.3)	1 (6.3)	295 (11.0)
Marital Status							
Married/Divorced	589 (95.6)	220 (86.3)	207 (95.0)	146 (100)	68 (89.4)	16 (100)	1844 (68.4)
Never married	27 (4.4)	35 (13.7)	11 (5.0)	-	8 (10.6)	-	851 (31.6)
Educational Level							
≥ High school	248 (40.2)	89 (34.9)	96 (44.0)	87 (59.6)	58 (76.3)	10 (62.5)	1218 (45.2)
< High school	368 (59.8)	166 (65.1)	122 (56.0)	59 (40.4)	18 (23.7)	6 (37.5)	1477 (54.8)
Total	616	255	218	146	76	16	2695

IUD: İntrauterine device, CI: Coitus interruptus, OCD: Oral contraceptive drugs, TS: Tubal Sterilization, Other: Long-acting injectables, implants

'other methods' that consist of depot injectables and implants (1.2%) (Table 4).

Amongst women that utilize contraception, 62.7% were older than 30. Contraception usage rates were low and there is no case that underwent a tubal sterilization younger than 20 years of age, amongst the included women (Table 1). The intrauterine device is the most commonly used method. The mean age of IUD users was 34.5 (±8.0) and 95.8% of this group consisted of femes covert or women that have had at least one previous marriage. Prevalence of IUD usage was highest amongst the women between the ages of 30-40 (36.9%, n=227). A male condom was the most commonly used method amongst the women younger than 30 (43.1%, OR:0.956, 95% CI:0.936-0.976, p<0.001) and tubal sterilization was the least preferred option in this group (13.8%). However the mean age of women preferring tubal sterilization as a contraceptive method, was 36.9 (±4.3) which was higher than other contraceptive methods (p<0.001, OR:1.091, 95% CI:1.062-1.122). The mean values as regards to contraceptive methods are given in Table 2.

Gravidity of included women were similar between all the groups and the majority of the women have had 3 or more previous pregnancies. In addition, nearly 90% of the sterilized women were found to have had more pregnancies and parities than 3. The percentage of women that have had 3 or more elective abortions was found higher in the sterilized group (9%).

Subjects were classified into two groups regarding their educational levels as including women to have at least a highschool degree, and including women that have less educational degree than highschool. In the comparison of these groups, women that have a higher educational level were found to use OC (76.3%, OR:5.970, 95% CI:3.233-11.022), tubal sterilization (59.6%, OR:4.110, 95% CI:2.694-6.271) and other methods (62.5%, OR:3.279, 95% CI:1.033-10.402) more commonly than the latter group (p<0.001). Rates of IUD and withdrawal method usage were similar between these two groups (40.3%, 44%). Relationship of contraceptive method choices with age and educational level are demonstrated in Table 3.

Discussion

The present study focused on the utilization and choice of contraception, and the change in preferred contraceptive method. Regarding the data obtained from the USA, approximately 62% of women between the ages pf 15 and 44 were currently using contraception in 2006-2008 (4) although this rate was found lower, as 33%, in our study. Our results showed that almost 59% of the women that do not use contraception were nulliparous and did not use any contraceptive method possibly owing to their wish for pregnancy (Table 1). This rate seems high compared to the literature (4-9).

Table 2. The clinical characteristics of women using contraceptive methods

	CI	IUD	OCD	Condom	Tubal sterilization	Other	**p
Age, year *	34.2 (8.3)	34.1 (8.0)	32.8 (8.5)	32.7 (8.4)	36.9 (4.3)	34.3 (5.8)	<0.05
Gravidy *	2.43 (1.7)	2.58 (1.8)	2.16 (1.8)	1.87 (1.7)	3.64 (2.1)	2.13 (1.05)	<0.05
Parity *	1.69 (1.0)	1.78 (1.05)	1.42 (1.07)	1.33 (1.15)	2.43 (1.26)	1.88 (0.95)	<0.05
Curettage *	0.42 (0.8)	0.52 (1.02)	0.52 (1.02)	0.34 (0.74)	0.86 (1.28)	0.56 (0.89)	<0.05
Marital status (%)	94.9	95.8	89.4	86.2	100	94.7	<0.05
Education (%)	44.1	40.3	76.0	34.9	59.4	60.3	<0.05

Values are *means (±SD) or percentage CI: Coitus interruptus, IUD: Intrauterine device, OCD: oral contraceptive drugs, Other: Long-acting injectables, implants, Education: at least high school, Marital Status: Married/divorced,**Kruskal Wallis

Table 3. Adjusted Odds Ratios from Multinomial Logistic regression

		OR	95% CI of OR (Lower-Upper)	p
OCP	Age	1.029	0.995-1.065	0.099
	Educational Status	5.970	3.233-11.022	<0.001
CI	Age	1.007	0.985-1.030	0.515
	Educational Status	1.237	0.865-1.768	0.243
Condom	Age	0.956	0.936-0.976	<0.001
	Educational Status	0.566	0.400-0.799	0.001
Other	Age	1.038	0.966-1.114	0.308
	Educational Status	3.279	1.033-10.402	0.044
TS	Age	1.091	1.062-1.122	<0.001
	Educational Status	4.110	2.694-6.271	<0.001

OR: Odds Ratio, CI: confidence Interval, Reference category was set to RIA, Age: One year increase, Educational Status: ≥ High school & < High school

Table 4. Trends of women using contraceptives

Method	(%)
Intra uterine device	46.4
Condom	19.2
Coitus interruptus	16.4
Tubal sterilization	11.0
Oral contraceptive drugs	5.7
Others	1.2

In this study, the most commonly used contraceptive methods were IUD (46.4%) and condom (19.2%). Similar to our results, in a study conducted in another city in Turkey, the most common contraception methods were IUD and male condom with rates of 38% and 19.4% respectively (5). However, in developed countries such as Spain and Germany, the commonly preferred methods are condom and pill, respectively (6, 7). In Canada, Australia and France, OC is reported as the leading method (8, 9). The OC and female sterilization have been the two leading methods in the United States since 1982 (4). In the United States, 11-13% of married couples were using male sterilization and 22-24% were using female sterilization. However OCD (6%) and tubal sterilization (11%) were the least preferred methods in our study. In the United States, 5.5% of women were currently using IUDs. Although this rate was estimated as 46.4% in our study, the actual IUD usage rate was approximately 20% in Turkey. As a relatively new option, subcutaneus implant applications were preferred by about 1% of women in our study, similar to the worldwide preference rate.

Current use of contraception is most prevalent among women aged 30-39 and older women (aged 40-44) are less likely to use family planning than younger women (6). The rate of oral contraception usage was found to have an inverse correlation with age, and 75% of users were younger than 40 years. The rate of IUD usage was found to be 2.1% in the youngest age group and this rate increases to almost 37% among women between 30-39 years of age. Condom and oral contraceptives were preferentially used by childless women, while tubal sterilization and IUDs were most often used by women with two or more children. Meanwhile, the use of contraception is also more common after at least two or three children.

In most countries, the women with higher educational levels were found to use one of the contraceptive methods, more than less educated women (10). As educational levels changed, the choice of contraceptive method also varied. In women with higher educational levels, IUDs, condom and coitus interruptus were used less frequently, whereas OCs and tubal sterilization were preferably used. Through the rise in educational level, people have become less fearful about the adverse effects of hormonal contraceptive methods and have realized the advantages of modern methods. In the study, there was a significant relationship between educational level and the preferred method of contraception. However, as the educational level improved, the prevalence of condom and IUD usage decreased and OCD and tubal sterilization preference rates increased.

Reasons for the injectable method preference of women were reported as their long-acting effect, lack of the concern about missing a daily pill and ease of appropriate use. We do not advise using long-acting methods in our daily practice due to their side effects such as amenorrhea, metrorraghia and menstrual irregularities. However, OC preference could be explicated by its reversibility, its plentiful efficency and convenience and the scarcity of side effects. Male condom preferring subjects explain their consideration by convenience, advantage of prevention of sexually transmitted diseases including HIV and easy accessibility of this method, whereas those preferring the implant mentioned long-lasting effects (11).

Unintended pregnancies are still a major public health issue. Thirty-seven out of every 100 live births are either undesired or unplanned and 23.6% of pregnancies result in induced abortions in Turkey (6). Although unsafe abortions are entirely preventable, they still occur in all developing regions. The major public health implications include, but are not limited to, maternal morbidity and mortality. In addition, unsafe abortions bring heavy financial costs to women and to health services for treating complications.

In conclusion, in our population, contraception usage rates were low. Thec most commonly preferred method was IUD, as a more effective way of contraception. Oral contraceptive utilization rates were even more meager. One in five women, in terms of contraception, preferred methods with high failure rates like male condoms. These results demonstrated that the rates of contraception utilization and more effective contraception methods usage need to be increased by providing better family planning systems and counselling opportunities.

Conflict of interest
No conflict of interest was declared by the authors.

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Comparison of preoperative endometrial biopsy grade and final pathologic diagnosis in patients with endometrioid endometrial cancer

Endometrioid endometriyum kanserli olgularda preoperatif endometriyal biyopsi grade ile postoperatif patolojik değerlendirmenin karşılaştırılması

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Abstract

Objective: To compare preoperative grading in endometrioid endometrial cancer with the final pathologic assessment of the hysterectomy specimen. The second objective of the study was to determine a high risk group who will be upgraded in the postoperative evaluation.

Material and Methods: A total of 335 patients with endometrioid endometrial cancer were retrospectively reviewed between June 2000 and January 2011. All pathology results were pre- and postoperatively reviewed at two institutions, and all patients underwent surgical therapy. Sensitivity, specificity, positive and negative predictive values and accuracy rates were calculated for all grades in the preoperative assessment.

Results: The mean age of the patients was 56.2±9.6 and the vast majority of the patients were postmenopausal (n=239, 71.3%). FIGO grade was determined to be greater in 75 patients in the final hysterectomy specimen. Fifty-five (32.9%) of the patients with preoperative grade 1 were found to be grade 2 and 3.6% of them were upgraded to grade 3. Fourteen of the patients with grade 2 (11.4%) were found to be grade 3. The accuracy rates of the preoperative grade assessment with endometrial sampling were 75.5%, 66.2% and 88.3% for grades 1, 2 and 3, respectively. There were no statistically significant differences in the preoperative demographic characteristics between patients with or without upgraded tumors.

Conclusion: A high percentage of preoperatively diagnosed grade 1 tumors were upgraded in the postoperative evaluation. The patients who would have been upgraded after hysterectomy could not have been predicted preoperatively using the characteristic features.

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Key words: Endometrial cancer, biopsy, grade, preoperative evaluation, postoperative evaluation

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Özet

Amaç: Endometrioid tip endometriyum kanserinde preoperatif ve postoperatif histerektomi materyalindeki grade'in karşılaştırılmasıdır. İkinci amaç ise postoperatif değerlendirmede upgrade olabilecek yüksek riskli grubun tanımlanmasıdır.

Gereç ve Yöntemler: Haziran 2000 ve Ocak 2011 tarihleri arasında endometrioid tip endometriyum kanserli 335 olgu retrospektif olarak incelendi. Tüm patolojik sonuçlar pre ve postoperatif olarak aynı merkezlerde değerlendirilerek, tüm olgulara cerrahi yapıldı. Preoperatif grade için sensitivite, spesifisite, pozitif ve negatif prediktif değerler ve doğruluk oranları hesaplandı.

Bulgular: Ortalama yaş 56.2±9.6 idi ve olguların çoğunluğu postmenapozal idi (n=239, %71.3). Olguların 75'i histerektomi spesmeninde daha yüksek grade'li olarak saptandı. Preoperatif grade 1 saptanan 55 olgu (%32.9) postoperatif olarak grade 2 saptanırken %3.6 olgu grade 3 tespit edildi. Grade 2 saptanan 14 olgu (%11.4) postoperatif olarak grade 3 saptandı. Endometriyal örnekleme ile preoperatif grade değerlendirilmesinin tanısal doğruluk oranları grade 1, 2 ve 3 için sırasıyla %75.5, %66.2 ve %88.3 idi. Upgrade olan ve olmayan olgular arasında demografik karakteristikler açısından istatistiksel olarak anlamlı fark bulunmadı.

Sonuç: Preoperatif olarak grade 1 tanısı almış olgularda, yüksek oranda postoperatif olarak daha yüksek bir grade saptanmaktadır. Histerektomi sonrası hangi olguların upgrade olabileceği preoperatif karakteristiklerle tahmin edilememektedir.

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Anahtar kelimeler: Endometriyum kanseri, biyopsi, grade, preoperatif değerlendirme, postoperatif değerlendirme

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Introduction

The grade of a tumor is a well-known prognostic factor for women with endometrial carcinoma and correlates with the depth of myometrial invasion, lymph node involvement, surgical stage and survival (1, 2). The staging for endometrial carcinoma has been suggested as a surgical-pathologic system which includes peritoneal cytology, pelvic and paraaortic lymphadenectomy (3). In 2005, the American College of Obstetricians and Gynecologists (ACOG) recommended surgical staging for women with endometrial cancer, except for young or perimenopausal women with grade 1 endo-

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metrioid adenocarcinomas, as well as atypical endometrial hyperplasia, and women at high risk of mortality secondary to comorbidities (4). The role of lymphadenectomy has not been clearly defined in the management of endometrial cancer, especially in patients with grade 1 and 2 disease that is limited in the uterus. Some authors advise performing a routine pelvic and/or para-aortic lymphadenectomy in all women (5), whereas others have questioned the clinical utility of this procedure because of the complications of lymphadenectomy, especially in patients at low risk of nodal involvement (grade 1 or 2 with no or minimal myometrial invasion) (6, 7).

Approximately 52% of women with endometrial carcinoma have a preoperative endometrial biopsy showing grade 1 (8). The accuracy of preoperative grading is an extremely important issue in young patients with well-differentiated endometrial carcinoma who desire future fertility and uterine preservation. In addition, preoperative endometrial biopsy is often the basis of referral to centers and most of the well-differentiated tumors are managed by general gynecologists and often without appropriate incision or surgical staging. Recently, two randomized multicenter studies reported no evidence of benefits in terms of overall or recurrence-free survival for pelvic lymphadenectomy in women with preoperative International Federation of Gynecology and Obstetrics (FIGO) stage I endometrial cancer (9, 10).

Most of the studies which have investigated preoperative tumor grading by various endometrial sampling methods have shown that these methods are poorly correlated with the final pathologic grade (8, 11-13). A higher FIGO grade on final uterine pathologic examination will be diagnosed in 24% of patients with preoperative FIGO grade 1 and the vast majority of cases will be upgraded to FIGO grade 2, but approximately 3% will be upgraded to FIGO grade 3 or be diagnosed as a serous or clear cell carcinoma on final pathologic assessment of the hysterectomy specimen (7-12). However, there are some studies that show nearly perfect agreement between preoperative and final pathologic grades (14, 15).

The objective of this study was to compare preoperative grading with the final pathological assessment of the hysterectomy specimen. The second objective of the study was to determine the high risk group who will be upgraded in the postoperative evaluation.

Materials and Methods

Between June 2000 and January 2011, a total of 335 patients with endometrioid endometrial cancer were reviewed retrospectively. These cases were identified from a database after approval was granted by the Institutional Review Board at the Bakirkoy Women's and Children's Teaching and Research Hospital and Haseki Teaching and Research Hospital. D&C was used as the method of endometrial sampling in all cases. All patients underwent hysterectomy and lymphadenectomy as the primary treatment for their endometrial cancer. All of the preoperative endometrial histological examinations were performed and reviewed at these two institutions by specialized gynecologic pathologists. Only the patients with preoperatively diagnosed endometrioid endometrial carcinoma were evaluated in this study. Cases of serous or clear cell adenocarcinoma, whether alone or mixed with the other subtypes and non-epithelial histology, were excluded.

Operative reports were reviewed to determine intraoperative findings. The pathology reports of the specimens revealed the FIGO grade, the depth of myometrial invasion, the FIGO stage of disease, the presence of extra-uterine metastases, the peritoneal cytologic results and the presence of lymphvascular space invasion (LVSI). Patients were classified as upgraded if the postoperative definitive grade was determined to be a greater then the preoperative grade.

The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy rates were calculated for all preoperatively assessed grades. Chi-square and Fisher's exact tests were used, as appropriate, to compare nominal variables. All statistical analyses were performed using SPSS for Windows version 15.0.1 (Chicago, IL).

Results

A total of 335 patients with endometrioid type endometrial cancer were evaluated. The mean age of the patients was 56.2±9.6 and the vast majority of the patients were postmenopausal (n=239, 71.3%). Table 1 summarizes the demographic and clinic characteristics of the patients. Most of the patients had grade 2 disease (n=152, 45.4%). 40.9% and 13.7% of them had grade 1 and grade 3 disease at the final pathologic examination, respectively.

Table 2 shows the distribution of the surgical outcomes according to the preoperative grades of the patients. FIGO grade was determined to be greater in 75 patients in the final hysterectomy specimen. Fifty-five (32.9%) of the patients with preoperative grade 1 were found to be grade 2 and 3.6% of them were

Table 1. Demographic and clinical characteristics of the patients

	n (%)
Age (mean±sd)	56.2±9.6
Gravida (median)	3.0
Parity (median)	3.0
Menopause	239 (46.0)
BMI ≥30	182 (35.0)
DM	88 (16.9)
HT	142 (27.3)
Operation	
TAH-BSO-PLND	193 (55.7)
TAH-BSO-PPLND	142 (42.3)

BMI: body mass index, DM: diabetes mellitus, HT: hypertension, TAH-BSO-PLND: total abdominal hysterectomy- bilateral salphingoopherectomy-pelvic lymph node dissection, TAH-BSO-PPLND: total abdominal hysterectomy- bilateral salphingoopherectomy-pelvic and para-aortic lymph node dissection

Table 2. Comparison of the surgical outcomes according to preoperative FIGO grade

	Preoperative Grade		
	1 n (%)	2 n (%)	3 n (%)
Final Grade			
1 (n)	106 (63.5)	28 (22.8)	3 (6.7)
2 (n)	55 (32.9)	81 (65.9)	16 (35.6)
3 (n)	6 (3.6)	14 (11.4)	26 (57.8)
Final FIGO stage			
I	134 (80.2)	93 (75.6)	23 (51.1)
II	10 (6.0)	11 (8.9)	4 (8.9)
III	15 (9.0)	8 (6.5)	13 (28.9)
IV	8 (4.8)	11 (8.9)	5 (11.1)
Postoperative Histology			
Endometrioid	166 (99.4)	120 (97.6)	44(97.8)
Non-Endometrioid	1 (0.6)	3 (2.4)	1(2.2)
LNI	19 (11.4)	16 (13.0)	15 (33.3)
Positive Cytology	15 (9.0)	14 (11.4)	11 (24.4)
LVSI	40 (24.0)	29 (23.6)	19 (42.2)
Depth of MI			
<1/2	126 (75.4)	77 (62.6)	20 (44.4)
>1/2	41 (24.6)	46 (37.4)	25 (55.6)

LNI: lymph node invasion, LVSI: lymphovascular space invasion, MI: myometrial invasion

Table 3. Sensitivity, specificity, PPV and NPV for preoperative grade prediction

	Grade 1	Grade 2	Grade 3
Sensitivity	77.3%	53.2%	56.5%
Specificity	67.5%	77.0%	93.4%
PPV	63.4%	65.8%	57.7%
NPV	80.3%	66.5%	93.1%
Accuracy	75.5%	66.2%	88.3%

PPV: positive predictive value, NPV: negative predictive value

upgraded to grade 3. Fourteen of the patients with grade 2 (11.4%) were found to be grade 3.

The vast majority of the patients with preoperative grade 1 had stage I disease (80.2%), 6.0% of them had stage II, 9.0% and 4.8% of the patients had stage III and IV disease. Lymph node involvement was detected in 11.4% and the depth of myometrial invasion (MI) was greater than 50% in 24.6% of the patients who had grade 1 tumors preoperatively.

The overall accuracy rate of preoperative histologic grade evaluation was 64.1%. The sensitivity, specificity, PPV and NPV rates of the preoperative grade prediction are summarized in Table 3. Among the preoperatively assessed grades, grade 1 had higher sensitivity (77.3%) and lower specificity rates (67.5%) compared with grade 2 and grade 3. The accuracy rates of the preoperative grade assessment with endometrial sampling were 75.5%, 66.2% and 88.3% for grades 1, 2 and 3, respectively.

If the patients with a preoperative diagnosis of grade 3 were excluded, 25.8% of the patients were found to have a higher grade in the final pathologic examination. A comparison of the demographic and pathologic characteristics between patients with or without upgraded cancer is summarized in Table 4. Upgraded tumors were significantly related to a higher stage of disease (p=0.003) and positive peritoneal cytology (p=0.04).

Discussion

The surgical approach for endometrial cancer varies from only total hysterectomy with bilateral oophorectomy to hysterectomy with full pelvic and para-aortic lymphadenectomy. Preoperative tumor grading with pre- and/or intraoperative assessment of the depth of myometrial invasion, as well as the histologic subtype, is frequently used to decide whether lymph node dissection is necessary at the time of hysterectomy. According to FIGO guidelines, lymphadenectomy should be performed when myometrial invasion is greater than 50% and/or when the tumor is undifferentiated (16). Similarly, Mariani et al. (17) reported that patients with FIGO grade 1 or 2 endometrial cancer with macroscopically no or superficial myometrial invasion (<50%) can be treated safely with only hysterectomy. However, pre- and

Table 4. Univariate analysis for the patients with or without upgraded tumors

	Upgraded n (%)	Not upgraded n (%)	p
Age (years)			
<70	72 (96.0)	200 (93.0)	0.35
≥70	3 (4.0)	15 (7.0)	
Menopause status			0.88
Premenopausal	22 (29.3)	65 (30.2)	
Postmenopausal	53 (70.7)	150 (69.8)	
BMI			0.19
<30	39 (52.0)	93 (43.3)	
≥30	36 (48.0)	122 (56.7)	
DM	15 (20.0)	58 (27.0)	0.23
HT	36 (48.0)	86 (40.0)	0.22
Final FIGO stage			0.003*
I	46 (61.3)	204 (78.4)	
II	9 (12.0)	16 (6.2)	
III	10 (13.3)	26 (10.0)	
IV	10 (12.3)	14 (5.4)	
LNI	59 (78.7)	226 (86.9)	0.07
Positive Cytology	14 (18.7)	26 (10.0)	0.04
LVSI	23 (30.7)	65 (27.0)	0.32
Depth of MI			0.59
<1/2	48 (64.0)	175 (67.3)	
>1/2	27 (36.0)	85 (32.7)	

BMI: body mass index, DM: diabetes mellitus, HT: hypertension, LNI: lymph node invasion, LVSI: lymphovascular space invasion, MI: myometrial invasion
*X^2 test for trend

intraoperative assessment of the myometrium is an inaccurate predictor of the actual depth of myometrial invasion (11). In a series of 112 patients, Frumovitz et al. (11) reported that a frozen section diagnosis of no myometrial invasion is not accurate in 72% of cases, and 26% of cases with a frozen section of myometrial invasion <50% will actually have deeper invasion, cervical invasion and/or extra-uterine disease.

Preoperative tumor grade based on endometrial sampling is also reported to be poorly correlated with the final pathologic grade (8, 11-13, 18, 19) and a greater FIGO grade on final hysterectomy pathological assessment will be diagnosed as high as in 30% of patients with preoperative FIGO grade 1 (12). In another study, which compared histological grades between D&C and the hysterectomy specimen in grade 1 tumors on the final hysterectomy pathological assessment showed an overall upgrade rate of 50% and a concordance rate of 32.5% (20).

On the other hand, Kang et al. (14) recently evaluated a total of 122 patients with low-risk endometrial cancer for the necessity of lymphadenectomy and showed nearly perfect agreement between pre- and postoperative grades, even when Pipelle was used for the preoperative diagnosis. Similarly, in a study with a very large series of only preoperatively detected as grade 1 endometrial cancer, almost 15% of the pathology specimens were upgraded in the final hysterectomy specimen (15).

In our study, nearly 35% of the patients with FIGO grade 1 endometrial adenocarcinoma prior to hysterectomy were diagnosed with a greater FIGO grade after hysterectomy. This finding may be explained by the fact that FIGO grading is based on the percentage of solid growth within a specimen and will therefore vary once the final specimen is obtained and a greater tissue volume is examined. In addition to this, 13.8% of the patients with preoperative grade 1 disease had advanced stage of disease (stage 3 and 4). Lymph node involvement was detected in 11.4% of the patients with preoperative grade 1 and 9% of them had positive peritoneal cytology. If the patients were selected for surgical staging according to preoperative grading, more than 10% of the patients with preoperative grade 1 would have been subjected to inappropriate surgery in our cohort. In an Italian multicenter study which evaluated the efficacy of systemic lymphadenectomy in patients with preoperative and intraoperative stage I disease, almost 25% of the total cohort was upstaged (FIGO II, III, IV) after definitive surgery and

patients undergoing systemic lymphadenectomy had a higher likelihood of being upstaged to FIGO IIIC disease compared the no lymphadenectomy arm (13.3% vs. 3.2%) (10). Another randomized trial (MRC ASTEC) also showed that 23% of patients with a preoperatively diagnosed stage I tumor were upstaged in both the standard surgery and lymphadenectomy arms (11). Our second objective in conducting this study was to preoperatively determine the high risk group in which patients will be upgraded in postoperative evaluation. However, there was no statistically significant difference in the demographic and clinical features between patients with or without upgraded tumors. We found a significant relation only between the stage of disease, positive abdominal cytology and upgrading. However, those were mostly detected after surgical staging. Thus, it is not possible to predict the high risk group for upgrading preoperative findings.

In conclusion, unpredictably, a high percentage of preoperatively diagnosed as grade 1 tumors were upgraded in the postoperative evaluation. According to our study, it is not possible to say that lymphadenectomy should be considered as comprehensive surgical staging in all patients with preoperatively diagnosed endometrial cancer, but it should be mentioned that patients with a preoperative diagnosis of grade 1 uterine cancers have a risk of extra-uterine spread, and the information achieved from an appropriate surgical staging procedure affects the adjuvant treatment decision.

Conflict of interest

No conflict of interest was declared by the authors.

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Low VEGF expression in conceptus material and maternal serum AFP and β-hCG levels as indicators of defective angiogenesis in first-trimester miscarriages

İlk trimester gebelik kayıplarında, yetersiz anjiogenez'in göstergesi olarak konseptus materyalinde düşük VEGF ekspresyonu ve maternal serum AFP ve β-hCG düzeyleri

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Abstract

Objective: The aims of this study were to assess the relationship between early miscarriages and vascular endothelial growth factor (VEGF) expression and to determine the serum levels of first-trimester maternal alpha-fetoprotein (AFP) and human chorionic gonadotropin (β-hCG) as markers of angiogenesis and predictors of abortion and intrauterine fetal loss.

Material and Methods: The present study was a prospective, single-center, randomized controlled clinical trial. Ninety-five women who were 6-10 weeks pregnant between May and June 2010 were included in the study. The subjects were divided into three groups, i.e., incomplete abortion (IA) (n=31), intrauterine death (IU-D) (n=32) and control (elective pregnancy termination) (n=32). Feto-placental materials were compared based on immune staining for VEGF in the pathology laboratory, and maternal serum samples were tested in the hormone laboratory.

Results: Serum β-hCG levels in the patient groups were significantly lower than the controls (p=0.001). The serum AFP level was lower than the controls in the IA group while it was higher than the controls in the IU-D (p=0.016). Immunohistochemistry showed that the cytotrophoblast, syncytiotrophoblast and endometrial gland epithelium were weakly stained for VEGF in the patient groups (IA and IU-D) in comparison to the control group (p=0.06, p=0.028, p=0.006).

Conclusion: Early pregnancy losses are related to insufficient angiogenesis, and maternal serum AFP and β-hCG can be used as markers of angiogenesis in the first trimester.

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Key words: Abortion, implantation, angiogenesis, VEGF, β-hCG, AFP

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Özet

Amaç: Erken gebelik kayıplarının vasküler endotelial growth faktör (VEGF) ekspresyonu ile ilişkisini değerlendirmek ve anjiogenez markırı olarak ilk trimester maternal serum alfa-fetoprotein (AFP) ve human chorionic gonadotropin (β-hCG) düzeylerinin abortusu ve intrauterin fetal ölümü öngörmedeki yerini tespit edebilmektir.

Gereç ve Yöntemler: Çalışmamıza, Mayıs 2010 ve Temmuz 2010 tarihleri arasında hastanemize başvuran, 6-10. gebelik haftalarındaki toplam 95 hasta dahil edildi. Hastalar inkomplet abortus (n=31), intrauterin ex (n=32) ve kontrol (n=32) olarak 3 grup halinde incelendi. Fetoplasental materyaller patoloji laboratuarında VEGF ile immün boyanma özellikleri açısından karşılaştırıldı. Maternal serum örnekleri hormon laboratuvarında çalışıldı.

Bulgular: Serum β-hCG değeri hasta gruplarında, kontrole göre anlamlı olarak düşük (p=0.001) ve serum AFP değeri de İA grubunda kontrole göre düşük, IUEX grubunda ise yüksek saptandı (p=0.016). İmmünhistokimya ile, sitotrofoblast, sinsityotrofoblast ve endometrial gland epitel hücrelerinde hasta gruplarında (İA VE İUEX) kontrol grubuna kıyasla VEGF için daha zayıf boyanma olduğu görüldü (p=0.06, p=0.028, p=0.006).

Sonuçlar: Erken gebelik kayıpları, yetersiz anjiogenezle ilişkilidir ve VEGF ile ilişkili olarak, ilk trimesterde maternal serum AFP ve β-hCG'nin anjiogenez markırı olarak kullanımı olasıdır.

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Anahtar kelimeler: Abortus, implantasyon, anjiogenez, VEGF, β-hCG, AFP

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Introduction

Implantation and development of a human embryo requires an increased level of angiogenesis. Various growth factors have been associated with placental angiogenesis and embryonic development. However, among these factors, vascular endothelial growth factor (VEGF) plays the key role (1). VEGF exerts angiogenic effects via two receptors; VEGFR-1/Flt-1(fms-like-tyrosine kinase) and VEGFR-2/flk-1 (fetal liver kinase)/KDR (kinase domain region) (2). The role of VEGF was first described in a gene deletion study by Carmaliet et al., (3) who reported in 1995 that embryonic mice which

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were unable to produce VEGF or were defective at the level of the VEGF receptor did not develop normal vascular structures and were aborted. Evans and coworkers showed that the concentration of VEGF in the maternal serum was elevated in early first trimester pregnancies (4). In an immunohistochemical study by Kaloglu et al., (5) the role of VEGF in placental angiogenesis was established. It has been reported that VEGF not only stimulates and regulates angiogenesis but also guides implantation by promoting the growth of the cytotrophoblasts and differentiation via these receptors (6). In addition to the well-defined angiogenic factors such as VEGF, recent studies have revealed that growth factors and hormones related to gestation, especially human chorionic gonadotropin (hCG), alpha-fetoprotein (AFP) and insulin-like growth factor II (IGF II), play important roles in the vascular development of the feto-placental unit (7-10). Laitinen et al. (11) showed the direct effect of hCG on VEGF expression via the hCG/LH receptor. Herr et al. (8) argued that hCG stimulates the proliferation of human placental micro vascular endothelial cells in a dose-dependent fashion and that it is critical for a successful pregnancy due to its role in immune tolerance. AFP is a protein synthesized in the yolk sac and liver of the fetus and plays an important role as a proangiogenic factor in VEGF-dependent angiogenesis, especially in the endothelial cells of the feto-maternal unit (9). There are a few papers in the literature on maternal serum AFP (MS-AFP) levels in the first trimester (9, 10, 12, 13). Previous studies have shown that the levels of endocrinological factors, such as hCG, progesterone (14, 15), pregnancy associated plasma protein-A (PAPP-A) and inhibin A (13) levels, are decreased in the first trimester in patients with symptoms of threatened miscarriage (TM) who subsequently had a complete miscarriage, compared to those with a normal obstetric outcome.

The aim of the present study was to detect and compare VEGF immunoreactivity among feto-maternal materials obtained as a result of spontaneous incomplete abortion (IA), intrauterine death (IU-D) and elective termination of pregnancy (control) and to determine the values of first-trimester maternal serum levels of AFP and β- hCG as markers of angiogenesis and predictors of abortion and intrauterine fetal losses.

Material and Method

The present study was a prospective, single-center, randomized controlled clinical trial assessing the VEGF immunoreactivity and the values of first-trimester maternal serum levels of AFP and β-hCG among feto-maternal materials obtained as a result of spontaneous incomplete abortion (IA), intrauterine death (IU-D) and elective termination of pregnancy (control). Ethical approval was obtained from the local research ethics committee prior to the study, and written informed consent were obtained from all patients. This study was conducted in accordance with the basic principles of the Helsinki Declaration.

Patient selection:

A group of 124 patients ranging from 6-10 gestational weeks in their pregnancies admitted to the Family Planning Unit of Zekai Tahir Burak Women Training and Research Hospital, Ankara, Turkey, between May 2010 and July 2010 were eligible for inclusion in this trial. Before the subjects were enrolled in the study, age, gravida, parity, abortus weight, height, body mass index (kg/height^2) (BMI), the presence of a systemic disease (such as diabetes, hypertension), smoking, alcohol consumption, caffeine consumption, medications, blood group incompatibility and first day of the last menstrual period were recorded. Subjects with a systemic disease or an etiological risk factor for recurrent abortion, subjects who conceived by assisted reproductive techniques or had Rh incompatibility and smokers were not included in the study (n=12). All subjects underwent pelvic examination in the dorsolithotomy position. Conditions that might cause vaginal bleeding, such as cervical carcinoma, ulcer, polyp, erosion, vaginal laceration, and vaginitis, were ruled out (n=11). Patients with trophoblastic disease, ectopic pregnancy and multiple pregnancies, identified by pelvic and ultrasound examination, were also excluded from the study (n=6). Therefore, the remaining 95 patients were included in the study.

Study Design:

Patients were divided into three groups. The IA group comprised 31 patients who had a live fetus within the uterine cavity but who had experienced spontaneous incomplete abortion within 12 hours before admittance to the hospital. (Gestational material for immunohistochemical examination was obtained only from 16 cases). Thirty-two patients were allocated into the IU-D group when the crown-rump length (CRL) was over 5 mm but a fetal heart beat was absent, based on trans-vaginal ultrasound (TVU) examination. The control group comprised 32 normal subjects who underwent elective termination of their pregnancies.

All pregnancies were terminated by vacuum aspiration, and two venous blood samples of 3 cc were taken from each patient's antecubital vein just before the procedure. Blood samples were centrifuged at 4500 rpm for 15 minutes to separate the serum. β-hCG and AFP were measured using these sera.

Diagnoses of the patients in the IA group were made by gynecological examination or observation with TVU of gestational material within the cervical canal and serial β-hCG measurements and were confirmed histopathologically after curettage. The IU-D group included patients with fetuses with a CRL≥5 mm but without a fetal heart beat on TVU exam. Subjects in the control group were evaluated by TVU to determine the location of the fetus, heart beat and biometric size (CRL).

β-hCG measurements: Sera were analyzed on the same day as sample collection using the β- hCG kit by the Heterogenous Enzyme Immunoassay method, and the results were expressed in mIU/ml. All samples were assayed in duplicate, and the intra- and inter-assay variations based on undiluted 170 mIU/ml Bio-Rad hCG control were 3.2% and 6.7%, respectively.

AFP measurements: Sera were analyzed on the same day as sample collections in the hormone laboratory for AFP by Enzyme-Linked Immunosorbent Assay (Genentech, Inc., San Francisco, California), and AFP levels were quantified as IU/ml. The intra- and inter-assay coefficients of variation were calculated as 2.8% and 3.8%, respectively.

Histopathological and Immunohistochemical Method: All feto-placental curettage material was sent to the Pathology

Laboratory. Specimens were fixed in formalin and embedded in paraffin after routine histological processing, and tissue blocks were obtained. Tissue blocks were then sectioned, deparaffinized and rinsed under running tap water. Sections were incubated in 3% hydrogen peroxide for 10 minutes, rinsed under distilled water and pretreated at a high temperature in a microwave oven in Tris-EDTA buffer (pH 9) for 20 minutes. After waiting at room temperature for 20 minutes, sections were washed in PBS (phosphate buffered saline, pH 7.6) for 5 minutes. After application of the protein block for 10 minutes, sections were incubated with the primary antibody at room temperature for one hour (VEGFAb-1 Rabbit Polyclonal Antibody, Thermo Scientific RB222) and then washed with PBS for 5 minutes. The sections were incubated for 20 min with a biotinylated secondary antibody, washed with PBS for 5 minutes, incubated with streptavidin/peroxidase complex for 20 minutes, washed with PBS for 5 minutes and incubated with AEC chromogen for 5 minutes. Slides were washed under tap water, counterstained with Mayer's Hematoxylin for 30 seconds, washed with distilled water and covered with a water-based cover material.

To reduce intra- and inter-observer variability, materials were numbered and examined by a single pathologist who was blind to the group to which the specimen belonged. Tissues that were immunostained and examined under light microscope included trophoblasts around the chorionic villi (syncytiotrophoblasts, cytotrophoblast), Hofbauer cells (fetal tissue macrophages) within the chorionic villi stroma, the vascular endothelium of the chorionic villi on the fetal side as well as the decidual stromal cells, the decidual vascular endothelium and the endometrial gland epithelium on the maternal side.

The tissue sections were compared based on immunostaining for VEGF. We observed that the VEGF antibody stained the cytoplasm and cell membrane, but not the nucleus. In other words, sections were evaluated based on positive staining or membranous staining of the cells. Sections were graded on a 4-point scale which is commonly used in immunohistochemical studies. Sections were scored as; 0: No staining, 1+: focal, weak staining, 2++: diffuse, weak staining, 3+++: diffuse, strong staining.

Outcome variable and statistical analysis:

To differentiate between the control, IA and IU-D groups using the AFP values, the power was calculated as 0.97 at ±4 units of deviation from the mean, and alpha was taken as 0.05 (Calculated by NCSS-PASS software package).

SPSS (Statistical Package for Social Sciences) for Windows 15.0 was used for statistical analyses. In addition to descriptive statistics (mean, standard deviation, median), one-way ANOVA, Kruskal-Wallis H, and Mann-Whitney U tests were used for comparison of quantifiable data. Differences between groups were considered significant when $p<0.05$ and $p<0.01$ at 95% and 99% confidence intervals.

Results

Table 1 shows the demographic and descriptive data of the patients, including age, gravida, parity, live births, abortus, dilation and curettage (D&C), and body mass index (BMI). There were no significant differences in age and BMI between groups (Table 1). The mean gestational ages of the groups according to last menstrual period and ultrasound were 7.6±1.3 and 6.5±0.81, respectively.

Significant differences in the mean β-hCG levels of the subjects were found between groups; the mean β-hCG level in the IA group was lower ($p=0.001$) (Table 2). There was also a significant difference in mean AFP levels between groups. Compared to the controls, the mean AFP was lower in the IA group, but higher in the IU-D group ($p=0.016$) (Table 2).

Comparison of tissue sections in terms of VEGF staining revealed that the cytotrophoblasts and syncytiotrophoblasts of the placental villi and endometrial gland cells stained significantly weaker in the patient groups (IA and IU-D) in comparison to the controls (Table 3, Figures 1-3). Hofbauer cells in the control group stained similarly to those in the IA and IU-D groups, and there were no statistically significant differences in staining intensity (Table 3). Vascular endothelial cells of the placental villi stained weakly in the control group as opposed to the IA and IU-D groups, and the differences between the patient groups and the controls in terms of VEGF staining intensity were significant (Table 3, Figures 4 and 5). Decidual stromal cells stained comparably in all groups with no statistically significant differences among them (Table 3, Figure 6). Decidual vascular endothelial cells presented weaker staining in the control and IA groups than the IU-D group, but the differences did not reach the level of significance (Table 3).

Table 1. Comparison of the patient demographics and descriptive data

	Control (Mean±SD)** n=32	IA (Mean±SD)** n=31	IU-D (Mean±SD)** n=32	p value*
Gravida	4.1250±1.8447	3.0000±1.9321	2.5939±1.5202	0.001*
Parity	2.4063±1.7387	1.6452±1.6030	0.9688±1.0920	0.001*
Live birth	2.2500±1.1639	1.5484±1.5671	0.9375±1.0453	0.001*
D&C	0.5000±0.1419	0.1290±0.1009	0.2813±0.1364	0.021*
Abortus	0.2813±0.6831	0.2258±0.6688	0.3125±0.7803	0.798
Age (years)	31.25±5.968	30.90±6.655	30.88±7.241	0.969
BMI (kg/height^2)	25.6594±4.8746	24.0290±3.6455	24.2188±5.1477	0.310

*p<0.05 statistically significant, **Data are expressed as the mean±standard deviation (SD)

Table 2. The means of serum β-hCG and AFP values in the groups

	Control (Mean±SD)* n=32	IA (Mean±SD)* n=31	IU-D (Mean±SD)* n=32	p value
β-hCG (mIU/ml)	71479±6453.57	9491.00±3118.871	34492.74±7799.917	0.001
AFP (IU/ml)	5.2594±2.6591	3.4645±2.3656	7.8000±2.0128	0.016

*Data are expressed as the mean±standard deviation (SD)

Table 3. The median and range of the intensity of VEGF staining of the groups

	CONTROL (Median) (Range)	IA (Median) (Range)	IU-D (Median) (Range)	p
CYTOTROPHOBLAST	3 2.15-2.66	2 1.40-2.35	2 1.67-2.33	0.066
SYNCYTIOTROPHOBLAST	3 2.15-2.66	2 1.40-2.35	2 1.57-2.22	0.028*
HOFBAUER CELLS	1 1.01-1.68	1 0.44-1.43	1 0.55-1.31	0.158
PLACENTAL VASCULAR ENDOTHELIAL CELLS	0.00 0.02-0.29	0.50 0.26-1.11	0.50 0.52-1.34	0.003**
STROMAL CELLS	2 1.87-2.45	2 1.48-2.39	2 1.58-2.42	0.736
DECIDUAL VASCULAR ENDOTHELIAL CELLS	0.50 0.38-1.00	0.50 0.26-1.11	1 0.74-1.55	0.165
ENDOMETRIAL GLAND CELLS	1 1.13-1.81	0.50 0.33-1.42	0 0.33-1.03	0.006**

*Kruskall Wallis Test, *p<0.05, **p<0.01

Discussion

Aiming to clarify the etiopathogenesis of first-trimester miscarriages, we examined VEGF staining in tissue sections prepared from the feto-placental materials collected from our patients and measured β-hCG and AFP levels in maternal serum. We constructed two patient groups, namely a spontaneous incomplete abortion group and an intrauterine death group, and we compared their results with those of the controls. Few studies exist in the literature that measured MS-AFP in the first trimester. It is usually investigated during the diagnoses of fetal chromosomal anomalies and neural tube defects in the later stages of pregnancy (13, 16). Previous studies have reported a strong association between low MS-AFP (<0.05 MoM) and gestational complications, such as fetal death, spontaneous abortion, anembryonic pregnancy, preterm labor and macrosomia (16-21). In addition to fetal chromosomal anomalies, high MS-AFP (AFP>2.5 MoM) has been shown to be related to placental pathology, multiple pregnancy and fetal death (13). In agreement with findings reported in the literature, the mean MS-AFP in the IA group was lower (AFP=3.4645 IU/ml), while that in the IU-D group was significantly higher (AFP=7.8000 IU/ml) (p=0.016). An immunohistochemical study on endothelial cell culture from the human feto-maternal units by Liang et al. showed that

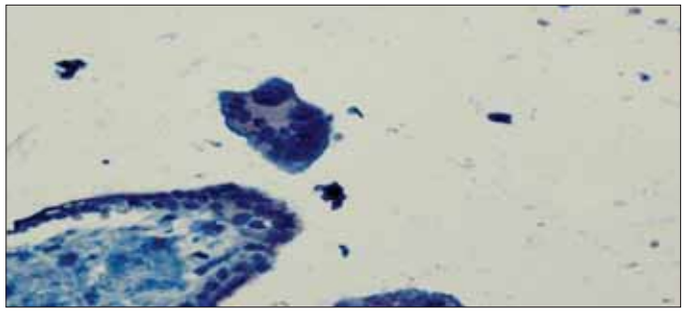

Figure 1. Cytotrophoblasts and syncytiotrophoblasts that show focal weak VEGF staining (1) in the IA group. 400X

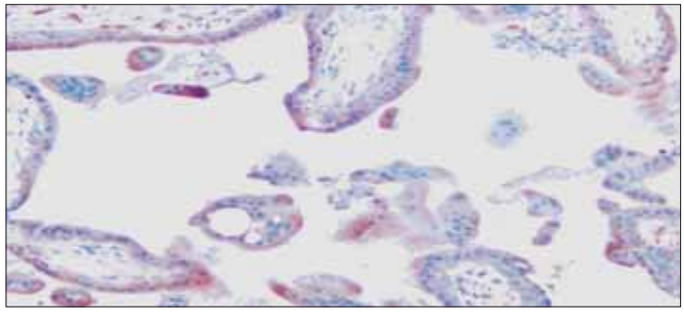

Figure 2. Cytotrophoblasts and syncytiotrophoblasts that show diffuse weak VEGF staining in the IU-D group. 400X

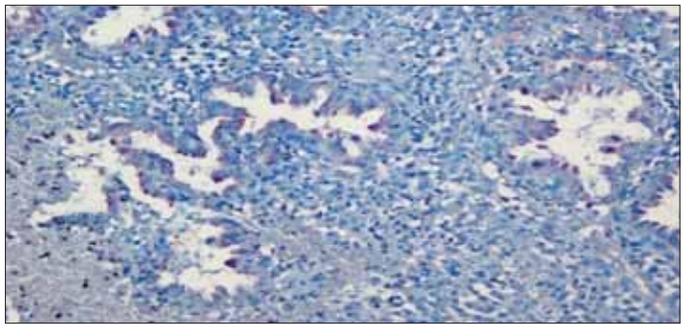

Figure 3. Endometrial gland cells that show focal weak VEGF staining in the IA group. 400X

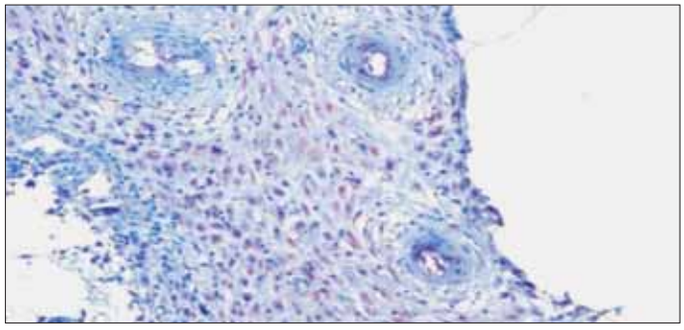

Figure 4. Decidual vascular endothelial cells that show diffuse weak VEGF staining (2) in the IA group. 400X

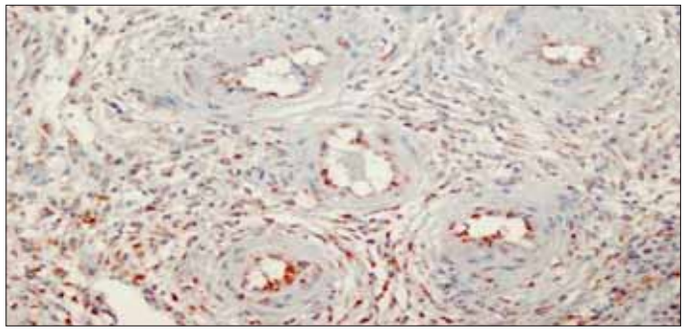

Figure 5. Decidual vascular endothelial cells that show diffuse weak VEGF staining (2) in the IU-D group. 400X

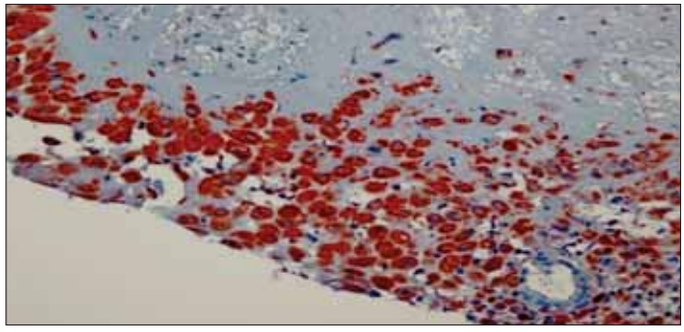

Figure 6. Decidual stromal cells that show diffuse strong VEGF staining in the control group. 400X

stimulation of VEGF-dependent proliferation depended on the dose of AFP and that the optimal dose should be at least 100 ng/ml (9). Sande et al. (22) argued that the best indicator of a threatened miscarriage is the β-hCG level, and that AFP and human chorionic somatomammotropin (HCS) levels were equal indicators but not as reliable as β-hCG. The authors also argued that the AFP level was more diagnostic than HCS because both high and low levels of AFP suggest that a pregnancy could progress unfavorably. In the present study, the mean serum β-hCG levels in the patient groups were significantly lower than in the control group, and the lowest level was measured in the IA group (β-hCG=9491 MIU/ml) (p=0.001). Johns et al. (23) reported that serum β-hCG levels in the first trimester were lower in pregnancies that ended in miscarriage than in those that reached term. Zygmunt et al. (24) highlighted the importance of angiogenesis in early pregnancy, showing that hCG not only had a trophoblast invasion stimulating effect but also was an important angiogenic factor for the feto-maternal unit (10). Numerous studies have shown that defective vascular development underlies many early pregnancy losses and incidents of intrauterine embryonic death (7, 22, 25). hCG stimulates VEGF via the LH receptor, and together they play roles in peritrophoblastic angiogenesis (25). Moreover, previous studies have demonstrated a positive correlation between serum hCG and serum VEGF levels during the early embryonic period, and this is important for a successful pregnancy (25, 26). In a review by Ferrara, the author reported that VEGF was the key regulator in normal and pathological angiogenesis (27). The authors also noted that loss of a single VEGF allele could result in early embryonic death due to insufficient vascularization (27). In this study, we noted that changes in VEGF levels in the 6th-10th gestational weeks, and the conceptus material was significant enough to show defective angiogenesis, which was consistent with concurrent serum hCG and AFP levels. Compared to the control group, weaker staining of cytotrophoblasts, syncytiotrophoblasts and endometrial gland epithelial cells was noteworthy in the both patient groups (IA and IU-D). At this stage, the lower level of β-hCG, which is released in particular from the syncytiotrophoblasts, in the patient groups was attributed to defective angiogenesis. Studies by Demir et al. (28, 29) demonstrated that, in a normal pregnancy, the villous cytotrophoblastic cells, followed by Hofbauer cells of the villus stroma, strongly express VEGF, although the villous endothelium lacked immunostaining for VEGF (10). In this study, we found that Hofbauer cells and decidual stromal cells were stained comparably in all groups. They suggested that vascular endothelium revealed a clear decrease in VEGF staining intensity in normal human placental villi sections from days 22 to 48 post conception of gestation (28). So, this normal developmental physiology can explain why vascular endothelial cells of the placental villi stained weakly in the control group in our study. Kayisli et al. (30) reported that, in normal early pregnancy, vascular endothelial cells of the placental villi revealed weaker VEGF immunoreactivity than trophoblasts in all pregnancy weeks. They evaluated placental vasculogenesis in their study and they evaluated angiogenic proteins (Tie-1 and Tie-2) in the different stages of vasculogenesis related to cell type, villous maturation and pregnancy age during very early placental development (30). They also found that vascular endothelium

displayed a gradual decrease from strong to weak for Tie-2 immunoreactivity. Demir et al. (29) sugessted that expression of VEGF and its receptors VEFR-1 and VEGFR-2, and angiopoietin receptors Tie-1 and Tie-2 in parallel to vascular maturation in human placental villi during very early stages of placental development. Vuorela et al. (31) described diminished placental trophoblastic VEGF immunoreactivity, reduced placental trophoblastic Tie-1 and Tie-2 expression and weaker VEGFR-1, VEGFR-2,Tie-1 and Tie-2 expression in decidual endometrium of spontaneous abortions and these results are similar of our results in which we found that the cytotrophoblasts and syncytiotrophoblasts of the placental villi and endometrial gland cells stained significantly more weakly for VEGF in the patient groups (IA and IU-D) in comparison to the controls. And also they found weak immunostaining for VEGF in vascular endothelium of the placental villi of the healthy controls similar with our study. In their study, decidual stromal cells showed faint VEGF and medium VEGFR-3 immunoreactivity in all study groups (31). They found negative reactions for VEGF and VEGFR-1 and VEGFR-3 of decidual vascular endothelium in all study groups, similar of our results. They reported that recurrent miscarriage might be associated with alterations in the expression of VEGF, VEGF receptors-1,-2,-3 and Tie-1 and Tie-2 receptors (31). Sugino et al. (32) reported that decidual stromal cells stained strongly for VEGF and its receptors between 6 and 8 weeks of gestation. An immunohistochemical study by Kaufmann (33) demonstrated that VEGF, especially in the early stages of pregnancy, is expressed by villous trophoblasts and Hofbauer cells, and the authors considered this to be the initial stage of normal angiogenesis. In the same study, the authors showed that, for both VEGF-A and its receptor VEGFR-2 (KDR/flk-1), this stage corresponded to the transition from secondary villi to tertiary villi, which also occurs at 21-32 days post conception (33). The soluble form of VEGF (VEGRF-1) and placental growth factor (PlGF) are expressed during later stages (branching angiogenesis phase), i.e., between 32 days and 25 weeks of gestation (28-33). Therefore, the levels of serum (soluble) VEGF would not be suitable to predict early pregnancy loss. Hence, we used serum AFP and β-hCG instead of serum VEGF as markers of early angiogenesis. There are no reliable assays available to measure 'total' VEGF in the circulation, and circulating levels of VEGF are almost undetectable in early pregnancy (34). Angiogenic growth factors (VEGF-A and PlGF) have been investigated extensively in normal and abnormal placental vascular development (35-37). Romero et al. (38) reported associations between PlGF and soluble VEGF and late gestational complications such as preeclampsia. Conversely, Muttukrishna et al. (39) demonstrated that soluble vascular endothelial growth factor receptor-1(sFlt-1) and PlGF could be new sensitive predictors of a subsequent miscarriage in patients with TM in the first trimester. They suggested that, with its short half-life in the maternal circulation, sFlt-1 could be a more sensitive marker than other molecules such as hCG, which have a longer half-life (39). They concluded that, whereas the lowering of P1GF may be related to a decreased syncytiotrophoblast synthesis, lower levels of sFlt-1 may be compensatory as the placenta may be producing more VEGF and less sFlt-1, which is bound to VEGF. On the other hand, both VEGF and the receptor production may be lower in patients who subsequently have a miscarriage, thus reflecting lower levels of sFlt-1 in maternal circulation in these cases (39).

Conclusion

At present, there is no reliable marker to predict the clinical outcome of women presenting with TM in the first trimester of pregnancy, although several potential markers have been studied (14, 15).

Our results indicate that early pregnancy loss is associated with low VEGF expression, and this association possibly originates from the villous cytotrophoblasts, syncytiotrophoblasts and endometrial gland epithelium. In line with these results, it is possible to use maternal serum β-hCG together with MS-AFP as markers of defective angiogenesis in the first trimester to predict early pregnancy losses. Randomized studies with larger sample size are needed to confirm this finding. To date, studies are underway to accomplish therapeutic angiogenesis with VEGF and VEGF gene transfer and to prevent pathological angiogenesis with anti-VEGF antibodies (40-44).

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Conflict of interest

No conflict of interest was declared by the authors.

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Pregnancy and trauma: analysis of 139 cases

Gebelik ve Travma:139 Olgunun Analizi

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Abstract

Objective: The aim of this study was to examine the diagnoses and treatment methods and demographical and clinical characteristics of pregnant women who were exposed to trauma and in additon, review of the literature was carried out in this regard.

Material and Methods: One hundred thirty-nine pregnant women who presented at the Yüzüncü Yıl University between January 2006 and September 2009 with local or general body trauma complaints were analysed retrospectively.

Results: The average age of the cases was 26.72±6.29 years and the age group ranging from 21-34 composed the majority. When they were studied according to their etiologies, falls during daily activities formed 43.9%. When they were analyzed in terms of their gestational weeks, 64.46% were in the 3rd trimester. Pregnant cases with trauma resulted in maternal (3 cases) and fetal (9 cases) loss. It was found that 19 cases who had imaging techniques involving radiation and whose gestation was continuing had a problem-free gestation period and healthy children.

Conclusion: It is mandatory to evaluate both mother and fetus together when trauma exposure is in question, the general well-being of the fetus should be provided and the mother should be informed about the presence of advanced trauma life support.

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Key words: Pregnancy, trauma, emergency department, radiation, etiology

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Özet

Amaç: Bu çalışmanın amacı travmaya maruz kalan gebe olguların demografik, klinik özelliklerini, tetkik ve tedavi yöntemlerini incelemek ve literatürü gözden geçirmektir.

Gereç ve Yöntemler: Ocak 2006-Eylül 2009 tarihleri arasında Yüzüncü Yıl Üniversitesi Acil servis' ine lokal veya genel vücut travması nedeniyle başvuran ve gebeliği olan 139 olgu geriye dönük olarak incelendi.

Bulgular: Olguların yaş ortalaması 26.72±6.29 yıl olup, çoğunluğunu 21-34 yaş arası grup oluşturmakta idi. Etiyolojilerine göre incelendiğinde %43.9'u günlük aktiviteler sırasında düşme olup, trimestera göre değerlendirildiğinde %64.46'sı 3. trimester idi. Travmalı gebe olguların 3'ü maternal, 9'u fetal kayıpla sonuçlandı. Radyasyon içeren görüntüleme yöntemi kullanılan ve gebeliği devam eden 20 olgunun gebeliklerini sorunsuz sürdürdükleri ve çocuklarının sağlıklı olduğu öğrenildi.

Sonuç: Travmaya maruz kalan tüm gebelerde, anne ile birlikte fetusun değerlendirilmesi gerekli olup, fetusun iyilik halinin sağlanması, annenin ileri travma yaşam desteğine uyulmasına bağlıdır.

(J Turkish-German Gynecol Assoc 2012; 13: 118-22)

Anahtar kelimeler: Gebelik, travma, acil servis, radyasyon, etiyoloji

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Introduction

The incidence of trauma during pregnancy is 5% and it is known to cause 6-7% of maternal deaths due to non-obstetric reasons. Although fetal mortality and morbidity increase in parallel with the severity of maternal injury, sometimes severe fetal injury may occur even with mild traumas, and trauma may lead to intrauterine fetal demise, abortions, preterm deliveryor ablatio placentae (1-4).

The approach to pregnant trauma patients is still a problem for health care providers due to the physiologic and anatomic changes in pregnancy, drugs that are considered to negatively affect the fetus and anxiety about radiologic tests (4, 5).

This study aimed to retrospectively evaluate the pregnant trauma patients which were significant for both the mother and the fetus and require a multidisciplinary approach, and to obtain epidemiologic data in the light of the literature.

Material and Method

A total of 139 pregnant subjects who were admitted to the Emergency Department (ED) of Yüzüncü Yıl University

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Medical Faculty due to local or multiple trauma (2 or/and other system injuries) between January 2006 and September 2009 were retrospectively screened using the ED registry. Age of the patients, gestational week, season of admission, etiology of the trauma, organ injuries, diagnostic methods like X-ray, computed tomography (CT), magnetic resonance imaging (MRI) and ultrasonography (USG), treatments, data about hospitalization, and maternal and fetal complications were evaluated. Contrast liquid for radiological evaluation was not used.

The analyses of treatments, surgical interventions, supportive therapies (fluids, blood and blood product replacements, tetanus prophylaxis, analgesics, steroids, antibiotic therapy, ice application, wound care, monitorization) were also performed. All patients were examined by the obstetric and gynecology department.

Statistical Analysis

Data analysis was performed using SPSS (Statistical Package for Social Science) 13.0 package program. Descriptive statistics for constant variables were defined as mean±standard deviation (SD), minimum and maximum values, and categorical variables were defined as number (n) and percent (%). Qui-square test was used to determine whether there was a statistically significant difference between groups in terms of categorical variables and student's t test was used to compare the mean values of constant variables.

Results

The mean age of the pregnant women exposed to trauma was 26.72±6.29 years (range 15-45 years) and the majority of the patients were between 21-34 years. Distribution of the cases according to age groups and gestational weeks is shown in Figures 1 and 2, while distribution according to etiology of trauma is presented in Table 1.

The kind of trauma was classified as "local and multiple trauma". While 9 (6.4%) cases were multiple trauma, 130 (93.6%) cases were local.

When the cases were analyzed according to the season they applied to the hospital, it was seen that hospital admissions were most frequent in the summer (33.1%) (n=46) followed by spring (28.8%) (n=40), winter (23%) (n=32) and autumn (15.1%) (n=21). There was no statistically significant difference between the groups (p>0.05).

When the subjects were evaluated according to the tests, it was seen that, while radiologic tests were not used for 110 (79.1%) subjects, radiologic tests for chest, pelvis, skull, vertebra and extremity, CT (cerebral, maxillofacial, lumbal, pelvis) and cerebral MRI were performed for 29 (20.9%) patients (Table 2). Radiation doses and postpartum outcomes of the subjects who had radiologic tests and whose pregnancies continued are shown in Table 3.

Consultations for all subjects were carried out in the Gynecology and Obstetrics Clinic and the fetus was evaluated with obstetric USG. While fetal or maternal complications were not detected in 133 (95.7%) cases, intrauterine fetal demise was detected in 6 cases.

Organ injuries and treatments are presented in Table 4.

Of the followed up pregnant subjects, 3 (2.2%) resulted in maternal and 9 resulted in fetal losses. While the etiology of trauma was a traffic accident in 5 of the fetal loss cases, falls

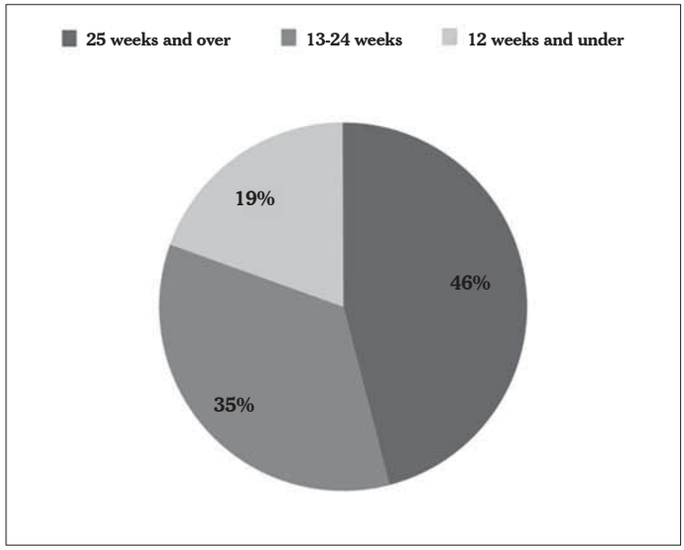

Figure 1. Distribution of the cases according to age groups

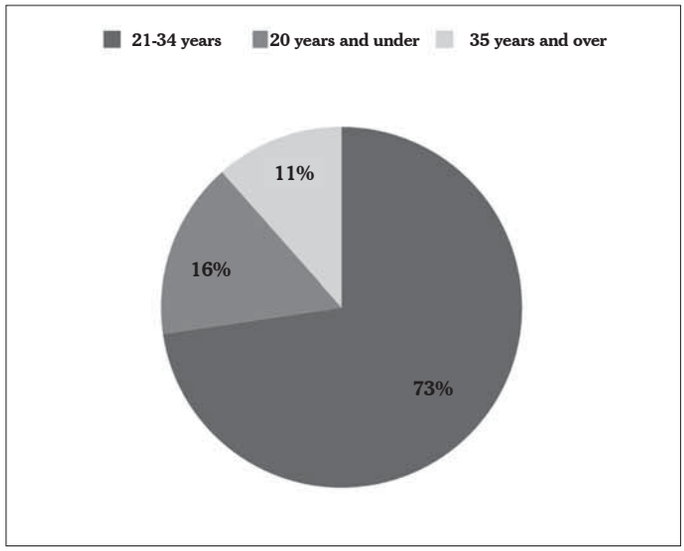

Figure 2. Distribution of the cases according to gestational weeks

Table 1. Distribution of the cases according to etiology

Etiology	n	%
Falls during daily activities	61	43.9
Motor vehicle accident	29	20.8
Falls off	17	12.2
Electrical shock	12	8.6
Pounding	9	6.5
Other	11	8
Total	139	100

were detected in 2, falls off were detected in 1 and burn in the genital area coexisting with spontaneous abortion was detected in 1 case. Causes of fetal exitus were direct fetal injury in 2, fetal hypoxia in 2, abortion in 3 and therapeutic abortion in 2. While the etiology of maternal deaths was traffic accident-related multi-organ injury and hemorrhagic shock in 2, cerebral edema due to cerebral trauma in the course of seizure in 1. While 2 of maternal deaths were 21-34 years group, 1 case was in the 20 years and under group. All three maternal death cases occurred in the third trimester of pregnancy. One of the cases resulting in maternal mortality passed away due to hemorrhagic shock while her operation was being planned and another died during the operation. The third case died owing to respiratory and circulatory failure during the patient's intensive care. There were no fetal heart beats determined in the course of first evaluation of all three cases ending in maternal mortaility.

Table 2. Radiological tests

	n	%
USG	139	100
X-Ray	25	17.9
CT	6	4.3
MRI	2	1.4

Table 3. Fetal outcome of patients with radiation exposure during the trauma evaluation

Radiation dose cGy/Rad	Healthy delivery	Therapeutic abortion	Fetal complication
0.001-0.1	14		-
0.1-0.5	6		-
0.5-5		2	

When the cases were evaluated according to the Glasgow Coma Scale (GSK) scoring, the GSK in134 cases was found to be 15 and between 9-14 in 5 cases.

When the cases were analyzed according to the clinics where they were followed up, it was seen that follow up and treatment of 117 (84.1%) were completed in the ED. One patient (0.7%) was referred to another hospital. Seven (5.1%) patients rejected follow up. Six (4.3%) patients were followed up in the Gynecology and Obstetrics Clinic, 8 (5.8%) patients were followed up in the other wards.

Mean duration of hospital stay was 24 hours.

Discussion

The incidence of trauma during pregnancy is increasing due to active participation in working life (6). However, trauma management in the gravida has been a continuous problem for centuries (2).

Trauma is reported to be seen in 3-7% of all pregnancies and 0.4% of these are reported to need hospitalization (2, 3).

El-Kady et al. (7) reported that motor vehicle accidents, falls and pounding were included in the etiology of trauma and more than half occurred during the last trimester, Tinker et al. (1) reported that the most common causes for trauma were falls (51.6%) followed by motor vehicle accidents, traumas most commonly occurred in the 2nd trimester and falls were more frequent during the 2nd and 3rd trimesters. Connolly et al. (8) and Nannini et al. (9) reported that the most frequent causes were motor vehicle accidents, falls, pounding and burns, respectively and especially falls were most frequent during the 2nd and 3rd trimesters.

The most common causes of trauma were reported as motor vehicle accidents (55%), falls (23%), assaults (21%) and burns (1%) (10, 11). The period when trauma is seen most frequently was the 3rd trimester in this study also, as in that of El-Kady et al. Trauma etiologies were detected as falls during daily activities

Table 4. Affected organs and therapeutic approaches

Organ injuries	n (%)	Treatments
None	78 (56.1)	-
Soft tissue trauma	43 (30.9)	*
Vaginal bleeding and skin incision	3 (2.1)	*, Suture
Maxillofacial trauma	4 (2.7)	*, close reduction of mandible fracture (in 1 case)
Femur fracture	3 (2.1)	*, close reduction
Clavile fracture	2 (1.4)	*, 8 bandage
Fracture of the tibiae and fibulae	2 (1.4)	*, close reduction
Fracture of pelvis and femur	1 (0.71)	*, pelvipedal splint, close IMN**
Pelvis Fracture	1 (0.71)	*, skeletal traction
1-2° burns	1 (0.71)	*
Cut wound of the hand	1 (0.71)	Suture
Vertebral fracture	1 (0.71)	*

* Analgesic, antibiotic, steroid treatment, tetanus prophylaxis, ice application, fluid and erythrocyte suspension replacement according to the indications, ** İntra-medullary nailing

(43.9%) and motor vehicle accidents (20.8%) similarly to that of Tinker et al. (1). The main cause of frequent falls in the 2nd and 3rd trimesters may be the displacing of the center of gravity due to weight gain and enlargement of the uterus.

While Chang et al. (12) reported that the major causes of fatal traumas were motor vehicle accidents, homicide and suicide, Harper et al. (13) reported homicide, motor vehicle accidents, pounding and assaults (gunshot wounds, stab wounds, drownings), falls and suicide attempts as the major causes of fatal cases. Tinker et al. (1) reported that maternal and fetal deaths were most commonly caused by motor vehicles. In our study, all maternal deaths occurred during the 3rd trimester and the most common etiologic factor was motor vehicle accidents. The mortality in motor vehicle accidents is high as they lead to high energy trauma.

Weiss et al. (14) and McFarlane et al. (15) reported known risk factors for trauma during pregnancy as young maternal age, drug and alcohol use and domestic violence. Tinker et al. (1) reported risk factors as young maternal age, smoking and alcohol use, seizures, obesity and women's participation in working life. In this study, the mean age of the subjects was 26.72±6.29 and alcohol and drug use were not detected. One of the dying subjects had a history of seizures. Absence of alcohol and drug use may be explained by the sociocultural properties of the region in which the study was conducted.

Risk factors for fetal deaths due to maternal trauma have been reported as high ISS (injury severity score), falling out of the motor vehicle, maternal pelvic fracture, crash, maternal alcohol use and smoking, young maternal age and motorbike accidents (7, 16). In the study presented here, the etiology of fetal losses was traffic accidents in 55.5% of the cases and complications like direct fetal injury, fetal hypoxia and therapeutic abortion related to traffic accident.

The ratio of trauma-related fetal mortality is 65%. While the most common cause of fetal losses had been accepted as maternal death in previous years, at present it is accepted as the result of developments in the approach to the trauma, the most common cause of fetal losses has been reported as fetal hypoxemia developing secondary to maternal shock (4, 17). Other causes of fetal losses have been reported as maternal hypotension, abruptio palcentae, rupture of the uterus, direct uterine trauma and disseminated intravascular coagulation (DIC) in various studies (18-21). Ali et al. (18) hold DIC developing due to circulating placental products responsible for fetal losses. In our study, the ratio of fetal losses is 6.5% and is caused by spontaneous abortion (3 cases), fetal hypoxia (2 cases), direct fetal injury (2 cases) and therapeutic abortion (2 cases).

Stafford (22) and Baed et al. (3) reported that the degree of maternal injury was not an important factor for permanent fetal injury and the ratio of trauma-related fetal losses was higher than the ratio of maternal deaths. Shah et al. (23) reported the maternal death rate as 3.5%, Esposito et al. (10) reported fetal death rate as at least 5%. In this study, while the ratio of fetal losses was 6.5%, maternal death rate was 2.2% and fetal losses were more than maternal deaths.

The ratio of hospitalization in pregnant trauma patients has been reported as 5-24% (24). In the United States, indications for hospitalization due to trauma during pregnancy not resulting in delivery are fractures, dislocations, sprains and hurts (6). In our study, consistent with literature, the most common indication for hospitalization was bone fractures and the ratio of hospitalization was 10.8%.

Despite the absence of specific literature concerning pregnant trauma patients, obstetrics consultation is recommended. In clinical studies, the patients with normal examination and monitorization findings are recommended to be followed up for at least 2-6 hours (2). Level 2 studies indicate that fetal heart monitorization should be carried out for at least 6 hours in a pregnant woman with a gestational age of over 20 weeks. Monitorization should be continued in cases of uterine contractions, vaginal bleeding, abnormal fetal heart rate pattern, uterine tenderness, severe maternal injury and rupture of amniotic membranes (2). Level 3 studies indicate that the fetus should be evaluated in the early period and optimum resuscitation of the mother according to advanced trauma life support should be obtained (2). Oxygenation should certainly be provided due to the harmful effects of hypoxemia on the fetus, even when there is no need for maternal intubation (6). Also in this study, all cases were consulted at the Gynecology and Obstetrics Clinic and the fetus was evaluated with urgent obstetric ultrasonography. Consistent with the literature, fetal cardiac monitorization was performed for evaluation of pregnant women in the 2nd and 3rd trimesters and adequate oxygenation of the mother was provided. All pregnant women were monitored for possible obstetric complications such as premature delivery, ablatio placentae. 84.1% of the cases were monitored in the ED for at least 2-6 hours and discharged thereafter. The mean duration of hospital stay was found to be 24 hours.

X-ray, tomography and nuclear imaging methods are a significant cause of anxiety for the patient herself, her family and physician (25). Serum β-hCG levels should be obtained for all females in the reproductive age who were exposed to trauma, and protected X-rays should be obtained as possible (26). The effects of ionizing radiation on an embryo and fetus can include: pregnancy loss, malformations, neurobehavioral abnormalities, fetal growth retardation, and cancer. However, there is no defined threshold and the amount of radiation does not predict the severity of the disease (27).

The American College of Obstetrics and Gynecology (ACOG) reported that 5 rad radiation does not lead to fetal loss, still birth, birth defects or childhood leukemia (2). Nevertheless, Groen et al. (27) stated that a low dose of radiation causes increased risk in childhood leukemia. On the other hand, the nature and extent of determining effects of radiation on pregnancy depend on the radiation dose and trimester of the pregnancy. Animal studies show that, during the first 2 weeks after conception, a dose as small as 10-20 rad can be lethal for an embryo. The threshold for fetal death increases throughout gestation as the fetus develops (27). Despite this, anxiety regarding the harmful effects of radiation is not a drawback for X-ray imaging necessary for making a diagnosis (28). In this study, various imaging methods have been used by preserving the abdomen when there was any indication. Except for 2 women who were exposed to trauma and survived, radiation dose was

below 0.5 rads. Two subjects who were subjected to 5 rads of radiation underwent therapeutic abortion and 20 subjects who were given radiologic tests and whose pregnancies continued were seen to experience no problems in their pregnancies and their babies had no pathologies.

In order to save the baby, caesarean section should be considered in pregnant women whose gestational age is above 24 weeks and who are about to die. Delivery of the baby in 4-20 min following maternal death is of great importance in terms of neurologic outcomes (29). In this study, urgent caesarean section was not considered as fetal heart sounds could not be heard in the initial evalaution of the subjects who died.

In conclusion, appropriate circulation and oxygenization should be obtained in all pregnant women exposed to trauma, required tests should be performed by taking advantages and disadvantages into account and patients should be monitored closely with a multidisciplinary approach. It should be kept in mind that securing the well being of the baby depends on optimum maternal respiratory and circulatory support and complying with recommendations for advanced trauma life support. The patient should be examined in the Obstetrics and Gynecology Clinic for evaluation of the well being of the baby. The pregnant women and relatives should be informed that maternal alcohol and cigarette use, and the presence of diseases like seizures would increase susceptibility to trauma and lead to poor post-traumatic fetal and maternal outcomes.

Conflict of interest

No conflict of interest was declared by the authors.

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This article will be credited by TMA within the scope of CME/CPD.

Evaluation and management of voiding dysfunction after midurethral sling procedures

Midüretral sling işlemi sonrası işeme disfonksiyonunun değerlendirilmesi ve yönetimi

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Abstract

Midurethral slings have become the most popular surgical procedure for the correction of stress urinary incontinence in women. Urinary retention or obstructive voiding symptoms may arise from partial urethral obstruction as a result of oversuspension of the urethra or exaggerated tension. Fortunately, most cases of voiding dysfunction are transient and resolve spontaneously within days. Clean intermittent self-catheterization is the mainstay of conservative treatment. If symptoms persist, tape mobilization, incision or urethrolysis may be performed. Recurrent stress urinary incontinence may occur in a small group of patients, who may benefit from another incontinence treatment. (J Turkish-German Gynecol Assoc 2012; 13: 123-7)

Key words: Incontinence, midurethral sling, voiding dysfunction, urinary retention, urethrolysis

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Özet

Midüretral slingler, kadınlarda stress idrar inkontinansının cerrahi tedavisinde en çok tercih edilen işlem haline gelmiştir. Üretranın fazla asılması ya da meşin daha sıkı yerleştirilmesi tam idrar retansiyonuna veya obstrüktif işeme semptomlarına neden olabilir. Akut idrar retansiyonu hemen müdahale gerektirir. Neyse ki, çoğu işeme disfonksiyonu geçicidir ve bir kaç gün ile hafta içinde kendiliğinden çözülür. Temiz, aralıklı self kateterizasyon, konservatif tedavinin temelini oluşturur. Konservatif tedaviye rağmen işeme disfonksiyonu devam ederse meş gevşetilebilir, kesilebilir ya da üretrolizis uygulanabilir. Bu da hastaların küçük bir kısmında tekrar tedaviyi gerektirebilecek düzeyde stres idrar inkontinansına yol açabilir.

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Anahtar kelimeler: İnkontinans, midüretral sling, işeme disfonksiyonu, idrar retansiyonu, üretrolizis

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Introduction

Midurethral slings have revolutionized the surgical management of stress urinary incontinence (SUI). Tension-free vaginal tape (TVT), introduced in 1996 by the Ulmsten and Petros, was the first widely available midurethral sling. Since its introduction over 10 years ago, it is estimated that approximately 1 million procedures have been performed worldwide (1). In addition, other techniques such as the suprapubic-arc sling (SPARC), which differs from TVT with respect to the direction of trocar passage, have also gained popularity. In 2001, Delorme described the transobturator tape (TOT) midurethral sling (2). Unlike TVT, it is placed using a transobturator approach rather than a retropubic one. This approach is generally considered to have the advantages of low morbidity, reduced costs and shorter hospital stay (3, 4).

Regardless of the technique, anti-incontinence surgery may change bladder outlet resistance. Voiding dysfunction (VD) is a well-recognized complication of midurethral sling procedures. However, the definition of VD is not consistent in the literature. The vague definition of "impaired bladder emptying immediately following surgery" is often used. Some researchers have studied failed voiding after outpatient midurethral sling as the outcome measure for postoperative voiding function. Most cases of mild postoperative voiding dysfunction appear to resolve with expectant or conservative management. Transient urinary retention after TVT has been reported in up to 17% of patients, but it is important to distinguish this from voiding dysfunction, which is commonly more clinically significant (5). For example, in the Stress Incontinence Surgical Treatment Efficacy Trial (SISTEr), voiding dysfunction was defined as any need for bladder catheterization after 6 weeks, or reoperation for sling takedown (6). The incidence of postoperative retention lasting longer than 4 weeks or requiring intervention following midurethral slings is reported as 2-4% (7). A recent systematic review and meta-analysis of 33 randomized controlled trials found lower rates of voiding difficulties after transobturator sling when compared to retropubic sling procedures. With regards to comparisons with retropubic tape, TVT and intravaginal slingplasty had similar complication rates, whereas SPARC was complicated by higher rates of voiding lower urinary tract symptoms and reoperations (8). However, the most recent Cochrane review and meta-analysis, which compared the incidence of postoperative VD by the midurethral sling approach, specifically between the transobturator and retropubic approaches, found no difference across 24 trials (9).

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Risk factors

The debate on the risk factors for VD following midurethral slings continues despite several studies which have focused on this topic.

Demographics and other associated factors

Due to variable results from different studies, it is difficult to make a decisive conclusion about the demographic predictors of VD after midurethral sling. Sokol et al. (10) found that older age, low body mass index (BMI) and postoperative urinary tract infections (UTI) were independently associated with prolonged time to adequate voiding; however, in this study, a previous history of incontinence surgery was the only independent variable predictive of urinary retention. Barron et al. (11) showed that parity over two and preoperative anxiety were independently associated with successful immediate voiding trial after a TVT procedure in their retrospective review of 126 patients. Barber et al. (12) have found that poor preoperative detrusor function may have a role as well. Women frequently have concurrent abdominal or pelvic surgery at the time of midurethral sling placement. Shukla et al. (13) described a trend toward long-term voiding difficulty when women with low preoperative flow rates underwent concurrent posterior vaginal repairs. Most recently, a multicenter case-control study by Molden et al. (14) reported that preexisting obstructive voiding symptoms, the retropubic approach and concurrent surgery at the time of sling placement were independent risk factors for sling revision.

Urodynamic parameters

According to several studies, low preoperative peak flow rates or abnormal uroflow can be predictive of postoperative VD after midurethral sling procedures. In a retrospective review of 59 women who underwent TVT, Wang et al. (15) described VD as the following: postvoid residual volume (PVR) of more than 100 ml, urinary frequency greater than six times per day or two times per night and urinary stream perceived as abnormal by the patient. In this study, abnormal uroflowmetry, which was defined as flow that did not have a normal configuration or pattern, was found to be an associated factor. A prospective trial of 89 women who underwent the midurethral sling procedure showed low peak flow rate to be the only independent variable for a successful initial voiding trial (16). This is consistent with another retrospective study of 375 patients by Hong et al. (17), which also found lower preoperative peak flow rates as a risk factor. In this study, the parameter for VD was defined as the need to catheterize for 72 hours or longer after surgery. The mean preoperative peak flow rates in the group with and without urinary retention were 22.3 and 29.7 ml/s, respectively. Sung-Tae et al. (18) suggested that a peak flow rate lower than 15 ml/s was the most predictive variable for postoperative VD.

Some studies investigated the effect of preoperative residual on postoperative VD. In a report of 205 TOT and 213 TVT, Barber et al. (12) found high preoperative PVR to be a consistent risk factor for prolonged postoperative catheterization and slow resumption to normal voiding. In contrast, Minassian et al. (19) retrospectively analyzed 138 patients who underwent anti-incontinence surgery, including TVT, Burch or pubovaginal slings and found that patients with early postoperative VD (defined as a residual of >200 ml at discharge) had lower preoperative PVRs than those who did not (50 vs. 75 ml).

Barron et al. (20) reported that a Valsalva leak point pressure of more than 60 cm H_2O and a maximum urethral closure pressure of more than 20 cm H_2O were associated with a successful immediate voiding trial.

Despite the aforementioned studies, numerous other studies have shown no association between postoperative VD and the parameters such as preoperative peak flow rate, preoperative PVR, Valsalva leak point pressureor severe intrinsic sphincter deficiency (15, 18, 20-24). We were not able to find any report which studied the type of voiding mechanism and detrusor pressures with respect to VD after midurethral slings (25).

Evaluation and diagnosis

Urethral obstruction after midurethral sling procedure surgery can manifest itself in a variety of ways. Patients may complain of slow urinary stream, splitting or spraying, hesitancy or intermittency with the urine flow, feelings of incomplete emptying, prolonged voiding, straining to void and elevated PVR. Urinary retention may also lead to overflow incontinence, recurrent UTI and painful urination. They may also develop de novo or worsening detrusor overactivity.

The optimal evaluation for patients with postoperative VD is poorly defined in the literature. One should start with a careful pelvic and rectal examination which may identify underlying findings such as abnormal urethral angulation, a foreshortened, non-pliable vagina, non-mobile urethra, pelvic hematoma or fecal impaction. During evaluation, UTI should be ruled out with urinalysis and culture as this can manifest itself with a variety of symptoms. There is a no general consensus on the appropriate PVR volume to diagnose urinary retention. In some studies, PVR cutoff for urinary retention has varied from 100 to 200 ml (23, 26). Some authors choose to use a percentage of total volume as an indicator. Techniques to evaluate the adequacy of postoperative bladder emptying also vary tremendously. In a prospective study, Kleeman et al. (27) found that the back fill technique after vaginal prolapse or continence surgery predicted adequate bladder emptying in 91% of women who voided 50% or greater of the amount instilled and in 100% who voided 68% or greater of the total volume.

The best location for cystourethroscopy and urodynamic studies is controversial. Some authorities advocate videourodynamic studies to diagnose obstruction prior to the reversal of anti-incontinence surgery. Under the ideal circumstances, urodynamic evaluation would differentiate patients with high-pressure, low-flow voiding consistent with obstruction and patients with detrusor hypocontractility. In a study by Carr and Webster, urodynamic parameters, previous surgery, time from suspension to urethrolysis and the surgical approach were not good predictors for urethrolysis (28). Cystourethroscopy may be useful to rule out bladder pathology, a hypersuspended bladder neck and foreign bodies such as retained sutures, mesh or stones. In another study by Petrou et al. (29), urethrolysis outcomes were not significantly different when urodynamic parameters were used instead of clinical criteria. At the present

time, there does not appear to be conclusive evidence to support routine implementation of these tests before any surgical corrective procedure.

Treatment

Conservative treatment

Transient postoperative urinary retention has been reported to be within the range of 2.5 to 36% after surgery for SUI and pelvic organ prolapse (POP) (30, 31). Suprapubic catheter placement, which was common before midurethral sling procedure was introduced, has been widely abandoned as prolonged postoperative VD is uncommon after this minimally invasive approach. Temporary Foley catheter drainage, timed voiding, biofeedback, pelvic floor muscle training, clean intermittent self-catheterization, selective medical treatment and urethral dilatation have been successful to some degree in managing postoperative VD. Expectant management is initially appropriate as early retention may be due to postoperative pain, edema and inflammation. Indeed, most patients with transient postoperative urinary retention resume normal voiding following midurethral sling within 1-2 days of the procedure. Return to normal voiding may be delayed for 1-2 weeks in women with a history of prior or concomitant surgery for SUI or POP (32, 33).

Behavioral treatment begins by encouraging the patient to create a relaxing environment and taking adequate time for voiding. They are instructed to slow down, take a deep breath, relax the body, relax the pelvic floor muscles and wait for the urine to flow. Rushing can inhibit pelvic floor relaxation. Valsalva voiding can increase pelvic floor tension, resulting in incomplete emptying. Anecdotally, some women have benefited from double voiding, or lingering until another detrusor contraction brings about more complete emptying. Perineal or vaginal biofeedback, which can be useful for restoring muscle tension, is a particularly important practice for patients with VD. To facilitate relaxation, these patients can focus more on the relaxation phase, which can be extended with a 1:2 ratio or longer as appropriate (34).

Medications play a small role in the treatment of postoperative VD. Diazepam 2-10 mg 1-3 times daily and baclofen 5-10 mg twice daily may also be used in an effort to reduce urethral sphincter and pelvic floor spasm from pain (35). Some may use an α-adrenergic antagonist such as terazocin or doxazocin, but there are limited scientific data. These antagonists, which can cause postural hypotension as a significant side effect, are also effective for functional rather than anatomic bladder outlet obstruction. Antimuscarinic medications may be helpful when there are predominantly irritative symptoms and a normal PVR. Specifically, oxybutynin has a combination of antimuscarinic, antispasmodic and local anesthetic properties. However, these medications are contraindicated in women with urinary retention. Vaginal estrogen may be useful for reducing irritative voiding symptoms and recurrent infections (36).

When a patient cannot empty two thirds of her bladder volume within a few hours after an outpatient midurethral sling procedure, the first appropriate step is catheterization. This initial treatment relieves the immediate distress of a full bladder and prevents permanent bladder damage. Continuous transurethral catheterization is less preferable as it is associated with higher rates of UTI, urinary tract irritation, development of bladder calculi and a decrease in bladder capacity over time. Therefore, many institutions adopted teaching patients how to perform self-catheterization either before or after the procedure. If urinary retention with voiding difficulty persists, further treatment will be necessary.

Clean intermittent self-catheterization (CISC) is catheterization performed by the patient or a caregiver on a periodic basis to empty the bladder. It is important to ensure that the bladder never holds more than 500 ml of urine at one time. Bladder distention can result in upper urinary tract reflux, reduced vesical blood flow and UTI. CISC is performed three or four times daily until the residual decreases to less than 100 ml, or at most 50% of the voided volume (37).

Although several reports have shown some benefit with urethral dilatation (17, 38), recent reports have proven urethral dilation to be ineffective in most patients with urethral obstruction after TVT procedures. Additionally, repeated urethral dilation may predispose to the development urethral erosion and could induce scarring of the urethra (24, 39, 40). The place of urethral dilatation for urethral obstruction is yet to be studied in a controlled and randomized fashion.

Surgical treatment

When these conservative measures fail, surgical intervention is indicated. Fortunately, persistent postoperative VD is a relatively rare complication after midurethral sling placement. Otherwise, some authors have reported that waiting too long may result in unresolved irritative bladder symptoms such as frequency, urgency and urge incontinence (41-43). In the era of traditional pubovaginal slings, which caused VD more often, most surgeons delayed a release procedure until about 3-6 months after the procedure. This has changed to 2 weeks with midurethral slings. Despite some contradicting reports, most of these release procedures have been effective in correcting VD. The mesh still provides support to the urethra laterally even after the obstruction is released at the midline (43).

After midurethral sling procedures, surgical release for refractory postoperative VD procedures has been indicated for 1-2% of women (8, 44, 45). This is more common after retropubic sling procedures (12, 44, 46). Surgical intervention for VD may consist of mobilization, division of the sling or urethrolysis typically through a vaginal approach. Retropubic or a combined vaginal and retropubic technique are rarely necessary. Successful sling mobilization is possible only in early interventions. If the mobilization attempt fails, the sling is cut at the midline or laterally. Urethrolysis entails more dissection and entry into the retropubic space. It may occasionally require mobilization of the urethra from the pubic bone. Unless the release procedure is delayed too long, urethrolysis is rarely necessary for today's slings. Although there are no well-designed and randomized studies comparing the abdominal and vaginal routes, retrospective data indicate success rates approaching 85%, comparable for retropubic and vaginal routes. Most surgeons prefer transvaginal urethrolysis rather than retropubic or suprameatal approaches (37).

Mobilization or incision of the midurethral sling is highly successful in improving voiding dynamics and should be considered the first line therapy. In a large review by Klutke et al. (24), 17 of 600 patients (2.8%) required reoperation for postoperative VD. Tape release was performed at a mean of 64 days after TVT placement and 16 patients remained continent. Hong et al. reported that 4 of 375 (1%) patients who underwent TVT required tape release or cutting at an average 61 days after the operation and three patients (0.8%) underwent a second TVT procedure for recurrent SUI (17). Sling loosening was reported by Nguyen within approximately 1 week after TVT placement. All patients were continent after mobilization, and quality of life scores of the non-voiders did not differ from those of voiders 1 year after surgery (47). In a retrospective study by Price et al. (48), 33 patients required mobilization of TVT to treat postoperative VD. In each case, the TVT was mobilized and loosened without dividing it within 2 weeks after the original procedure. Voiding function subsequently returned to normal in 29 out of 33 women with no recurrence of original stress incontinence. The four remaining women had the tape divided.

Croak et al. (49) reported that TVT tape dissection using a midline incision for obstructive urinary retention was successful in five (6.4% of 109 TVTs) patients; four of these (80%) remained continent. The incision was performed within 4 weeks of initial placement. A nationwide analysis of obstruction after surgery was performed by Laurikanien and Kilholma. A retrospective review of 9040 patients who underwent a TVT procedure was reviewed. The sling was transected at the midline, uni- or bilaterally, or the sling was resected. Forty-nine percent of the patients were completely cured of their retention and four patients (12%) continued to have retention after lysis. Repeat sling lysis and urethrolysis were options used for refractory retention (50).

A lateral incision technique might be particularly beneficial for avoiding urethral injury in cases whose tape cannot be identified. Long et al. (51) described a technique transecting the tape lateral to the midline on the right side of the periurethral fascia, leaving the tape in the shape of a J underneath the urethra. This procedure had a success rate of 100% with VD in seven women utilizing a lateral incision, but stress incontinence recurred in 28.6% of them. Game et al. (52) presented results from a series of 30 women requiring sling lysis with a single lateral incision over a four-year period. 70% were continent after intervention, and two women developed recurrent SUI. Recently, Kasturi et al. (53) reported 100% success in 15 women undergoing the J cut technique for postoperative VD following midurethral sling. Zubke et al. (54) managed three patients with urethral obstruction after TVT with a novel technique. They cut the tape at the midline with a transvaginal approach and sutured the edges of the tape to a Prolene mesh, thus lengthening the tape. All three patients were continent and resumed normal voiding after intervention.

Conclusion

Surgery for stress incontinence has increasingly shifted towards minimally invasive approaches. Although there are no well-designed and prospective randomized studies which evaluated VD following midurethral sling procedures as the primary outcome, we have gained significant experience over the last decade. Hypersuspension of urethra by sling can cause symptoms of bladder emptying and low urinary tract. Most cases respond to conservative treatment with temporary indwelling catheter and CISC. If symptoms persist, as occurs in 1-2% of patients, sling mobilization and/or incision almost always resolve the problem. Urethrolysis is rarely necessary for VD after midurethral sling procedures. In a small group of women, another intervention operation may be needed for recurrent stress urinary incontinence.

Conflict of interest

No conflict of interest was declared by the authors.

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Three-dimensional ultrasound as a predictor of pregnancy in patients undergoing ART

ART uygulanan hastalarda gebeliği öngörmeye yarayan bir araç olarak üç boyutlu ultrason

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Abstract

Different ultrasound parameters have been used to assess endometrial receptivity during ART treatment, including endometrial thickness, endometrial pattern, endometrial volume, Doppler of uterine arteries and endometrial blood flow. However, conflicting results have been reported with regard to their role in the prediction of pregnancy in ART treatment. The 3D ultrasound with power Doppler provides a unique tool with which to examine the blood supply of the whole endometrium and subendometrial region. Volume assessment can also be precisely performed by 3D ultrasound. Based on a med-line research and on our experience, the clinical use of 3D ultrasound is discussed in this review article.

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Özet

ART tedavisi sırasında endometriyumun kabul ediciliğini değerlendirmek için farklı ultrason parametreleri kullanılmaktadır. Bunlar içinde endometriyal kalınlık, endometriyal patern, endometriyal hacim, uterus arterlerinin ve endometriyal kan akımının Doppler'i yer almaktadır. Bununla beraber, ART tedavisinde gebeliğin öngörülmesindeki rolleri ile ilgili olarak birbiriyle çelişen sonuçlar bildirilmiştir. Bütün endometriyumun ve subendometriyal bölgenin kan akımının incelenmesinin mümkün olduğu power Doppler'li 3D ultrason yegane bir araç sağlamaktadır. 3D ultrason ile hacim değerlendirmeleri de kesin olarak yapılabilmektedir. Med-line araştırması ve kendi deneyimimize dayanarak, bu derleme makalede 3D ultrasonun klinik kullanımı tartışılmaktadır. (J Turkish-German Gynecol Assoc 2012; 13: 128-34)

Anahtar kelimeler: 3D, ultrason, power Doppler, IVF, ART

Geliş Tarihi: 13 Mart 2012 **Kabul Tarihi:** 23 Nisan 2012

Introduction

Three-dimensional ultrasound (3D-US) is a rapidly developing area of clinical imaging. The ongoing research and continuous improvements in 3D-US have a significant impact on many areas of clinical application (1-6).

Successful implantation depends on the interaction between the blastocyst and the endometrium. Thickness of endometrium and a good blood supply are considered to favour pregnancy (7-9). Increased endometrial and subendometrial vascularity have been found to be higher in patients with live births following Assisted Reproductive Technology (ART) than in those who have suffered a miscarriage (10). However, conflicting results are reported with regard to their role in the prediction of pregnancy in ART treatment (11-13).

We developed this review through the use of Medline, a digital database, articles on three-dimensional ultrasonography and pregnancy outcomes in patients undergoing ART. In addition, we used the data we collected over the past 12 years and our clinical experiences.

Volume calculation

Volume calculation by 3D-US will be performed by Virtual Organ Computer-Aided Analysis (VOCAL) program. VOCAL is the combination of 3D ultrasound tissue presented as voxels and geometric information of surfaces in a 3D dataset. It is defined by rotating an image plane around a fixed axis and defining 2D contours of each plane. The 2D contours of the polygonal area in each plane can be defined automatically or manually. There are four rotation angles to choose from: 6°, 9°, 15° and 30°, and because the entire dataset is rotated about 180,° these result in 30, 20, 12 and 6 planes, respectively, being available for measurements. The result is converted to mL or cm^3 ultrasound units (Figure 1).

In a previous study we documented the reproducibility of the endometrial volume measurement in 57 consecutive patients undergoing in-vitro fertilization (14). The interobserver reliability was 0.96 with an intraobserver reliability of 0.94. High reproducibility was also obtained for ovarian volume and power Doppler indices (15-19).

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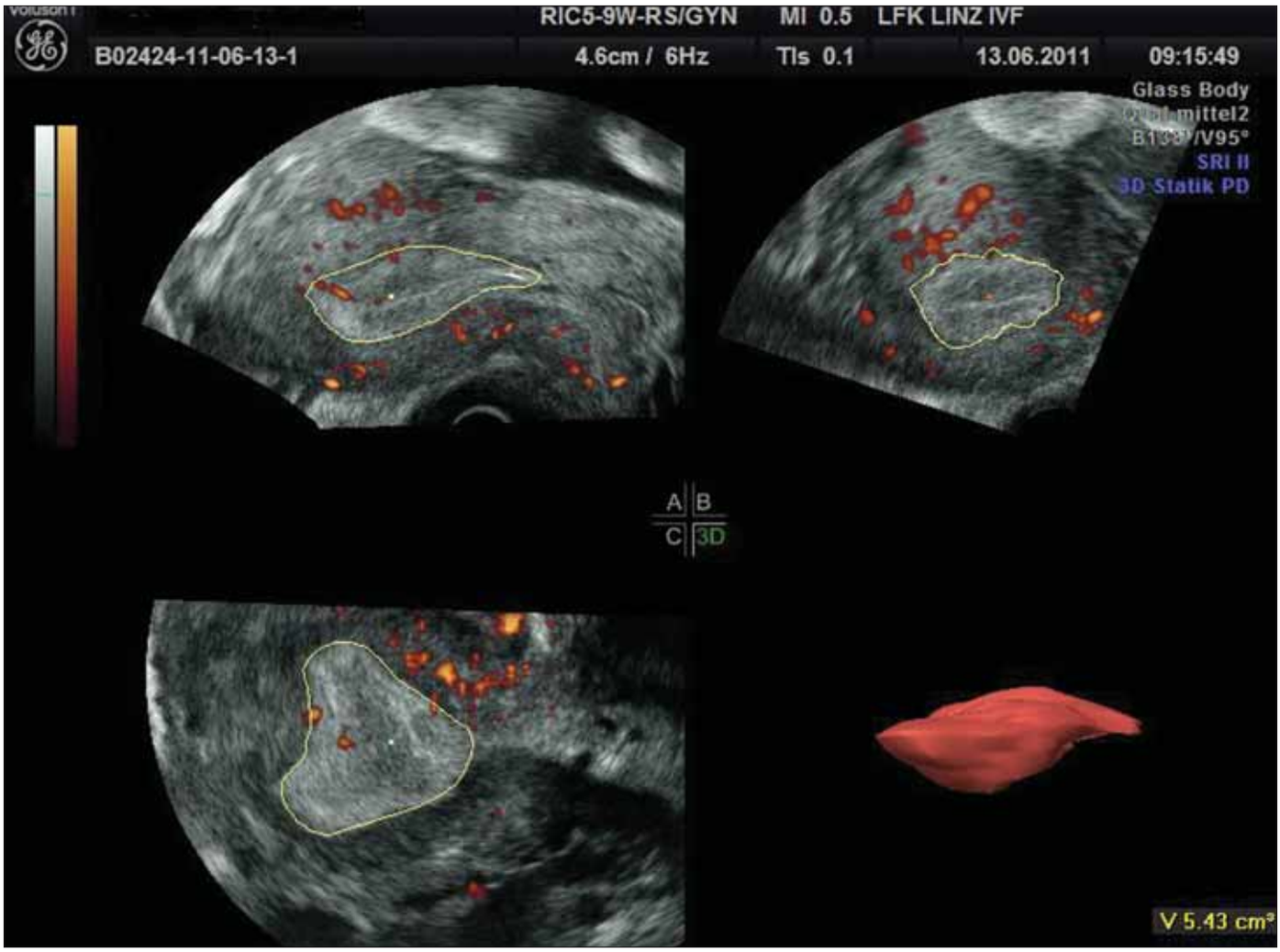

Figure 1. 3D-volume calculation in a VOCAL program. Note the 2D contours of the endometrium have to be defined in different planes

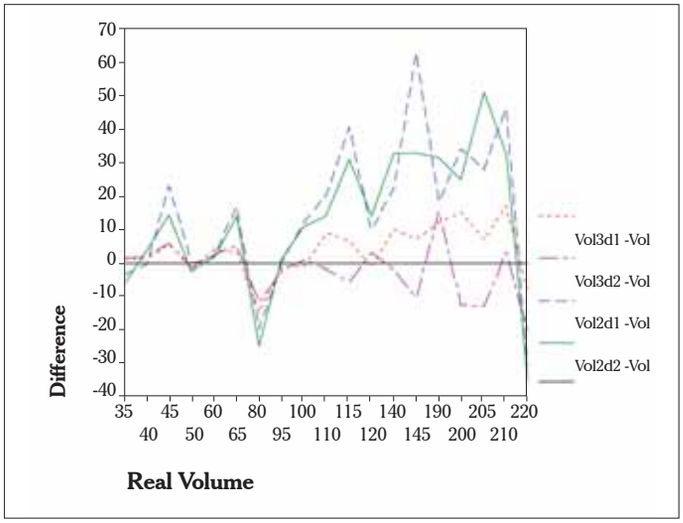

Figure 2. Differences of estimated volumes and real volumes (vertical axis) are plotted against the real volumes (horizontal axis). For a better view, the single points of each method (2D, 3D, first, second measurement) were connected by lines

We evaluated the in-vivo accuracy of 3D volume measurements of the uterus (20). In this study, transvaginal ultrasound examinations were performed in 48 consecutive patients before hysterectomy. Immediately after hysterectomy, the true volume was measured in a water bath. Although the volumes estimated by the 3D method were not significantly different ($p=0.126$), the volumes estimated by the 2D method were significantly different ($p=0.005$). The mean error rate of the 3D volume measurement was 7.4%, and 22.2% for the 2D volume measurement (Figure 2, Table 1). The limitation of the uterine volume measurement by 3D was the uterine size. An uterus more than 220 ml. could not be measured accurately. The high accuracy of volume measurements by 3D ultrasound was also confirmed by other studies (21-25).

Volume storing

Although 2D ultrasound makes it possible for physicians to make important contributions to patient management, there are occasions when it is difficult to develop a 3D impression of the patient's anatomy. The typical approach to overcome this problem is to scan repeatedly through the region-of-

Table 1. Shows that the median of the absolute differences for 3D (estimated volume-real volume) lies between 6.4 and 6.9, whilst for 2D the median lies between 16.9 and 17.4

	Number	Minimum	Median	Maximum	Mean	Standard-deviation	Variance
2D Vol 1	35	31.2	113.7	274.2	121.6	69.8	4871.2
2D Vol 2	35	28.8	114.0	299.3	120.5	70.2	4931.9
3D Vol 1	35	36.2	102.7	237.6	111.8	61.0	3719.1
3D Vol 2	35	35.4	104.5	241.6	108.5	56.5	3192.8
Real Volume	35	35	100	220	109	57	3199
Vol3D1-Vol*	35	-20.10	3.40	44.30	2.98	11.35	128.74
Vol3D2-Vol*	35	-21.10	-1.50	51.60	-.34	12.37	153.09
Vol2D1-Vol*	35	-47.60	15.50	84.20	12.79	27.26	743.15
Vol2D2-Vol*	35	-45.80	14.00	109.30	11.65	28.03	785.45
ABS(Vol3D1-Vol)**	35	.20	6.40	44.30	8.20	8.29	68.68
ABS(Vol3D2-Vol)**	35	1.10	6.90	51.60	8.46	8.92	79.48
ABS(Vol2D1-Vol)**	35	3.20	16.90	84.20	23.98	17.88	319.63
ABS(Vol2D2-Vol)**	35	5.20	17.40	109.30	23.20	19.26	370.99

*Difference of estimated volume-real volume, **Absolute difference of estimated volume-real volume

interest (ROI) to make an exact diagnosis. This process can be time consuming and tedious. Furthermore, time consuming examinations can alienate the patients. In contrast to 2D ultrasound, which allows particular planes, 3D volume acquisition enables the presenting of the whole organ simply, so that the whole organ can be stored for later examinations. In addition, this ability has an important "teaching effect" as it allows a re-evaluation of the examination after histologic findings of tumors and such.

3D-power Doppler

Quantitative 3D power Doppler angiography represents the acquisition and measurement of power Doppler data within a 3D data set. This technique is being used to compare pregnant and non-pregnant patients undergoing ART. The majority of these studies use the 'histogram' tool, which displays the distribution of the power Doppler data and uses specific algorithms to derive indices of blood flow: vascularisation index (VI) characterises vessel density: the ratio of the number of colour voxels to the total number, flow index (FI) describes the intensity of blood flow: the ratio of the sum of colour intensities to the colour voxels and the vascularisation flow index (VFI) assesses both vascularisation and perfusion: the ratio of the sum of colour intensities to the total number of voxels (Figure 3).

These vascular indices depend on, and relate to, the total and relative amounts of power Doppler information within the target organ and the intensity of the signals. The power Doppler signal is dependent on the presence of blood flow within the target organ and its intensity is dependent on the number of blood cells within the blood vessels. The intensity of the power Doppler spectrum is determined by several settings: gain, pulse repetition frequency (PRF), line density, wall motion filter, signal rise and persistence and speed of acquisition.

Limitations and artifacts

Understanding of how artifacts occur, and what can be done to detect and correct for them, is important in order to avoid mistaking them for a pathology and to make correct interpretations of clinical 3D ultrasound.

Three types of artifacts can be caused by different sources in 3D ultrasound imaging. Some artifacts occur due to the 2D imaging process. Other artifacts are unique to 3D ultrasound, arising from patient motion or rendering method, which alter the appearance of the anatomy. Lastly, there are artifacts that arise as the result of operator choice in selecting which part of the volume to display (26). Each of these artifact sources may alter the displayed images and lead to incorrect diagnosis. Consequently, differentiation of the endometrial border from neighboring structures (e.g. myometrium), may be very difficult, especially in obese women. As a result, volume measurements cannot be performed accurately. In cases where power Doppler signal artifacts exist, power Doppler indices of target organ cannot be measured accurately.

Using power Doppler, it is essential to maintain identical settings if different subjects, or if changes over time within the same subject, are to be compared. One of the most important Doppler settings is color gain. Doppler gain appears to be directly correlated with all the 3D power Doppler indices, and the use of higher gains may lead to false signals that could be interpreted as real blood flow (Figure 4a, b).

Raine-Fenning et al. (27) evaluated how different settings affect the Doppler signal in terms of its quantification by these three indices within a 3D dataset. They found that the gain and signal power have the greatest effect on the power Doppler signal, followed closely by the PRF. The other settings and speed of acquisition also influence the signal, but to a much lesser degree. It is essential to maintain constant Doppler settings if any meaningful comparisons are to be made within and between subjects.

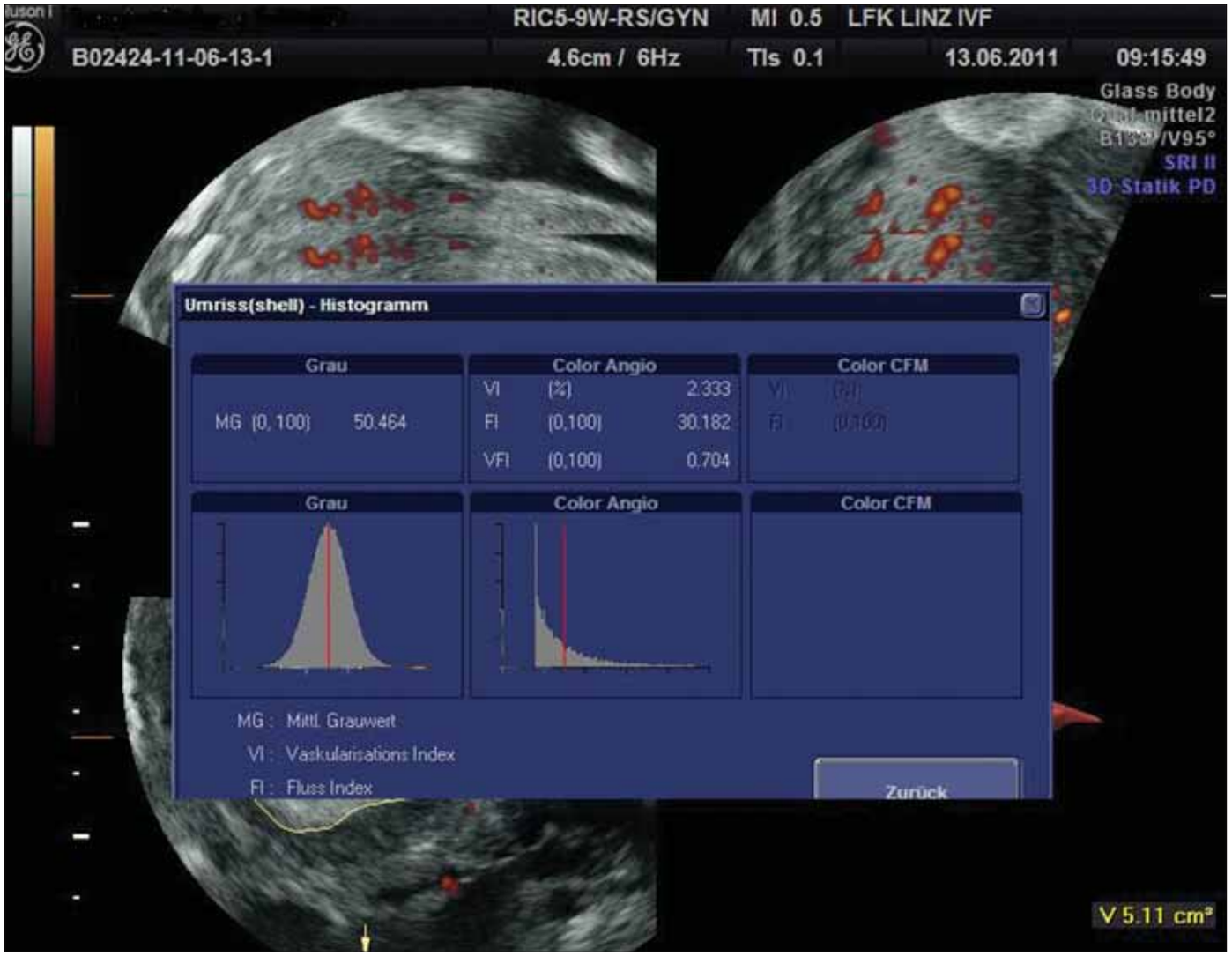

Figure 3. Vascularisation index (VI), flow index (FI) and the vascularisation flow index (VFI) assessed both vascularisation and perfusion

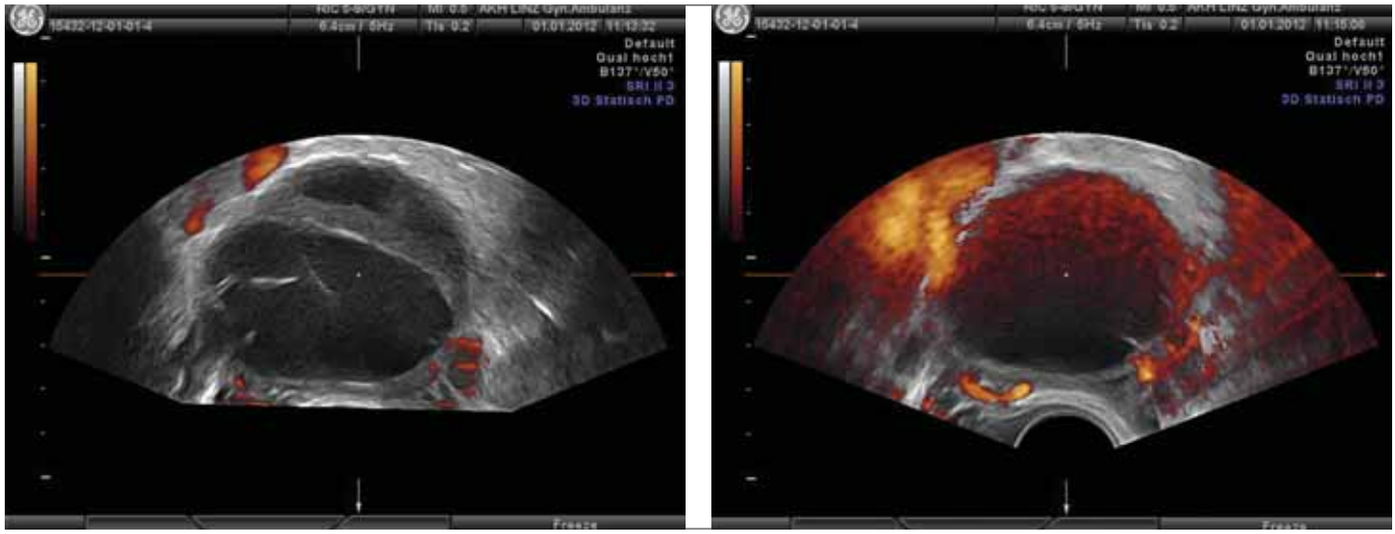

Figure 4. a) Vascularisation of ovarian cyst with low gain. b) Vascularisation of the same ovarian cyst with high gain. Note high grade artifacts

Standardizing the color gain between different machines is almost impossible, as the parameters used to define it differ widely among different companies and on different scales within the same company (28).

Endometrial receptivity

Endometrial receptivity is an important factor in human reproduction. It has usually been assessed by endometrial biopsy. However, such an invasive method is not acceptable when evaluating endometrial receptivity. Ideally, it should be evaluated by a non-invasive method.

Lee et al. (29) first reported endometrial volume changes during spontaneous menstrual cycles assessed by 3D US. These authors performed a longitudinal study on 18 nullipara regularly menstruating women, at 3-6 day intervals during a single menstrual cycle, measuring the endometrial and uterine volume and calculating the "uterus-endometrium" ratio. The mean endometrial volume was 1.23 cm^3 (SD: 0.98), ranging from 0.25 cm^3 to 5.5 cm^3. They found that this ratio decreased throughout the menstrual cycle, reaching a nadir around the 20^{th} day of the cycle, reflecting that endometrial volume was highest at mid luteal phase.

Raine-Fenning et al. (30) analysed the endometrial volume longitudinally in a series of 30 fertile women, having regular menstrual cycles. They found a steady increase of the endometrial volume throughout the follicular phase until ovulation occurs and then remained relatively constant throughout the luteal phase. These findings would be in agreement with histological data in which endometrial growth is restricted to the follicular phase of the menstrual cycle when expansion of the stratum functionalis of the endometrium occurs. This in turn is directly related to the increase of serum estradiol levels. In this study, endometrial volume was found to be greater in parous women. Two parameters are considered to predict pregnancy: a) endometrial volume and b) (sub) endometrial flow.

a) The first studies reported a good correlation between endometrial volume and pregnancy (31-33). Although it has been shown that the endometrium must attain at least 2.0-2.5 ml to achieve a pregnancy, recent studies did not confirm the relation between endometrial volume and pregnancy outcome (33-37). In our study, the area under the receiver operating characteristic (ROC) curve was statistically significant for endometrial volume when no grade 1 embryos or only one were transferred but not significant when two or three grade 1 embryos were transferred (34).

In conclusion, endometrial volume is also unlikely to be predictive of pregnancy, although the pregnancy rate may be significantly reduced in patients whose endometrial volume is less than 2.0-2.5 ml. The suggestion that endometrial thickness is determined by the individual uterine architecture, and therefore not predictive of the likelihood of implantation, may be related to endometrial volume (38).

b) A good blood supply to the endometrium is usually considered as an essential requirement for implantation. Therefore endometrial and subendometrial blood flows were evaluated in several studies. The first study was reported by Schild et al. (39), who measured the subendometrial blood flow on the first day of ovarian stimulation in 75 infertile patients after pituitary down-regulation was confirmed, i.e. endometrial thickness <5 mm, no ovarian cyst of >2.5 cm and serum estradiol concentrations of <60 pg/ml. Subendometrial VI, FI and VFI were significantly lower in pregnant cycles than non-pregnant ones. Logistic regression analysis found that the subendometrial FI was the strongest predictive factor for the outcome among the tested 3D Doppler flow indices.

A recent study by Kim et al. (40) evaluated whether endometrial and subendometrial blood flow parameters measured using three-dimensional power Doppler ultrasound (3D PD-US) can predict pregnancy after intrauterine insemination (IUI). They diagnosed higher endometrium VI, FI, and VFI scores in the pregnant group than in the non-pregnant group. In contrast, the subendometrial region VI, FI, and VFI scores did not differ between the groups. Pregnancies did not occur when endometrial blood flow had not been detected. Therefore, they concluded that three-dimensional PD-US was useful for evaluating endometrial and subendometrial neovascularization in IUI cycles. Similar results were reported by other authors (41, 42).

Ng et al. (43) evaluated endometrial and subendometrial blood flows on the days of human chorionic gonadotrophin (HCG) administration and embryo transfer. They also assessed the percentage change in endometrial and subendometrial blood flows between these two days as a predictor of pregnancy during IVF treatment. A 3D ultrasound examination with power Doppler was performed in 293 patients undergoing the first IVF cycle to determine endometrial thickness, endometrial volume, vascularization index, flow index and vascularization flow index of endometrial and subendometrial regions on the days of HCG administration and embryo transfer. Patients in non-pregnant and pregnant groups had comparable endometrial thickness, endometrial volume and 3D power Doppler flow indices of endometrial and subendometrial regions measured on each day. Percentage changes in endometrial and subendometrial 3D power Doppler flow indices were also similar. In conclusion, endometrial and subendometrial blood flows on the days of HCG treatment and embryo transfer and the percentage change in endometrial and subendometrial blood flows between these 2 days were not predictive of pregnancy.

Vlaisavljević et al. (44) examined whether we might predict the outcome of unstimulated IVF/ICSI cycles with quantitative indices of perifollicular blood flow assessed with three-dimensional power Doppler images. This prospective study included an analysis of 52 unstimulated cycles. Color and power Doppler ultrasound examinations of a single dominant preovulatory follicle were performed on the day of oocyte pick-up. They hypothesized that the follicles containing oocytes able to produce a pregnancy have a distinctive and more uniform perifollicular vascular network.

Conclusion

3D Ultrasound has been proposed as a promising tool for evaluating the endometrium, but a review of the literature regarding its role for assessing endometrial function did not confirm the suggested benefits of this technique. Endometrial volume,

endometrial and subendometrial flows have been shown to be ineffective for predicting pregnancy. Interactions between blastocyst and endometrium, e.g. embryo quality, seem to play a more important role than endometrial volume or (sub) endometrial blood flow.

Variable machine settings, differences in examination timing, different Doppler parameters or determination of endometrial volume by uterine architecture may explain why 3D is not predictive in the assessment of pregnancy in patients undergoing ART.

Conflict of interest

No conflict of interest was declared by the authors.

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Joubert syndrome and related disorders, prenatal diagnosis with ultrasound and magnetic resonance imaging

Joubert sendromu ve ilişkili bozuklukların ultrasonografi ve manyetik rezonans görüntüleme ile prenatal tanısı

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Abstract

Joubert syndrome (JBTS) is an autosomal recessive disorder characterized by intellectual disability, hypotonia, ataxia, tachypnea/apnea, and abnormal eye movements. A pathognomonic midbrain-hindbrain malformation seen on cranial magnetic resonance imaging (MRI), which consists of hypoplasia of the midline cerebellar vermis that resembles the cross-section through a molar tooth, has been described previously. The molar tooth sign is defined by a peculiar appearance resembling a molar tooth secondary to an abnormally deep interpeduncular fossa and enlarged superior cerebellar peduncles on axial images at the pontomesencephalic level. The term Joubert Syndrome and Related Disorders (JSRD) has recently been adopted to describe all disorders presenting the "molar tooth sign" (MTS) on brain imaging. JSRD is characterized by lack of decussation of the superior cerebellar peduncles, central pontine tracts and corticospinal tracts suggesting defective axon guidance. Prenatal sonographic findings in fetuses with JSRD are relatively nonspecific and include increased nuchal translucency, enlarged cisterna magna, cerebellar vermian agenesis, occipital encephalocele, ventriculomegaly and polydactyly. We report a case of JSRD detected prenatally at 23 weeks of gestation. The fetus in the present case had a normal karyotype. Sonographic features of the fetus included polydactyly, partial vermian hypoplasia, dilated 4th ventricle and mild ventriculomegaly which were also confirmed by prenatal MRI. MTS was demonstrated in a postnatal MRI after pregnancy termination.

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Key words: Joubert syndrome, prenatal diagnosis, ultrasonography, polydactyly, cerebellar vermian agenenesis

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Özet

Joubert sendromu entellektüel bozukluk, hipotoni, ataksi, takipne/apne ve anormal göz hareketleri ile karakterize otozomal resesif bir hastalıktır. Önceki çalışmalarda kraniyal manyetik rezonans görüntüleme ile hastalığa ait patognomonik bir görüntü saptanmıştır. Bu görüntü molar diş görünümü olarak ifade edilmiştir. Molar diş görüntüsü anormal derin yerleşimli interpedünküler fossa ve genişlemiş superior serebellar pedünkülllere bağlı olarak pontomezensefalik seviyedeki aksial kesitlerde ortaya çıkmaktadır. Joubert sendromu ve ilişkili bozukluklar son dönemde molar diş görünümünün olduğu tüm bozukluklar için kullanılmaktadır. Joubert sendromu ve ilişkili bozukluklar, superior serebellar pedünküllerde, santral pontin yollarda ve kortikospinal yollarda çaprazlaşmanın olmaması ile karakterize bir grup hastalıktır. Bu hastalığa ait prenatal sonografik bulgular görece non spesifiktir. Başlıca bulgular arasında artmış nukal saydamlık, genişlemiş sisterna magna, serebellar vermian agenezi oksipital ensefalosel ve polidaktili vardır. Biz, 23. haftada sonografik olarak polidaktili, vermian agenezi, dilate 4. ventrikül ve hafif ventrikülomegali saptanan normal karyotipli bir Joubert sendromu olgusu sunmaktayız. Bu olguda molar diş işareti doğum sonrası manyetik rezonans görüntüleme ile saptanmıştır.

(J Turkish-German Gynecol Assoc 2012; 13: 135-8)

Anahtar kelimeler: Joubert sendromu, prenatal tanı, ultrasonografi, polidaktili, serebellar vermian agenez

Geliş Tarihi: 28 Temmuz 2011 **Kabul Tarihi:** 08 Ekim 2011

Introduction

Ciliopathies are a group of disorders characterized by defective primary ciliary function (1). Exploring the role of primary cilia in humans has enabled categorization of certain syndromes under the umbrella term "ciliopathy". Joubert Syndrome (JBTS) is a ciliopathy which was initially described by the triad of cerebellar vermis hypoplasia, oculomotor apraxia and intermittent hyperventilation (2). The prevalence of Joubert Syndrome and Related Disorders JSRD has been estimated as approximately 1:100,000 (3). Molar tooth sign (MTS) is a pathognomonic magnetic resonance imaging (MRI) finding of JBTS. MTS refers to hypoplasia of the midline cerebellar vermis that resembles the cross-section through a molar tooth. JSRD, like many of the disorders considered as ciliopathies, shows considerable heterogeneity in clinical features and molecular basis (4). JSRD defines a group of disorders that encompasses classic JBTS as well as other features such as central nervous system anomalies, ocular coloboma, retinal dystrophy, renal disease and hepatic fibrosis (5). The description of MTS has greatly facilitated both prenatal and postnatal diagnosis of this syndrome. We report a case of JSRD detected prenatally at 23 weeks of gestation based on demonstration of the MTS and postaxial polydactyly.

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Case

A 27-year-old woman, was referred to our perinatology department for routine second trimester genetic sonogram at 19 weeks of gestation according to her last menstrual period. She was gravida 1 and she denied consanguinity with her husband and had no history of teratogen exposure during or immediately preceding pregnancy.

On ultrasound examination, a singleton viable intrauterine pregnancy was detected. The fetus was female and fetal biometric measurements were consistent with 19 weeks gestation. At this gestational age hypoplasia of cerebellar vermis, mild ventriculomegaly, postaxial polydactyly in both hands as well as left foot were detected (Figure 1). Amniocentesis revealed a 46 XX karyotype. The patient was scheduled for control sonography 2 weeks later with which the previous findings were confirmed. Fetal MRI was performed at 22nd gestational week and also confirmed ventriculomegaly and hypoplasia of cerebellar vermis (Figure 2). Dilatation of the 4th ventricle was also demonstrated by MRI. A presumptive diagnosis of ciliopathy was then made. MRI and sonographic examination of the fetus did not reveal any coexisting abnormalities. Based on these findings parental counseling was made and the family opted for pregnancy termination at the 23rd gestational week. Gross exami-

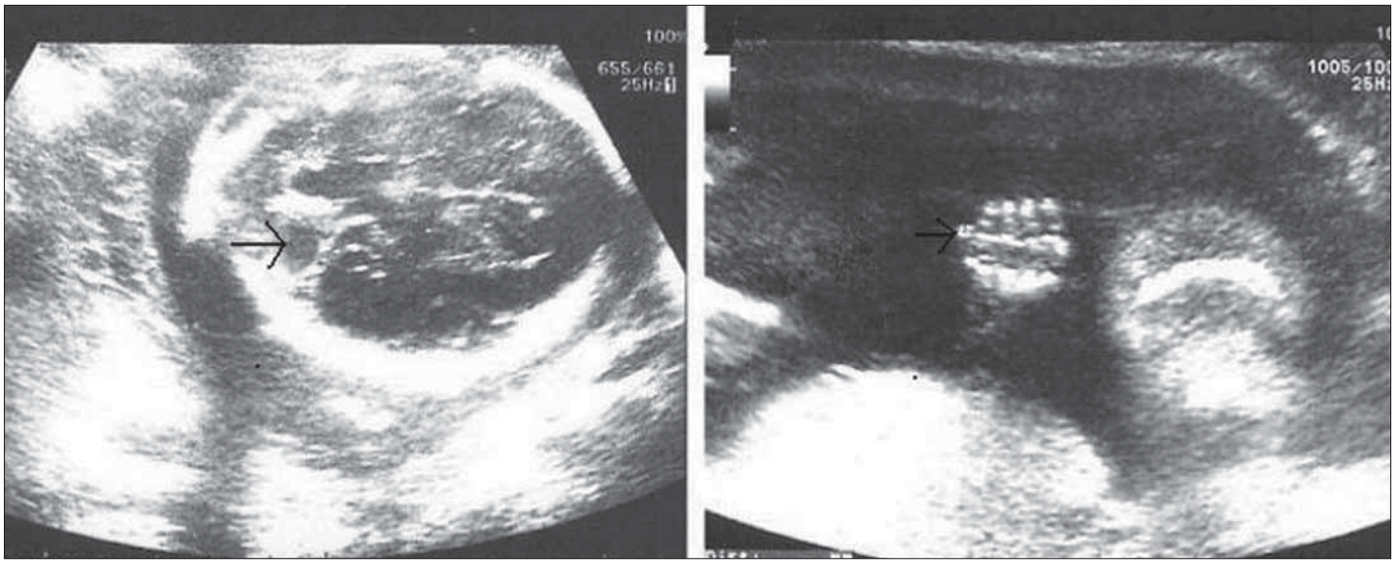

Figure 1. Prenatal sonographic view of postaxial polydactyly (right) and cerebellar vermian hypoplasia (left)

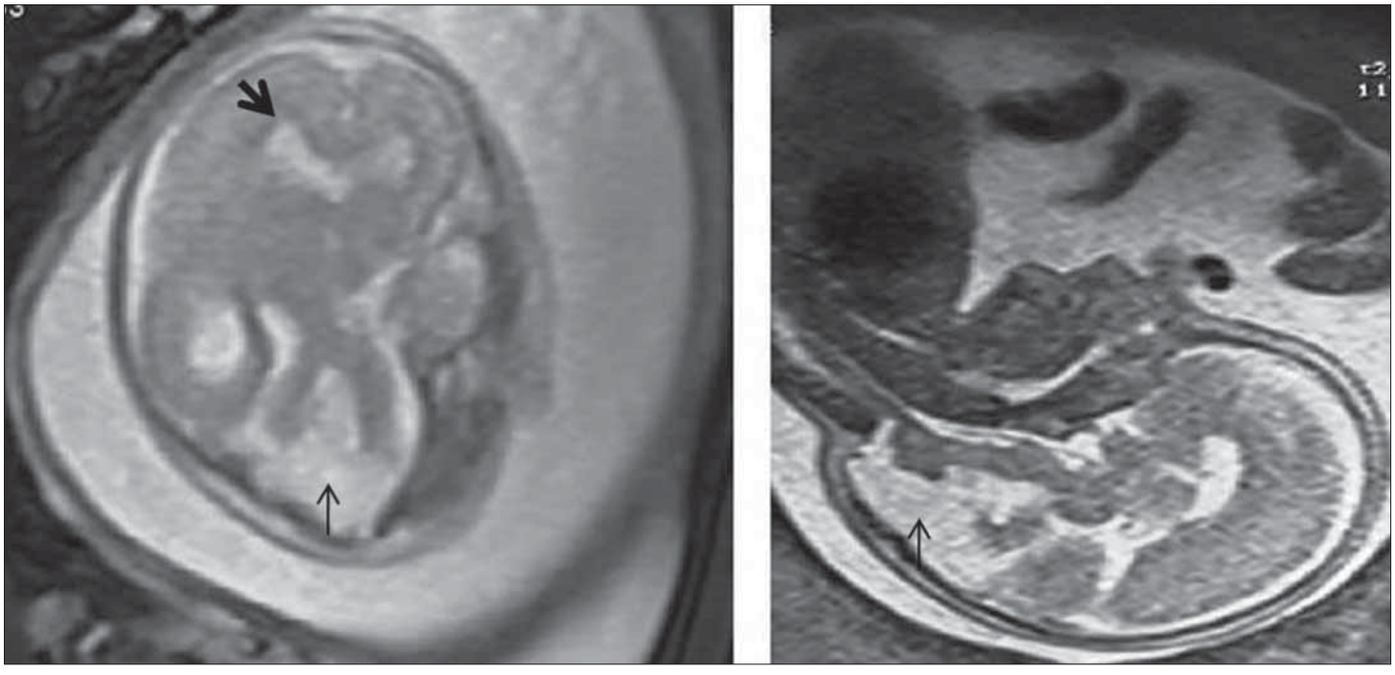

Figure 2. Axial (left) and sagittal (right) prenatal MR images demonstrating hypoplastic cerebellar vermis and ventriculomegaly

nation after pregnancy termination revealed a female fetus weighing 700 grams with postaxial polydactyly in both hands and left foot. Postabortal MRI examination of the fetus revealed the molar tooth sign owing to a deep interpeduncular fossa, elongated, thick and mal-oriented superior cerebellar peduncles combined with cerebellar vermis hypoplasia (Figure 3). A diagnosis of JSRD was made based on demonstration of MTS and postaxial polydactyly.

Discussion

Primary cilia are sophisticated organelles found in almost all vertebrate cell types. Primary cilia were first observed in the epithelium of renal tubules and thyroid gland more than a century ago (6). Cells of many other organs and tissues in the body (e.g. kidney, liver, pancreas, brain, and oviduct) display primary cilia on their surface (7-9). It has been recently found that primary cilia perform fundamental tasks in developmental processes. These organelles are thought to serve as sensory units that detect and transmit signals from the surrounding environment to the cell body in order to regulate embryonic development (6). The term 'ciliopathy' describes a class of rare human genetic diseases whose etiologies lie in defective cilia. Joubert syndrome belongs to the group of disorders which are collectively considered as ciliopathies (1). JS was initially described by the triad of cerebellar vermis hypoplasia, oculomotor apraxia (jerky eye movements with inability to visually fixate) and intermittent hyperventilation (2). A pathognomonic midbrain-hindbrain malformation seen on cranial MRI was described in 1997. This consists of hypoplasia of the midline cerebellar vermis that resembles the cross-section through a molar tooth (4). Contemporary diagnostic criteria of JBTS include characteristic brainstem malformation and demonstration of MTS (10). The term JSRD has been recently adopted to describe all disorders presenting the MTS on brain imaging (11). JSRD are genetically heterogeneous, and all known genes encode proteins localized at or near the primary cilium. Ten causative genes have been identified to date. JSRD has an estimated prevalence of 1 in 100.000 live births (3, 12). Only a few cases have been described prenatally. The neurological features of JSRD include hypotonia, ataxia, psychomotor delay, irregular breathing pattern and oculomotor apraxia and are variably associated with multi-organ involvement, mainly retinal dystrophy, nephronophthisis (NPH) and congenital liver fibrosis (5).

Prenatal sonographic findings in fetuses with JSRD are relatively nonspecific and include increased nuchal translucency, enlarged cisterna magna, cerebellar vermian agenesis, occipital encephalocele, ventriculomegaly, hypoplastic phallus, renal cysts, and polydactyly (13). Molar tooth sign associated with JSRD has previously been demonstrated by fetal MRI in three cases. Saleem and associates were able to identify the molar tooth sign as early as 22 weeks of gestation (14). MTS was identified at 27 weeks of gestation in two other cases (13, 15). MTS was demonstrated in two cases before the 24th gestational week by sonography alone in a recent study (16). In the present case we were able to identify the molar tooth sign following pregnancy termination at 23 weeks. Increased nuchal translucency (NT) has also been reported to be associated with JSRD (17). Increased NT, together with other extracranial findings such as polydactyly, may aid earlier diagnosis especially when a prior family history is present. However, it is not possible to demonstrate Vermian hypoplasia before the 18th gestational week (18).

Due to the marked heterogeneity in this group of disorders and the relatively high frequency of associated medical condi-

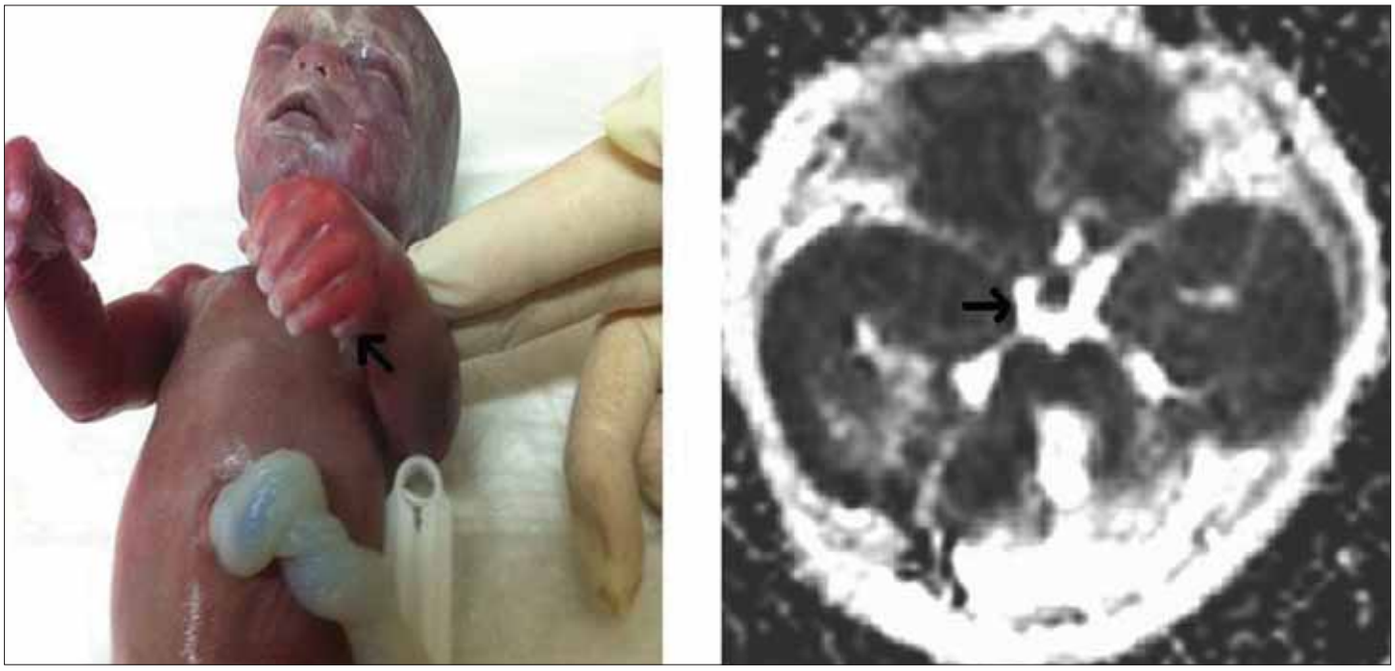

Figure 3. Polydactyly in both hands demonstrated in the photograph of fetus following abortion (left). Axial postnatal MR image demonstrating the " molar tooth appearance" (right)

tions, it is difficult to make generalizations about outcomes. Cognitive impairment in JSRD is highly variable, with many children exhibiting moderately severe disability (19). Moreover behavioral problems, typically impulsivity, perseveration, and temper tantrums, appear to be relatively common, particularly with increasing age (20). Close surveliance for retinal, renal and hepatic involvement is also necessary since the prognosis largely depends on the presence of these conditions (21).

Given the fact that these group of disorders are genetically heterogeneous and not all the causative genes are identified, the molecular diagnosis of JSRD is mainly for research purposes. It has been reported that currently identified genes account for an estimated 50% of causative mutations in JSRD (22). In addition, clinical features can vary between affected siblings within the same family. Also, many genotype-phenotype correlations that may require molecular diagnosis are age-dependent and may not be present in infants or young children (22). Other conditions to consider in the differential diagnosis of Joubert syndrome are those with cerebellar vermis hypoplasia or dysgenesis without the molar tooth sign on MRI. These include: Dandy-Walker malformation, X-linked cerebellar hypoplasia, congenital disorders of glycosylation, cranio-cerebello-cardiac syndrome, the ponto-cerebellar hypoplasias/atrophies, oral-facial-digital syndromes II and III and Meckel-Gruber syndrome (23).

Conflict of interest

No conflict of interest was declared by the authors.

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Iliofemoral-popliteal deep vein thrombosis at 35th week of pregnancy: treated with cesarean section and vena cava blockage plus thrombectomy

Gebeliğin 35. haftasında iliofemoral-popliteal derin ven trombozu olan sezaryen seksiyo, vena kava blokajı ve trombektomi ile tedavi edilen olgu sunumu

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Abstract

Pregnancy, due to its adaptive physiological changes, is a risk factor for deep vein thrombosis. Incidence of thromboembolic complications during pregnancy ranges from 0.76 to 1.72 per 1000 births. We present in this case report a pregnant woman with iliofemoral-popliteal deep vein thrombosis diagnosed at the 35th week of her pregnancy, who was treated with vena cava blockage and thrombectomy followed by cesarean section. Unfortunately, a rethrombosis developed in the patient after three days. We determined that the a-v fistula was blocked and not working. We found additionally that the deep vein thrombosis was closing the iliac vein completely on the left side and the blockage descending down through the inferior vena cava inlet with MRI. The patient underwent insertion of a retrievable vena cava filter, two stent implantation to the venous narrowings and surgical iliofemoral venous thrombectomy with concomitant re-creation of a temporary femoral arterio-venous fistula. Anticoagulation therapy with enoxaparine was started after the operation. The patient was discharged with warfarin under control of the INR value, and also with additional compression therapy (compression stockings) from the clinic. Without jeopardizing the mother and the baby, planning a combined surgical procedure, with a multidisciplinary approach is the best way to eliminate the risks of serious complications such as pulmonary embolism and mortality.

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Key words: Deep vein thrombosis, pregnancy, complications, thrombectomy, inferior vena cava

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Özet

Gebelik, bu dönemdeki fizyolojik değişikliklere bağlı olarak, derin ven trombozu açısından bir risk faktörüdür. Gebelik sırasındaki tromboembolik komplikasyonların insidansı her 1000 doğumda 0.76 ila 1.72 arasında değişir. Biz bu olgu sunumunda, gebeliğin 35. haftasında iliofemoral-popliteal derin ven trombozu tanısı konan ve vena kava blokajı ve trombektomiyi takiben sezaryen seksiyo ile tedavi edilen bir gebeyi sunuyoruz. Ne yazık ki bu hastada üç gün sonra tekrar tromboz gelişti. Arterio-venöz fistülün tıkandığını ve çalışmadığını saptadık. Ayrıca MR görüntüleme ile sol tarafta iliak venin tamamen tıkandığını ve tıkanıklığın aşağıda inferior vena kavanın girişine kadar uzandığını tespit ettik. Hastaya çıkarılabilir vena kava filtresi yerleştirildi, venöz daralma bölgelerine iki stent yerleştirildi, cerrahi olarak iliofemoral venöz trombektomi yapıldı ve eşzamanlı olarak geçici femoral arterio-venöz fistül yeniden oluşturuldu. Operasyondan sonra enoxaparine ile antikoagulan tedavi başlandı. Hasta INR kontrolü altında warfarin ve ek olarak kompresyon tedavisi (kompresyon çorapları) ile klinikten taburcu edildi. Pulmoner emboli ve ölüm gibi ciddi komplikasyon risklerini, anne ve bebeğin hayatını tehlikeye atmadan, elimine etmenin en iyi yolu multidisipliner yaklaşımla kombine cerrahi işlemlerin planlanmasıdır.

(J Turkish-German Gynecol Assoc 2012; 13: 139-41)

Anahtar kelimeler: Derin ven trombozu, gebelik, komplikasyonlar, trombektomi, inferior vena kava

Geliş Tarihi: 13 Eylül 2011 **Kabul Tarihi:** 20 Kasım 2011

Introduction

Pregnancy, due to its adaptative physiological changes in hormone concentrations, the position of the enlarged uterus in the vicinity of large veins, as well as the physiological alterations in the coagulation system, is a risk factor for deep vein thrombosis. The incidence of thromboembolic complications in pregnancy ranges from 0.76 to 1.72 per 1000 deliveries (1). Deep vein thrombosis (DVT) is classically associated with pulmonary embolism and chronic venous insufficiency, which are the leading causes of mortality in the USA and Europe; between 1.1 and 1.5 per 100000 pregnant women (2).

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We present a case of a pregnant woman with iliofemoral-popliteal deep vein thrombosis diagnosed at the 35th week of her pregnancy, who was treated with vena cava blockage and thrombectomy followed by cesarean section.

Case

A 41 year -old woman, at the 35th week of gestation, was admitted as an emergency with acute pain in her left leg accompanied by edema. During pregnancy the patient was regularly followed-up by an obstetrician and gynecologist. Two weeks earlier, the patient had initially experienced a slight pain in her left leg, than recognized slight edema a few days previously. Hemodynamic findings were normal and there were no signs of pulmonary embolism when she was admitted. Laboratory tests following admission revealed: HGB 10.2 g/dl, HCT 29.8%, platelets 329.000 /mm^3, WBC 11900 /l, D-dimer 0.89 μg/l, Creatinine 0.34 mg/dl, sodium 134.0 mmol/l, potassium 3.71 mmol/l APTT 35.1 s, INR 1.05, antithrombin III 76.9%, Protein C free >150%, Protein S 79.7%, CRP 10.06 MG. We searched also for thrombophilic factors, there were no Factor V Leiden or prothrombin G mutations.

Both ECG and diagnostic cardiac echography revealed no significant abnormalities. Coloured duplex compression ultrasonography revealed left iliofemoral-popliteal phlebothrombosis. In line with these findings, left external iliac and femoro-popliteal deep vein thrombosis (DVT), was diagnosed by compression ultrasonography and magnetic resonance imaging (Figure 1a, 1b and Figure 2).

As a first intervention, an inferior vena cava blockage applied through the transfemoral passage through the left iliac vein. There was no difficulty in passing the occluded iliac vein by a thrombectomy catheter. We saw no pulmonary embolism by this procedure. The vena cava filter was not necessary when occluding the inferior cava vein by thrombectomy catheters and a Cesarean section was performed thereafter under the control of vascular surgeons.

After the delivery of the baby, first thrombectomy and then arterio-venous (a-v) femoral fistula were performed by there vascular surgeons. The complete procedure was carried out without any complication. The treatment started immediately with Enoxaparin (Clexane 0.8 2*1 sc) after surgery. Factor Xa levels were checked daily to see whether they were within the level of treatment or not.

Unfortunately, a rethrombosis developed in the patient after three days. We determined that the a-v fistula was blocked and not working. After this, we decided to carry out a new thrombectomy operation. During the thrombectomy, two venous narrowings were found and two different stents, one of 14 mm. diameter and 6 cm. in length and the other one of 12 mm. diameter and 4 cm. in length, were implanted into these narrowed parts and also the a-v fistula was again made functional.

We found additionally that the deep vein thrombosis was closing the iliac vein completely on the left side, with the blockage descending down through the inferior vena cava inlet with MRI. The patient underwent insertion of a retrievable vena cava filter, two stent implantations to the venous narrowings and surgical iliofemoral venous thrombectomy with concomitant re-creation of a temporary femoral arterio-venous fistula. The inferior vena cava filter was inserted before the venous thrombectomy to prevent pulmonary embolism from clots dislodged

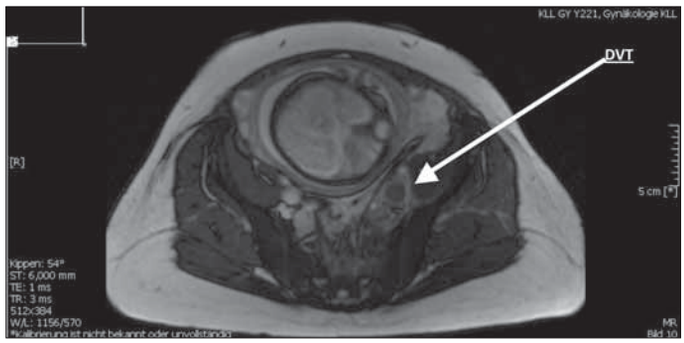

Figure 2. MRI image of the 41 year-old woman case showing the DVT

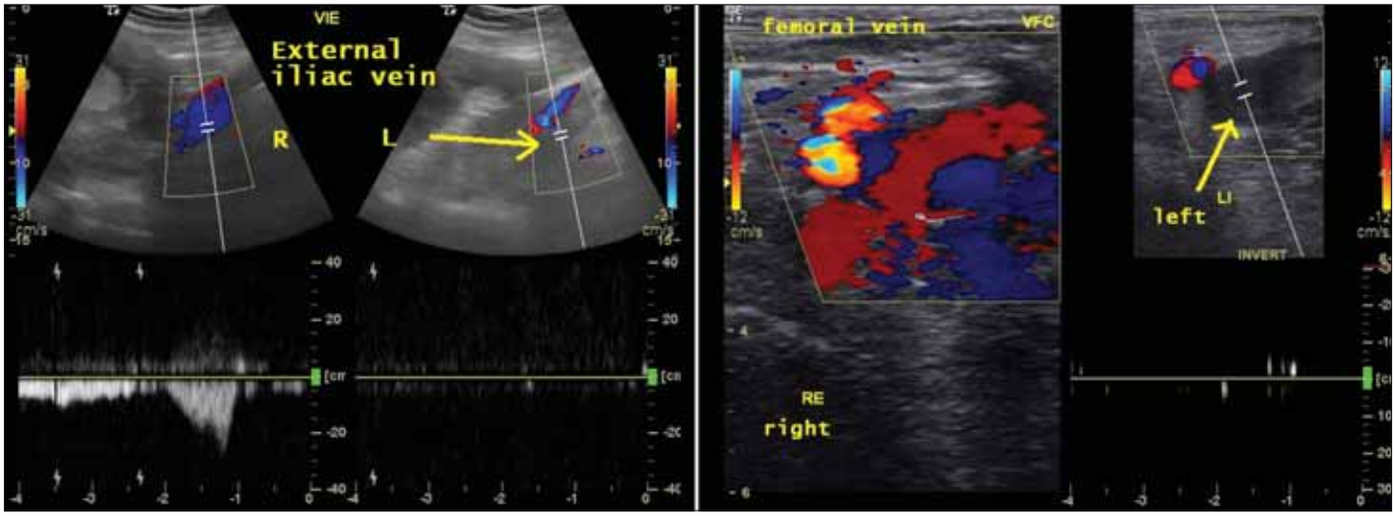

Figure 1. a) Ultrasonographic picture showing absence of flow in the left external iliac vein, b) Ultrasonographic picture showing absence of flow in the left femoral vein

during thrombectomy. Anticoagulation therapy with warfarin and enoxaparine, (clexane 0.8 ml 2*1 sc for 5 days with Factor Xa level were controlled during the therapy, until INR value reached between 2 to 3) was started after the operation. After a 5-day treatment with warfarin and enoxaparine, enoxaparine was stopped. The patient was discharged with warfarin (coumadin) under control of the INR value, and also with additional compression therapy (compression stockings) from the clinic.

Discussion

Although thromboembolism is not so common during pregnancy and the postpartum period, physicians should be alert for the possibility because the complications like pulmonary embolism, can be life threatening. Nonetheless, DVT is one of the most common cause of death among women in the puerperium (1, 2).

Pregnant women who present with thromboembolic occlusion are particularly difficult to treat because thrombolysis is hazardous to the fetus and surgical intervention by any of several approaches is controversial (3, 4).

Pregnancy may increase the risk of thrombosis through a number of factors, singly or in combination: mechanical obstruction of venous drainage by the enlarging uterus and descending fetal head, decreased activity in late pregnancy and especially intrapartum, intimal injury from vascular distention or surgical manipulation, and abnormal levels of procoagulant or anticoagulant plasma factors. Protein S serves as a cofactor for activated protein C, which has anticoagulative activity. Protein S deficiency leads to spontaneous, recurrent thromboembolic complications in adulthood. Protein S levels are substantially reduced during pregnancy and puerperium and during use of oral contraceptives (5, 6).

D-Dimer has lost its importance during pregnancy as well as Protein S and Protein C, when diagnosing thrombosis of a pregnant woman. Furthermore clinical examination, Duplex sonography and MRI become the most important diagnostic tools (2). We have also preferred these effective tools to the others in our case.

In order to reduce both maternal and fetal risks, combined surgical procedure is planned for the treatment of thrombosis. In these types of cases, the equipment and facilities of the hospital play a critical role, as well as the cooperation and coordination between related departments (6).

As discussed in our case, in cases of acute iliofemoro-popliteal thrombosis developing towards the end of the gestational period (7), the high risk for pulmonary embolism and mortality secondary to pulmonary embolism makes it almost impossible to plan the delivery with by normal vaginal route (8, 9).

Conclusion

Without jeopardizing the mother and the baby, planning a combined surgical procedure with multidisciplinary approachis the best way to eliminate the risks of serious complications like pulmonary embolism and mortality.

Conflict of interest

No conflict of interest was declared by the authors.

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Bilateral megalocystic ovaries following in vitro fertilization detected during cesarean section: a case presentation

In Vitro Fertilizasyonu Takiben Sezaryen Esnasında Tespit Edilen Bilateral Megalokistik Overler: Olgu Sunumu

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Abstract

We present a patient with persistent bilateral megalocystic ovaries following in vitro fertilization which was detected during cesarean section. A 24 year-old primigravida presented to our clinic at the 36th week of a twin pregnancy with labour pain and cervical dilatation. On ultrasound examination, 2 masses of 90x60 and 60x70 mm were seen in the right and left adnexal regions respectively. Her history showed that she had unexplained infertility for 4 years and had undergone IVF with gonadotropin releasing hormone (GnRH)-agonist stimulation. Two embryos were transferred. Twin pregnancy was detected on ultrasound examination. The patient was delivered by emergency caesarean section due to transverse presentations at 36th weeks of gestation. During the operation, both adnexae were markedly enlarged, the right ovary measuring about 15x18 cm and the left about 16x18 cm. There was minimal ascites in the abdominal cavity. Ovarian biopsy was performed and the final pathology report showed bilateral follicle cysts. The patient was discharged on the postoperative 4th day. The patient was seen 4 weeks later. She had no complaints and ultrasound follow-up revealed a normal size uterus and ovaries. We should keep in mind that hyperstimulated, enlarged ovaries and its complication may be seen in the late weeks of pregnancy, even at term, in cases of in vitro fertilization cases. Therefore, close follow-up of pregnant IVF patints is recommended whether they had OHSS or not, because ovarian torsion caused by hyperstimulated ovaries may be difficult to diagnose during pregnancy.

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Key words: Bilateral megalocystic ovaries, in vitro fertilization, term pregnancy, OHSS, cesarean delivery

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Özet

İn Vitro Fertilizasyon (IVF) sonrası sezaryen esnasında persiste bilateral megalokistik overlerin tespit edildiği bir hastayı sunuyoruz. 24 yaşında 36. gebelik haftasında ikiz gebelik ve ilk gebeliği olan hasta doğum sancısı ve servikal dilatasyon ile kliniğimize başvurdu. Ultrasonografik incelemesinde sağ ve sol adneksiyal bölgede 90x60mm ve 60x70 mm boyutunda iki adet kitle izlendi. Hastanın öyküsünden 4 yıllık açıklanamayan infertilitesinin olduğu ve GnRH agonist stimülasyonla IVF tedavisine alındığı öğrenildi. İki embryo transferi yapıldı ve ultrasonografide ikiz gebelik tespit edildi. Hasta transvers presentasyon sebebi ile 36. gebelik haftasında acil sezaryen ile doğum gerçekleştirildi. Operasyonda, her iki adneksial bölge büyümüş, sağ over 15x18cm sol over 16x18cm olarak ölçüldü. Abdominal kavitede minimal asit mevcuttu. Ovarian biopsi yapıldı ve son patolojik tanı follikül kisti olarak geldi. Hasta postoperatif 4. gününde taburcu edildi. Hasta 4 hafta sonra tekrar görüldü. Hastanın şikayeti yoktu ve ultrasonografi takibinde uterus ve overler normal boyutta idi. IVF olgularında, hiperstimüle, büyümüş overler ve komplikasyonlarının geç gebelik haftalarında veya termde gözlenebileceği de akılda tutulmalıdır. Hiperstimüle overlerin ovarian torsiyona sebep olabileceği ve gebelikte tespiti zor olması sebebi ile IVF gebelerinin OHSS olsun veya olmasın sıkı takibi yapılmalıdır.

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Anahtar kelimeler: Bilateral megalokistik overler, in vitro fertilizasyon, term gebelik, OHSS, sezaryen doğum

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Introduction

Ovarian hyperstimulation syndrome (OHSS) is a potential complication of ovarian stimulation in the treatment of infertility. Severe forms of OHSS appear in 0.5-5.0% of *in vitro* fertilization (IVF) cycles (1). The syndrome has been known since 1943 when gonadotrophins were first used to induce ovulation (2).

Typically, iatrogenic OHSS is diagnosed immediately following conception. One of the presentations of ovarian hyperstimulation syndrome (OHSS) is an increase in ovarian size and the presence of numerous luteal cysts (3). Hyperstimulated ovaries often subside when the hCG levels start to decline at 10-12 weeks and rarely continue until 20 weeks. Pregnancies complicated by OHSS were observed in the 2nd and 3rd trimesters (2, 4, 5); but only two cases were reported with OHSS recognized during cesarean section or during the postpartum period (3, 6).

We aimed to present a patient with persistent bilateral megalocystic ovaries detected during cesarean section which was

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performed for transverse presentation in the 36th weeks of a twin pregnancy induced by gonadotropins.

Case Presentation

A 24 year-old primigravida presented to our clinic on 36th week of a twin pregnancy, with labour pains and cervical dilatation. On ultrasound examination, two viable fetuses with biometrical measurements consistent with 35 weeks were seen, the amniotic fluid was normal and the placenta anteriorly located. Two masses of 90x60 and 60x70 mm were seen in the right and left adnexal regions, respectively. The large uterus due to the 36 week gestation limited the ultrasonographic evaluation of the ovaries so they were measured as smaller than the actual size encountered during operation. Her history showed that she had unexplained infertility for 4 years and had undergone several attempts for ovulation induction and intrauterine insemination. These were unsuccessful, so she underwent IVF with gonadotropin releasing hormone (GnRH)-agonist stimulation, and 225 IU recombinant follicle-stimulating hormone (Gonal-F; Serono, Istanbul) was started on the second day of the menstrual cycle. Transvaginal oocyte retrieval was carried out on day 16, yielding 17 mature oocytes. Two embryos were transferred. The patient did not have any signs or symptoms of OHSS during her pregnancy. Twin pregnancy was detected on ultrasound examination. Deep vein thrombosis was detected at the 32nd week and subcutaneous Enoxaparin Sodyum 0.8cc 1x2 (Clexane®, Aventis, Istanbul) was started twice daily. There was no other problem during pregnancy. The IVF procedure and pregnancy follow up were carried out in another centre. The patient was delivered in our hospital by emergency caesarean section due to transverse presentations and she had labour pain and cervical dilatation at the 36th week of gestation. A male and a female baby were delivered. During the operation, both adnexae were markedly enlarged, the right ovary measuring about 15X18 cm and the left about 16x18 cm (Figure 1). There was minimal ascites in the abdominal cavity. Ovarian biopsy was performed and the final pathology report showed bilateral follicular cysts. The postoperative course was uneventful, and the patient was discharged on the 4th postoperative day. The patient was seen 4 weeks later. She had no complaint and an ultrasound follow-up revealed a normal sized uterus and ovaries.

Figure 1. Both ovaries were markedly enlarged, the right ovary measuring about 15x18 cm and the left about 16x18 cm

Discussion

OHSS continues to be a serious complication of assisted reproductive therapy (ART). There are well-known risk factors that must be considered during the administration of medications to treat infertility (1).

Ovarian enlargement secondary to hyperstimulation is common. Human chorionic gonadotropin (hCG) stimulates the ovaries to continue to grow (3). If no pregnancy occurs, the syndrome will typically resolve within 1 week. If the pregnancy continues, slow resolution of symptoms of luteal cysts usually occurs over 1-2 months and rarely persists until 5 months of gestation. This is probably because of continuous exposure of the ovaries to endogenous hCG. Ovarian enlargement with multiple follicular and lutein cysts persists for a longer period if pregnancy continues. Hyperstimulated ovaries often subside in the 20th week of gestation (3). Endogenous hCG is secreted by the trophoblast starting 7-8 days after fertilization. In a normal singleton pregnancy hCG concentration in the maternal serum reaches a peak level of 100 000 IU/L between 8-10 weeks of gestation, and declines to 40 000 IU/L from 20 weeks up to delivery (4, 7).

He et al. (6) presented an interesting case of spontaneous severe OHSS after delivery. Ling et al. (3) reported a case of persistent megalocystic ovaries during the cesarean section in a patient with an IVF pregnancy. The megalocystic ovaries persisted after delivery so the patient was operated on again and biopsies from both ovaries were performed, and the histopathological result was follicular cyst. Our case was interesting because the patient was not diagnosed as OHSS and there was no symptom of OHSS or enlarged ovaries during pregnancy. We expect bilateral megalocystic ovaries to subside after the first trimester. However, in this case, enlargement of ovaries continued until the 36th week of gestation. The ovaries in our patient regressed in the 1st month of postpartum period.

Some researches show that, in patients with regular ovulatory cycles, improvement of symptoms of OHSS is obtained in a shorter time than in patients with anovulatory cycles before pharmacological induction (8). In our case, inducing ovulation by gonadotropins, and high hCG due to twin pregnancy could be factors that delayed the decrease of ovarian size. However, in our search of the literature, we did not find any case report of persisting megalocystic ovaries reaching term in IVF patients.

A variety of cystic ovarian conditions may develop during pregnancy. The differential diagnosis of multicystic ovaries during pregnancy includes ovarian hyperstimulation, hyperreactioluteinalis, theca lutein cysts, and polycystic ovarian syndrome (PCOS). Some researchers demonstrated a relationship between infertility treatment and the risk of inducing ovarian cancer (9). This risk of malignancy should be kept in mind but should not lead to unnecessary surgery. In our case; because

the patient had infertility treatment, we thought that the ovarian enlargement may be due to OHSS secondary to ovulation induction.

Many rare complications of ovarian enlargement, such as ovarian torsion and labor dystocia, may be seen in ovary-expanding conditions (4). Ovulation induction techniques predispose to ovarian cyst formation, particularly if ovarian hyperstimulation syndrome (OHSS) is present; therefore, it is to be expected that women undergoing gonadotropin ovulation induction are at increased risk of adnexal torsion (10). Cornfeld et al. (11) reported two cases of ovarian torsion complicating ovarian hyperstimulation in 7 week pregnant patients, one of them was a twin pregnancy.

The reduction in ovarian volume and the resolution of ascites, along with gradual symptomatic relief, observed during careful clinical and ultrasonic follow-up, contribute to the decision for close observational management (4). Our patient had normal ovarian size on ultrasound examination after one month.

In conclusion, we should keep in mind that hyperstimulated, enlarged ovaries and its complications may be seen in the late weeks of pregnancy even at term in cases of in vitro fertilization cases. So close follow-up of pregnant IVF patients is recommended whether they had OHSS or not because ovarian torsion caused by hyperstimulated ovaries may be difficult to diagnose during pregnancy.

Conflict of interest

No conflict of interest was declared by the authors.

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Prenatal diagnosis of Cantrell pentalogy in first trimester screening: case report and review of literature

Birinci trimester anöploidi taramasında Cantrell pentalojisinin erken tanısı: olgu sunumu ve literatür taraması

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Abstract

Pentalogy of Cantrell is a heterogeneous and rare thoraco-abdominal wall closure defect with the estimated prevalence of 1/65.000 to 1/200.000 births. Supraumbilical midline wall defect (generally omphalocele), deficiency of the anterior diaphragm and diaphragmatic peritoneum, defect of the lower sternum and several intracardiac defects are the components of Cantrell pentalogy. Etiology is unknown but a defect on the lateral mesoderm during the early stage of pregnancy is the most accepted hypothesis. Nowadays both 2- dimensional (2D) and 3-dimensional (3D) sonography are commonly used in diagnosis. In our case, a fetus with 11 weeks of gestation was reported as Cantrell pentalogy during first trimester screening. Additionally, unilateral limb defect and lumbar lordoscoliosis were detected through 3D sonography. Pregnancy was terminated according to parental desire. Karyotype was 46 XY. Early diagnosis is feasible in the first trimester if ectopia cordis and omphalocele exist. Additionally, development in ultrasound technology provides us with better visualization and early diagnosis. Prognosis seems to be poor in patients with complete Cantrell syndrome and patients with associated anomalies. Termination is the choice of treatment. Early diagnosis gives us a chance to reduce maternal morbidity and mortality related to termination.

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Key words: Ectopia cordis, omphalocele, lower sternal defect, 3D sonography, Cantrell pentalogy

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Özet

Cantrell Pentalojisi tahmini prevalansı 1/65.000 ile 1/200.000 doğumda bir izlenen heterojen ve nadir bir torako-abdominal duvara ait kapanma defektidir. Supraumblikal orta hat defekti (genellikle omfalosel), anterior diyafram ve diyafragmatik periton defekti, sternumun alt kısmına ait defektler ile kalbe ait anomaliler Cantrell Pentalojisini oluşturan bileşenlerdir. Etyolojisi bilinmemekle beraber erken gebelik haftalarında lateral mezoderme ait defektlerden kaynaklandığı hipotezi en geçerli olanıdır. Günümüzde tanıda hem iki hem de üç boyutlu sonografi kullanılmaktadır. Olgumuz birinci trimester taramasında Cantrell Pentalojisi tanısı alan 11. gebelik haftasındaki fetüs idi. Ek olarak tek taraflı alt ekstremite defekti ve lumbar lordoskolyoz üç boyutlu sonografide tespit edildi. Gebelik ailenin isteği üzerine termine edildi. Karyotip 46 XY idi. Olgularda eğer ektopia kordis ve omfalosel mevcut ise birinci trimesterde erken tanısı mümkündür. Ek olarak ultrasonografi teknolojisindeki gelişmeler de bize daha iyi görüntüleme ve erken tanı imkanları sunmaktadır. Ek anomalilerin varlığında veya Cantrell Pentalojisinin tüm komponentlerini içeren olgularda prognoz kötüdür. Gebelik sonlandırması bu nedenle bir alternatif olarak göz önünde bulundurulmalıdır. Erken tanı bize gebelik sonlandırmasına ait mortalite ve morbiditenin azaltılması imkanı tanımaktadır.

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Anahtar Kelimeler: Ektopia kordis, omfalosel, alt sternal defekt, 3 boyutlu sonografi, Cantrell pentaloji

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Introduction

Pentalogy of Cantrell is a heterogeneous and rare thoraco-abdominal wall closure defect with the estimated prevalence of 1/65.000 to 1/200.000 births (1). Supraumbilical midline wall defect (generally omphalocele), defect of the anterior diaphragm and diaphragmatic peritoneum, defect of the lower sternum and several intracardiac defects are the components of Cantrell pentalogy (1, 2). Primary anomalies are the ectopia cordis (EC) and omphalocele in this syndrome. Etiology is unknown but defect on the lateral mesoderm during the early stage of pregnancy is the most accepted hypothesis (3). Recently, both 2- dimensional (2D) and 3-dimensional (3D) sonography are commonly used in diagnosis. Differential diagnosis consists of isolated thoracic ectopia cordis, amniotic band syndrome, body stalk anomaly, Beckwidth-Wiedemann syndrome and physiologic midgut herniation (2, 3). Differential diagnosis is simple in physiologic midgut herniation related to the non-existent liver in the abdomen. Prognosis depends on the severity of lesions and associated anomalies. Therefore detailed anatomic assessment is essential for optimal prenatal counseling, pregnancy outcome and treatment policy (1-3).

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Case report

A 29-year-old pregnant woman gravida: 1 para: 0 was referred to the perinatalogy service for fetal posture anomaly at 11+0 week of gestation. Ultrasonographic examination revealed ectopia cordis, herniated liver with large omphalocele including bowel loops, stomach and spleen (Figure 1). No cardiac anomaly was detected. The left unilateral femur was hypoplastic, tibia and fibula were absent, the left foot was directly connected to the left femur (Figure 2). Also, clubfoot deformity was detected on the left side. Thereafter, lumbar lordoscoliosis was identified (Figure 3). Umbilical cord appeared normal and there was no amniotic band. Pentalogy of Cantrell with limb defects was initially diagnosed. Genetic counseling was afforded and the parents opted for pregnancy termination. Single dose misoprostol was administered and 30 gr male fetus was aborted.
After abortion, macroscopic examination revealed the same findings as prenatal ultrasonography and also the lower limbs were adherent to each other (Figure 4a, b). Fetal karyotype was evaluated by dermal biopsy and detected 46 XY.

Discussion

Pentalogy of Cantrell is a very rare congenital anomaly with an estimated prevalence of 1/65.000 to 1/200.000 births (1). The etiology is unknown but defective formation, differentiation and migration of the lateral mesoderm at 14-18 days of embryonic life is the most accepted hypothesis (3). Most previous reported cases were sporadic but X chromosome gene mutation was involved in midline ventral disorders and in the literature, X linked inheritance has been suggested in some families (3).
Cantrell pentalogy may be present in different variations ranging from the protruding heart through the chest with omphalocele to anterior diaphragmatic hernia underdiagnosed until birth. In severe cases; the fetal heart protrudes through a wide sternal cleft but in mild forms, patients with small defects have partial anterior or transient or intermittent displacement of fetal heart. Abdominal wall defects present in many forms ranging from diastasis recti to large omphaloceles. A 'V' shaped defect is observed in diaphragm herniation in Cantrell syndrome and a connection is present between peritoneal and pericardial cavity. Sternal defect should be partial or complete and may range from an absent xyphoid to various degrees of clefting (4, 5).
Cardiac anomalies such as ventricular septal defect, atrial septal defect, tetralogy of Fallot and ventricular diverticulum may accompany pentalogy of Cantrell. Ventricular septal defect (VSD) is the most commonly seen cardiac anomaly (6). Anencephaly, encephalocele, exencephaly hydrocephalus and craniorachischisis has been reported to be associated with Cantrell syndrome (6). Cleft lip and/or palate is the craniofacial anomaly accompanying Cantrell syndrome. Abdominal organ defects such as gallbladder agenesis and polysplenia may be the other attending anomalies. Vertebral anomalies such as dorsolumbar kyphoscoliosis and scoliosis are rare (6, 7). Clubfoot, absence of tibia or fibula or radius, hypodactily, ectrodactyly, phocomelia are associated limb defects and are reported only in a few papers in the literature (8). Pivnick et al. (9) reported an infant

Figure 1. Large omphalocele and ectopia cordis are seen in color Doppler sonography

Figure 2. Left femur was hypoplastic, tibia and fibula were absent, left foot was directly connected to left femur

Figure 3. 2D sonographic appearance of lumbar lordoscoliosis

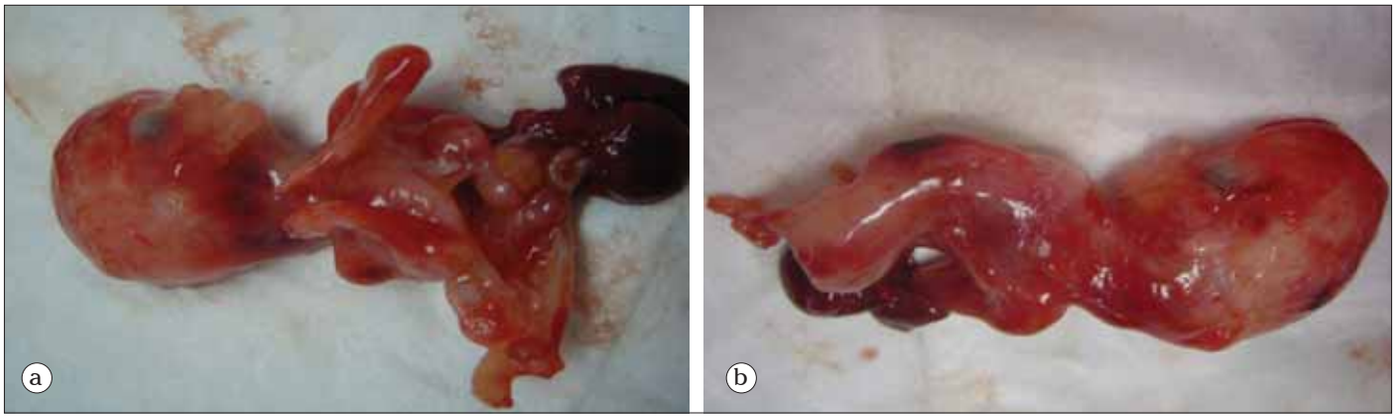

Figure 4. a) Defects which were diagnosed at the initial period were identical at pathologic examination, b) Prenatal sonographic examination of vertebral anatomy was consistent with pathologic examination

with midline thoracoabdominal syndrome with ectrodactyly and absence of right fibula and foot. Uygur et al. (10) reported an infant of Cantrell syndrome with limb defects. Chen et al. (11) reported a fetus with pentalogy of Cantrell and associated ectrodactyly and right upper limb hypoplasia. In our case report we observed a large omphalocele containing both bowels and liver. The heart protruded out and no cardiac anomaly was detected. In lower extremities left femur was hypoplasic, left tibia and fibula were absent and bilateral legs were adherent to each other (syrenomelia) which was reported rarely in literature. Also we identified lumbar lordoscoliosis by 3D scanning.

Prenatal diagnosis in the first trimester is simple if ectopia cordis and large omphalocele are detected with 2D ultrasonography. However, sometimes this may be difficult particularly in minor forms of ectopia cordis such as anterior, partial or transient displacement of the heart. Therefore transient pericardial effusion is an adjunct sonographic marker in diagnosis. 2D ultrasonography is commonly sufficient in diagnosis, but 3D scanning provides us with more detailed information about the fetal anatomy and malformations. The 3D mode is better in visualizing fetal bones because of greater contrast difference compared with adjacent organs. If pentalogy of Cantrell is suspected, detailed fetal anatomic assessment is necessary. In many cases a combination of 2D and 3D ultrasonography provide us with more details and sufficient images. MRI seems to be a complementary screening method for fetal anomalies. Fetal cardiac assessment should be done through fetal echocardiograpy. Chromosomal analysis is highly recommended due to the association with aneuploidy, particularly trisomy 18. In our case, Cantrell syndrome was diagnosed at 11+0 weeks of gestation with both 2D and 3D ultrasonography. In the differential diagnosis amniotic band syndrome must be kept in mind (12).

Prognosis depends on the severity of cardiac lesions and associated anomalies. Treatment consists of corrective or palliative cardiovascular surgery, correction of diaphragmatic defects, ventral hernia and other associated anomalies. Success is related to the size of the omphalocele, ectopia cordis and associated heart anomalies (13, 14).

In such cases of fetal anomaly postmortem investigation must be performed. However, in our case the parents did not agree to an autopsy examination.

In conclusion, early diagnosis is feasible in the first trimester if ectopia cordis and omphalocele exist. Development in ultrasound technology provides us better visualization and early diagnosis. Prognosis seems to be poor in patients with complete Cantrell syndrome and patients with associated anomalies. Termination is the choice of treatment. Early diagnosis gives us a chance to reduce maternal morbidity and mortality related to termination.

Conflict of interest

No conflict of interest was declared by the authors.

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Genetic pathogenesis of Perrault Syndrome

Perrault Sendromunun genetik patogenezi

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Dear Editor,

Premature ovarian insufficiency (POI) is defined as the occurrence of hypergonadotropic hypoestrogenic amenorrhoea in women under the age of 40 years and it is part of well described autosomal recessive syndromes (Perrault, Richard Rundle, Alstrom, Wolfram syndromes and Mitochondriopathies) (1).

The association of hypergonadotropic hypogonadism (HH) in females and sensorineural hearing loss (SNHL) in females and males was described as Perrault syndrome (PS). Some patients also have neurological manifestations, but their exact frequency cannot be ascertained since several reports did not include a description of a neurological examination. More recent studies have investigated whether the neurological signs in some of the patients are a coincidental finding or part of the syndrome. Some researchers proposed a possible classification of PS to type I, without neurological disease, and type II or AAHH (The association of ataxia, hypergonadotropic hypergonadism and hearing loss), with progressive neurological disease (2, 3).

Previously, partial deficiency of the mitochondrial enzyme cytochrome c oxidase and muscle coenzyme Q10 (CoQ10) deficiency was reported in cases with PS (4, 5). Recently, mutations in 17 beta-hydroxysteroid dehydrogenase type 4 (also known as D-bifunctional protein (HSD17B4/DBP)) which is also involved in Zellweger syndrome, one of three leukodystrophies and mitochondrial histidyl tRNA synthetase (HARS2) also implicated, in the leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL), have been proposed as the genetic causes of PS (6-8). The "ovarioleukodystrophies" comprise a group of rare leukodystrophies associated with POI. Some of the patients have a variant of "vanishing white matter disease" with mutations in subunits of eukaryotic initiation factor 2B (EIF2B) (9). Although HSD17B4, mitochondrial histidyl tRNA synthetase (HARS2) and EIF2B should be examined in other cases, it may be time to classify PS type II under the leukodystrophies. The report of Pierce et al. (8), represents a valuable contribution, because recent findings in genetic research have suggested that a large number of genetic disorders are highly related in the genotypical root. For example; Alstrom syndrome has begun to be classsified as a ciliopathy (10). The late-onset form of GAII and the myopathic form of CoQ10 deficiency are allelic diseases and chylomicron retention disease and Marinesco-Sjogren syndrome are related (11, 12). We suggest that, before proceeding with further laboratory investigations, clinical and neurological examinations must be fully performed and a correct diagnosis of the cases made as there are many syndromes sharing several findings. Long term follow up is very important, since some clinical manifestations appear later in life. Pierce et al. (8) evaluated the sisters MK and LK, whose clinical manifestations had been thoroughly described previously by Fiumara et al. (13) and Mc Carthy and Opitz (14). Therefore, these sisters are the only cases who have such a detailed clinical history, multidiciplinary approach and long term follow up. At the end, a causative mutation was discovered (6). This simple approach will provide an opportunity to recognize associated syndromes and evidence requiring the initiation of further laboratory investigations.

Before making high cost moleculer analysis; simple blood tests for glucose, vitamin E, folate and B12 levels, alpha-fetoprotein, very long chain fatty acids and phytanic acid, lysosomal enzymes, amino and organic acids, serum ammonia, arterial pH levels, and X-ray of the skeleton could be carried out. Performing ECG, muscle biopsy, MRI, measurement of mitochondrial enzyme cytochrome c oxidase and CoQ10 levels and DNA analysis for trinucleotide expansions at the SCA 1, 2, 3, 6, 7 and FrieDreich's Ataxia loci, mutations analysis of FMR1, HSD17B4/DBP, mitochondrial HARS2 and EIF2B for a number of similar cases will give valuable information about the pathogenesis of PS (3, 15).

PS type II seems to be caused by both a malfunction of the mitochondria and of myelination. The question remains whether there is one gene or at least two different genes responsible for two different clinical entities.

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What is your diagnosis?

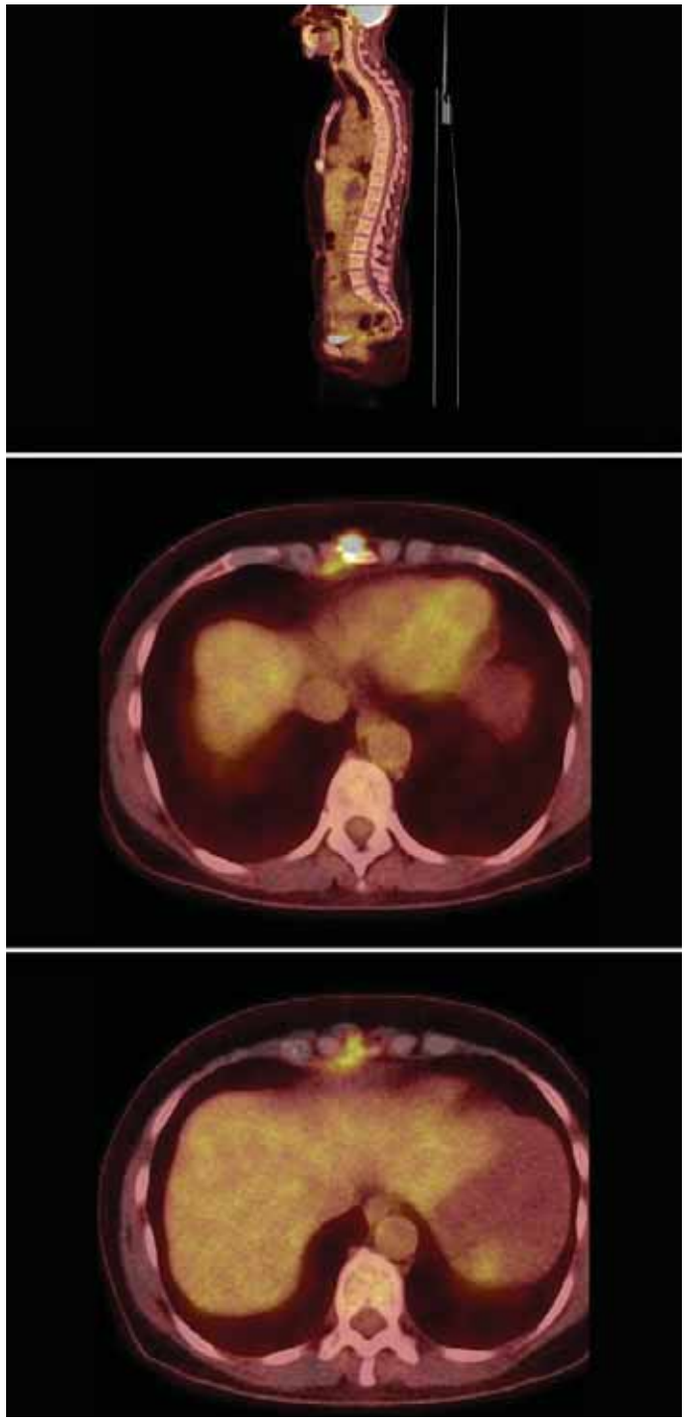

Figure 1. Metastatic lesion in the xyphoid bone

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Among the gynecological cancers, ovarian cancer is the leading cause of death. According to estimates of the American Cancer Society, ovarian cancer accounts for 3% of new cases of female malignancies and 5% of cancer-related deaths in 2009 in the United States (1). Imaging, especially ultrasound and CT, has become a critical part of the evaluation of patients with ovarian cancer.

The diagnosis of recurrent ovarian cancer can be difficult, and variable sensitivities and specificities have been reported for positron emission tomography (PET).

^{18}F-Fluoro-deoxyglucose (FDG) PET/CT has become a critical tool for the preoperative evaluation of women with primary ovarian cancer and for postoperative follow-up assessment for evidence of recurrence in these patients.

(a) To assess the accuracy of FDG-PET/CT in distinguishing malignant from benign pelvic lesions, compared to transvaginal ultrasonography (TVUS) and (b) to establish the role of whole-body FDG-PET/CT, compared to contrast-enhanced computed tomography (CT), in staging patients with ovarian cancer, Castelluci et al. (2) examined fifty consecutive patients with pelvic lesions. The sensitivity, specificity, NPV, PPV and accuracy of FDG-PET/CT were 87%, 100%, 81%, 100% and 92%, respectively, compared with 90%, 61%, 78%, 80% and 80%, respectively, for TVUS. In staging ovarian cancer, FDG-PET/CT results were concordant with final pathological staging in 22/32 (69%) patients, while the CT results were concordant in 17/32 (53%) patients. CT incorrectly downstaged four out of six stage IV patients by missing distant metastases in the liver, pleura, mediastinum and in the left supraclavicular lymph nodes, which were correctly detected by FDG-PET/CT. Based on these results, they concluded that FDG-PET/CT provides additional value to TVUS for the differential diagnosis of benign from malignant pelvic lesions, and to CT for the staging of ovarian cancer patients.

Thrall et al. (3) reported on a retrospective chart review on 39 ovarian cancer patients who underwent a total of 59 FDG-PET/CT scans. Twenty-four FDG-PET/CT scans were performed in 22 patients with previously negative or indeterminate CT scans, but rising CA-125 levels, providing a sensitivity of 90% for localizing disease. Nine FDG-PET/CT in eight patients with clinical symptoms of recurrence, but normal CA-125 levels, detected all three patients who had recurrent disease confirmed within 6 months of follow-up. In addition, four FDG-PET/CT scans performed as a routine follow-up with no clinical evidence of recurrent disease were truly negative in all cases. Fourteen FDG-PET/CT scans in 12 patients with recurrent disease already identified by conventional CT imaging were useful in guiding treatment decisions such as radiation therapy, surgery or chemotherapy by confirming the recurrence and more precisely localizing the site(s) of disease. FDG-PET/CT helped to avoid surgery in four patients who had additional disease detected in unresectable anatomic areas. A total of 51 FDG-PET/CT scans were performed in the patients described above with an overall sensitivity and specificity of 94.5% and 100%, respectively. Eight FDG-PET/CT scans in five patients performed for the assessment of treatment response following chemotherapy or radiation were useful as the disease was not clearly visualized by conventional CT imaging at baseline. According to these data, the authors concluded that FDG-PET/CT has the greatest utility in determining suspected ovarian cancer recurrence, particularly in patients with rising CA-125 levels and negative conventional imaging. FDG-PET/CT was specifically helpful in optimizing the selection of patients for site-specific treatment, including radiation treatment planning, and aided in the selection of optimal surgical candidates. These findings were also confirmed by other studies (4-6).

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Questions on the article within the scope of CME/CPD

1. How was voiding dysfunction defined after anti-incontinence surgery according to the Surgical Treatment Efficacy Trial (SISTERs)?
   a) Need for bladder catheterization after 4 weeks
   b) Need for bladder catheterization after 6 weeks
   c) Need for reoperation for sling takedown
   d) a or c
   e) b or c

2. Which of the following is not specified as a risk factor for postoperative voiding dysfunction?
   a) Preoperative low peak flow rates
   b) Preoperative high PVR
   c) Valsalva leak point pressure <60 cm H2O
   d) Maximum urethral closure pressure >20 cm H2O
   e) Concurrent abdominal or pelvic surgery

3. What percentage of women requires surgical release for refractory postoperative VD after midurethral sling procedures?
   a) %1-2
   b) %2.5-5
   c) %2.5-10
   d) %2.5-36
   e) %10-25

4. Which of the following is not used in medical treatment for postoperative VD with urinary retention?
   a) Diazepam
   b) Baclofen
   c) Terazocin
   d) Oxybutynin
   e) Vaginal estrogen

5. Which of the following is not true for the management of the postoperative VD?
   a) Most surgeons prefer transvaginal urethrolysis rather than retropubic or suprameatal approaches
   b) Mobilization or incision of mid-urethral sling is highly successful in improving voiding dynamics and should be considered first line therapy
   c) Most surgeons delayed a release procedure until about 6-12 months after the procedure.
   d) The mesh would still provide support to the urethra laterally even after the obstruction is released at the midline
   e) In a small group of women, another intervention operation may be needed for recurrent stress urinary incontinence

6. Which of the following is appropriate for the optimal evaluation for patients with postoperative VD?
   a) Pelvic and rectal examination
   b) To rule out urinary tract infection by urinalysis and culture
   c) Evaluation of high pressure, low-flow voiding by videourodynamic studies
   d) Evaluation of bladder pathology, a hypersuspended bladder neck and foreign bodies by cystourethroscopy
   e) All of the above

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2nd Question	A	B	C	D	E

3rd Question	A	B	C	D	E

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6-8 June 2012	**28th Annual Meeting of ESHRE** Istanbul Congress Center – ICC/ Istanbul www.eshre2012.net
24-28 June 2012	**World Congress in Fetal Medicine by Fetal Medicine Foundation** Island of Kos , GREECE www.fetalmedicine.com
19-22 July 2012	**16th World Congress on Controversies in Obstetrics, Gynecology & Infertility (COGI)** Singapore (Fairmont Singapore & Swissôtel) , SINGAPORE www.congressmed.com/cogisingapore
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26 -30 September 2012	**8th Obstetrics and Gynecologic Ultrasonography Congress and Ian Donald Advanced Ultrasound Course** Lykia World Oludeniz Hotel-Antalya www.usgkongre2012.org
27-30 September 2012	**5.TSRM** Sheraton Çeşme Hotel-İzmir www.2012.tsrm.org.tr
11-14 October 2012	**The 8th National Congress of Turkey Maternal Fetal Medicine and Perinatology Association** İstanbul, Turkey www.tmftpkongre2012.org
9-11 November	**2nd Asian Conference on Endometriosis** İstanbul, Turkey www.ace-2012.org