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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/),

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

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Article type	Abstract Length	Manuscript Word Count*	Maximum Number of Authors	Maximum Number of References$^{\Phi}$
Original Research	250 words	5,500 words (~22 pages)$^{\Psi}$	NA	30
Case report	150 words	2,000 words (~8 pages)	4	8
Systematic review	300 words	6,250 words (~25 pages)	4	60
Current commentary	250 words	3,000 words (~12 pages)	4	12
Procedure and Instruments	200 words	2,000 words (~8 pages)	4	10
Letters	NA	350 words	4	5

*Manuscript length includes all pages in a manuscript (ie, title page, abstract, text, references, tables, boxes, figure legends, and appendixes). $^{\Phi}$Suggested limit. $^{\Psi}$The Introduction should not exceed 250 words. ~approximately; NA, not applicable.

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TURKISH JOURNAL OF OBSTETRICS AND GYNECOLOGY

LETTER FROM THE PRESIDENT

Dear Colleagues,

After the end of summer, in autumn we are ready for the congresses. In 5-9 October, we are going to have the TSOG congress.

In 11-12 November we are going to have the "Nutrition in Women Congress."

As you also know we have the general assembly of TSOG in November. We are going to elect the new board.

As president of TSOG and the official owner of this magazine, we had changed the editor, I want to thank Prof. Dr. Eray Çalışkan very much.

Our aim was to be a part of SCI, unfortunately we could not manage this yet.

I hope in the near future Turkey's most important Obstetrics and Gynecology society's magazine will be an international magazine.

If you are going to send your papers first to our magazine rather than after rejection in international papers, you will be a part of this success.

During my presidency I tried to change this magazine, partially we did it (English version, change of editor).

We began the assistant school project and did 7 schools. Many young doctors attended and had been a part of TSOG, I know that they are TSOG's future.

We had done 3 congress and in a few days will do the 4th one.

We had done the TSOG Rising Star project young doctors got an enthusiastic education and we will do it this year again.

We had done sessions in International Federation of Gynecology and Obstetrics, Ebcog congresses. In International Federation of Gynecology and Obstetrics, Turkey had been one of the four countries that decreased the maternal mortality rates efficiently worldwide.

We had gone to many cities for local meetings.

We had many ethics meetings and tried to solve the problems of many colleagues.

I want to thank all the members of the board of TSOG for the collaboration and hope that TSOG will be more powerful in the future.

I want to thank all friends for being a member of TSOG.

Best wishes to all of you.

Cansun Demir, Prof. MD

President of TSOG

TURKISH JOURNAL OF OBSTETRICS AND GYNECOLOGY

EDITORIAL

Dear Colleagues,

Scholarly publishing is an area of great competition. On one side there are the classical journals that publish scientific papers for decades and are supported by renowned publishing companies. Academicians and their supporters pay all the costs of a research and gain no money from the copyright of their paper. On the contrary journal owners and publishing companies own the copyright of the manuscripts only in the expense of publishing costs. Companies and journal owners sell the manuscripts at high cost, earn money from subscriptions, advertisements and pay nothing for the time of editors, reviewers who are expected to spend their time for scientific acceptance and idealism. As the number of new journals and published manuscripts increases renowned journals are cited more than the others and get high impact factors. As the impact factor increases more scientists sent their manuscripts for evaluation to these journals which enables them to select best research which will even accelerates their impact factor. This is a vicious circle that prevents new journals to compete with renowned journals for copyrighted citation indexes. This is such a high profit sector that publishing companies are launching new journals every day. This situation while increasing the profit of the publishing companies decreases the income of the scientific societies whose primary function should be promoting scientific productivity independently. The present situation is leading to a monopoly of big publishing companies.

Among the new journals an alternative way of appearing in the front rows is open journal publishing strategy. Professional publishing companies provides a venue of independent publishing for the researchers and takes the publishing cost with unreasonably high profits from the researchers. The bill differs from 500 to 2000 dollars for a seven page manuscript and even e-journals take the same amount of money despite the lack of hard copy printing costs. Some may argue that this provides an independent scholarly publishing but the conflict of interest arises from the fact that the more manuscripts open journals publish the more profit they get so there is the possibility of quick and a non-rigorous scientific evaluation process.

Not all the open journals are the same of course. Like our journal some open journals are fully sponsored by scientific societies. The idealism dominates in every step. Researchers pay no money for publishing, evaluation and language editing. The editors and reviewers donate their time and knowledge free of charge. The manuscripts appearing in the journal can be freely down loaded and distributed which enables the scientists, students and all target readers to reach up to date knowledge easily and freely. We hope that these efforts will find a platform of real independent knowledge sharing and awarded by higher citation numbers.

Hope to see your support in the new issues.

Best wishes,

Eray Çalışkan, Editor

Clinical Investigation / Araştırma

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Role of inflammation and oxidative stress in the etiology of primary ovarian insufficiency

Primer ovariyan yetmezliğin etiyolojisinde oksidatif stres ve enflamasyonun rolü

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Abstract

Objective: The aim of this study was to elucidate the etiology and treatment of primary ovarian insufficiency, which is of unknown cause in 95% of the cases.

Materials and Methods: Thirty patients aged 18-40 years who presented to Dicle University Faculty of Medicine Clinic of Obstetrics and Gynecology between June 2012 and January 2014 and were diagnosed as having primary ovarian insufficiency based on their clinical and endocrinologic data, and 30 healthy controls were included in this study.

Results: No significant differences were found between patients with primary ovarian insufficiency and control subjects in demographic data and lipid profile levels, thyroid- stimulating hormone, prolactin, and glucose. However, the neutrophil to lymphocyte ratio and levels of follicle-stimulating hormone, luteinizing hormone, total antioxidant status, total oxidant status, and oxidative stress index were significantly higher in patients with primary ovarian insufficiency than in control subjects. In the correlation analysis, follicle-stimulating hormone exhibited a positive correlation with total oxidant status, oxidative stress index, and the neutrophil to lymphocyte ratio (r=0.573** p<0.001, r=0.584** p<0.001, r=0.541 p<0.001, respectively) and correlated negatively with total antioxidant status (r=-0.437** p<0.001).

Conclusion: The neutrophil to lymphocyte ratio, total oxidant status, and oxidative stress index levels are elevated in primary ovarian insufficiency. Therefore, anti-oxidative and anti-inflammatory treatment might be administered to patients in the early stage of primary ovarian insufficiency. However, larger studies are needed to clarify whether these elevated levels are a cause or a consequence of primary ovarian insufficiency.

Keywords: Premature ovarian insufficiency, oxidative stress, inflammation

Öz

Amaç: Bu çalışmayla amacımız %95 etiyolojisi bilinmeyen prematür ovariyan yetmezliğin etiyolojisine ve tedavisine ışık tutabilmektir.

Gereç ve Yöntemler: Haziran 2012-Ocak 2014 yılları arasında Dicle Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum Kliniği'ne klinik ve endokrinolojik olarak prematür ovariyan yetmezlik tanısı ile başvuran 18-40 yaş arası 30 hasta dahil edildi.

Bulgular: Çalışmamızın sonucunda her iki gruptada pelvik ultrasonografide herhangi bir patoloji yoktu ve her iki grubunda kromozom analizleri normaldi. Demografik veriler açısından gruplar arasında anlamlı bir farklılık izlenmedi. Glukoz, lipit profili, tiroid stimülan hormon, prolaktin düzeyleri açısından anlamlı bir farklılık izlenmedi. Ancak, luteinize edici hormon, total antioksidan statüs, total oksidan statüs ve oksidative stres indeks düzeyleri ve neutrofil lenfosit oranı hasta grupta anlamlı olarak yükseklik izlendi. Estradiol hasta grupta anlamlı olarak düşük tespit edildi (p<0,001). Yapılan korelasyon analizinde folikül stimülan hormon ile total oksidant statüs ve oksidative stres indeks ve neutrofil lenfosit oranı arasında pozitif korelasyon izlendi. Sırasıyla r=0,573** p<0,001, r=0,584** p<0,001, r=0,541 p<0,001. Folikül stimülan hormon ve total antioksidan statüs, arasında negatif korelasyon izlendi r=-0,437** p<0,001.

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Öz

Sonuç: Prematür ovariyan yetmezliği olan hastalarda neutrofil lenfosit oranı, total antioksidan statüs, total oksidan statüs düzeyinin yüksek olduğunu söyleyebiliriz ve bu nedenle prematür ovariyan yetmezliğin tedavisinde antioksidatif ve antienflamatuvar tedaviler verilebilir. Ancak bunun prematür ovariyan yetmezliğin etiyolojisinde mi yoksa prematür ovariyan yetmezliğin sonucu mu olduğunu söylemek için daha geniş çalışmalara ihtiyaç vardır.
Anahtar Kelimeler: Prematür ovariyan yetmezlik, oksidatif stres, enflamasyon

Introduction

The age of normal menopause, which occurs as a result of the depletion of functional primordial follicles in ovaries, is 50±4 years[1]. Loss of normal ovarian functions before the age of 40 years is referred to as primary ovarian insufficiency (POI)[2]. In women under the age of 40 years who experience amenorrhea for longer than 4 months, and follicle-stimulating hormone (FSH) levels found at the menopausal range on two consecutive occasions with an interval of at least one month suggests POI[3]. Ovaries do not cease all function in approximately 50% of affected women, and 5-10% of these women can get pregnant and give birth after the diagnosis of POI[3-5].

POI is a common disorder that afflicts 1-2% of women younger than 40 years and 0.1% of women aged less than 30 years[6]. It is a heterogeneous disorder that demonstrates great variations in causes and phenotypes. The focus of the present study was the etiology of POI, which affects one out of every 100 women under the age of 40 years.

Follicle depletion is caused by insufficient formation of the primordial follicle pool in the intrauterine period, increased follicle consumption, and autoimmune or toxic follicle degradation. Follicle dysfunction, on the other hand, occurs when normal functions of ovarian follicles are blocked by a pathologic process, such as mutations of the FSH receptor[7] either mechanism results in functional insufficiency of the ovary.

POI comprises various diseases with a wide variety of pathogenesis such as genetic chromosomal, mitochondrial, enzymatic, iatrogenic, and immunologic aberrations, or infections[8]. These causes may effect the ovary at each period of life, including prepubertal, pubertal, and reproductive periods[9]. However, POI in patients is generally idiopathic, and the principal mechanisms are unknown.

Oxidative stress (OS) causes lipid peroxidation, functionally and structurally. It changes protein and DNA, supports apoptosis, and conduces the risk of chronic diseases such as cancer and heart disease by the agency of effects on redox status and/or redox-sensitive signaling pathways and gene expression[10]. Findings from in vitro, animal model, and clinical studies proposed that OS was implicated in the etiology of reverse reproductive cases in both women and men[11].

The neutrophil to lymphocyte ratio (NLR), which is an indicator of systemic inflammation, demonstrates the balance between neutrophil and lymphocyte concentrations in the body. Inflammatory cytokines induce DNA damage and inhibit DNA repair[12]. Studies showed that inflammatory mediators were increased in patients with premature ovarian failure (POF)[13]. There are many rat studies in the literature regarding anti-inflammatory treatments in the treatment of POF[14]. This is the first study in the literature to investigate NLR, total antioxidant status (TAS), and total oxidant status (TOS) in POI, which is of unknown cause in 95% of the cases. The purpose of this study was to elucidate the etiology and therapeutic approaches of POI.

Materials and Methods

A total of 30 patients aged 18-40 years of age (mean: 28.9±6.8 years) who presented to Dicle University Faculty of Medicine Clinic of Obstetrics and Gynecology between June 2012 and January 2014 and were diagnosed as having POI based on their clinical and endocrinologic data, and 30 healthy controls who were matched for ethnic background and age were included in the study. The features of 30 patients with presumptive primary ovarian insufficiency were investigated. The initial diagnosis was based on a serum FSH level higher than 40 mIU/mL in karyotypically normal women aged younger than 40 years who experienced menstrual irregularity or amenorrhea. Following the provision of written informed consent, FSH, luteinizing hormone (LH), estradiol (E2), thyroid-stimulating hormone (TSH), prolactin (PRL), triglyceride (TRG), total cholesterol (total-C), and glucose tests, as well as complete blood count were performed in the patients with POI and control subjects. Patients with thyroid diseases, hyperprolactinemia, Cushing's disease, congenital adrenal hyperplasia or infectious diseases (pulmonary diseases, peritonsillar abscesses), cardiovascular diseases, endometrial lesions, malignant neoplasm), and patients that were administered such agents as hormonal agents, ovulation-inducing agents, glucocorticoids, anti-androgens, and anti-hypertensives over the six months prior to the study were excluded. The patients were enrolled if they were not on any drugs, had no history of recent infection or inflammation, were nonsmokers, and also had normal weight. Patients with secondary amenorrhea or pregnancy were also excluded.

In addition to family history of metabolic disorders, a detailed history including menstrual cycle pattern, temporal profile, severity of unwanted hair growth, and drug intake was taken at the time of enrollment. Weight and height measurements were made. Body mass index (BMI) was determined using the following formula: Weight (kg)/height (m^2). One single observer performed transabdominal ultrasonography (USG) in all the participants to demonstrate ovarian morphology. To reveal possible gynecologic abnormalities, transvaginal USG was performed as appropriate using a Voluson 730 expert sonography 1.8 GHZ probe. The parameters examined in this

study were as follows: Age, BMI, smoking, family history, co-existing conditions, complete blood count results, baseline hormone levels, NLR, TAS, and TOS values, and findings on sonography. This study, which was approved by the Local Ethics Committee of the university, was performed in the Obstetrics and Gynecology Clinic of Dicle University.

Laboratory Tests

Participants gave blood samples between the third and the fifth days of the normal menstrual cycle, i.e. in the early follicular phase. Venous blood was taken from the forearm between 08:00-10:00 AM following a fast of eight hours. Blood samples were centrifuged without delay, and sera were kept at a temperature of -80 °C before laboratory testing.

Levels of serum glucose, TRG, and total-C were determined using an Architect C 16000 autoanalyzer (Abbott Laboratories, Abbott Park, IL, USA).

FSH, LH, E2, PRL, TSH levels were determined using electrochemiluminescence immunoassay on a Cobas 601 analyzer (Roche Diagnostics, Mannheim, Germany).

For the determination of NLR, complete blood counts of patients with POI and controls were studied using a CELL-DYN automated hematology analyzer (Ruby-Abbott Diagnostics, USA).

TAS levels were measured using Erel's[15] recently developed automated technique. In Erel's[15] technique, a hydroxyl radical is generated, which is the most potent biologic radical. A solution of ferrous ion in Reagent 1 is combined with Reagent 2 that containing hydrogen peroxide in the assay. The radicals generated by the hydroxyl radical in this way are also potent radicals. As a result, the anti-oxidative action of the sample against the potent-free radical reaction is determined, which is triggered by the hydroxyl radical. The findings are reported in mmol Trolox Eq/L.

TOS levels were measured using Erel's[16] automated technique. In this technique, a ferrous ion-o-dianisidine complex is oxidized to ferric ion by oxidants found in the sample. Glycerol molecules, which are found in large amounts in the reaction medium, increase the oxidation reaction. In acidic material, the ferric ion creates a colored complex with xylenol orange. The intensity of color is measured spectrophotometrically and is related to the total amount of oxidant molecules in the sample. Calibration of the assay is performed using hydrogen peroxide. The findings are reported in μmol H_2O_2 Eq/L.

The division of TOS by TAS yields the oxidative stress index (OSI) value. The following formula is used to calculate OSI: OSI (arbitrary unit)=TOS (μmol H_2O_2 Eq/L)/TAS (mmol Trolox Eq/L)[17].

The analysis of chromosomes was conducted in the Department of Medical Biology-Genetics. Blood samples were taken into heparinized vacutainers for cytogenetic analysis, and the lymphocyte cultures were organized in duplicates[18]. Two sets of slides were arranged from each culture. Karyotyping was conducted on routine peripheral blood lymphocyte cultures using G-banding following Trypsin and Giemsa staining (GTG)[19]. A minimum of 30 GTG-banded metaphases were scored from each patient. Considering the criteria of the International System for Human Cytogenetic Nomenclature, three cells were karyotyped[20]. In general, chromosome counts of 30 cells were undertaken; however, 50 or more cell counts were performed in the event that mosaicism was suspected[21].

Statistical Analysis

Statistical Package for the Social Science (SPSS 21) (IBM SPSS Version 8.5.0.0021 Licensed Materials Property of IBM Corp. Copyright IBM Corporation and others) was used for data analyses. Data analyses are expressed as mean and standard deviation. Student's t-test and Mann-Whitney U test were used to compare clinical and biochemical data between the groups. Whether intra-group variables demonstrated normal distribution was determined using the Kolmogorov-Smirnov test. The investigation of correlation between the values was conducted using Spearman's analysis. P values less than or equal to 0.05 were considered statistically significant.

Results

No participants in this study had a pathologic presentation on pelvic ultrasound or a chromosomal abnormality. In addition, none of the participants had a family history of POI. No significant differences were found between the patients with POI and control subjects in age, marital status, gravidity, smoking and BMI (Table 1). No significant differences were found between the groups in lipid profile levels, TSH, PRL, or glucose. E2 levels were lower in patients with POI than in the control subjects p<0.001 (Table 2). However, NLR and levels of FSH, LH, TOS, and OSI were higher in patients with POI than in the control subjects (Table 3) (Figure 1). The levels of FSH were directly correlated with TOS, OSI, and NLR (r=0.573** p<0.001; r=0.584** p<0.001; r=0.541 p<0.001, respectively) and indirectly correlated with TAS (r=-0.437** p<0.001) (Figure 2).

Discussion

In our study, we hypothesized that there would be increased OS, and investigated the presence of inflammation in patients

Table 1. Demographic data of the groups

Demographic data		POI (n=30)	Control (n=30)	p
Age		28.9±6.8	29.2±5.0	0.864
Marital status (married)		22±0	26±0	0.200
Gravidity		1.13±1.3	1.43±1.4	0.408
BMI		24.1±4.2	23.2±3.3	0.090
Smoking	Yes	11 (36.7%)	10 (33.3%)	0.791
	No	19 (63.3%)	20 (66.7%)	

Data are presented as mean±standard deviation. Mann-Whitney U test, p: p values denoting the outcomes of comparison of the parameters of biochemical premature ovarian insufficiency and control groups, p<0.05 was considered statistically significant, POI: Premature ovarian insufficiency, BMI: Body mass index

with POF. Many studies have been conducted on ovarian reserve and OS. However, there are few studies in patients with POF. We determined increased OS and inflammation in patients with POF.

Table 2. Levels of hormonal parameters in the groups

Hormonal parameters	POI (n=30)	Control (n=30)	p
FSH (mU/mL)	60±20	5.9±1.9	<0.001
LH (mU/mL)	38±21.2	6.3±3.7	<0.001
E2 (pg/mL)	17.0±7.2	52.6±39.9	<0.001
PRL (ng/mL)	13.6±5.4	16.8±3.2	0.222
TSH (uIU/mL)	2.4±1.6	1.6±0.8	0.082
Glucose (mg/dL)	96.0±17.4	89.8±17.9	0.180
Total-C (mg/dL)	184.5±25.4	170.5±46.9	0.099
TRG (mg/dL)	124.4±25.6	110.8±37.0	0.106

Data are presented as mean ± standard deviation, Mann-Whitney U test, p: P values denoting the outcomes of comparison of the parameters of biochemical POI and control groups, p<0.05 was considered statistically significant, POI: Premature ovarian insufficiency, TRG: Triglyceride, Total-C: Total cholesterol, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, E2: Estradiol, PRL: Prolactin, TSH: Thyroid-stimulating hormone, BMI: Body mass index

Various etiologic factors are associated with POI: Autoimmune ovarian damage, genetic aberrations, infectious agents, toxins, iatrogenic factors, and environmental factors. Nevertheless, the majority of cases are idiopathic with no identifiable etiologic factors, even after a thorough examination[22].

POI is usually sporadic; however, one of the first-degree relatives of 10-15% of patients also has this disorder[23]. Therefore, patients should be asked about their family history. In addition, hypothyroidism, adrenal insufficiency, hypoparathyroidism, and other autoimmune diseases should be questioned. A family history of mental retardation, tremor-ataxia, and Parkinson-like symptoms might lead to consider Fragile X syndrome associated with FMR1 gene mutation[24]. However, no patients with POI in the present study had a family history or an autoimmune disease.

Chronic low-grade inflammation is a major contributor to the pathogenesis of POI. NLR, which is an indicator of systemic inflammation, demonstrates the balance between neutrophil and lymphocyte concentrations in the body. Compared with

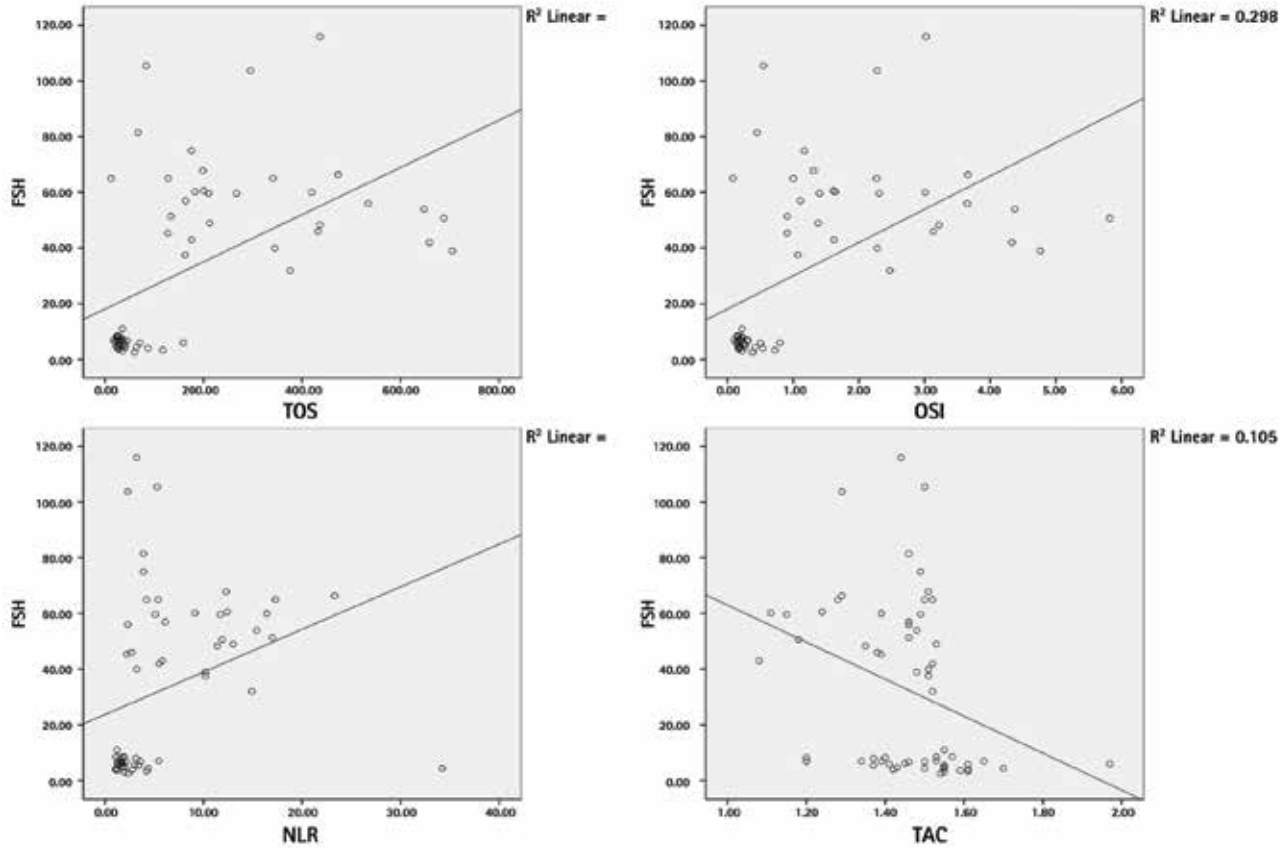

Figure 1. Correlation analysis between follicle-stimulating hormone, total antioxidative capacity, total oxidative capacity, oxidative stress index, and neutrophil to lymphocyte ratio

NLR: Neutrophil to lymphocyte ratio, OSI: Oxidative stress index, FSH: Follicle-stimulating hormone, TOS: Total oxidant status

many other inflammatory markers, NLR adds no extra cost because it is inexpensive. It is widely available and routinely measured on admission. In the present study, NLR was found to be significantly elevated in patients with POI, which might indicate the potential role of increased inflammation in the etiology of POI. Previous studies reported that patients with POI had an increased risk of atherosclerosis and CVD[25] which might also be associated with increased inflammation in these patients.

Table 3. Levels of oxidative stress and inflammation markers in the groups

Oxidative stress and inflammation markers	POI (n=30)	Control (n=30)	p
TAS (mmol trolox eqv/L)	1.3±0.1	1.5±0.1	0.006
TOS (μmol H_2O_2 eqv/L)	309.4±195.9	42.6±30.7	<0.001
OSI	2.2±1.4	0.2±0.1	0.001
NLR	8.9±5.6	3.2±5.9	<0.001

Data are presented as mean ± standard deviation, p: P values denoting the outcomes of comparison of the parameters of biochemical POI and control groups, p<0.05 was considered statistically significant, POI: Premature ovarian insufficiency, TAS: Total antioxidative capacity, TOS: Total oxidative capacity, OSI: Oxidative stress index, NLR: Neutrophil to lymphocyte ratio

The effect of OS in the etiopathogenesis of POF has not been widely studied. A recent study reported that administration of coenzyme Q in patients with POF who had high reactive oxygen species (ROS) levels improved the embryo quality[26]. High superoxide ion amounts lead to a decline in the bioavailability of nitric oxide, an accrete in ROS levels, and OS. As compared with spermatozoa, female germ cells improve under hypoxic conditions in the ovarian cortex. However, exposure to supraphysiologic levels of ROS are deleterious to developing oogonia. Another study proposed that increased production of OS contributed to oophoritis associated with POF[27]. High ROS levels stimulate mitochondrial DNA modifications. In addition, high ROS levels lead to mitochondria abnormality, which could lead to low adenosine triphosphate production due to disrupted oxidative phosphorylation and oogenesis, low oocyte number, and POF[28].

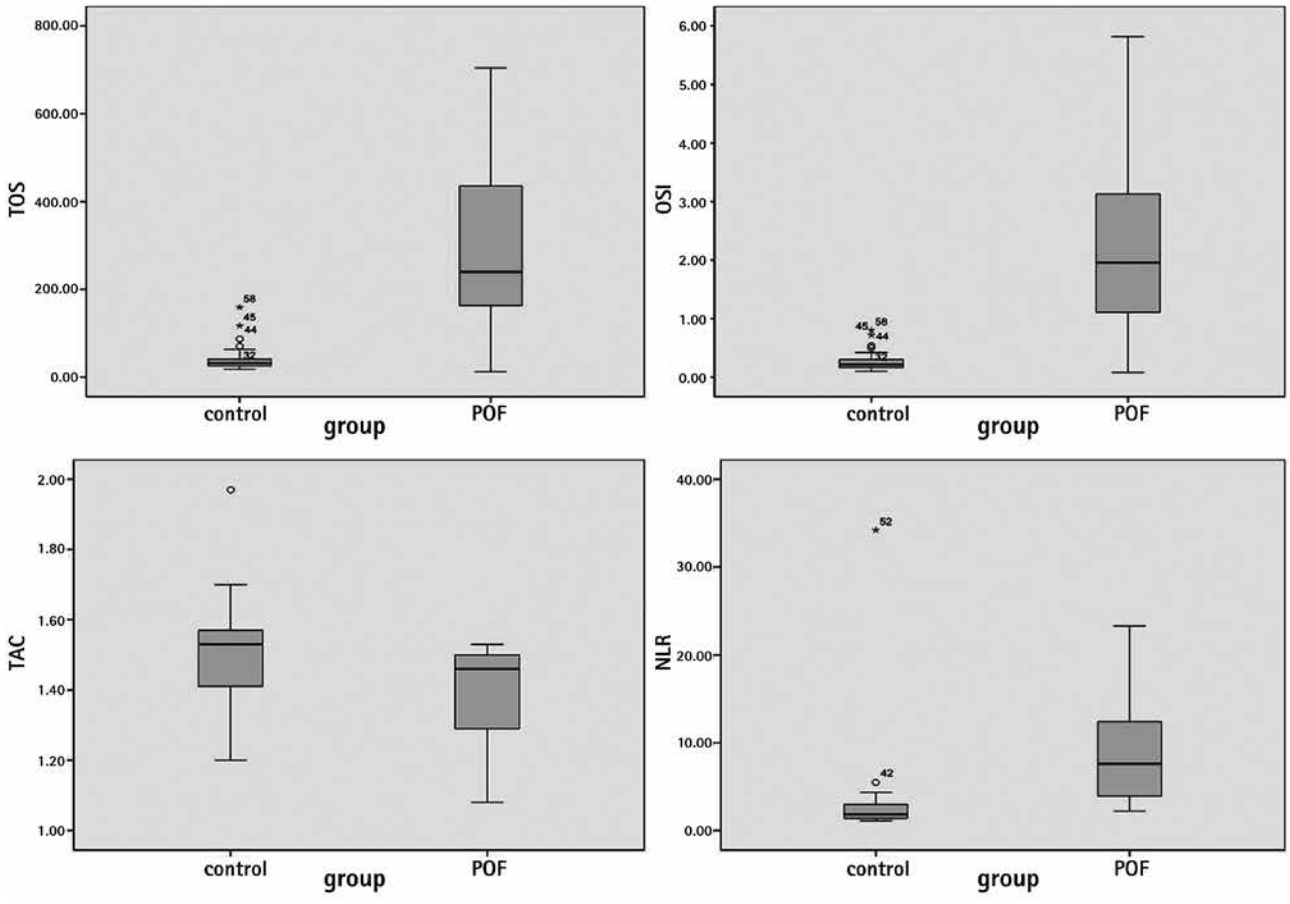

Figure 2. Neutrophil to lymphocyte ratio, total antioxidative capacity, total oxidative capacity, oxidative stress index levels in patients with premature ovarian insufficiency and controls

POF: Premature ovarian failure, TOS: Total oxidant status

OS is involved in the etiology of diverse degenerative conditions such as diabetes, atherosclerosis, arthritis, cancer, and aging[29]. In addition, it was shown that ROS such as hydroxyl radicals, hydrogen peroxide, and superoxide anions are a part of the pathogenesis of bone loss caused by osteoclast differentiation and bone resorption[30]. Furthermore, two previous studies suggested that ROS levels were elevated in POI, and OS may be a part of the etiology of idiopathic POI[31,32].

The role of OS in female fertility is an area worthy of sustained research. Preliminary research that analyzes the complete mitochondrial genome and OS should be tracked in different populations and in broader studies. This research should also investigate the ovary for mitochondrial nucleotide change because they develop in a different microenvironment in the ovary and are of different embryologic origin. However, owing to ethical constraints, such research is not feasible. In a study of male infertility from our laboratory, we found systemic blood ROS levels correlated with seminal ROS levels[33]. Hence, the present study on blood TAS, TOS, and OSI in POI is significant, although it would be ideal to conduct further, similar studies on oocytes. The therapeutic tools currently available for the treatment of mitochondrial diseases due to mitochondrial deoxyribonucleic acid mutations are very few, and their efficacy is not yet well established[34].

In a large series of 357 patients with POI, the median E2 level was only 10 pg/mL[35]. In the present study, estrogen levels were found significantly lower in patients with POI compared with the control subjects.

There is no family history in the vast majority of women with POI. The chromosomes are normal, and there is no sign of auto-immunity in these women, which renders the mechanism of damage unknown. Therefore, hidden environmental damage from the past might be considered in these women. In men, it is known that viruses such as mumps might cause testicular inflammation and lead to permanent damage and lack of sperm. In addition, it is widely believed that sperm counts in men have reduced in recent years because of testicular exposure to environmental toxins and drugs. In this respect, it is probable that the ovaries are similarly affected by viruses and toxins. Viruses in particular are a potential cause of ovarian insufficiency in women with no identifiable cause. Anecdotal reports of virus infections that are rapidly followed by ovarian insufficiency provide support for this causal relationship[35]. In the present study, NLR was found significantly elevated in patients with POI who had no history of inflammation or medication. As a result, idiopathic POI might be explained by inflammation caused by environmental toxins. Smoking is known to be detrimental to ovarian functions. On average, smokers experience menopause earlier than nonsmokers, which indicates a potential harmful effect of smoking on ovarian functions[36]. Our study demonstrated no significant difference between patients with POI and healthy control subjects regarding smoking.

Previous studies reported that a diet rich in glucose and free fatty acid could trigger OS and an inflammatory response from mononuclear cells[37]. The present study found no significant difference between patients with POI and controls in lipid profile and glucose levels. Therefore, increased OS observed in patients with POI might be associated with increased inflammation.

Study Limitations

A limitation of our study is that we did not measure anti-Müllerian hormone (AMH) levels. The AMH test is the best to evaluate the ovarian reserve, but it cannot be performed in our hospital; instead ovarian reserve was evaluated through FSH, LH, and E2 measurements. FSH and E2 are important markers of ovarian reserve, especially in the absence of known AMH levels.

As far as we know, no other studies have investigated NLR, TAS, TOS, and OSI in patients with POI. The present study revealed elevated levels of NLR, TOS, and OSI in patients POI. Therefore, anti-oxidative and anti-inflammatory treatment might be administered to patients in the early stage of POI. However, larger studies are needed to clarify whether these elevated levels are a cause or a consequence of POI.

Ethics

Ethics Committee Approval: The study were approved by the Dicle University of Local Ethics Committee, Informed Consent: Consent form was filled out by all participants.
Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Elif Ağaçayak, Neval Yaman Görük, Concept: Hakan Küsen, Design: Elif Ağaçayak, Data Collection or Processing: Hakan Küsen, Ahmet Yıldızbakan, Analysis or Interpretation: Serdar Başaranoğlu, Mehmet Sait İçen, Hatice Yüksel, Sevgi Kalkanlı, Literature Search: Senem Yaman Tunç, Talip Gül, Writing: Elif Ağaçayak.
Conflict of Interest: No conflict of interest was declared by the authors.
Financial Disclosure: The authors declared that this study received no financial support.

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Non-invasive prediction of implantation window in controlled hyperstimulation cycles: Can the time from the menstrual day at embryo transfer to expected menstrual cycle give a clue?

Kontrollü hiperstimülasyon sikluslarda implantasyon penceresinin non-invaziv tespiti: Embriyo transferi yapılan menstürasyon günü ile beklenen menstürasyon siklusu arasındaki zaman ipucu verir mi?

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Abstract

Objective: The aim of this study was to assess whether the time from the menstrual day at embryo transfer to expected menstrual cycle (TETEMC) is associated with the implantation in women with regular cycles or not.

Materials and Methods: Forty women with successful implantation and forty women without implantation with regular cycles were randomly selected from prospectively collected database of assisted reproductive technology clinic of Zeynep Kamil Women And Children's Health Training and Research Hospital. TETEMC was calculated for each case to assess relationship with the successful implantation.

Results: Comparison of groups revealed significant differences with regard to TETEMC and the menstrual period ($p<0.05$).

In ROC analyses both the TETEMC (AUC=0.824, $p<0.001$) and the menstrual period (AUC=0.797, $p<0.001$) were significant predictors for clinical pregnancy. Cut off value for the menstrual period was found to be 27.5 days with 82.6% sensitivity and 65% specificity. Cut off value for TETEMC was 11.5 days with 75% sensitivity and 63.2% specificity.

Conclusion: Longer menstrual cycle and the TETEMC seem to be associated with the implantation failure.

Keywords: Day of embryo transfer, artificial reproductive techniques, implantation

Öz

Amaç: Bu çalışmanın amacı düzenli mens olan hastalarda embriyo transferi yapılan gün ile beklenen siklus günü arasındaki sürenin (TETEMC) implantasyon ile ilişkisini değerlendirmektir.

Gereç ve Yöntemler: Zeynep Kamil Eğitim ve Araştırma Hastanesi İnfertilite Kliniği'ne başvuran hastalar çalışmaya dahil edildi. Rastgele seçilmiş, adet siklusları düzenli ve başarılı implantasyon elde edilmiş 40 hasta ile, adet süreleri düzenli başarısız implantasyon elde edilen 40 hastanın tıbbi kayıtları prospektif olarak toplandı. Hastaların implantasyon ilişkisini değerlendirebilmek için TETEMC süreleri hesaplandı.

Bulgular: Gruplar karşılaştırıldığında menstrüel siklus günü ile TETEMC arasında anlamlı fark bulundu ($p<0,05$). ROC analizinde TETEMC (AUC=0,824, $p<0,001$) ve menstrüel gün (AUC=0,797, $p<0,001$) klinik gebeliğin anlamlı belirteçleri olarak bulundu. Menstrüel gün için cut off değeri hesaplandığında 27,5 gün için sensitivite %82,6 spesifite %65 bulundu. TETEMC için cut off değer %75 sensitivite ve %63,2 spesifite ile 11,5 gün bulundu.

Sonuç: Uzun menstrüel siklus ile TETEMC implantasyon başarısızlığı ile ilişkili görünmektedir.

Anahtar Kelimeler: Embriyo transfer günü, yardımcı üreme teknikleri, implantasyon

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Introduction

Window of implantation is defined as the period of an optimal synchronization between the embryo and the endometrium. In physiological menstrual cycles, this period corresponds to the menstrual days of 21-24 days in a women with regular 28 days of cycles. In other words, implantation can be achieved in a period of 4-7 days to next expected cycle. This period of implantation is determined by the sensitive balanced stimulation of steroids hormones of estrogen and progesterone secreted through the cycle[1-3]. However; in stimulated cycles, it was reported that endometrial maturation can be 3 days early compared to unstimulated cycles[4]. In the current practice, window of implantation was tried to be predicted indirectly by endometrial thickness measurement. Cut off value for the endometrial thickness for successful implantation was reported to be 6 mm[5-7]. However according to our experience and the reports from literature, 50% of patients with optimal endometrial thickness and high grade embryos fail to conceive. Endometrial receptivity is determined by several factors and these factors were reported to be under the effect of gonadal hormones, so it is expected to see a change in receptive period with changing endocrine milieu. In ovarian stimulation cycles gonadal hormones are secreted in high levels compared to physiological states so this may change the implantation period. The aim of this study was to assess whether the time from the menstrual day at embryo transfer to expected menstrual cycle (TETEMC) is associated with the implantation in women with regular cycles or not.

Materials and Methods

Between January 2014 and December 2015, women with regular cycles who underwent artificial reproduction in the in vitro fertilization (IVF)/intra-cytoplasmic sperm injection unit of Zeynep Kamil Women and Children's Health Training and Research Hospital were recruited from prospectively collected database. Age, body mass index matched groups of women with (n=40) and without (n=40) successful implantation after grade 1 embryo transfer were randomly selected and compared in terms of some demographic and clinical characteristics including TETEMC, endometrial thickness at embryo transfer and duration of regular cycles. Embryo grading was determined according to the review by Alpha Scientists in Reproductive Medicine and European Society of Reproduction and Embryology Special Interest Group of Embryology[8]. All the participants had regular menstrual cycles, as well as normal serum prolactin levels and without hormone treatment within three months. The patients' ages ranged from 24 to 39 years. In all patients artificial reproductive techniques (ART) were indicated for unexplained infertility. Unexplained infertility was diagnosed when a patient was infertile with normal ovulatory and tubal functions along with a normal sperm count for her partner. These were determined by the regularity of menstrual cycles, hysterosalphingography, and semen analysis, respectively. Women with low ovarian reserve, irregular cycles, polycystic ovarian syndrome and the endometriosis were excluded from the study.

Antagonist protocol was used in all cases; on the second day of the menstrual cycle, recombinant follicle stimulating hormone (rFSH), depending on patient's response, were administered and follicular growth was monitored using transvaginal sonography. The dosage of rFSH was adjusted from day 5 of stimulation according to the ovarian response. Antagonist Cetrorelix (Merk-Sereno, Geneva, Switzerland) 0.25 mg/day was administered when the follicular size was 12 mm. After the follicular size reached >18 mm, recombinant human chorionic gonadotropin (HCG) 250 µg was administered, and follicular puncture was performed after 34-36 hours. Then we started the application of 8% vaginal progesterone gel twice/daily. Serum HCG level was measured two weeks later, and if serum HCG level was more than or equal to normal level, we performed ultrasonography to detect the pulse of fetus to confirm clinical pregnancy. TETEMC was divided into 4 groups as group 1: 0-4 days, group 2: 5-8 days, group 3: 9-13 days, group 4: >14 days. Groups were compared in terms of successful implantation.

TETEMC was the number of days from the day at embryo transfer to the first day of expected menstrual cycle determined from regular cycles.

Statistical Analyses

Data was analyzed using SPSS 15.0 for Windows. Pearson's correlation analysis or Spearman's correlation analysis was performed to assess the correlation between different variables and ovarian response and the correlation between one variable and another as appropriate. Student t test was used to compare continuous variables between the groups. Multivariate regression analyses were used to assess the adjusted associations. Receiver operating characteristic (ROC) analyses were used to assess the predictive value of the test and to calculate sensitivity and specificity. P value <0.05 was accepted to be statistically significant.

Results

Group comparisons

Comparison of groups with and without successful implantation revealed significant differences in between groups with regard to TETEMC and menstrual period (Table 1). There were 11 three day embryo transfers where as the number of five day embryo transfer was 69 (p>0.05).

Correlation analyses

Correlation analyses revealed significant correlations in between the successful implantation and TETEMC, duration of menstruation and the age (Table 2).

Multivariate regression analyses

Multivariate analysis revealed significant association in between the TETEMC and clinical pregnancy after adjustment for age and the duration of menstruation (Table 3).

Receiver operating characteristic analyses

In ROC analyses both the TETEMC (AUC=0.824, p<0.001) and the menstrual period (AUC=0.797, p<0.001, Figure 1) were significant predictors for clinical pregnancy. Cut off value for the menstrual cycle was found to be 27.5 days with 82.6% sensitivity and 65% specificity. Cut off value for TETEMC was 11.5 with 75% sensitivity and 63.2% specificity.

Subgroup comparisons

Comparison of groups with TETEMC ≤11.5 and >11.5 days for successful implantation revealed a significant difference indicating higher rates in group with TETEMC ≤11.5 (75.9% vs. 35.3%, p<0.05, Table 4). Comparison of groups with duration from the menstrual period ≤27.5 and >28 days for successful implantation revealed a significant difference indicating higher rates in group with menstrual period ≤27.5 (82.6% vs. 36.8%, p<0.05, Table 5).

Table 1. Comparison of some demographic and clinical characteristics between groups

	Implantation	n	Mean	Standard deviation	
Age (years)	Negative	40	31.88	4.783	
	Positive	40	29.83	4.050	NS
Antral follicle count	Negative	40	13.03	5.785	
	Positive	40	13.03	4.886	NS
Peak estradiol (pg/mL)	Negative	40	1415.60	1.006.976	
	Positive	40	1519.25	790.780	NS
Duration of stimulation	Negative	40	9.88	1.786	
	Positive	40	10.50	1.725	NS
Menstrual day at ET	Negative	40	15.73	1.754	
	Positive	40	16.35	1.875	NS
Of oocytes	Negative	40	8.33	5.385	
	Positive	40	7.65	3.759	NS
Total gonadotropin dose	Negative	40	2163.75	1.138.191	
	Positive	40	2366.88	1.111.729	NS
Initial dose	Negative	40	253.13	90.968	
	Positive	40	246.25	78.762	NS
Of embryos	Negative	40	4.5	3.4	
	Positive	40	3.7	2.05	NS
FSH U/mL	Negative	39	6.3	2.6	
	Positive	40	5.7	2.1	NS
Estradiol pg/mL	Negative	40	45.6	26.4	
	Positive	40	45.5	20.8	NS
AMH (ng/mL)	Negative	10	5.6	5.1	
	Positive	10	2	1.8	NS
End line transfer (mm)	Negative	24	10	2.5	
	Positive	28	9.4	1.8	NS
TETEMC (days)	Negative	40	13.5	2.6	
	Positive	40	10.6	2.2	<0.001
Menstrual period (days)	Negative	40	29.30	2.989	
	Positive	40	26.95	1.753	<0.001

TETEMC: Transfer to expected menstrual cycle, NS: Non significant, AMH: Anti mullerian hormone, FSH: Follicle stimulating hormone, ET: Embryo transfer

Comparison of successful implantation among the group with 4 different TETEMC revealed 100% implantation rate in group with TETEMC ≤8 days (Table 6).

Discussion

In this study, we tried to assess the effect of menstrual day at embryo transfer on the implantation rates in ovarian stimulation cycles. Our data revealed an early maturation of endometrium, however more sooner transfers especially 11.5 days before the next expected menstruation was associated with unsuccessful implantation with 75% sensitivity and 63.2% specificity. Besides estrogen and the progesterone, gonadotropin-releasing hormone (GnRH) receptors were shown in extra pituitary tissue including the endometrium[9-11], studies reported the presence of GnRH mRNA gene expression in the endometrium throughout the menstrual cycle, with a significant increase in the secretory phase. These data indicate the possible physiological role of GnRH in the early stages of implantation via paracrine/autocrine pathways. Due to this physiological effect, clinicians have become suspicious for the possible negative effect of GnRH antagonists in combination with gonadotropin on the assisted reproductive technology success[12,13]. Some evidence showed detrimental effects of GnRH antagonist that may interfere with the embryo implantation. Consequently[14], high dosages of GnRH antagonist (1 or 2 mg once daily) were found to be associated with low implantation rate (8.8 and 1.5%, respectively) in fresh cycles. Due to this data, in order to prevent ovarian hyper stimulation syndrome and for more receptive endometrium, freeze all policies were introduced and the review on this issue indicated reduced risk of ovarian hyper stimulation syndrome and improved outcomes with frozen embryo transfer[15].

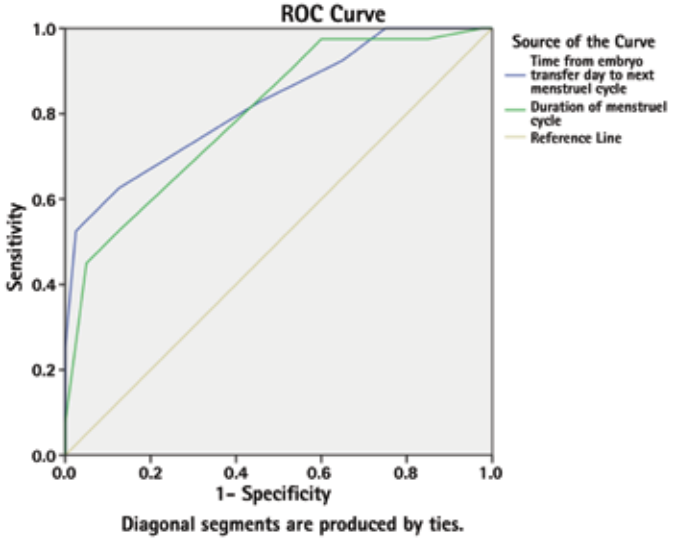

Figure 1. Receiver operating characteristic curve of transfer to expected menstrual cycle and menstrual period to predict implantation

ROC: Receiver operating characteristic

Table 2. Summary of correlation analyses between successful implantation and some variables

		TETEMC	Menstrual period	Age
Implantation	Correlation coefficient	-0.569**	-0.534**	-0.220*
	Significant (2-tailed)	0.000	0.000	0.050
	N	80	80	80

TETEMC: Transfer to expected menstrual cycle

Table 3. Multivariate regression analyses for successful implantation

	Standardized coefficients Beta	t	Significant
(Constant)		3.649	0.000
Age	-0.176	-1.825	0.072
Menstrual period	-0.089	-0.574	0.568
TETEMC	-0.435	-2.800	0.006

TETEMC: Transfer to expected menstrual cycle

Reduced implantation rates in IVF cycles were shown in some studies compared to natural ones[16], however, there is still some controversy regarding this issue. A large retrospective analysis, showed similar implantation rates between donor and recipient IVF patients[17].

In IVF cycles, the day of oocyte retrieval was thought to be the equivalent to day 14 in a natural cycle in women with 28 days regular cycles[18,19]. However, in ovarian stimulation cycles, an advanced endometrial maturation has been shown in some studies, this advancement was reported to be around 2±4 days[20] and seen in 45.5%[21] of cycles. As a consequence, an early and increased progesterone concentrations were blamed for early secretory transformation[22] and followed by mid-luteal glandular maturation arrest[23]. High serum estradiol concentrations in stimulated cycles were also thought to result in glandular ± stromal dyssynchrony that may interfere with the endometrial receptivity[24]. Another data showed the direct effect of HCG that might lead to the advanced endometrial maturation[25,26]. Finally, studies showed that ovarian stimulation changed the luteal phase endometrial development. Luteal phase support was thought to significantly improve clinical outcomes in in-vitro fertilization cycles by the correction of these detrimental effects of ovulation induction[27]. There is a consensus on the detrimental effect of ovarian stimulation on the endometrial receptivity and some measures have been introduced to overcome this issue like luteal phase support however, we hypothesized that despite advanced endometrial maturation, earlier transfers may be the main problem that lead

to failed implantation, therefore timing of embryo transfer may be the cornerstone of this problem.

Study assessed the histological features of endometrium both at the 6th day after luteinising hormone (LH) surge and the 10 days after LH surge. Study revealed similar histological features with regard to endometrial maturation[28], in another study, pinopodes were observed at 20th day of menstruation and indicated period of implantation window started to open at days of 22-23 in women with 28 day regular cycles[29], as we mentioned above there is two to four days maturation advancement in stimulated cycles. Our data also showed some advancement in endometrial maturation but more sooner embryo transfers failed to implant. Significant predictive value of longer menstrual cycles also confirm this argument which increase possibility of high TETEMC.

A cochrane review on the comparison of ART success between the cases with two different embryo transfer days revealed significant difference in live birth rates in favour of blastocyst transfer (day 5 to 6) compared to cleavage stage transfer (day 2 to 3)[30]. This data supports our arguments that three days delay in timing of embryo transfer seem to increase success rate. Recently published well designed study showed a suboptimal endometrial development in ART cycles, and indicated a altered regulation of specific endometrial receptors compared to the the natural cycle. Similar to our end point authors concluded to modify ovarian stimulation not only to yield the optimal

Table 4. Comparison of implantation rates between groups with high and low transfer to expected menstrual cycle

			Implantation		Total
			Negative	Positive	
TETEMC (days)	≤11.5	Count	7	22	29
		% within luteal eleven point five	24.1%	75.9%	100.0%
	>11.5	Count	33	18	51
		% within luteal eleven point five	64.7%	35.3%	100.0%
Total		Count	40	40	80
		% within luteal eleven point five	50.0%	50.0%	100.0%

TETEMC: Transfer to expected menstrual cycle

Table 5. Comparison of implantation rates between groups with long and short menstrual period

		Implantation		Total
		Negative	Positive	
Menstrual period	≤27.5	4	19	23
		17.4%	82.6%	100.0%
	>27.5	36	21	57
		63.2%	36.8%	100.0%
Total		40	40	80
		50.0%	50.0%	100.0%

Table 6. Comparison of implantation rates among groups with different transfer to expected menstrual cycle intervals

		TETEMC				Total
Days		0-4	5-8	9-13	>13	
Implantation	Negative	0	0	19	21	40
		0.0%	0.0%	37.3%	95.5%	50.0%
	Positive	1	6	32	1	40
		100.0%	100.0%	62.7%	4.5%	50.0%
Total		1	6	51	22	80
		100.0%	100.0%	100.0%	100.0%	100.0%

TETEMC: Transfer to expected menstrual cycle

number of oocytes, but also to achieve serum hormonal levels that promote an optimal endometrial development and better pregnancy outcomes with fresh cycles. In addition to this study proposed cancellation of fresh embryo transfer and vitrification of embryos and postponing the transfer to more suitable endometrial development such as reached during natural cycles or controlled endometrial maturation[31]. Our data showed that TETEMC lower than eight days resulted in 100% implantation where as there were 62.7% successful implantation in groups with TETEMC between the 9-13 days. The rate was 4.5% in group with TETEMC >13 days, we thought that this group of cases may be the appropriate candidates for freeze all policy.

Expression of HOXA10 varies in the human endometrium throughout the menstrual cycle, rising dramatically in the luteal phase at the time of implantation[32]. This pattern of expression suggests a role for HOXA10 in the process of cyclic endometrial development and endometrial receptivity.

We thought that there is a sensitive gene expression regulation during menstrual cycle that determines the duration of menstruation and the time of implantation window, with ovarian stimulation, it seems that this regulated gene expression is not easily adapt this new microenvironment, previous study indicated the minimum period required to achieve a new level is directly proportional to product half-lives because rates of decay control the ratio between the rate of synthesis and the concentration of gene products at steady state[33].

Endometrial receptivity array have recently been introduced to assess the endometrial receptivity via genetic evaluation[34], however this test needs invasive procedures.

Conclusion

In conclusion, longer menstrual cycle and the TETEMC seem to be associated with the implantation failure. According to this data it is reasonable to take account the duration of regular menstruation and TETEMC to determine the candidates for freeze all policy.

Ethics

Ethics Committee Approval: The study were approved by Zeynep Kamil Training and Research Hospital Local Ethics Committee, Informed Consent: Study was approved by institutional review board and inform constent was obtained by each participant.
Peer-review: Internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İlhan Şanverdi, Enis Özkaya, Tayfun Kutlu, Yavuz Şahin, Concept: Enis Özkaya, Tayfun Kutlu, Ateş Karateke, Design: Enis Özkaya, İlhan Şanverdi, Data Collection or Processing: Taylan Şenol, Munip Akalın, Eda Sayar Akalın, Analysis or Interpretation: Enis Özkaya, Taylan Şenol, Literature Search: Enis Özkaya, Taylan Şenol, Writing: Enis Özkaya, Taylan Şenol.
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Do vitamin D and high-sensitivity-C reactive protein levels differ in patients with hyperemesis gravidarum? A preliminary study

Hiperemezis gravidarum hastalarında vitamin D ve yüksek hassasiyetli-C reaktif protein seviyeleri değişir mi? Preliminer çalışma

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Abstract

Objectives: The high sensitivity-C reactive protein (hs-CRP) is an inflammatory marker and vitamin D is an immune modulator that might play a critical role in the pathogenesis of hyperemesis gravidarum. Therefore, in the current study, we tested the hypothesis that suggests women with hyperemesis gravidarum have lower 25-hydroxyvitamin D levels and higher hs-CRP levels, compared to controls.

Materials and Methods: This prospective case-control study included 30 women with hyperemesis gravidarum (study group) and 30 age- and body mass index-matched healthy women (control group). The levels of 25-hydroxyvitamin D and hs-CRP were compared between two groups.

Results: Both the serum 25-hydroxyvitamin D (5.30 µg/L vs. 6.44 µg/L; p=0.09) and hs-CRP levels (0.29 mg/dL vs. 0.47 mg/dL; p=0.93) were not significantly different between the study and control groups. Vitamin D deficiency was present in 27 (90.0%) women in the study group and 22 (73.3%) women in the control group (p=0.181). There was also no correlation between 25-hydroxyvitamin D and hs-CRP levels in both groups.

Conclusion: Although it did not reach statistical significance, vitamin D levels were lower in the study group compared with controls. Therefore, vitamin D might be speculated to play a crucial role in controlling the inflammatory status associated with hyperemesis gravidarum. Larger studies are required to clarify whether there is a relation between vitamin D deficiency and hyperemesis gravidarum.

Keywords: C-reactive protein, hyperemesis gravidarum, inflammation, vitamin D

Öz

Amaç: Yüksek hassasiyetli C reaktif protein (hs-CRP) bir enflamatuvar belirteçtir ve vitamin D ise hiperemezis gravidarum patogenezinde kritik rol oynayan bir immünmodülatördür. Bu nedenle, bizde bu çalışmada hiperemezis gravidarumlu kadınlarda kontrollere göre daha düşük 25 hidroksivitamin D ve daha yüksek hs-CRP seviyeleri olma hipotezini test ettik.

Gereç ve Yöntemler: Bu prospektif olgu kontrol çalışmasına hiperemezis gravidarumlu 30 gebe (olgu grubu) ve yaş, vücut kitle indeksi ile eşleştirilmiş 30 sağlıklı gebe (kontrol grubu) dahil edildi. İki grup arasında 25-hidroksivitamin D ve hs-CRP seviyeleri karşılaştırıldı.

Bulgular: Olgu ve kontrol grupları arasında serum 25-hidroksivitamin D (5,30 µg/L vs. 6,44 µg/L; p=0,09) ve hs-CRP (0,29 mg/dL vs. 0,47 mg/dL; p=0,93) seviyeleri farklı değildi. Olgu grubunda vitamin D eksikliği 27 (%90) hastada görülür iken, kontrol grubunda 22 (%73,3) hastada görülmekte idi (p=0,181). İki grupta da 25-hidroksivitamin D ve hs-CRP seviyeleri arasında korelasyon yoktu.

Sonuç: İstatistiksel olarak anlamlı olmasa da vitamin D seviyeleri olgu grubunda kontrollere göre daha düşüktür. Bu nedenle vitamin D'nin hiperemezis gravidarumdaki enflamatuvar süreci kontrol etmekte etkin bir rol oynadığı speküle edilebilir. Vitamin D eksikliği ve hiperemezis gravidarum arasındaki ilişkiyi netleştirmek için daha geniş hasta sayılı çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: C-reaktif protein, hiperemezis gravidarum, enflamasyon, vitamin D

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Introduction

Hyperemesis gravidarum (HG) is a common medical problem that affects nearly 1 percent of pregnant women, and causes morbidity both for the mother and fetus[1]. The etiology is still unclear and until now, many theories have been introduced. Psychological factors, hormonal changes, gastrointestinal dysmotility, and immunologic dysregulation have been proposed as possible causes[2,3]. In recent years, a close relationship was also recently found between HG and inflammation caused by helicobacter pylori infection[4,5].

Vitamin D is a well-known immunomodulator and anti-inflammatory agent in the body. Vitamin D deficiency is shown as the one of the major causes of many diseases in the reproduction system[6,7]. Sugito et al.[8] found that pregnant women with HG had increased cell-free DNA levels in blood, which was believed to emerge as a result of hyperactivity of the maternal immune system and destruction of trophoblasts. However, fasting, which is a feature of HG and pregnancy, are also known to weaken the human and cell-mediated immune system. Although both pregnancy and fasting are features of HG, in contrast to expectations, the immune system was activated in women with HG. It might be speculated that vitamin D has a key role in the etiopathogenesis of HG, and vitamin D deficiency might explain the immune theory of HG because vitamin D deficiency might lead to problems in immune regulation.

Therefore, in the current study, our objective was to compare the 25-hydroxyvitamin D [25 (OH) D] and C reactive protein (CRP) levels between women with HG and controls.

Materials and Methods

A total of 30 women hospitalized with a diagnosis of HG as a study group and another 30 pregnant women who were matched to the HG group in terms of age, body mass index (BMI), and gestation period as a control group were enrolled into this prospective case-control study. The Institutional Review Board of the hospital (24.07.2013/, number 8) approved the current study and all patients gave written informed consent. This study was performed in accordance with the Declaration of Helsinki and patients were reviewed from a tertiary referral center between January 1st, 2013 to March 3rd, 2013. The inclusion criteria were as follows; age 18-35 years, between 6 and 12 gestational weeks, singleton pregnancy with healthy fetus, persistent nausea and vomiting (more than 4 times/day), presence of ketosis (>80 mg/dL in a urine specimen), and weight loss (more than 5% weight loss since pregnancy).

Patients who had multiple pregnancy; trophoblastic disease; habitual abortus; any systemic disease such as diabetes hypertension or thyroid disease; psychiatric disorder; any inflammatory disorder such as urinary tract infection; and those who used antiemetic medication or any kind of medication that could potentially affect hormones were excluded from the study. All participants underwent sonographic examination to confirm the gestational week, fetal heart rate, and the absence of placental pathology. When the difference between sonographic measurement and last menstrual date were more than 3 days, crown rump length measurement was used. Weight and height measurement were used to calculate BMI.

Biochemical measurement of vitamin D and high sensitivity-C reactive protein

Patients gave venous blood for biochemical tests following overnight fasting. Serum samples were centrifuged at 5000 revolutions/minute for 10 minutes within 20 minutes of blood sampling. Samples are stored at -80 °C. Total 25-OH-vitamin D levels in the plasma were measured using an ImmuChrom column (IC 3401 rp) kit with immune chromatographic methods. According to the instructions, the analytic detection limit of kit was 5.8 nmol/L and reference intervals were 10-60 µg/L in winter. High sensitivity-CRP (hs-CRP) levels were measured in serum using immunonephelometry (Cardio Phase hs-CRP, Siemens, Germany). In accordance with a statement for healthcare professionals from the American Heart Association/Centers for Disease Control and Prevention, hs-CRP levels were classified as follows: hs-CRP <1.0 mg/dL as low, hs-CRP between 1.0-3.0 mg/dL as intermediate, and hs-CRP >3.0 mg/dL as high levels[9].

Statistical Analysis

The study data were analyzed using the Statistical Package for Social Sciences (SPSS) version 15.0 for Windows (SPSS, Chicago, IL). In order to see if the variables had normal distribution, histogram and Shapiro-Wilk tests were used. The mean plus/minus standard deviation, median (minimum-maximum), count and percentile are presented in accordance with the distribution of the data. Categorical variables were analyzed using Fisher's exact test and chi-square tests. As a statistical method, Student's t-test was performed for normally distributed variables and the Mann-Whitney U test was used to analyze non-normally distributed variables. Spearman's correlation test was used to test the strength of correlation between the variables. A p value less than 0.05 was considered as statistical significance.

Results

Age, gestational period, parity, and BMI were similar in the study and control groups (p>0.05) (Table 1).

The was also no difference in hs-CRP and vitamin D concentrations between the study and control groups. Table 2 shows the comparison of hs-CRP levels and vitamin D levels in both groups. In the study group, 23 (76.7%) patients had low hs-CRP levels, 3 (10.0%) had intermediate, and 4 (13.3%) had high levels of hs-CRP. For the control group, 27 (90.0%) patients had low levels of CRP and 3 (10.0%) had intermediate levels of CRP; no significant difference was detected between the study and control groups regarding CRP levels (p=0.115). In the study group, 27 (90%) patients had low vitamin D levels, and 3 (10.0%) had high vitamin D levels. In control group, 22

(73.3%) patients had low levels of vitamin D, and 8 (26.7%) had high vitamin D levels; no significant differences were found between the study and control groups regarding vitamin D levels (p=0.181) (Table 2). No correlation was found between vitamin D and hs-CRP concentration in either the HG group or controls (p>0.05) (Table 3).

Discussion

Immune dysregulation and inflammation are suggested to have a critical role in the etiopathogenesis of HG[10,11]. hs-CRP is a well-known inflammatory marker and vitamin D is an immune modulator and anti-inflammatory that plays a crucial role in the reproductive system. Therefore, we hypothesized that pregnant women with HG should have lower 25 (OH) D levels and higher hs-CRP levels compared with controls, and tested this hypothesis in this prospective case-control study. To our knowledge, the current study is the first trial in the existing literature to investigate the association between vitamin D concentrations and HG. Although it did not reach statistical significance, vitamin D levels were lower in the HG group compared with controls (p=0.090). In addition, no difference was found in hs-CRP concentrations between the two groups.

In a review that analyzed various factors that contribute to the diagnosis of HG, only helicobacter pylori was identified as having a definitive impact in the etiopathogenesis of the disease[4]. Endoscopy conducted on women with HG proved that 90% had mucosal inflammation and helicobacter pylori activation in the stomach[12]. However, not all pregnant women with helicobacter pylori exhibit the signs of HG and these women are possibly inclined to helicobacter pylori because of the problems in humoral and cell-mediated immunity[13]. Leylek et al.[10] supported this hypothesis by showing an increase in immunoglobulin, complement, and lymphocyte counts in patients with HG, as a result of immunologic activation. Vitamin D has a pivotal role in many diseases of the reproductive system as an immune modulator and anti-inflammatory agent. Vitamin D receptors might be found on a large number of immune cells. Vitamin D helps fetal immune adaptation by inhibiting the secretion of cytokines from T-helper cells[14]. In addition, it inhibits the secretion of pro-inflammatory cytokines from the placenta and suppresses the inflammatory response. Recent studies focused on the possibility that deficiency of vitamin D might be related with many maternal and fetal adverse outcomes such as spontaneous abortion, preterm labor, intrauterine growth restriction, and preeclampsia[15,16]. The present study emphasizes the possibility that vitamin D, which is known to have numerous roles in the reproductive system, might also have an impact on HG CRP is an acute phase reactant and its synthesis is primarily stimulated by IL-6 and tumor necrosis factor as a reaction to infection and inflammation[17]. Kuscu et al.[18] also reported that women with HG had increased levels of IL-6 levels and successful treatment of resistant cases with steroid treatment might be explained by the fact that steroids have anti-inflammatory effects. Therefore, hs-CRP levels might be speculated to increase in women with HG. To our knowledge, there is only one published study that investigated hs-CRP concentrations in women with HG[19]. In that case-control study, researchers evaluated 56 women and described an increase in hs-CRP levels in women with HG. However, in the current study, no difference was detected in hs-CRP levels between the study group and controls. Many factors such as socioeconomic status, dietary intake of carbohydrates, and smoking were also related to variations in CRP concentrations[20]. The present study is a preliminary study and had a small number of patients; therefore, we might not have homogenized the two groups with these factors and thus failed to detect the difference in hs-CRP levels.

Table 1. Distribution of age, body mass index, and gestational age according to the study and control groups

	Hyperemesis gravidarum (n=30)	Control group (n=30)	p
	Mean ± SD	Mean ± SD	
Age (years)	25.73±3.88	24.87±4.43	0.424
BMI (kg/m^2)	25.23±3.57	25.97±4.31	0.634
Gestational age (weeks)	8.73±1.17	8.63±1.49	0.774

BMI: Body mass index; SD: Standard deviation

Table 2. Distribution of the high sensitivity-C reactive protein and vitamin D levels in the study and control groups

	Hyperemesis gravidarum (n=30)	Control group (n=30)	p
hs-CRP (mg/L)	0.29 (0.03-4.73)	0.47 (0.02-1.82)	0.923
25 (OH) vitamin D (µg/L)	5.30 (3.0-17.5)	6.44 (2.49-20.70)	0.090

CRP: C-reactive protein, 25 (OH) vitamin D: 25-hydroxyvitamin D, hs-CRP: High sensitivity-C reactive protein, Data are presented as median (minimum-maximum)

Table 3. The correlation between high sensitivity-C reactive protein and vitamin D levels in the study and control groups

		hs-CRP	
		Hyperemesis gravidarum (n=30)	Control (n=30)
25 OH Vitamin D	Rho	0.040	0.112
	p	0.834	0.554

Rho: Spearman's correlation coefficient, 25 (OH) vitamin D: 25-hydroxyvitamin D, hs-CRP: High sensitivity-C reactive protein

Conclusion

In the present study, vitamin D concentrations were lower in the HG group compared with controls, albeit the relation was not statistically significant. We might not have been able to reach definite results and clearly explain the role of vitamin D in the etiopathogenesis of HG because our study had a small number of patients. However, whether vitamin D has an impact on the etiopathogenesis of hyperemesis or inflammation underlies the disease that causes vitamin D levels to drop needs to be clarified. Therefore, further studies with higher numbers of patients are required to investigate the association between vitamin D and HG.

Ethics

Ethics Committee Approval: The study were approved by the Local Ethics Committee of Zekai Tahir Burak Women's Health Training and Research Hospital, Informed Consent: Consent form was filled out by all participants.
Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Saynur Yılmaz, Canan Demirtaş, Hakan Timur, Concept: Saynur Yılmaz, Dilek Uygur, Nuri Danışman, Design: Saynur Yılmaz, Dilek Uygur, Nuri Danışman, Data Collection or Processing: Saynur Yılmaz, Ayşe Şahin, Analysis or Interpretation: Saynur Yılmaz, Hakan Timur, Derya Akdağ Cırık, Literature Search: Derya Akdağ Cırık, Canan Demirtaş, Ayşe Şahin, Writing: Derya Akdağ Cırık, Saynur Yılmaz.
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The views of nulliparous pregnant women on the types of delivery

Hastanemiz gebe polikliniğine başvuran nullipar gebelerin doğum şekillerine bakış açısı

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Abstract

Objective: To evaluate the relevant thoughts of nulliparous pregnant women in the second trimester without an absolute indication for cesarean on delivery preferences.

Materials and Methods: This study was conducted on pregnant women who presented to the Ankara University Faculty of Medicine, Department of Obstetrics and Gynecology Pregnant Outpatients Department for antenatal follow-up between May 2014 and February 2015. A total of 237 nulliparous patients voluntarily completed the survey form and the data were evaluated using various parameters. Parameters consistent with normal distribution were evaluated using the t-test, and parameters that were not normally distributed were evaluated using the Mann-Whitney U test. Parameters with a p value <0.05 were considered significant.

Results: We found that 221 (93.2%) of the 237 nulliparous pregnant women preferred vaginal delivery and the remaining 16 (6.8%) preferred delivery by cesarean section.

Conclusion: Women should be informed on the type of birth and both methods should be explained in a realistic and scientific manner in terms of benefit and risk. An effort is being made to increase vaginal birth rates worldwide and the same effort should be made in Turkey.

Keywords: Vaginal delivery, nulliparous, cesarean section

Öz

Amaç: Bu çalışmada sezaryen için mutlak endikasyonu olmayan ikinci trimesterdeki nullipar gebelerin doğum tercihlerini sorgulayan bir anket uygulayarak kadınların bu konudaki düşüncelerini değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Bu çalışma Mayıs 2014 ve Şubat 2015 tarihleri arasında Ankara Üniversitesi Tıp Fakültesi, Kadın Hastalıkları ve Doğum Anabilim Dalı Gebe Polikliniği'ne antenatal takip amacıyla başvuran gebeler üzerinde yapıldı. Anket doldurma yöntemi ile yapılan bu çalışma nullipar gebeler üzerinde ikinci trimesterde gerçekleştirildi. Doğum şekli tercihi ve nedenleri sorgulandı. Bu amaçla 237 gönüllü nullipar hastaya anket formu doldurtuldu ve elde edilen veriler çeşitli parametrelere göre değerlendirildi. Normal dağılıma uyan parametreler t test ile normal dağılıma uymayan parametreler ise Mann-Whitney U testi ile değerlendirilmiştir. P<0,05 olan parametreler anlamlı kabul edildi.

Bulgular: Çalışma sonucunda yapılan analizde 237 nullipar gebenin 221'i (%93,2) vajinal doğumu, geri kalan 16'sı (%6,8) ise sezaryen ile doğumu tercih ettiği görülmüştür.

Sonuç: Sonuç olarak kadınlar doğum şekli açısından detaylı olarak bilgilendirilmeli, yarar ve zarar açısından her iki yöntem gerçekçi ve bilimsel olarak ortaya konulmalıdır. Özellikle vajinal doğum oranları tüm dünyada yaygınlaştırılmaya çalışılırken, ülkemizde de bu çaba gösterilmelidir.

Anahtar Kelimeler: Vajinal doğum, nullipar, sezaryen

Introduction

Pregnancy and birth are some of the most important physiologic processes in a woman's life[1]. The approach to birth varies in each society according to the sociologic structure. Pregnancy and the subsequent delivery are important events that should be evaluated biologically as well as physiologically and socially. Many views of pregnancy and especially the type of delivery are influenced by the characteristics of the society. The increase in the self-confidence of women as a result of their increased involvement in work life and relative financial independence in recent years has led to determination of their own delivery type. It is commonly believed that a history of a difficult birth

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experienced by the pregnant woman or her relatives has great influence on the issue[2]. Requests by pregnant women for cesarean section delivery have increased despite the high risk of complications because of the fear of birth pains experienced during vaginal delivery and the knowledge that the risk of complications has decreased with current advanced technology[3]. Concern that the infant and pelvic floor may be damaged is also a factor in vaginal delivery being preferred less. The fear of birth is the most important factor in preferring cesarean section delivery.

Another factor in the increase of the cesarean section rate is malpractice, a serious concern for physicians. The number of legal cases due to complications during delivery is constantly increasing. The medical and legal responsibilities regarding both the mother and infant of a physician helping the delivery cannot be denied. However, the fear of litigation inevitably leads to self-protection attempts and a general avoidance of the scientific approach by the physician.

In conclusion, the belief that cesarean section delivery with will be less painful and more reliable for the mother and less harmful for the infant directs women away from vaginal delivery. However, evidence-based medical practice has revealed that cesarean section delivery increases perinatal risk and morbidity and mortality, whereas vaginal delivery is more reliable[4]. It is also self-evident that cesarean section delivery will have a negative effect on healthcare expenses, considering its cost and effect on returning to work.

In this study, we administered a survey querying the delivery preferences of nulliparous pregnant women in the second trimester without an absolute indication for cesarean section with the aim of evaluating the relevant thoughts of the women.

Materials and Methods

This study was conducted on pregnant women who presented to the Ankara University Faculty of Medicine, Department of Obstetrics and Gynecology pregnant outpatients department for antenatal follow-up between May 2014 and February 2015. We used the survey completion method on nulliparous pregnant women in the 2nd trimester. None of the pregnant women included in the study had any contraindication in terms of vaginal delivery. The age, gestational week, educational level, information on birth methods, income level of the patient, and the delivery preference and reasons were questioned. A total of 237 nulliparous patients voluntarily completed the survey form and the data obtained were evaluated using various parameters. The pregnant women were divided into two groups as those requesting vaginal delivery and those requesting cesarean section. Data were evaluated using SPSS version 21. Parameters consistent with normal distribution were evaluated using the t-test, and non-normally distributed parameters were evaluated using the Mann-Whitney U test. Parameters with a p value <0.05 were considered significant. Ethics Committee Approval for the study was obtained from the Ankara University Faculty of Medicine Ethics Committee on 12 May 2014 (decision no; 08-348-14).

Results

We found that 221 (93.2%) of the 237 nulliparous pregnant women preferred vaginal delivery, and the remaining 16 (6.8%) preferred delivery by cesarean section. The reasons for the pregnant women's choice of delivery are presented in detail in Tables 1 and 2.

The pregnant women were queried on being informed on birth previously, educational levels, monthly income level, occupational status, and preference for delivery according to occupation (Table 3).

When the delivery preferences were investigated according to the rates of being provided information, 54 (90%) of the

Table 1. Reasons of the pregnant women for preferring vaginal delivery

Pregnant women preferring vaginal delivery (n=221)	n	%
1. Pressure by others	5	2.26
2. Fear of anesthesia or surgery	53	23.98
3. Lower cost	5	2.26
4. Desire to recover early and return home more quickly	138	62.44
5. Desire to have more than three children	8	3.61
6. Less bleeding and infection	58	26.4
7. To be able to breastfeed earlier	40	18.09
8. Other	17	7.69

Table 2. Reasons of the pregnant women for preferring cesarean delivery

Pregnant women preferring cesarean section (n=16 pregnant women)	n	%
1. Not to put the baby at risk	8	50
2. Fear of injury of sexual organs (episiotomy)	1	6.25
3. Not to experience birth pain	4	25
4. To be able to determine the birth time beforehand	3	18.75
5. Fear of normal delivery	9	56.25
6. Fear of future urinary and fecal incontinence	3	18.75
7. Prolapse of the uterus and other organs and concern regarding protection of sexuality	3	18.75
8. Request for tube ligation and advanced age	3	18.75
9. Previous history of infertility, or pregnancy following treatment	1	6.25
10. Other	-	-

61 patients who were informed previously preferred vaginal delivery and 7 (10%) preferred cesarean section. Similarly, 167 (94.8%) of 176 patients who were not informed on the type of delivery preferred normal delivery and 9 (5.2%) preferred cesarean section (p=0.083).

When educational levels were investigated, 65 (87.8%) of 74 patients who were university graduates preferred vaginal delivery, 99 (94.2%) of 105 patients who were high school graduates preferred vaginal birth, and 56 (98.2%) of 57 patients who were primary school graduates preferred vaginal delivery (p=0.016).

When occupational status was evaluated, 168 (94.9%) of 177 pregnant women who were not working preferred vaginal delivery and 53 (88.3%) of 60 pregnant women who were employed preferred vaginal delivery (p=0.077). According to the occupational groups, 135 of 143 pregnant women who had a specific occupation, the majority of which consisted of university graduates, preferred vaginal birth. The majority of the other professional groups also preferred vaginal delivery (p=0.50).

Discussion

We found that 6.8% of the pregnant women included in our study preferred cesarean section delivery. Chong and Mongelli[5] reported that 3.7% of pregnant women requested elective cesarean section in their study. The World Health Organization (WHO) reported that the primary cesarean section ratio in all pregnant women should be less than 15%[6]. Among the studies reported in Turkey, Yıldız et al.[7] conducted on nulliparous and multiparous (who had undergone vaginal delivery and cesarean section previously) pregnant women, 74% of nulliparous pregnant women preferred vaginal delivery but this rate was 97.3% in pregnant women who had experienced vaginal delivery previously. The same study reported a vaginal delivery request rate of 52.5% even in pregnant women who had undergone cesarean section in a previous delivery[7]. Vaginal birth preference was reported to be due to early recovery (54.1%) and early return to routine activities (20.3%) [7]. Vaginal delivery was similarly preferred by 84.1% in the study of Buyukbayrak et al.[8] Bektaş[9] also reported a vaginal delivery preference rate of 84%. The reasons offered by the women for preferring vaginal delivery in these studies were similar to our findings and those reported in other studies in the literature[8,10-12].

Table 3. Characteristics of pregnant women according to vaginal or cesarean section delivery preference

	Vaginal birth preference (n=221)	Cesarean section preference (n=16)	p
Age (years)	23.8±3.96	27±4.9	0.48
Gravida	1.15±0.45	1.12±0.5	0.59
Abortus	0.10±0.30	0.12±0.5	0.50
History of abortion	0.06±0.25	0	0.021
Gestational week	26.67±10.2	25.5±8.6	0.10

A sociological review of delivery preference showed that it varied according to the society. This preference was affected by many factors such as the physiological status of the woman, as well as the social environment, experiences of others, economic status, and customs and traditions[10].

Vaginal birth has been considered a normal human physiologic stage since mankind first appeared and is the basic delivery form. The preferred type of birth was vaginal delivery in our study as in many other studies.

Although the request rate for cesarean section delivery was higher in university graduate women, no statistically significant difference was found. Similarly, it has been reported that the cesarean section request rates increased as the age and educational level of women increased by Koc[13], and as the income level and educational level increased by Behaque et al.[14]. Women are becoming more actively involved in work life with their changing role in society, and their resultant increasing financial power has increased the age of pregnancy. This in turn has led to a concern regarding putting the infant at risk with pregnancies becoming more and more important. The request for cesarean section is therefore increased at advanced ages. However, various rates have been reported in studies on populations with different socio-economic levels[14]. This demonstrates that the approach to birth has a sociocultural background.

The basic reason why the majority of our patients preferred vaginal delivery is that pregnancy is accepted as a natural and normal process in our society as in most other societies. Pregnant women who preferred vaginal delivery expressed that they find vaginal birth healthier additional comments section of the survey.

Although vaginal delivery is preferred in studies, the cesarean section delivery rate was found as 48% in the latest statistical study conducted in Turkey[15]. However, we know that delivery with cesarean section should be used as an alternative in cases where vaginal delivery is not possible or constitutes a danger for the infant and/or the mother. It was reported that cesarean sections should be performed with medical indications at the American Congress of Obstetricians and Gynecologists 2006[16]. It was also emphasized in 1999 by International Federation of Gynecologists and Obstetricians that performing cesarean section for non-medical reasons was not ethical[17]. The Turkish Ministry of Health aims for pregnant women with a medical indication to give birth with cesarean section under the best possible conditions while minimizing cesarean section delivery with non-medical indications. The cesarean section rates reported in Turkey are much higher than the 15% recommended in "Health for Everybody in 2000" as publicized

by the WHO[6]. A legislation released in 2012 stated that cesarean section could be preferred if the situation mandates it for the safety of the either mother or baby.

We think that if pregnant women receive detailed information from physicians regarding the forms of delivery during follow-up this will decrease cesarean section delivery rates. The low cesarean section rate, short hospitalization duration, lower birth induction requirement, and lower analgesia requirement in a study conducted on pregnant women who had been provided information by midwives demonstrated the importance of informing these women[18]. The Turkey Population Health Research 2013 data revealed that physicians undertake the follow-up and delivery for most pregnant women. High cesarean section rates may stem from physicians seeing too many patients and not having time to inform pregnant women due to time constraints. The fear of malpractice also plays a role[15].

The reasons for preferring cesarean section in our study were mainly fear of birth, avoiding putting the infant at risk, avoiding pain, and fear of prolapse. Seventy-two percent of the women preferred optional cesarean section due to normal fear of birth in a study that evaluated the opinions on cesarean section in Turkey[19]. The majority of patients preferred delivery with cesarean section due to stress and fear at similar rates in the study of Yıldız et al.[7] Fear of birth was found to be the most common (59%) among the reasons for requesting cesarean section in a study conducted in Iran[20]. The rate of preferring cesarean section delivery for the same reason was found as 36% in Sweden[21]. Half of the women who preferred delivery with cesarean section due to fear of birth in Sweden and Finland changed their preferences to vaginal delivery after effective anxiety training[22]. Decreasing the fear of normal delivery with training in pregnant women who request delivery with cesarean section may increase the request rate for vaginal delivery.

Patients should be informed on the types of birth during pregnancy and healthcare staff should be supportive during the birth process considering the psychological dimension of pregnancy. This would help decrease the cesarean section rates and the related mortality and morbidity while encouraging vaginal birth.

Although most women in our society are aware that birth is a normal process, there has been a significant increase in the cesarean section rate. The pregnancy process should be evaluated biologically, physiologically, and socially, and pregnant women should be encouraged regarding vaginal delivery in this period. Physicians who emphasize cesarean section delivery because of time pressure and increasing malpractice cases also affects these rates. The Ministry of Health should therefore consider increasing support for physicians and increasing the number of healthcare staff when evaluating birth-related policies. A retrospective evaluation of our results shows that the cesarean section rate was 48.1% (114 pregnant women). One hundred thirty-one of the women in our study comprised patients who presented to the clinic when active delivery had started, 106 women presented due to reasons such as a delay in delivery, request for a cesarean section or cesarean section requirement. Cesarean section became necessary in 29% (38 women) of the 131 pregnant women who presented during active delivery. Delivery with cesarean section was realized in 71.6% (79 women) of the remaining 106 pregnant women. This indicates that most of the women who gave birth by cesarean section were women in whom active delivery had not started and they underwent elective cesarean section. We believe that most of these women were directed to cesarean section with reasons such as environmental pressure, patient request, fear of birth, or physician guidance. The current proliferation of private hospitals has had a great effect on the increasing cesarean section rates. Cesarean section rates up to 90% have been reported when the data of private hospitals are evaluated. This creates an impression that healthcare policies implemented in state and private hospitals are different.

Conclusion

In conclusion, women should be informed on the type of birth and both methods should be explained in a realistic and scientific manner in terms of benefit and risk. An effort is being made to increase vaginal birth rates worldwide and the same effort should be made in Turkey. Physicians feel a serious threat of malpractice and this should be decreased through regulations by the Ministry of Health and informing society. Physicians need to monitor the health of the mother and baby in the best way during pregnancy and birth, and they should support pregnant women in choosing vaginal delivery if there is no contraindication.

Ethics

Ethics Committee Approval: The study were approved by the Ankara University Ankara University Medical Faculty Ethics Committee on 12 May 2014 with decision no. 08-348-14, Informed Consent: Consent form was filled out by all participants.

Peer-review: External and Internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Dilek Yüksel, Tuncay Yüce, Acar Koç, Concept: Tuncay Yüce, Acar Koç, Design: Tuncay Yüce, Acar Koç, Data Collection or Processing: Dilek Yüksel, Erkan Kalafat, Seda Şahin Aker, Analysis or Interpretation: Tuncay Yüce, Literature Search: Dilek Yüksel, Writing: Dilek Yüksel.

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The optimal analgesic method in saline infusion sonogram: A comparison of two effective techniques with placebo

Salin infüzyon sonogramda en ideal analjezik yöntem: İki etkin tekniğin plasebo ile karşılaştırılması

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Abstract

Objective: Operations performed with local anesthesia can sometimes be extremely painful and uncomfortable for patients. Our aim was to investigate the optimal analgesic method in saline infusion sonograms.

Materials and Methods: This study was performed in our Clinic of Obstetrics and Gynecology between March and August 2011. Ninety-six patients were included. Patients were randomly divided into groups that received saline (controls, group 1), paracervical block (group 2), or paracervical block + intrauterine lidocaine (group 3). In all groups, a visual analogue scale score was performed during the tenaculum placement, while saline was administered, and 30 minutes after the procedure.

Results: When all the patients were evaluated, the difference in the visual analogue scale scores in premenopausal patients during tenaculum placement, during the saline infusion into the cavity, and 30 minutes following the saline infusion sonography were statistically different between the saline and paracervical block groups, and between the saline and paracervical block + intrauterine lidocaine group. However, there was no statistically significant difference between paracervical block and paracervical block + intrauterine lidocaine groups.

Conclusion: As a result of our study, paracervical block is a safe method to use in premenopausal patients to prevent pain during saline infusion sonography. The addition of intrauterine lidocaine to the paracervical block does not increase the analgesic effect; moreover, it increases the cost and time that the patient stays in the dorsolithotomy position by 3 minutes.

Keywords: Saline infusion sonography, pain, topical anesthesia, lidocaine

Öz

Amaç: Sadece lokal anestezi ile uygulanan işlemler hastalar için bazen son derece ağrılı ve rahatsızlık verici olabilmektedir. Amacımız salin infüzyon sonogramlarda en ideal analjezik yöntemi araştırmaktır.

Gereç ve Yöntemler: Bu çalışmaya Mart-Ağustos 2011 tarihleri arasında hastanemiz Kadın Hastalıkları ve Doğum Kliniği'nden 96 hasta dahil edildi. Hastalar randomize olarak; serum fizyolojik kontrol grubu (1. grup), paraservikal blok (2. grup), paraservikal blok + intrauterin lidokain (3. grup) gruplarına ayrıldılar. Tüm gruplara, tenakulum sırasında, salin infüzyonu sırasında ve işlem uygulandıktan 30 dakika sonrasında vizüel analog skala skorları yapıldı.

Bulgular: Tüm hastalar değerlendirildiğinde; premenopozal hastalarda tenakulum yerleştirildiğinde, kaviteye salin infüzyonu sırasında ve işlem yapıldıktan 30 dakika sonra uygulanan vizüel analog skala skorları arasında, serum fizyolojik grubu ile paraservikal blok grubu arasında ve serum fizyolojik grubu ile paraservikal blok + intrauterin lidokain grubu arasında anlamlı derecede fark tespit edilmiştir. Fakat paraservikal blok ile paraservikal blok + intrauterin lidokain grubu arasında anlamlı bir fark tespit edilmemiştir.

Sonuç: Araştırmamızın sonucunda, salin infüzyon sonogram sırasında paraservikal blok uygulaması premenopozal hastalarda ağrıyı etkin bir şekilde tek başına kesen, güvenle kullanabileceğimiz bir yöntem olarak gözükmektedir. Paraservikal blok sonrasında intrauterin lidokain eklenmesi işlem sırasındaki ağrıyı anlamlı şekilde kesmediği gibi, ekstra analjezik maliyetine ve hastanın 3 dakika daha fazla litotomi pozisyonunda kalmasına sebep olmaktadır.

Anahtar Kelimeler: Salin infüzyon sonogram, ağrı, topikal anestezi, lidokain

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Introduction

There is a necessity to evaluate the endometrial cavity in many different gynecologic conditions. Pre and post-menopausal bleeding, endometrial lesions found with ultrasound, and evaluation of endometrial cavity before performing hysterectomy are some indications that may require saline infusion sonography (SIS)[1,2].

The specificity and sensitivity of SIS for detecting endometrial pathology were 81-100% and 85-100%, respectively. For detecting submucosal myoma, it has sensitivity of 57-100% and specificity of 96-100%. For detecting endometrial hyperplasia or cancer it has sensitivity of 29-80% and specificity of 82-100%[3]. In sum, SIS is a valuable and indispensable method in gynecology practice.

Unfortunately, SIS may cause pain and discomfort depending on the technique and methods of anesthesia. Grasping the cervix with a tenaculum, movement of cannulas in the uterus, and distention of the uterine cavity with saline may cause pain in the procedure. Hence, active cooperation of patients is highly desirable to obtain maximum efficacy, and effective anesthesia becomes very important. Paracervical block (PCB) is the most frequently used method to prevent pain in the procedure. Previous reports showed that intrauterine lidocaine (IUL) is also a safe and effective method for preventing pain in outpatient gynecologic procedures[4-9].

We designed a randomized controlled trial to compare the efficacy of PCB vs. IUL, and also with placebo.

Materials and Methods

We conducted this study between March 2011 and August 2011 in a tertiary reference center. The study was approved by our ethical committee. All participants gave their written informed consent for the study. We included 120 women who underwent SIS for various reasons. We excluded women with severe systemic medical conditions such as heart failure and uncontrolled severe hypertension, and cervical stenosis, acute cervicitis and/or vaginitis, and lidocaine allergy. The remaining 96 women were randomized into three groups: saline controls (group 1), PCB (group 2), and PCB + IUL (group 3); randomization was performed using computer-generated random number tables.

We collected data about patient characteristics including age, gravidity, parity, history of abortion, any known allergy, current drug use, and medical and gynecologic history from patient records.

All women underwent a bimanual pelvic examination to determine the size and position of the uterus. The cervix was exposed using a bivalve speculum and washed with povidone-iodine solution. In the PCB group, 2 mL 2% lidocaine (Iekaine Ampoule, IE Ulagay, İstanbul, Turkey) was injected into the cervix at 4- and 8 o'clock positions at a depth of 2-3 cm after confirming the tip of needle was not inside a vessel lumen. Five minutes were allowed to pass to ensure the anesthetic effect of lidocaine had started. In the PCB + IUL group, an 18-gauge intravenous catheter was gently inserted into the cervical canal up to the internal os. Two milliliters of 2% lidocaine was injected into the uterine cavity. Again, 5 minutes were allowed to pass to ensure that the anesthetic effect of the lidocaine had begun. All forms of anesthetic methods were applied before grasping the cervix with a tenaculum. We used no anesthetic in the control group. Two milliliters of 0.9% saline solution was injected into the cervix at 4- and 8 o'clock positions instead of lidocaine. Five minutes were allowed to pass to create similar circumstances with the other groups. The cervix was grasped with a tenaculum at 11- and 1 o'clock positions. A number 4 carmen cannula was inserted in the uterine cavity. The uterine cavity was filled with 50 mL of normal saline solution. The same operator performed all SIS procedures in the same way with help of the same nurse. Therefore, other variables that may affect pain score were controlled. A tenaculum was used in all patients in the standard procedure technique. Difficulty during passing the cervix and SIS findings were not recorded in our study.

We evaluated pain scores using a 10-cm visual analogue scale (VAS), where 0 cm represented no pain and 10 cm represented worst pain imaginable. We evaluated pain scores at three different points: Immediately after installation of normal saline, at the end of the procedure, and 30 minutes after the procedure. All patients were prescribed 500 mg azithromycin as prophylaxis.

Statistical calculations were performed using the Statistics Package for the Social Sciences (SPSS) for Windows version 13.0. Descriptive data are presented as mean ± standard deviation or standard error. One-way ANOVA and Post-hoc Tukey tests were used to compare parametric variables and to compare differences between groups, respectively. A value of $p<0.05$ was accepted as statistically significant.

Results

The ages of the 96 patients who participated in the study ranged from 23 to 62 years. The mean age of group 1 was 38.38±7.48 years, group 2 was 35.25±8.08 years, group 3 was 37.03±7.27 years. There was no statistically significant difference between the mean ages of the groups ($p>0.05$).

Of the patients included in the study, 16 were postmenopausal and 80 were premenopausal; group 1 (n=32) 26 premenopausal, 6 postmenopausal patients; group 2 (n=32) 27 premenopausal, 5 postmenopausal; and group 3 (n=32) 27 premenopausal, 5 postmenopausal patients.

The median scores of the groups were gravida (2, 3, 3), living child (2, 2, 2), abortion (0, 0, 0), and curettage (0, 0, 0) respectively. It has been found to disperse in accordance with the average of all these groups.

We found significant differences between groups at tenaculum placement. We used the Post-hoc Tukey test to determine which group had the statistically significant score. We found that pain

scores were significantly higher in the control group (p=0.002), but there was no significant difference between either study group (p=0.596).

After the injection of sterile saline solution, the control group had significantly increased pain scores, different from both study groups (p=0.045). We found no significant difference between either study group at this point (p=0.835). During tenaculum use, the mean pain in the group 1 was 27.40±25.58, group 2 was 21.74±23.25, and group 3 was 11.74±11.54 (Graphic 1). During saline infusion, the mean pain in the group 1 was 25.20±27.66, group 2 was 29.12±14.56, and group 3 was 20.63±19.50 (Graphic 2) (Table 1, 2, 3).

Discussion

Patients experience pain in gynecologic outpatient diagnostic interventions. We aimed to determine whether it was correct to use different anesthetic methods in daily clinical practice, and thus we compared PCB and PCB + IUL with placebo.

In the study of Guney et al.[5], IUL that was applied just after buccal misoprostol was found effective preventing pain. IUL failed to prevent pain in procedures such as endometrial biopsy or hysterosalpingograhy in other studies[6,7]. Guney et al.[5] attributed this difference to the combined use of lidocaine with other drugs. Though there was no significant difference between study groups, we also find that lidocaine decreased pain with statistical significance. The reason of this result may be the limited local effect of lidocaine. Patients feel pain the most at the time of grasping the cervix with a tenaculum and the insertion of a carmen cannula. Lidocaine shows its anesthetic effect through free nerve endings as described in previous studies. Guney et al.[5] found that pain was decreased in their IUL group during endometrial curettage. We did not perform endometrial biopsy, instead only the uterine cavity was distended in our study. We found no significant differences, probably because we performed a less painful procedure than that of Guney et al.[5].

PCB and PCB + IUL were effective at preventing pain in all premenopausal women in our study. The same effect could not be shown in postmenopausal women. To our knowledge, no studies have compared pain scores of women according to their menopausal status. Only Guney et al.[5] noted that combined use of IUL and misoprostol was effective at preventing pain in premenopausal women, whereas it was not effective in postmenopausal women. More randomized

Table 1. Demographic characteristics of the groups

	Group 1 Saline (n=32)	Group 2 PCB (n=32)	Group 3 PCB + IUL (n=32)	p
Gravid*	2	3	3	NS
Living child*	2	2	2	NS
Abortus*	0	0	0	NS
Curettage*	0	0	0	NS
Premenopausal (n)	26	27	27	NS
Postmenopausal (n)	6	5	5	NS
Age**	38.38±7.48	35.25±8.08	37.03±7.27	NS

*Medians, **Mean ± standard deviation, NS: Non significant, PCB: Paracervical block, IUL: Intrauterine lidocaine

Table 2. The visual analogue scale scores of all patients during tenaculum use during saline infusion sonogram

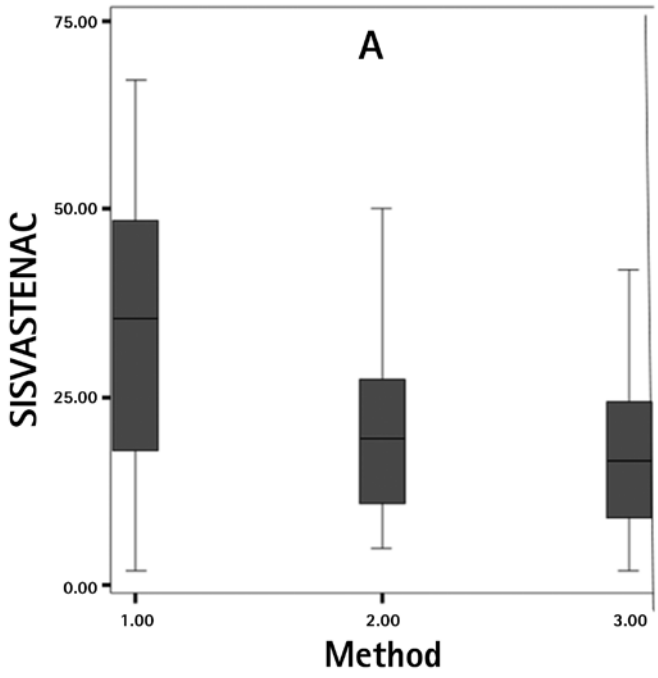
	Saline	PCB	PCB + IUL
Saline	-	p=0.002 [95% CI: (4.33-21.91)]	p<0.001 [95% CI: (7.92-25.51)]
PCB	-	-	p=0.596 [95% CI: (-5.20-12.38)]

PCB: Paracervical block, IUL: Intrauterine lidocaine, CI: Confidence interval

Table 3. Visual analogue scale scores of all patients during saline infusion into the uterine cavity

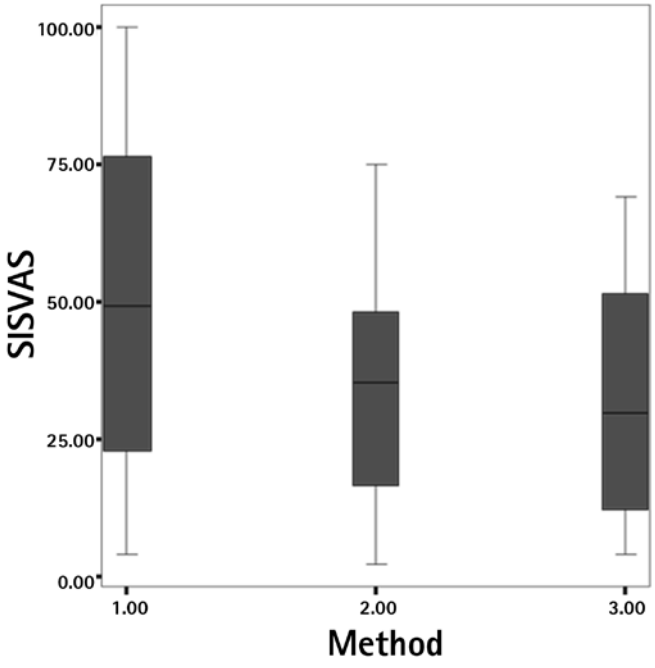
	Saline	PCB	PCB + IUL
Saline	-	p=0.045 [95% CI: (0.28-29.15)]	p=0.010 [95% CI: (3.75-32.6)]
PCB	-	-	p=0.835 [95% CI: (-10.9-17.9)]

PCB: Paracervical block, IUL: Intrauterine lidocaine, CI: Confidence interval



Graphic 1. Graph showing the mean ± standard deviation D values of pain visual analogue scale scores during tenaculum application

SIS: Saline infusion sonography, VAS: Visual analogue scale, TENAC: Tenaculum



Graphic 2. The graph showing the mean ± standard deviation values of pain visual analogue scale scores during saline infusion into the uterine cavity

SIS: Saline infusion sonography, VAS: Visual analogue scale

studies are warranted to determine which anesthetic method would be appropriate for postmenopausal women in outpatient gynecologic procedures.

Van den Bosch et al.[8] compared gel infusion sonography with SIS in their study of 2009. They found both methods were similar in use but pain caused by the procedure was heightened in SIS. They attributed this difference to the lubricant effect of gel, which made it easier to pass the instrument through the cervix. In their second study, they compared gel infusion sonography alone with gel infusion sonography plus IUL. The authors could not show significant differences in the mean VAS scores. Performing SIS is much easier than gel infusion sonography in outpatient settings. Moreover, the long-term effect of gel use remains unknown[9].

The effect of different anesthetic methods on endometrial curettage, hysterosalpingograhy, and hysteroscopy has been extensively studied. The results are conflicting because of the different natures of the procedures. We think our study will help those who need an effective method to prevent pain in SIS.

Conclusion

In conclusion, paracervical block is effective at preventing pain in premenopausal women undergoing SIS. The addition of IUL to PCB does not decrease pain but increases both the time and cost of the procedure.

Ethics

Ethics Committee Approval: The study were approved by the Dr. Lütfi Kırdar Training and Research Hospital Local Ethics Committee,
Informed Consent: Consent form was filled out by all participants.
Peer-review: External and Internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Sadullah Özkan, Aylin Onan Yılmaz, Yaren Tuba Bektaş, Concept: Sadullah Özkan, Bülent Kars, Design: Sadullah Özkan, Bülent Kars, Data Collection or Processing: Sadullah Özkan, Aylin Onan Yılmaz, Yaren Tuba Bektaş, Analysis or Interpretation: Sadullah Özkan, Önder Sakin, Halim Ömer Kaşıkçı, Literature Search: Sadullah Özkan, Önder Sakin, Writing: Sadullah Özkan, Önder Sakin, Halim Ömer Kaşıkçı.

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A comparison of clinico-pathologic characteristics of patients with serous and clear cell carcinoma of the uterus

Seröz ve berrak hücreli endometriyum kanseri olan hastaların kliniko-patolojik özelliklerinin kıyaslanması

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Abstract

Objective: Serous carcinoma and clear cell carcinomas account for 10% and 3% of endometrial cancers but are responsible for 39% and 8% of cancer deaths, respectively. In this study, we aimed to compare serous carcinoma and clear cell carcinoma regarding the surgico-pathologic and clinical characteristics, and survival, and to detect factors that affected recurrence and survival.

Materials and Methods: We retrospectively analyzed patients with clear cell and serous endometrial cancer who underwent surgery between January 1993 and December 2013 in our clinic. We used Kaplan-Meier estimator to analyze survival.

Results: The tumor type in 49 patients was clear cell carcinomas and was serous uterine carcinoma in 51 patients. Advanced stage (stage III and IV) disease was present in 42% of the patients in the clear cell group, whereas this rate was 62% in the serous group (p=0.044). Lymph node metastasis was detected in 37% of the patients with clear cell carcinomas and 51% of the patients with serous carcinoma (p=0.17). The adjuvant therapies used did not differ significantly between the groups (p=0.192). The groups had similar recurrence patterns. Five-year progression-free survival and the 5-year overall survival were 60.6% and 85.8%, 45.5% and 67.8% in the patients with clear cell carcinomas and serous tumor, respectively.

Conclusion: With the exception that more advanced stages were observed in patients with serous carcinoma endometrial cancers at presentation, the surgico-pathologic features, recurrence rates and patterns, and survival rates did not differ significantly between the groups with clear cell carcinoma and serous carcinoma endometrial cancers.

Keywords: Uterine serous carcinoma, uterine clear cell carcinoma, survival, recurrence

Öz

Amaç: Endometriyumun seröz ve berrak hücreli kanserleri, endometriyum kanserlerinin sırasıyla %10 ve %3'ünü oluştururlar ve endometriyum kanserine bağlı ölümlerin sırasıyla %39 ve %8'inden sorumludurlar. Bu çalışmada bu kanserleri cerrahi, patolojik ve klinik özellikleri ve sağkalım açısından karşılaştırmayı ve rekürrensi ve sağkalımı etkileyen faktörleri belirlemeyi amaçladık.

Gereç ve Yöntemler: Seröz kanser ve berrak hücreli kanseri olan ve kliniğimizde Ocak 1993 ve Aralık 2013 tarihleri arasında ameliyat olan hastalar retrospektif olarak incelendi. Sağkalım analizi için Kaplan-Meier metodu kullanıldı.

Bulgular: Kırk dokuz hastada berrak hücreli ve 51 hastada seröz uterin kanser saptandı. Berrak hücreli grupta hastaların %42'sinde ileri evrede (evre III ve IV) hastalık varken bu oran seröz grupta %62 idi (p=0,044). Berrak hücreli hastaların %37'sinde, seröz kanserli hastaların %51'inde lenf nodu metastazı vardı (p=0,17). Kullanılan adjuvant tedavi açısından gruplar arasında fark yoktu (p=0,192). Rekürrens paterni gruplar arasında benzerdi. Beş yıllık hastalıksız sağkalım ve 5-yıllık genel sağkalım berrak hücreli ve seröz gruplarda sırasıyla %60,6 ve %85,8; %45,5 ve %67,8 idi.

Sonuç: Seröz endometriyum kanserli hastaların daha ileri evrelerde başvurması dışında berrak hücreli ve seröz gruplar arasında cerrahi, patolojik faktörler, rekürrens oranları ve paternleri ve sağkalım oranları açısında istatistiksel anlamlı fark yoktu.

Anahtar Kelimeler: Uterin seröz karsinom, uterin berrak hücreli karsinom, sağkalım, rekürrens

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Introduction

Endometrial cancer (EC) is the sixth most common cancer in women worldwide and the twelfth most common cancer overall[1]. Bokhman[2] first suggested that there were 2 types of ECs that had different microscopic, clinical, epidemiologic, and genetic properties in 1983. Type I ECs, represented by endometrioid carcinomas, constitute 80% of all ECs. Type II tumors are composed of other cell types of ECs that are less frequently observed. Most common cell types included in type II ECs are serous carcinoma (SC) and clear cell carcinoma (CCC). Type II tumors are estrogen independent, seen in older and thinner patients, diagnosed at more advanced stages, and the likelihood of recurrence and death of the disease is much higher with type II compared with type I tumors[3].

SC and CCCs account for 10% and 3% of ECs but are responsible for 39% and 8% of cancer deaths, respectively[4]. Therefore, it is important to approach these tumors differently and to separate them from endometrioid tumors in studies that analyze patients with ECs. They are usually analyzed together in studies that investigate characteristic features, management, and survival of patients with these tumors they are rare are more aggressive than endometrioid ECs. This may also explain the disparate results obtained in the literature, because these two tumors are also different with distinct clinical behavior and pathogenetic properties. They have different molecular alterations and separate ways of spreading. Most serous tumors have p53 mutation because only 14% of clear cell tumors have this mutation. Serous tumors have a tendency to spread intraperitoneally just like its ovarian counterparts, whereas clear cell tumors show a propensity for distant metastasis[5]. Many studies have compared these tumors with type I or poorly-differentiated ECs. However, there is little data in the literature with regard to the differences between these 2 tumors. In this study, we aimed to present a comparison of SC and CCC in terms of surgico-pathologic and clinical features, and survival, and to determine factors that affect recurrence and survival.

Materials and Methods

Patients with clear cell and serous EC who underwent surgery in our clinic between January 1993 and December 2013 were retrospectively analyzed. The data related to demographic characteristics, intraoperative findings, surgico-pathologic results, patients' treatments, recurrence and the site of recurrence, and survival were collected from the electronic gynecologic oncology clinic database system, pathology reports, and surgical records. Patients were staged according to the 2009 International Federation of Gynecology and Obstetrics criteria. Institutional review board approval was obtained.

In our clinic, patients with a preoperative or intraoperative pathologic diagnosis of clear cell or serous tumor undergo staging surgery directly. Staging surgery involves total abdominal hysterectomy, bilateral salpingo-oophorectomy, systematic pelvic and paraaortic lymphadenectomy, abdominal cytology, and omentectomy as standard. Omentectomy was performed as total, infracolic or omental biopsy according to the cell type, intraoperative examination, and decision of the surgeon. Cytoreductive surgery was performed in addition to staging surgery in case there was macroscopic disease intraoperatively.

In terms of adjuvant therapy, only radiotherapy or sandwich therapy (3 cycles of chemotherapy followed by radiotherapy, and then 3 cycles of chemotherapy) or only chemotherapy or radiotherapy followed by chemotherapy were applied at the discretion of the surgeon and according to the stage of the disease. Patients were followed-up every 3 months in the first 2 years after adjuvant therapy, within every six months until the fifth year, and yearly thereafter. Pelvic examination, complete blood count and blood chemistry, and abdominal ultrasonography were performed at every follow-up. Chest X-ray was performed yearly or in the event of clinical suspicion. Thoracic and/or abdominal computerized tomography was used when needed. In the follow-up, a Papanicolaou smear and cancer antigen-125 (Ca) level tests were used, even though we did not use them routinely.

Pelvic recurrence was defined as recurrence distal to the pelvic inlet (true pelvis), upper abdominal recurrence as recurrence between the pelvic inlet and the diaphragm, and extraabdominal recurrence as all other recurrences. Ascites and peritonitis carcinomatosa were included in the upper abdominal recurrences, whereas recurrence in the liver parenchyma and bone were included in the extraabdominal recurrences. The period from surgery to recurrence or last visit was defined as progression-free survival (PFS), and the period from surgery to death or last visit was defined as overall survival (OS). Follow-up time was evaluated as the time between surgery and the time of the patient's last examination (death or last visit).

Statistical Analysis

Statistical data were analyzed using Statistical Package for Social Sciences (SPSS) version 17 (SPSS Inc., Chicago IL, USA). Descriptive statistics are presented using median and range or mean and standard deviation where appropriate. Student's t-test and the Mann-Whitney U test were used to compare means and medians, respectively, in different groups. The chi-square test or Fisher's exact test were used where appropriate to compare proportions and percentages in different groups. Kaplan-Meier estimation was used for the analysis of survival. The logrank test and univariate Cox regression analysis were used for analysis of categorical and continuous variables that affect survival, respectively. The possible factors identified with univariate analysis were entered into multivariate Cox regression analysis. Statistical significance was considered as $p<0.05$.

Results

Surgico-pathologic factors

In our clinic, 1640 patients with EC underwent surgery between January 1993 and December 2013. In the defined time period,

100 (6.1%) patients were diagnosed as having either clear cell or serous uterine tumor. Among these, 49 patients had clear cell and 51 patients had serous uterine carcinoma. The mean age at diagnosis was 63±8.2 years. All but seven patients were staged surgically. Forty-two patients had stage 1 disease, five patients had stage 2, 32 patients had stage 3 and 19 patients had stage 4 disease. Forty-two percent of patients had advanced stage (stage III and IV) disease in the clear cell group, and 62% had advanced stage disease in the serous group (p=0.044).

The median number of harvested lymph nodes was 50 (range, 2-118), and these numbers were 16 (range, 1-55) and 37 (range, 2-69) for paraaortic and pelvic regions, respectively. Among the patients with lymphadenectomy, 41 (44%) patients had lymph node metastasis. Of these patients, 16 patients had only pelvic involvement, 8 patients had only paraaortic involvement, and 16 patients had both pelvic and paraaortic involvement. In one patient the region of involvement was not defined. Thirty-seven percent of patients with CCC and 51% of patients with SC had lymph node metastasis (p=0.17). Lymphovascular space invasion (LVSI) was positive in 40 patients; it was positive in 40% and 61% of patients with CCC and serous tumor, respectively (p=0.07). Abdominal cytology was positive in 23 patients. Omental metastasis was observed in 21 patients. Twenty-one (22%) patients had ovarian involvement. The median Ca-125 level was 28 (range, 1-915).

There was no difference between the 2 tumor types in terms of number of harvested lymph nodes, myometrial invasion, cervical involvement, cytologic positivity, tumor size, ovarian involvement, omental metastasis, preoperative Ca-125 level, and the site of recurrence (abdominal vs. extraabdominal) (Table 1).

Adjuvant therapy

Nine patients had no adjuvant therapy, and 71 patients completed adjuvant therapy. Twenty-one patients had radiotherapy only, 34 patients had chemotherapy only, 11 patients received sandwich therapy, and 5 patients had radiotherapy followed by chemotherapy. Platin- based chemotherapy was used (paclitaxel + carboplatin, n=31; paclitaxel + cisplatin, n=9; cisplatin, n=3; paclitaxel, n=1, doxorubicin + cisplatin, n=5; paclitaxel + carboplatin + epirubicin, n=1). Thirty-five patients completed six cycles of chemotherapy. Eighteen were lost to follow-up following surgery. Eighty percent of patients with CCC and 65% of patients with serous tumor received adjuvant therapy (p=0.08). Details of the adjuvant therapy in patients with CCC and serous tumor are defined separately in Table 2. Radiotherapy seemed to be used more commonly in patients with CCC; however, there was no statistical difference between the groups regarding the type of adjuvant therapies used (p=0.192).

Recurrence

Recurrence was observed in 22 patients (27.5%). This number was 9 (24%) and 13 (31%) for patients with CCC and SC, respectively (p=0.47). The mean time to recurrence was 12 months (range, 1-45 months). The time to recurrence and site of recurrence were similar in the two tumor types. Recurrence was

Table 1. Comparison of clinico-pathologic characteristics of patients

Parameter		Clear cell tumor (n=49) mean (range)	Serous tumor (n=51) mean (range)
Age (years)		62 (32-77)	64 (46-76)
Ca-125 level (IU/mL)		23 (5-411)	42 (1-915)
Number of total harvested lymph nodes		47 (2-102)	55 (10-118)
		n (%)	n (%)
2009 FIGO stage			
	I-II	28 (58)	19 (38)
	III-IV	20 (42)	31 (62)
Omental metastasis			
	Negative	34 (81)	34 (74)
	Positive	8 (19)	12 (26)
Lymph node metastasis			
	Negative	29 (63)	23 (49)
	Positive	17 (37)	24 (51)
Lymphovascular invasion			
	Negative	22 (60)	16 (39)
	Positive	15 (40)	25 (61)
Abdominal cytology			
	Negative	36 (80)	34 (71)
	Positive	9 (20)	14 (29)
Ovarian metastasis			
	Negative	39 (83)	36 (74)
	Positive	8 (17)	13 (26)
Depth of myometrial invasion			
	No invasion	10 (21)	7 (14)
	<½	20 (42)	15 (30)
	≥½[1]	14 (29)	21 (42)
	Serosal involvement	4 (8)	7 (14)
Cervical involvement			
	Negative	39 (85)	34 (72)
	Positive	7 (15)	13 (28)

FIGO: International Federation of Gynecology and Obstetrics, [1]: Except for uterine serosal invasion

only in the upper abdomen in nine patients, only extraabdominal in four patients, only in the pelvis in two patients, in the upper abdomen and extraabdominal in three patients, in the pelvis and extraabdominal in two patients, in the pelvis and upper abdomen in one patient, and in the pelvis, upper abdomen, and extraabdominal in one patient. The recurrence pattern of the 2 tumor types is defined in detail in Table 3.

In the subgroup analysis of patients with clear cell tumors, only lymph node involvement was associated with recurrence (p=0.04). Depth of myometrial invasion, LVSI, ovarian involvement, omental metastasis, cervical invasion, age, number of lymph nodes harvested, tumor size, and taking adjuvant therapy were not associated with recurrence. The patients who had recurrence had higher preoperative Ca-125 levels (p=0.014).

In the group with serous tumor, paraaortic lymph node metastasis, presence of LVSI, ovarian and omental metastasis, and higher preoperative Ca-125 level were associated with a higher risk of recurrence (p=0.017, p=0.004, p=0.007, p=0.001 and p=0.007, respectively). On the other hand, pelvic lymph node metastasis, myometrial invasion, positivity of peritoneal cytology, cervical invasion, age, number of lymph nodes harvested, tumor size, and taking adjuvant therapy were not associated with recurrence.

Table 2. Comparison of adjuvant therapies between the tumor types

Therapy type	Clear cell tumor (n=49)	Serous tumor (n=51)	All patients (n=100)
Only CT	16	18	34
Only RT	15	6	21
Sandwich therapy	4	7	11
RT followed by CT	3	2	5

CT: Chemotherapy, RT: Radiotherapy, Sandwich therapy: 3 cycles of chemotherapy followed by radiotherapy followed by 3 cycles of chemotherapy

Survival Analysis

The median follow-up time was 18.5 months (range 1-156 months), and was 39 months (range, 1-156 months) and 28 months (1-96 months) for patients with CCC and SC ECs, respectively (p=0.035). Five patients with CCC and eight patients with SC ECs died in the follow-up period; one patient with CCC died during adjuvant therapy and the other who had SC died before the adjuvant therapy (1 following 3 cycles of chemotherapy and 1 before adjuvant therapy-renal insufficiency).

Five-year PFS was 53.6%; 60.6% and 45.5% for CCC and serous tumor, respectively (p=0.465) (Figure 1). Five-year OS was 77.1%; 85.8% and 67.8% for CCC and serous tumors, respectively (p=0.565) (Figure 2).

In the univariate analysis of the clear cell subgroup, omental metastasis, paraaortic involvement, peritoneal cytology positivity, and taking no adjuvant therapy were associated with worse 5-year OS (p=0.002, p=0.003, p<0.001, p=0.035 respectively), and omental metastasis, paraaortic involvement, pelvic involvement, positivity of peritoneal cytology, preoperative Ca-125 level and ovarian metastasis were associated with 5-year PFS (p<0.001, p=0.014, p=0.044, p<0.001, p=0.016 and p=0.006, respectively) (Tables 4 and 5). Multivariate analysis could not be performed in this subgroup.

In the univariate analysis of the serous subgroup, lower number of harvested lymph nodes, paraaortic metastasis, and LVSI were associated with worse 5-year OS (p=0.017, p<0.001, p=0.041 respectively), and paraaortic metastasis, omental metastasis, and LVSI were associated with worse 5-year PFS (p<0.001, p=0.004, p=0.006, respectively) (Tables 4 and 5). Multivariate analysis could not be performed for OS and it could not detect any independent prognostic factor for 5-year PFS.

Discussion

Type II ECs differ from endometrioid tumors with their less favorable characteristics. They have a tendency to present at more advanced stages and to recur earlier[6,7]. In the present

Table 3. Pattern of recurrence

	Clear cell tumor (n=49)	Serous tumor (n=51)	p
Patients with recurrence	9 (24%)	13 (31%)	0.47
Time to recurrence	14 months (1-45)	12 months (7-24)	0.927
Site of recurrence			
Only pelvic	-	2	
Only upperabdominal	2	7	
Only extraabdominal	2	2	
Upperabdominal + extraabdominal	1	2	
Pelvic + extraabdominal	2	-	
Pelvic + upperabdominal	1	-	
Pelvic + upperabdominal + extraabdominal	1	-	

study, 42% of patients had advanced stage (stage III and IV) disease in the clear cell group, and 62% had advanced stage disease in the serous group (p=0.044). The rate of advanced stage disease is reported between 40% to 56% in the literature for both serous and clear cell tumors[3,4,6,7]. The different rates may be explained by the different rates of comprehensive surgical staging in these studies. SC, ECs seem to present at more advanced stages than CCCs according to our results.

There was no difference between the 2 tumor types in terms of number of harvested lymph nodes, myometrial invasion, cervical involvement, cytologic positivity, tumor size, ovarian involvement, omental metastasis, preoperative Ca-125 level, and the site of recurrence (abdominal vs. extraabdominal). LVSI was positive in 40% and 61% of patients with CCC and serous tumor, respectively (p=0.07). This difference seems clinically significant. However, it did not reach statistical significance. Omental metastasis was observed in 24% of the patients. Although omentectomy is controversial in the staging surgery

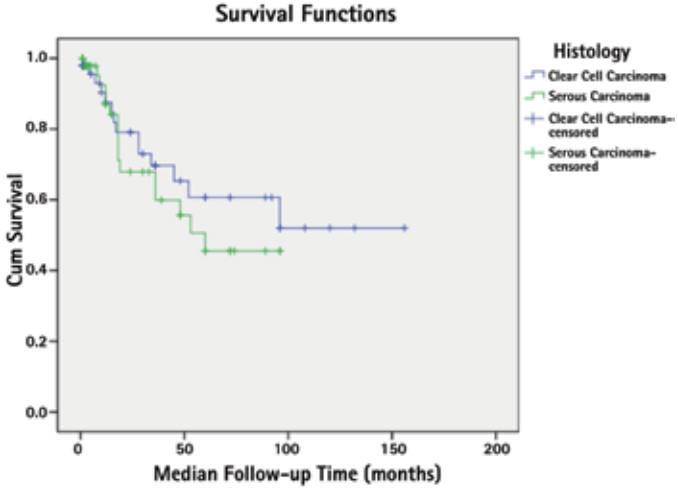

Figure 1. Five-year progression-free survival

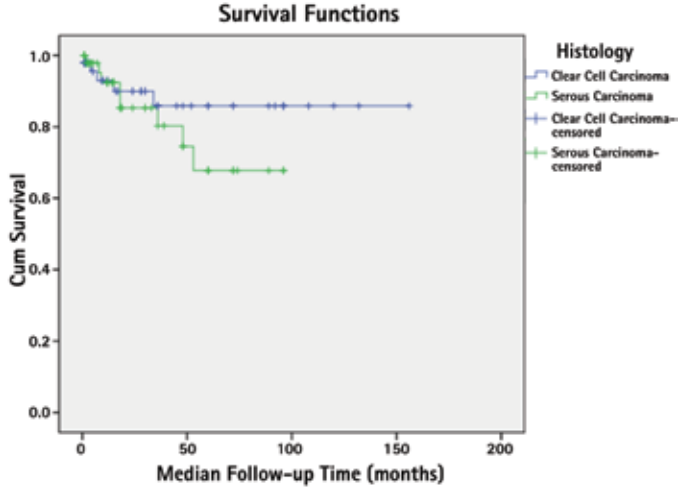

Figure 2. Five-year overall survival

Table 4. Five-year overall survival

Parameter	Univariate analysis	
	Serous tumor	Clear cell tumor
	p	p
PALN metastasis*,1	p<0.001	p=0.003
PLN metastasis*,1	p=0.10	p=0.93
Ovarian metastasis*,1	p=0.16	p=0.40
Omental metastasis*,1	p=0.068	p=0.002
Peritoneal cytology*,1	p=0.43	p<0.001
Stage#,1	p=0.33	p=0.003
Total number of harvested LN2	p=0.017	p=0.22
Age2	p=0.94	p=0.72
Lymphovascular space invasion1	p=0.041	p=0.62
Cervical invasion*,1	p=0.61	p=0.50
Adjuvant therapy**,1	p=0.45	p=0.035
Myometrial invasion£,1	p=0.57	p=0.660
Preoperative Ca-125 level2	p=0.12	-

PALN: Paraaortic lymph node, PLN: Pelvic lymph node, LN: Lymph node, *positive versus negative, **applied versus not applied, #stage I, II, III, IV; £<1/2 versus ≥1/2, 1: Logrank, 2: Cox regression, univariate analysis

Table 5. Five-year progression-free survival

Parameter	Univariate analysis	
	Serous tumor	Clear cell tumor
	p	p
PALN metastasis*,1	p<0.001	p=0.014
PLN metastasis*,1	p=0.12	p=0.044
Ovarian metastasis*,1	p=0.20	p=0.006
Omental metastasis*,1	p=0.004	p<0.001
Peritoneal cytology*,1	p=0.78	p<0.001
Stage#,1	p=0.065	p<0.001
Total number of harvested LN2	p=0.25	p=0.93
Age2	p=0.84	p=0.80
Lymphovascular space invasion1	p=0.006	p=0.39
Cervical invasion*,1	p=0.065	p=0.25
Adjuvant therapy**,1	p=0.31	p=0.51
Myometrial invasion£,1	p=0.21	p=0.47
Preoperative Ca-125 level2	p=0.18	p=0.016

PALN: Paraaortic lymph node, PLN: Pelvic lymph node, LN: Lymph node, *positive versus negative, **applied versus not applied, #stage I, II, III, IV, £<1/2 versus ≥1/2, 1: Logrank, 2: Cox regression, univariate analysis

of type II ECs, omental metastasis was reported as 13% and up to 25% for CCC and SC, respectively, in different studies[8,9].

There is no consensus regarding adjuvant therapy for type II ECs. Adjuvant chemotherapy is usually suggested for patients with type II ECs for all stages, because even patients with uterine SC without myometrial invasion treated with observation alone were shown to have a risk of recurrence, which varied from 0 to 30%[10] and clear cell tumors were reported to have a tendency for distant recurrence[5]. Although there are different results in the literature, adjuvant radiotherapy is usually accepted to decrease local recurrence, but an exact effect on survival has not been shown[3,6]. In our study, 80% of patients with CCC and 65% of patients with serous tumor received adjuvant therapy (p=0.08).

Recurrence was observed in 22 (27.5%) patients; the recurrence pattern was similar between the 2 groups. Twenty-two percent to 38% of patients were reported to have recurrence in the literature[11-13]. In the subgroup analysis of patients with CCC, only lymph node involvement was associated with recurrence. In the group with serous tumor, paraaortic lymph node metastasis, presence of LVSI, and ovarian and omental metastasis were associated with a higher risk of recurrence. Additionally, the patients who had recurrence in both groups had higher preoperative Ca-125 levels. Preoperative Ca-125 was also associated with 5-year PFS in patients with CCC in our study (p=0.016). There are no data in the literature on the relation between Ca-125 level and uterine clear cell tumors. On the other hand, the association of uterine SC and Ca-125 level has been studied in several trials. In a study that analyzed the relation between preoperative Ca-125 level and uterine SCs in 41 patients, Olawaiye et al.[14] showed that preoperative Ca-125 was associated with disease stage at diagnosis and with the likelihood of death. In addition, Abramovich et al.[15] reported that a rising Ca-125 was associated with relapse.

In the present study, 5-year PFS was 60.6% and 45.5% for CCC and serous tumor, respectively (p=0.465). These rates were 85.8% and 67.8% for 5-year OS (p=0.565). In the study by Scarfone et al.[13] these rates were reported as 67% and 55% for 5 year PFS, and 77% and 71% for 5-year OS, respectively. Thomas et al.[16] found that 5-year PFS and OS were 46% and 55% in 99 patients with CCC. There is a wide range of survival rates reported in the literature. Different complete staging and cytoreduction rates, and different adjuvant therapies may account for this situation. Complete surgical staging including lymphadenectomy and cytoreduction are recommended to be performed for all patients with these tumors, because more than half of these patients are upstaged during these procedures and residual disease was shown to be associated with worse survival[6,7]. Ninety-three percent of our patients underwent complete surgical staging and cytoreductive surgery and the numbers of lymph nodes removed were quite high. These may be the reasons for the high survival rates in our study.

In the current study, in the univariate analysis of the clear cell subgroup, omental metastasis, paraaortic involvement, peritoneal cytology positivity, and receiving no adjuvant therapy were associated with worse 5-year OS, and omental metastasis, paraaortic involvement, pelvic involvement, peritoneal cytology positivity, preoperative Ca-125 level, and ovarian metastasis were associated with 5-year PFS. However, in the study by Thomas et al.[16] age more than 60 years, LVSI, and myometrial invasion equal to or greater than half were reported associated with both 5-year PFS and OS in the univariate analysis that included 99 patients with uterine CCC. In the same study, a multivariate analysis revealed that stage and adjuvant radiotherapy were independent prognostic factors for both PFS and OS, and systemic lymphadenectomy was an independent prognostic factor for OS only. Abeler and Kjørstad[17] showed in a study of 97 patients with uterine CCC that 17% of patients with LVSI survived 5 years, in contrast to 49% of patients without this finding. In the univariate analysis of the serous subgroup of our study population, lower number of harvested lymph nodes, paraaortic metastasis, and LVSI were associated with worse 5-year OS, and paraaortic metastasis, omental metastasis, and LVSI were associated with worse 5-year PFS. Similar findings were shown in a study that analyzed 129 patients with uterine SC. In that study, worse 5-year OS was reported associated with LVSI and positive lymph nodes in the univariate analysis. Different to other studies, the same study also showed that myometrial invasion was related to OS[18]. Myometrial invasion was also reported associated with PFS in 83 women with stage I uterine SC. The authors could not show a relation between LVSI, number of harvested lymph nodes, age, and survival[11]. Similarly, Fader et al.[19] were unable to demonstrate an association between LVSI and PFS.

Study Limitations

The retrospective nature of the study was one of our limitations. Additionally, the adjuvant chemotherapy and radiotherapy protocols could not be standardized during the study period. However, this study included 100 patients with CCC and SC ECs from a single institution and the clinico-pathologic features of the patients could be obtained in detail. Most patients in this study underwent complete staging and cytoreductive surgery including comprehensive lymphadenectomy. These are considered to be the advantages of our study.

Conclusion

In this study, with the exception that SC ECs presented at more advanced stages, we could not show a statistically significant difference between patients with CCC and SC ECs regarding surgico-pathologic features, recurrence rates and patterns, and survival rates. However, patients with SC ECs had a tendency to have less favorable characteristics compared with CCC. We also demonstrated factors that affected recurrence and survival.

Ethics

Ethics Committee Approval: Institutional review board approval was obtained, Informed Consent: None, retrospective.
Peer-review: External and Internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Nurettin Boran, Gökhan Tulunay, Taner Turan, Concept: Nurettin Boran, Gökhan Tulunay, Taner Turan, Design: Taner Turan, Data Collection or Processing: Derya Akdağ Cırık, Tolga Taşçı, Analysis or Interpretation: Taner Turan, Işın Üreyen, Literature Search: Günsu Kimyon Cömert, Tolga Taşçı, Osman Türkmen, Writing: Işın Üreyen, Alper Karalok.

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Long- and short-term complications of episiotomy

Epizyotominin uzun ve kısa dönem komplikasyonları

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Abstract

Although extensively applied in obstetrics practice to facilitate delivery by increasing the vaginal birth conduit, most episiotomy studies are in the context of short- or medium-term outcomes, and the number of studies investigating the long-term effects is insufficient. Episiotomy is often considered associated with urinary and/or anal incontinence and dyspareunia; however, there is no concrete evidence for this issue. Current meta-analyses and reviews that assessed the studies available in the literature revealed that episiotomy does not decrease the rates of urinary incontinence, perineal pain, and sexual dysfunction and that routine episiotomy does not prevent pelvic floor damage; thus, the recommended use of mediolateral episiotomy is restricted, rather than routine. According to the limited number of studies on sexual function, there seems to be a linear relationship between the degree of perineal laceration and postpartum dyspareunia. It is still not clear whether episiotomy has any impact on pelvic floor relaxation, pelvic organ prolapse, and sexual dysfunction in the long term.

Keywords: Episiotomy, urinary incontinence, anal incontinence, sexual dysfunction

Öz

Obstetrik pratiğinde doğum kanalı çapı artırarak doğumu kolaylaştırmak amacıyla sıklıkla uygulanmasına rağmen epizyotomi ile ilgili çalışmaların çoğu kısa veya orta vadeli sonuçlar üzerinedir ve uzun dönem etkileri inceleyen çalışmalar yetersizdir. Epizyotomi uygulaması sıklıkla üriner ve/veya anal inkontinans ve disparoni ile ilişkili olduğu düşünülse de günümüzde bunlara dair somut kanıt bulunmamaktadır. Literatürdeki çalışmaların incelendiği derleme ve meta-analizler epizyotominin üriner inkontinans, ağrı veya seksüel disfonksiyon oranlarını azaltmadığını ve rutin epizyotominin pelvik taban hasarını önlemediğini belirtmekte, bu nedenle rutin yerine kısıtlı mediolateral epizyotomi kullanılmasını tavsiye etmektedirler. Seksüel fonksiyon ile ilgili yapılan kısıtlı sayıdaki çalışma sonuçlarına göre ise perineal laserasyonun derecesi ile postpartum disparoni sıklığı arasında doğrusal bir ilişki var gibi görünmektedir. Epizyotomi uygulamasının uzun dönemde pelvik taban relaksasyonu, pelvik organ prolapsusu ve seksüel disfonksiyon üzerine etkisi olup olmadığı halen net değildir.

Anahtar Kelimeler: Epizyotomi, üriner inkontinans, anal inkontinans, seksüel disfonksiyon

PRECIS: The long-term influences of episiotomy on urinary and/or fecal incontinence, pelvic floor dysfunction, sexual function, and dyspareunea are still not clear and studies on these issues are necessary.

Introduction

For a succesful vaginal birth, vaginal and cervical expansion should occur slowly and the tissue should be allowed to stretch in a proper manner. At this time, spontaneous tears may ensue in rapid descent, particularly during the fetal head descent and the formation of vaginal dilatation. Even if these tears, as described by Fernando who divided them into four degrees, most frequently involve perineal skin and mucosa (1st degree), they may extend to perineal muscle (2nd degree), anal sphinchter complex (3rd degree), and anal mucosa (4th degree). Another reason for vaginal tears at birth is controlled and properly made perineal incisions performed at the end of the second stage of labor to ease parturition by increasing the vaginal diameter, known as episiotomy[1]. Two types have been described; median (from the posterior fourchette to the anus) and mediolateral (from hymenal ring downwards with at least a 45-degree angle). However, standardization in the method of application and repair of episiotomy is still lacking today. Additionally, in the majority of studies conducted on this issue to date, the parameters likely to influence the healing process and long-term outcomes are not clear.

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Early studies and short-term effects

After being described by Ould[2] in 1741, episiotomy was first recommended to be applied in a mediolateral fashion in all births of nulliparous women in order to protect the fetal head from trauma and the pelvic floor from extreme lacerations in 1921[3]. For years, episiotomy was believed to be repaired more easily and to reduce the risk of severe lacerations in the short term, and to protect against pelvic floor relaxation, sexual dysfunction, and long-term urinary and/or fecal incontinence, as compared with spontaneous vaginal or perineal tears. It was also considered associated with neonatal benefits such as lower incidences of asphyxia, cranial trauma, cerebral hemorrhage, mental retardation, and shoulder dystocia. Consequently, episiotomy was used extensively until the first half of the nineteenth century and the frequency of application gradually increased. However, in the second half of the twentieth century, increasing evidence that episiotomy did not actually provide these benefits began to be published[4]. Thereupon, Thacker and Banta[4] reviewed the related studies conducted between 1860 and 1980 and analyzed the results to investigate whether episiotomy provided any benefits. As a result, they reported that the number of studies available was insufficient and that the studies were not reliable enough to substantiate their hypotheses; thus, the results did not support the routine use of episiotomy. Moreover, it was indicated that postpartum pain and discomfort became evident and serious complications, and maternal death might even occur after episiotomy[4]. During the defined period and the following 10 years, publications mostly originated from the United States and were of minor scale, in addition, as almost all dealt with midline episiotomy. There is a very limited number of publications on mediolateral episiotomy and the most comprehensive study was from Argentina, a randomized controlled trial that included 2.606 women from 8 centers[5]. In that study, routine, restrictive or selective episitotomies were compared and episiotomy rates were reported to be 82.6% and 30.1% in the restrictive and routine groups, respectively. Perineal lacerations of 3rd or 4th degree were reported lower in the restrictive group than in the routine group (1.2% vs. 1.5%). Subsequently, the review by Homsi et al.[6] indicated the possible drawbacks of routine episiotomy to be the extension of the episiotomy incision, unsuitable anatomic outcomes, increased blood loss and hematoma formation, pain, inflammation, infection and dehiscence within the episiotomy region, sexual dysfunction, and increased costs (Table 1).

Episiotomy and long-term effects

A significant proportion of the studies relevant to episiotomy actually assessed short- and medium-term period outcomes; long-term complications associated with episiotomies were not explicit. In a systematic review published in 2005 in the Journal of the American Medical Association that included only 26 prospective randomized controlled trials even though 986 publications had been published between 1950 and 2004, data beyond the postpartum first year was only provided in two studies,[7] one of which was conducted by Sleep and Grant[8] in 1987 who compared routine versus restrictive episiotomy during spontaneous vaginal delivery within a single center. That study, which was initiated with 1.000 women in 1984, was terminated with 674 women in the 3rd postpartum year and reported that there was no significant difference between the two groups in terms of dyspareunia and urinary incontinence. The other study was conducted by Rockner[9] in 1990 and reported no statistically significant difference in the incidence of urinary incontinence between groups with and without episiotomy at the postpartum 4th year. However, no study has provided data on anal incontinence beyond the 1st postpartum year. As a result, there is no evidence to support the maternal benefits of routine episiotomy.

One of the largest studies on the long-term complications of episiotomy was conducted in France with the participation of two hospitals that adopted diverse policies regarding episiotomy[10]. Long-term outcomes of restrictive and routine episiotomy were compared in this study, including deliveries of 774 nulliparous women with singleton and cephalic presentation pregnancies between 37 and 41 gestational weeks. Four postpartum years later, 627 women responded with a 81% return rate and the patient distribution was 320 versus 307 women; the episiotomy rates were 49% and 88% in the restrictive and routine episiotomy groups, respectively. The rates of urinary incontinence, perineal pain, and dyspareuneu were lower in the restrictive group than in the routine episiotomy group with rates of 26% vs. 32%, 6% vs. 8%, and 18% vs. 21%, respectively, but not there was no significant difference. Similarly, fecal and flatus incontinences were lower in the restrictive group than in the routine episiotomy group with rates of 11% vs. 16%, and 8% and 13%, respectively; statistical significance was reached only for flatus incontinence. Consequently, the authors stressed that routine episiotomy did not protect against anal and urinary incontinence, there was even a increased risk of anal incontinence in the long term, and that restrictive episiotomy should be preferred to routine episiotomy.

In the early 2000s, publications reporting the increasing incidence of severe obstetric lacerations began to emerge and in the United Kingdom, and the incidence of perineal lacerations of grade 3 or 4, with a reported incidence of 1.8% in 2000, was reported to rise to 5.9% in 2011, which exhibited a 3-fold increase[11]. An increased risk for severe perineal lacerations were indicated associate with increased maternal age, instrumental delivery, Asian race, higher socio-economic status, birth weight of 4.000 g or above, and shoulder dystocia. Some publications reported that selective episiotomy decreased the likelihood of 3rd or 4th degree perineal lacerations;[12] whereas, in a large observational study that included approximately 3.000 births, risk of perineal lacerations was reported associated with a set of factors, mainly including median episiotomy[13]. Today, there

are two remarkable retrospective studies regarding mediolateral episiotomy. The first is a retrospective population-based study conducted in 2001, which comprised 284.000 vaginal births[14]. In that study, risk factors for 3rd degree perineal tears were investigated and episiotomy rate was reported as 35.1%, the rate of 3rd degree perineal tears was presented much lower than those in previous reports (1.94% vs. 4-5%). The authors concluded that forceps delivery was the most remarkable risk factor for 3rd degree perineal laerations [odds rate (OR), 3.33; 95% confidence Interval (CI): (2.97-3.74)] and that mediolateral episiotomy should be performed as a primary measure in case of fetal macrosomia to prevent 3rd degree perineal lacerations. The latter was a retrospective study conducted by Baumann et al.[15] in 2006 that included 40.000 vaginal births. In contrast to the previous study, the rate of anal sphincter laceration in primiparous women was reported as high as 5.2% and 17 obstetric risk factors, which may result in sphincter injury. Moreover, it was emphasized that anal sphincter laceration was most strongly associated with episiotomy [OR, 3.23; 95% CI: (2.73-3.80)] and forceps delivery [OR, 2.68; 95% CI: (2.17-3.33)].

Beyond the causes of severe obstetric lacerations, there were no concrete data on repair and long-term outcomes. In a retrospective case-control survey study, 171 women who underwent anal sphincter rupture surgery between 1971 and 1990 were matched with 171 control women for time and number of deliveries and all women were interrogated twice in both 1996 and 2005 as to whether there had been any increase in sexual and anorectal symptoms, regardless of the menopausal state; a statistically significant increase was determined in study group[16]. In particular, the rates of anorectal symptoms in 1996, when questioned for the first time, were 16% and 38% in control and study groups, respectively, whereas in 2005, they were 22% and 61%, respectively, which revealed that the increase in the variation of rates, as the years advanced, was statistically significant in the study group ($p<0.0001$). Additionally, in the questionnaire in 2005, dyspareunia and fecal incontinence during intercourse were investigated and found significantly different between the controls and study patients (13% vs. 29%, $p=0.01$ and 1% vs. 13%, $p=0.05$, respectively). Similar results were reported in another study conducted in 1988; the anal incontinence rate in women with complete perineal rupture occuring at vaginal delivery, as declared after a mean of 78 months was 22%, whereas it was 0% in the control women ($p<0.01$)(17). Even though perineal laceration was succesfully repaired, Poen et al.[18] also affirmed the anal incontinence rate after 5 years to be 40%.

Restricted instead of routine episiotomy?

The first Cochrane review available in the literature, in the context of benefits and possible risks of routine episiotomy, which aimed to compare routine versus restricted episiotomy as well as midline versus mediolateral episiotomy, was published in 1999, and revised in 2004 and 2009[19]. The authors included only 8 randomized controlled trials, comprising a total of 5.541 women, because most of the studies were of low-quality[5,20-26]. The frequency episiotomy was 75.15% in the routine group, and 28.40% in restrictive group. The limitations of the review were the limited data for episiotomy technique and lack of high-quality studies included in the review, although there were 3 studies available comparing midline and mediolateral episiotomies. Based on the results of the review, the incidence of any anterior trauma was significantly higher in the restrictive group than in the routine group [relative risk (RR), 1.84; 95% CI: (1.61-2.10)]. However, the only data on long-term episiotomy complications available was dyspareunia at 3 postpartum years and there was no significant difference between the groups [RR, 1.21; 95% CI: [0.84-1.75)]. Consequently, it was reported that routine episiotomy did not reduce the rates of urinary incontinence, pain, and sexual dysfunction, and that it has no benefit to the newborn. The recommendations of both National Institute of Clinical Excellence and Royal College of Obstetricians and Gynaecologists are similar and compatible with each other. In 2006, the American College of Obstetricians and Gynecologists stated that the frequency of anal sphincter and rectal mucosa injury in vaginal deliveries with median episiotomy was higher than in those with mediolateral episiotomy and they recommended restrictive mediolateral episiotomy, if necessary (Level A), and also expressed that routine episiotomy did not prevent pelvic floor damage (Level B)[27].

Table 1. Short and long-term consequences of performing an episiotomy

Short term effects
• Perineal lacerations
• Hemorrhage and increased blood loss
• Wound site edema
• Wound site infection
• Anal sphincter and rectal mucosal damage
• Urethral injury
• Bladder injury
• Hematoma formation
• Pain
• Episiotomy dehissence
Long-term effects
• Chronic infections
• Anorectal dysfunction
• Urinary incontinence
• Pelvic organ prolapse
• Sexual dysfunction
• Pain

Prophylactic episiotomy still continues to be widely used today, although the number of publications that recommend against its routine use is higher. Obstetricians' perception that episiotomy decreases the risk of perineal trauma as compared with spontaneous tears, apparently without having any basis of scientific evidence, constitutes the most substantial justification for this practice[28]. The implementation of episiotomy is likely to be influenced by the physician's working environment, conditions and individual diversities as well as mother and fetal factors. One study reported that midwives were more prone to perform episiotomies than physicians,[29] and another indicated that faculty providers performed episiotomies at a lower rate than private providers[30]. The study by Gossett and Dunsmoor Su[31] revealed individual differences more clearly.

Episiotomy and sexual dysfunction

Postpartum sexual life has recently been a subject of research. Studies have also demonstrated that postpartum sexual problems are common in the short term. Although perineal pain and dyspareunia that occur in the postpartum period are considered the main issues that prevent normal sexual activity, our knowledge on this issue is lacking because there are insufficient studies comparing ante- and postpartum sexual activity. According to the results of the study conducted by Abdool et al.[32] in 2009, perineal pain and dyspareunia results from perineal trauma, lacerations, episiotomy and forceps or vacuum use at delivery. Moreover, the authors also reported that perineal pain develops in 42% of patients in the early postpartum period and declines to 22% and 8% in the postpartum 8th and 12th weeks, respectively. Another study that included 921 primiparous women stated that 25% of women had lower sexual desire and functioning at the postpartum 6th month and 42% and 22% of women had dyspareunia at the 3rd and 6th postpartum months, respectively[33]. In the same investigation, it was reported that women with a second degree perineal trauma had 80% more dyspareunia symptoms, and those who had third degree perineal trauma had 270%, as compared with women who had no perineal trauma. However, there is very limited high-level evidence regarding long-term postpartum sexual dysfunctions. A limited number of studies that compared routine and restrictive episiotomy outcomes reported that the frequency of dyspareunia at the 3rd and 4th postpartum years did not differ between the groups[8,10,19]. A study from the Netherlands stressed that dyspareunia was significantly more common in women who underwent repair surgery for anal sphincter rupture than in those who did not, when the patients were questioned 15 years after their delivery (dyspareunia 13% vs. 29%, respectively, p=0.01)[16].

Conclusion

Even though a substantial number of publications do not recommend the implementation of routine prophylactic episiotomy, it still continues to be widely performed. It is not clear as to which approach should be adopted in operative delivery; however, the hitherto gathered data supports restrictive rather than routine episiotomy. Moreover, data as to whether routine episiotomy reduces the incidence of severe obstetric lacerations is lacking, as well as whether episiotomy improves the long-term risks of pelvic floor relaxation, pelvic organ prolapse, urinary incontinence, and dyspareunia remains unclear, and further studies on this issue are still warranted.

Ethics

Peer-rewiev: External and Internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İsmet Gün, Bülent Doğan, Özkan Özdamar, Concept: İsmet Gün, Özkan Özdamar, Design: İsmet Gün, Data Collection or Processing: İsmet Gün, Bülent Doğan, Özkan Özdamar, Analysis or Interpretation: İsmet Gün, Bülent Doğan, Literature Search: Bülent Doğan, Özkan Özdamar, Writing: İsmet Gün, Özkan Özdamar.

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Review / Derleme

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The role of *ADAMTS* genes in preeclampsia

ADAMTS genlerinin preeklampside rolü

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Abstract

Preeclampsia is a complex disease that increases both maternal and fetal morbidity and mortality in both developed and developing countries. It complicates around 5-10% of all pregnancies..The pathophysiology of preeclampsia includes both maternal and fetal/placental factors. Implantation of embryo and placentation are crucial steps for development of pregnancy involving trophoblast invasion. Abnormalities of spiral artery invasion, trophoblast function, inflammatory process, and biologic functions of angiogenic/anti-angiogenic factors early in pregnancy result in pregnancy diseases, including preeclampsia. *ADAMTS* genes are members of the family of matrix metalloproteinase, which have important tasks in extracellular matrix (ECM) degradation and repair processes. The roles of *ADAMTS* in preeclampsia may include regulation of spiral artery invasion and ECM arrangement of the placenta.
Keywords: *ADAMTS* genes, placentation, preeclampsia

Öz

Preeklampsi, gelişmiş ve gelişmekte olan ülkelerde maternal ve fetal morbidite ve mortaliteyi arttıran kompleks bir hastalıktır. Gebeliklerin %5-10'unu komplike eder. Maternal, fetal ve plasental faktörler preeklampsi patofizyolojisinde rol oynarlar. Trofoblast invazyonu, embriyo implantasyonu ve plasentasyon gebelik gelişimi için kritik aşamalardır. Anormal gelişen spiral arter invazyonu, trofoblast fonksiyonu, enflamatuvar süreç ve erken gebelik döneminde anjiyogenik/anti-anjiyogenik faktörlerin biyolojik fonksiyonları preeklampsi gibi gebelikle ilişkili hastalıkların oluşmasına neden olur. *ADAMTS*, ekstraselüler matriksin (ECM) degradasyonu ve tamir aşamalarında önemli görev yapan matriks metalloproteinaz ailesinin üyesidir. *ADAMTS*'lerin preeklampsideki rolü, spiral arterlerin invazyonu ve plasentada ECM'nin regülasyonu olabilir.
Anahtar Kelimeler: *ADAMTS* genleri, plasentasyon, preeklampsi

Introduction

Preeclampsia is defined as the clinical condition associated with hypertension (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg) and proteinuria or end-organ dysfunction in a woman who was normotensive before 20 weeks gestation[1,2]. Hypertensive diseases in pregnancy account for 16% of maternal deaths in developed countries[1]. According to data in the United States in 2010, 12% of pregnancy-associated maternal deaths are due to preeclampsia and eclampsia[1]. The main characteristics of hypertensive disorders and fetal growth restriction in pregnancy are gestation-specific restructuring of spiral arteries and defects in trophoblastic invasion[3-5]. In normal implantation, highly invasive trophoblast cells migrate to the decidua and myometrium and invade the endothelium of spiral arteries along with the muscularis tunica media. Smooth muscle structures at the distal part of uterine spiral arteries disappear. Terminal branches of the uterine artery transform into vessels that bear high capacity and low resistance, and provide the blood flow needed for development of the placenta[6,7]. Although gestation-specific restructuring of the spiral arteries begins at the end of the first trimester and is completed by the 18-20th weeks, it is not known when trophoblastic invasion is terminated. Although they infiltrate the decidual spiral arteries, cytotrophoblasts cannot penetrate into the myometrium and pseudovasculogenesis does not occur[8,9]. This in turn leads to undesirable conditions such as placental hypoperfusion, placental infarction and atherosclerosis, fetal demise during the second trimester, placental abruption, preeclampsia, intrauterine growth restriction (IUGR), preterm labor, and premature rupture of membranes[1,10,11]. Invasion of spiral arteries by trophoblasts, release of special matrix metalloproteinases, and embodiment of the extracellular matrix (ECM) structure are necessary[12]. ECM has an active role in

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regulating cellular activity and behaviors such as shaping the cell, differentiation, division and programmed cell death. Matrix metalloproteinases are a member of the *ADAM* and *ADAMTS* zinc-dependent proteinases family. *ADAMTS* degrade molecules that act on regulation of the tissue microenvironment. Some of these molecules belong to the ECM (collagen, proteoglycan, and many other glycoproteins), and others do not (receptors, growth factors, and cytokines). It was shown that spiral artery invasion was limited in preeclampsia (Figure 1).

Changes in the ECM in the placentas and umbilical cords of the pregnant women with preeclampsia are different than those in normal pregnancies; however, the etiology is not yet clear[13-15]. The roles of cellular adhesion molecules, angiogenic proteins, and the inflammation system on microvascular dysfunction are undeniable in patients with preeclampsia[16]. Impairment of trophoblastic cell differentiation accounts for the inability of spiral arteries to invade into trophoblasts. Cytokines, adhesion molecules, ECM metalloproteinases, and class 1b major histocompatibility complex molecules released during trophoblastic invasion of endothelial cells and changes in HLA-G expression act on trophoblast differentiation[17,18].

Preeclampsia can result in maternal complications such as eclampsia, edema, hypertensive encephalopathy, stroke, kidney and liver failure, liver rupture, retinal detachment, blindness, disseminated intravascular coagulation, and death[19]; and fetal outcomes such as IUGR, oligohydramnios, asphyxia, prematurity, preterm labor, and perinatal death. Studies on biological markers are needed in order to understand the etiology of this disease and predict preeclampsia.

ADAMTS genes were discovered in 1997 and were first defined by Kuno et al.[20] as associated with colon cancer and inflammation. *ADAMTS* proteinases currently involve many physiologic and pathologic processes such as the those of the female reproductive system (Figure 2)[21,22].

ADAMTS play a role in events such as restructuring of tissue, coagulation, angiogenesis, degradation of the ECM and basal membrane, and tumoral cell invasion and metastasis[23,24]. *ADAMTS* should be expressed, and the ECM must be degraded and formed so that trophoblasts can invade maternal tissues and spiral arteries. Invasion of the ECM is provided by the release of complicated proteases. *ADAMTS*-1, -2, -4, -6, -7, -9, and -12 subtypes are expressed during the first trimester in human placenta[25]. In addition, *ADAMTS*-1, -4, -5, -6, -7, -9, and -10 mRNA expressions were detected in term placenta[26-30]. Therefore, it is important to interpret the molecular organization and function of *ADAMTS*.

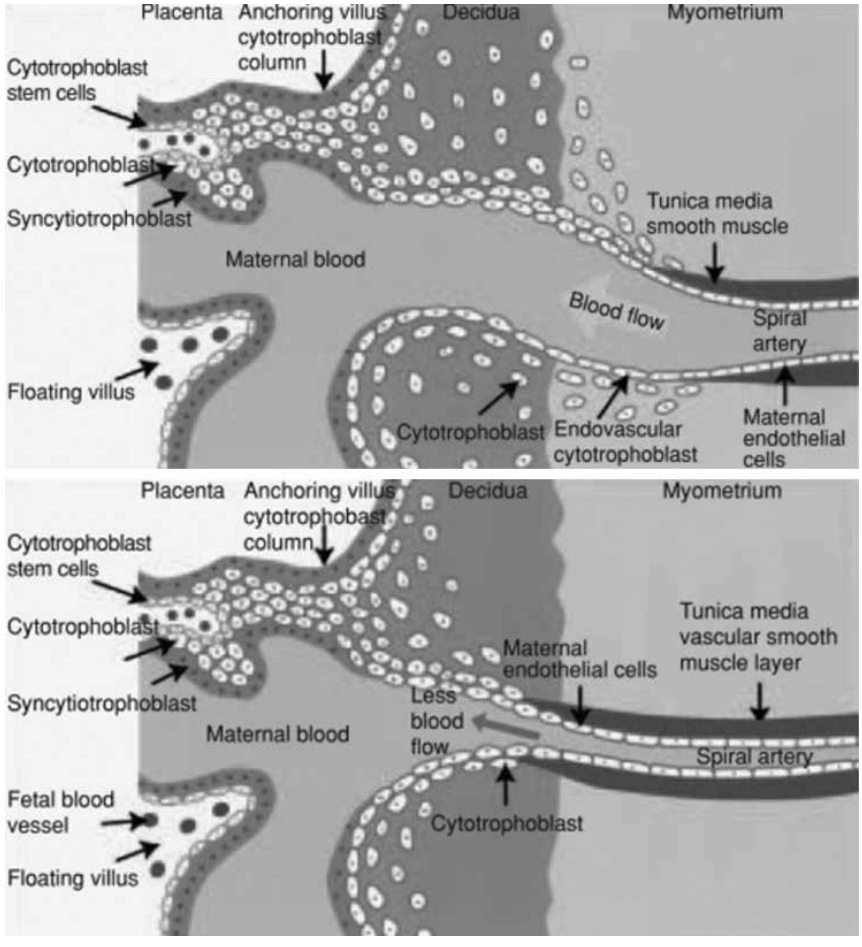

Figure 1. Normal placentation-pseudovasculogenesis (upper panel) and abnormal placentation in preeclampsia (lower panel)[11]

ADAM-12 is among factors that predict preeclampsia[1]. One of two types of ADAM-12 is secreted (ADAM-12s), which interferes with the function of insulin-like growth factor-binding protein 3 (IGFBP-3) and IGFBP-5, which in turn leads to the development of preeclampsia[31]. The difference between *ADAMTS* and *ADAM* is the thrombospondin (TSP) portion, which resides at the molecular level. TSP is the ECM adhesion glycoprotein secreted from thrombocytes and is an angiogenesis inhibitor[32]. *ADAMTS-12* is expressed in precedence by extravillous trophoblasts as compared with other ADAMTS[33]. Independent from the proteolytic activity of the enzyme, loss or decrease of *ADAMTS-12* function diminishes the trophoblastic invasion. *ADAMTS-12* regulates the cell invasion by regulating the avβ3 integrin heterodimer function and expression, and controls the trophoblast invasion by affecting the in vitro level of *ADAMTS-12*-transforming growth factor-β1 and interleukin-1β[33]. As a result, compared with other *ADAMTS*, *ADAMTS-12* is secreted in precedence from the placental tissues and increases the invasion of trophoblasts. Deficiency of *ADAMTS* enzymes leads to several pregnancy complications, mainly preeclampsia. Eda Gokdemir et al.[34] provided evidence that *ADAMTS-12* levels were significantly decreased in the serum of patients with preeclampsia. Deficiency of *ADAMTS-12* may cause defective trophoblast differentiation, abnormal remodeling of spiral arteries, and abnormal development of the placenta, which induces preeclampsia. Thus, *ADAMTS* proteinases play crucial roles in a variety of normal and pathophysiologic processes of placentation (Figure 3).

Daglar et al.[35] studied placental levels of *ADAMTS-12* to determine whether levels of enzymes differed among early-onset and late-onset severe preeclampsia. Early-onset preeclampsia was more likely associated with placental factors in impaired implantation and invasion than maternal factors. However, there were no significant differences in *ADAMTS-12* levels between the groups. Also, *ADAMTS* genes are associated with other diseases such as ovarian cancer, polycystic ovarian syndrome, and premature ovarian failure[36,37]. These genes play multiple roles in male and female fertility[38].

Result

Preeclampsia is one of the important complications of pregnancy. Early prediction of the disease is crucial in order to prevent maternal and fetal morbidity and mortality. A simple, cost-effective test performed in pregnant women with high-risk of developing preeclampsia would have significant effects on maternal and fetal morbidity and mortality of this disease. In *ADAMTS* function deficiency, impairments in differentiation of trophoblasts, invasion of spiral arteries, angiogenesis, and ECM restructuring ensue. Implantation failure can lead to abortion, preterm labor, early membrane rupture, pregnancy-associated hypertensive diseases, and preeclampsia.

Conclusion

ADAMTS genes are potential candidates in the pathophysiology of preeclampsia. Further studies are needed to determine whether these molecules can predict preeclampsia.

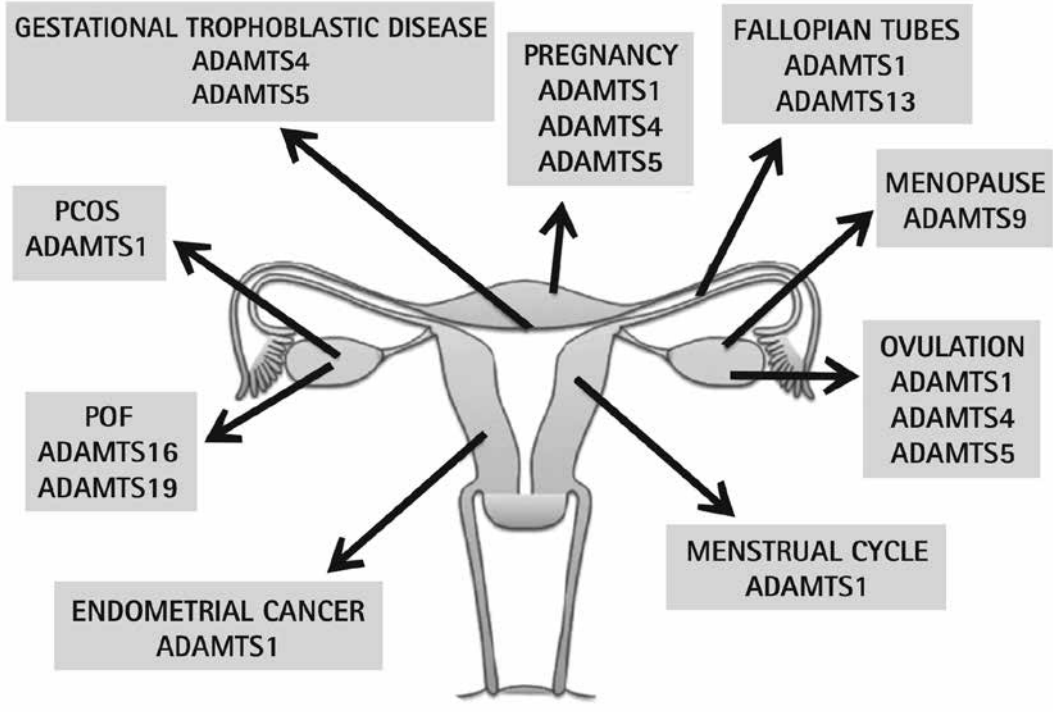

Figure 2. The role of the *ADAMTS*: A new biological marker candidates in physiological and pathological processes in female reproductive system[22]

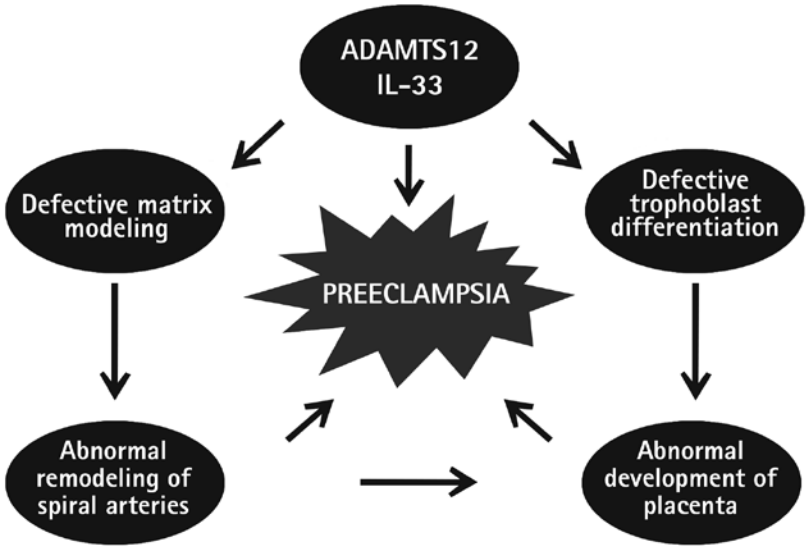

Figure 3. Deficiency of *ADAMTS-12* may cause defective trophoblast differentiation and matrix reshaping, abnormal remodeling of spiral arteries and finally abnormal development of the placenta that induce preeclampsia[34]

IL: Interleukin

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İrem Eda Gökdemir, Concept: İrem Eda Gökdemir, Buğra Çoşkun, Design: Buğra Çoşkun, Data Collection or Processing: Özlem Evliyaoğlu, Analysis or Interpretation: İrem Eda Gökdemir, Özlem Evliyaoğlu, Literature Search: İrem Eda Gökdemir, Özlem Evliyaoğlu, Writing: İrem Eda Gökdemir, Buğra Çoşkun.

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Case Report / Olgu Sunumu

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Clitoral keloids after female genital mutilation/cutting

Kadın genital sakatlama/kesme sonrası klitoral keloid

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Abstract

We aimed to describe the presentation of long-term complications of female genital mutilation/cutting and the surgical management of clitoral keloids secondary to female genital mutilation/cutting. Twenty-seven women who underwent surgery because of clitoral keloid between May 2014 and September 2015 in Sudan Nyala Turkish Hospital were evaluated in this retrospective descriptive case series study. The prevalence of type 1, type 2, and type 3 female genital mutilation/cutting were 3.7%, 22.2%, and 74.1%, respectively (type 1: 1/27, type 2: 6/27, and type 3: 20/27). All patients had long-term health problems (dysuria, chronic pelvic pain, vaginal discharge, and chronic pruritus) and sexual dysfunction. Keloids were removed by surgical excision. There were no postoperative complications in any patient. Although clitoral keloid lesions can be seen after any type of female genital mutilation/cutting, they usually develop after type 3 female genital mutilation/cutting. Most of these keloids were noticed after menarche. Keloids can be removed by surgical excision and this procedure can alleviate some long-term morbidities of female genital mutilation/cutting.

Keywords: Female genital mutilation, infibulation, circumcision, keloids, vulvar mass

Öz

Kadın genital sakatlama/kesme işleminin uzun dönem komplikasyonlarının tanımlanması ve işleme bağlı gelişen klitoral keloidlerin cerrahi eksizyon ile yönetimi. Mayıs 2014 ile Eylül 2015 tarihleri arasında Sudan Nyala Türk Hastanesi'nde klitoral keloid için opera edilen yirmi yedi hasta bu retrospektif tanımlayıcı olgu serisi çalışması için değerlendirilmiştir. Tip 1, tip 2 ve tip 3 prevalansı sırası ile 3,7%, 22,2% ve %74,1'dir (tip 1: 1/27, tip 2 6/27 ve tip 3 20/27). Tüm hastalarda uzun dönem sağlık problemleri ve seksüel disfonksiyon mevcuttur (dizuri, kronik pelvik ağrı, vajinal akıntı, kronik kaşıntı). Keloidler cerrahi eksizyon ile çıkarılmıştır. Postoperatif komplikasyon izlenmemiştir. Klitoral keloid kadın genital sakatlama/kesme işleminden sonra görülebilmesine rağmen genelde tip 3 ardından gelişmektedir. Keloidlerin çoğu menarş sonrası farkedilmektedir. Cerrahi eksizyon ile keloidler çıkarılabilir ve bu prosedür bazı uzun dönem morbiditeleri hafifletebilir.

Anahtar Kelimeler: Kadın genital sakatlama, infibulasyon, sünnet, keloidler, vulvar kitle

Introduction

Female genital mutilation/cutting (FGM/C) is the medically unnecessary modification of the female external genitalia for cultural reasons, which leads to dysfunction[1]. Historically, there have been references to its existence in Ancient Egypt; no one actually knows when, how or why FGM/C began. It is important to note that there have been no medically documented justifications that show the benefits of this practice for the purpose of enhancing woman's health. The procedure is named "female circumcision" in countries where it is practiced, but the term "FGM" is used in medical literature because of its harmful physical and psychological consequences[2]. It is often performed before adolescence. FGM/C is still known to be practiced in approximately 30 countries in Africa, in a few countries on the Arab Peninsula, among some communities in Asia, and among immigrants from these areas who have settled in Europe, Australia, and North America[2]. It affects approximately 100 million women worldwide and another 2 million procedures are performed each year[2,3].

Although the practice may show variations from one country to another, it is performed secretly because it is an illegal practice. Typically, the procedure is undertaken by a traditional circumciser using a sharp blade or razor, which is not sterilized, and without any anesthesia[4-6].

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The World Health Organization (WHO) has categorized FGM/C into four main groups:

Type 1: Amputation of the prepuce, sometimes along with partial or total removal of the clitoris (sunna).

Type 2: Amputation of the clitoris and part or all of the labia minora (excision).

Type 3: Amputation of the clitoris and labium minora. Cutting of the labium majora and sutured wound edges. A small opening is created to allow the flow of urine and menstrual blood (infibulation).

Type 4: A new category that encompasses a group of other operations on the external genitalia including piercing or incising the clitoris and/or labia, stretching the clitoris and/or labia, cauterization, scraping and/or cutting of the vagina, introduction of corrosive substances and herbs into the vagina, and similar practices[7].

Pain, hemorrhage, and infections are the three most important early complications. The long-term complications, especially as related to type 3 (infibulation) and these are infertility, vulvar mass-keloids, vesicovaginal fistula, and vesicourethral fistula, menstrual irregularities, chronic cystitis and dysuria, chronic pelvic pain, and dyspareunia. Maternal and fetal mortality and morbidity is also increased due to dystocia[8,9]. A number of studies also concluded that FGM/C had adverse effects on circumcised women's sexual life, leaving them feeling inadequate at intercourse[10,11]. This study describes the presentation of long- term complications of FGM/C and the surgical management of clitoral keloids.

Case Report

This was a retrospective study of the case notes on 27 patients with FGM/C who had clitoral masses and were referred to Sudan Nyala Turkish Hospital between May 2014 and September 2015. Gynecologic history, long-term complications of FGM/C, size of masses, and short-term complications after surgery were recorded. Surgical excision was performed for all patients by the same surgeon and all specimens were evaluated by the same pathologist.

Twenty-seven patients with clitoral mass were admitted to our gynecology outpatient clinic. All of the patients had a history of undergoing FGM/C. All masses were pre-diagnosed as clitoral keloid before surgery. The demographics and gynecologic history of the patients are shown in Table 1. The mean age of the patients were 18.07±7.16 years. FGM/C had been performed on all patients when they were aged between 7 to 9 years. The mean time between the procedure and notification of vulvar mass was 4.37±1.96 years. The sizes of the masses varied between 3 to 10 centimeters. The mean time between notification of the mass and referral to a gynecologist was 6.15±5.76 years.

The percentages of FGM/C types and symptoms are shown in Table 2. Most of the patients had type 3 FGM/C (n=20), which is the most destructive procedure and has the worst prognosis. The most common symptoms were dysuria with chronic cystitis and dyspareunia. All patients had at least two long-term health problems.

Surgical excision was performed for all patients. There were no early complications recorded in any of the patients. Pathologically all masses were reported as keloid. Pictures of one patient before and after the surgery are shown in Figures 1 and 2.

Discussion

Currently, over 100 million women throughout the world have been subjected to the practice of FGM/C. Likewise, 66.000 women in the United Kingdom and 50.000 women in France have been reported[12]. The age at which girls undergo FGM/C is mostly before 12 years[1,2,7]. In our study, all patients underwent FGM/C between the ages of 7 and 9 years.

FGM/C is accepted as an assault on the human rights of women by the WHO because the practice deprives women of their rights to experience their sexuality. Its detrimental psychological and psychosexual lifelong effects on women's sexual life have

Table 1. The demographics and gynecologic history of the patients

	Range	Mean ± SD
Age (years)	10-39	18.07±7.16
Gravidity	0-3	0.59±0.79
Age of menarche	11-14	12±0.93
Age of FGM/C	7-9	7.56±0.57
Age of keloid notification	9-17	11.93±1.85
Time between FGM/C and keloid notification	2-10	4.37±1.96
Time between keloid notification and referral to hospital	0-24	6.15±5.76

FGM/C: Female genital mutilation/cutting, SD: Standard deviation

Table 2. Percentages and numbers of female genital mutilation/cutting types and symptoms

Type	Number of patients	Percentage
Type 1	1	3.7
Type 2	6	22.2
Type 3	20	74.1
Symptom		
Dysuria	17	63
Dyspareunia	14	52
Pruritus	10	37
Chronic pelvic pain	7	26
Infertility	3	11

been examined in many studies. The psychotherapist and social activist Leila Hussein's case can be given to show the seriousness of this non-medical practice. In her report to the Guardian, she stated that she recalled every single detail: She was cut when she was seven years old, four women held her down, she felt every single cut, and she screamed so much that she fainted[13]. Girls who have not been circumcised are considered sexually active and labeled as "ghalfa," which is used for a woman who is sexually free and not respectful, who has the potential not to show fidelity to her family; as such these girls would be a target for abuse in their schools and social environments[12]. In order to protect their daughters from this kind of abuse, families choose to have their daughters circumcised for concerns of virginity when their daughters marry.

A significant number of children undergo FGM/C when under 1 year of age, which concurs with the global trend of FGM/C occurring at an increasingly younger age. This reduces the chance of the child remembering or being aware that the practice has taken place, thus reducing the chances of presenting to a physician[14]. In our study, all patients were aged between 7 to 9 years when FGM/C was performed.

Figure 1. Vulvar mass before surgery

Figure 2. After surgery

The dermatologic findings of FGM/C have been extensively reported in case reports and include keloids, epidermoid cysts, clitoral neuromas, and scarification. Women may delay treatment of keloids in the genital region for years because of embarrassment or fear of surgical options. Large keloids can contribute to obstetric complications[15]. We found that the mean time between notification of keloid and referral to a gynecologist was 6.15±5.76 years; this delay was more than ten years in six patients.

Allah et al.[16] performed surgical excision for 149 patients with keloids. The recurrence rate was 100%. The authors concluded that keloids were not homogeneous biologic entities and were related with increased immunologic factors. The best prevention is to avoid the scar itself[16]. Gurunluoglu et al.[17] reported a case of clitoral keloid that developed after a traumatic laceration. The keloid was treated with surgical excision, followed by silastic sheet application for six months. The sizes of keloid lesions were between 3 to 10 centimeters in our study. We performed surgical excision for all patients. There were no early complications recorded in any patients, but we did not have results for long-term follow-up.

Women with FGM/C have a significantly higher prevalence of long-term health problems such as dysmenorrhea, vulvar or vaginal pain, problems related to anomalous healing (e.g., fibrosis, keloid, synechia), and sexual dysfunction. They are also much more likely to suffer complications during delivery (perineal tear, obstructed labor, episiotomy, cesarean, stillbirth), and complications associated with anomalous healing. Similarly, newborns were found more likely to suffer complications such as fetal distress and caput of the fetal head[18]. In our study, the patients' most common symptoms were dysuria, dyspareunia, and pruritus. All case notes were obtained from the gynecology clinic; therefore, we had no data about obstetric complications. Despite prohibition, FGM/C is performed on girls illegally. These women have significantly higher prevalence of long-term health problems related to the genitourinary system. In cases of vulvar mass, keloid development secondary to FGM/C should be considered for immigrant patients. Keloids can be removed by surgical excision and this procedure can alleviate some long-term morbidities of FGM/C.

Ethics

Informed Consent: Consent form was filled out by all participants.
Peer-review: External and Internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ertuğrul Gazi Özbey, Özer Birge, Concept: Murat Akbaş, Özer Birge, Design: Murat Akbaş, Özer Birge, Data Collection or Processing: Ertuğrul Gazi Özbey, Özer Birge, Analysis or Interpretation: Murat Akbaş, Mehmet Adıyeke, Literature Search: Murat Akbaş, Özer Birge, Writing: Murat Akbaş.
Conflict of Interest: No conflict of interest was declared by the authors.

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Case Report / Olgu Sunumu

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Prenatal diagnosis of pectus excavatum

Pektus ekskavatumun prenatal tanısı

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Abstract

Pectus excavatum (PE) is the depression of the lower part of manubrium sterni and xiphoid process. The main problem of PE depends on the cardiopulmonary morbidity caused by the narrowing of the thoracic space. To date, prenatal diagnosis of this deformity has been reported only once and was associated with Down syndrome. We present another case which we diagnosed as PE during a second-trimester fetal anatomic scan. The pectus severity index is used for these patients in postnatal life; however, prenatal adaption of this index is reported for the first time in our case.
Keywords: Funnel chest, prenatal diagnosis, ultrasonography, prenatal

Öz

Pektus ekskavatum (PE) manubrium sterninin alt kısmının ve ksifoid çıkıntının içe doğru çöküntüsü olarak tanımlanır. PE'li hastaların esas problemi torasik boşluğun daralmasına bağlı gelişen kardiyopulmoner morbiditedir. Günümüze kadar bu deformitenin prenatal tanısı sadece bir kez ve Down sendromu ile ilişkili olarak bildirilmiştir. Biz, ikinci trimester fetal anatomik tarama sırasında tespit ettiğimiz bir diğer olguyu sunuyoruz. Pektus şiddeti indeksi, bu hastalar için postnatal dönemde kullanılan bir indekstir; fakat bunun prenatal döneme uyarlanması ilk kez bizim olgumuzda gerçekleştirildi.
Anahtar Kelimeler: Çukur göğüs, prenatal tanı, ultrasonografi, prenatal

Introduction

Pectus excavatum (PE) is the depression of the lower part of manubrium sterni and xiphoid process. It is the most common anterior chest wall deformity. It's incidence is 1 in 400 to 1.000 live births and it is three to five times more common in males[1]. PE is usually sporadic but can also be associated with connective tissue disorders, such as Marfan syndrome and Ehlers-Danlos syndrome, neuromuscular disease, and a variety of other genetic conditions, including Noonan syndrome and Turner syndrome.

The main problem of PE depends on the cardiopulmonary morbidity caused by the narrowing of the thoracic space. The severity of the chest wall deformity determines the morbidity. Another problem with PE is the psychosocial problems caused by the cosmetic concerns.

One third of PE patients present during infancy[2]. Spontaneous regression is rare and progression may continue until the end of adolescence[3]. The main symptoms of these patients are exertional intolerance, chest pain, and shortness of breath. Respiratory problems may even begin during infancy.

Until now, prenatal diagnosis of this deformity has been reported only once by Salamanca et al.[4] in two patients who postnatally diagnosed as having Down syndrome. In this report, we present another case which we diagnosed as PE during a second-trimester fetal anatomic scan.

Case Report

A pregnant woman aged 35 years presented during her 23rd week of gestation for a routine fetal anatomic scan. Her medical history was not significant for any clinical condition. She had a healthy boy aged 11 years delivered by cesarean section. The ultrasound examination was performed using a Voluson 730 Pro with RAB2-5L 3D abdominal transducer (2-5 MHz) probe. Fetal biometric measures were compatible with the gestational age. The fetus had a normal anatomic scan except for the depression at the lower part of the sternum. The depression at this level was seen in both the transverse and sagittal sections of the lower thorax (Figure 1). The defect did not deteriorate the cardiac functions of the fetus. Pectus severity index (PSI) as adopted from postnatal method was calculated as 1.44 (Figure 1). There was no family history for any anterior chest wall deformity. The patient delivered a 3.100 g male baby during the 39th week of gestation by cesarean section with an Apgar score of 9/10. Postnatal examination confirmed the diagnosis of PE and he

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had no cardiopulmonary complications during the two-year follow-up period (Figure 2). The child was otherwise healthy. Therefore, surgical correction of the deformity was postponed until after the end of adolescence.

Discussion

PE is an anterior chest wall deformity that primarily compromises cardiopulmonary functions in severe cases. However, cosmetic problems are the major problem for most patients. Currently, surgery is the only treatment approach for these patients. Severe chest wall restriction could initiate symptoms during infancy and may require surgical treatment during this period. For other patients, surgery is usually postponed until the end of adolescence, because the deformity may worsen during the growth spurt of adolescence.

Severity of PE is defined by PSI, which is measured using a computerized tomography scan of the thorax[5]. PSI is the ratio of the lateral diameter of the chest to the distance between the sternum and spine at the point of maximal depression[5].

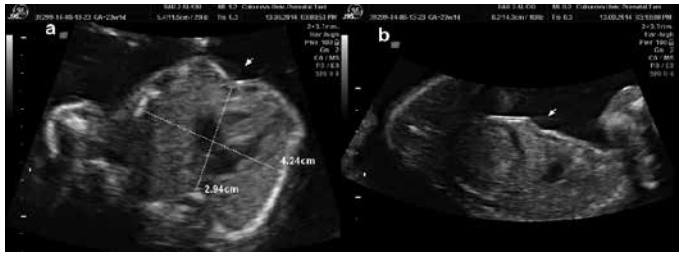

Figure 1. Ultrasonographic images of pectus excavatum, a) Axial thoracic section, pectus severity index is calculated by the ratio of the lateral diameter of the chest to the distance between the sternum and spine at the point of maximal depression (pectus severity index: 4.24 cm/2.94 cm=1.44), b) Sagittal thoracic section (arrows indicate the defect)

Figure 2. Postnatal photograph of the child with pectus excavatum

Surgery is offered to patients with a PSI of >3.25[5]. Prenatal adaption of this index is reported for the first time in our case. The PSI of our fetus (1.44) was consistent with good prognosis (PSI<3.25), which can be defined as deferability of surgery at least until the end of adolescence. Other tests needed for these patients are electrocardiography, echocardiography, and exercise tests in order to establish preoperative cardiopulmonary functions.

To the best of our knowledge, prenatal diagnosis of PE has been reported only once in the literature, in 1992[4]. In that report, two cases were described and both were later diagnosed as having Down syndrome, even though children with Down syndrome rarely have PE. In our case, PE was not associated with any genetic syndrome like Down, Turner or Noonan. Routine karyotyping may not be necessary for prenatally-diagnosed cases. Congenital cardiac anomalies (atrial/ventricular septal defects, partial atrioventricular septal defects), cardiac malpositioning or pericardial effusion are associated with PE[6]. Therefore, these fetuses should be examined thoroughly for any cardiac anomaly.

Consequently, chest wall examination should be incorporated into the routine fetal anatomic scan during the second trimester. Accompanying abnormal findings may require karyotyping. Patients should be counseled that this is rarely associated with genetic syndromes and prognosis depends mainly on the severity of the defect and cardiopulmonary complications it causes. PSI might be a promising marker for determining the prognosis of such fetuses if it can be supported by other studies.

Ethics

Informed Consent: It was taken from the patient.
Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Cihan Çetin, Concept: Cihan Çetin, Selim Büyükkurt, Cansun Demir, Design: Cihan Çetin, Mete Sucu, Mehmet Özsürmeli, Cansun Demir, Data Collection or Processing: Cihan Çetin, Analysis or Interpretation: Cihan Çetin, Selim Büyükkurt, Mete Sucu, Literature Search: Cihan Çetin, Mete Sucu, Mehmet Özsürmeli, Cansun Demir, Writing: Cihan Çetin, Selim Büyükkurt, Mehmet Özsürmeli.

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

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Case Report / Olgu Sunumu

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Placental, hepatic, and supraclavicular lymph node metastasis in pancreatic adenocarcinoma during pregnancy: A case report

Gebelikte plasental, hepatik ve supraklaviküler lenf nodu metastazı ile giden pankreatik adenokarsinom: Olgu sunumu

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Abstract

The occurrence of coexisting cancer in pregnant women is not a common phenomenon. It complicates approximately 1 in 1000 to 1500 pregnancies. We present a multiparous woman aged 27 years in her 28th week of pregnancy who was admitted to our clinic with right upper quadrant pain and was finally revealed to have multiple metastatic pancreatic adenocarcinoma. To the best of our knowledge, this is the first documented case of pancreatic adenocarcinoma to metastasize both to the placenta and multiple maternal sites (liver, supraclavicular, para-aortic lymph nodes) in a pregnant patient. Unpredictable metastases to the placenta may be encountered and may even lead to definitive diagnosis, as in our case. Therefore, the placenta in any patient with known malignancy should be sent for pathologic evaluation.

Keywords: Pancreatic carcinoma, malignancy, pregnancy

Öz

Gebeliğe kanserin eşlik etmesi çok sık rastlanan bir durum değildir. Yaklaşık gebeliklerin 1/1000 ile 1/1500'ünü komplike etmektedir. Çalışmamızda 27 yaşında, 28 haftalık gebeliği bulunan, sağ üst kadran ağrısı ile kliniğimize başvuran ve sonuçlarında multipl metastazı olan pankreas adenokarsinomu saptanan olgu sunulmaktadır. Bizim bilgimize göre bu olgu hem plasenta hem de maternal multipl odağa metastaz yapan (karaciğer, supraklaviküler, paraaortik lenf nodları) ilk dökümente edilen olgudur. Plasentaya bizim olgumuzda olduğu gibi beklenmeyen metastazlar olabilir ve kesin tanıyı koymamızı sağlayabilir. Bu yüzden malignitesi bilinen her hastada plasenta patolojik incelemeye gönderilmelidir.

Anahtar Kelimeler: Pankreas karsinomu, malignite, gebelik

Introduction

The occurrence of coexisting cancer in pregnant women is not a common phenomenon. It complicates approximately 1 in 1.000 to 1.500 pregnancies[1]. It is estimated that about 3.500 new cases of cancer are diagnosed annually in pregnant women in the United States of America, which corresponds to 1 case for every 1.000 gestations[2]. The most frequently diagnosed malignancies in pregnancy are breast cancer, cervical cancer, malignant melanoma, and lymphomas, respectively[3]. The most common tumor that metastasizes to the fetus or placenta is malignant melanoma, which accounts for 30% of all pregnancy-associated tumors[4]. The second most frequently metastasizing malignancies are leukemia and lymphoma, followed by carcinoma of the breast and lung[4]. Herein, we present a multiparous woman aged 27 years in her 28th week of pregnancy who was admitted to our clinic with right upper quadrant pain and was finally revealed to have multiple metastatic pancreatic adenocarcinoma.

Case Report

A multiparous patient aged 27 years in her 26th week of gestation presented with right upper quadrant pain, nausea, and vomiting. The patient was admitted to the hospital with a preliminary diagnosis of acute cholecystitis. Murphy's sign

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was positive. There were no signs of acute peritoneal irritation and she was initially managed with a nil-by-mouth status, intravenous hydration, and antispasmodic medication for abdominal cramps. She had a serum indirect bilirubin titre of 0.7 mg/dL (direct 0.2 mg/dL), and alkaline phosphatase titre of 123 u/L. Serology against viral hepatitis antigens were all negative. Levels of cancer antigen (Ca) 19-9, Ca 125, and alpha-fetoprotein tumor markers were all elevated to >2.064 U/mL, 985 U/mL, and 45 ng/mL respectively. Obstetric ultrasonography revealed an intrauterine male fetus with normal biometric measurements and biophysical profile scores. Right upper-quadrant abdominal ultrasound revealed a normal gallbladder, no dilatation of the common bile duct, and no periportal mesenteric pathologic lymphadenopathy. However, cervical ultrasound revealed bilateral cervical and left supraclavicular conglomerate lymphadenopathy. Supracervical lymph node excisional biopsy was performed. The pathologic diagnosis was reported to be anaplastic carcinoma, possibly originating from the gastrointestinal tract, gallbladder or pancreas. Due to relatively advanced gestational age of the fetus and poor prognosis of the mother if left untreated, corticosteroids were administered to enhance fetal lung maturity and cesarean section was performed at 28 weeks to deliver a 1.000-g male fetus with Apgar scores of 6-8, 1-5 minutes. The neonate was transferred to the neonatal intensive care unit but died of sepsis 30 days post-partum. The family refused autopsy of the neonate and mother; therefore, no pathologic condition could be observed in the neonate.

Intraperitoneal massive ascites was observed perioperatively, a sample of which was sent to pathologic examination together with the placenta. Pathology revealed malignancy-positive ascites cytology and metastasis of pancreatic adenocarcinoma to the placenta (Figure 1). Postoperatively, the patient was referred to medical oncology. Abdominopelvic computerized tomography (CT) demonstrated cervical, mediastinal, hilar, mesenteric, inguinal, parailiac and para-aortic multiple lymphadenopathies. The pancreatic head was impossible to visualize because of massive lymphadenopathy and a metastatic 6x7 cm mass was observed in the caudal lobe of liver (Figure 2). The patient experienced cardiac arrest during the immediate post CT period but returned to sinus rhythm after proper resuscitation. However, she succumbed to her cancer after two weeks. In this case, no familial cancer syndromes, cigarette smoking, genetic tendency or diabetes mellitus were identified, and there were no known toxic exposure.

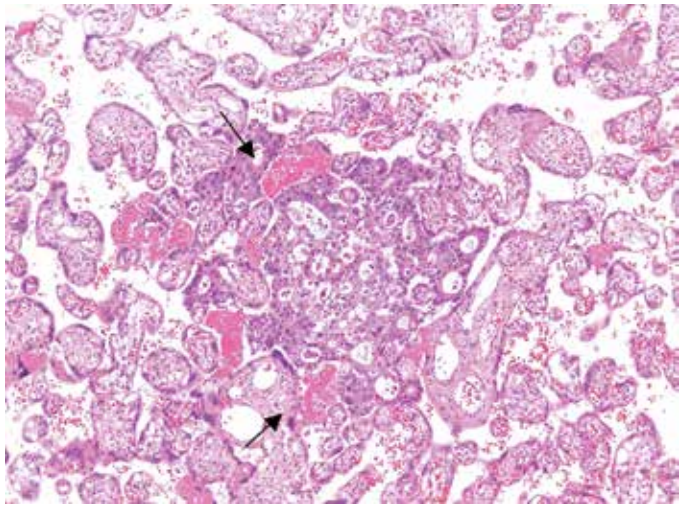

Figure 1. Small cribriform-forming atypical tumoral cells in placental chorionic villi

Discussion

Cancer-complicated pregnancy is a rare coexistence and presents in approximately 1 in 1.000 to 1.500 pregnancies. Among those, pancreatic cancer is even rarer in a pregnant patient[5]. Risk factors for pancreatic cancer include cigarette smoking, advanced age, male sex, African-American ethnicity, family history, genetic background/tendency, diabetes mellitus, and chronic pancreatitis[5]. The most common presenting symptoms in patients with pancreatic cancer are abdominal and epigastric pain, dark urine, jaundice, nausea, back pain, diarrhoea, and vomiting[6]. Ultrasound and magnetic resonance imaging are the mainstays of imaging during pregnancy. Other options may be used if necessary. Fetal outcomes are generally very good, with iatrogenic prematurity being the most common complication. Surgical resection followed by adjuvant therapy is the standard of care for early-stage disease. Surgical intervention in the first trimester carries a risk of spontaneous abortion, and the size of the uterus is prohibitive in the third trimester; therefore, the second trimester is the ideal time for

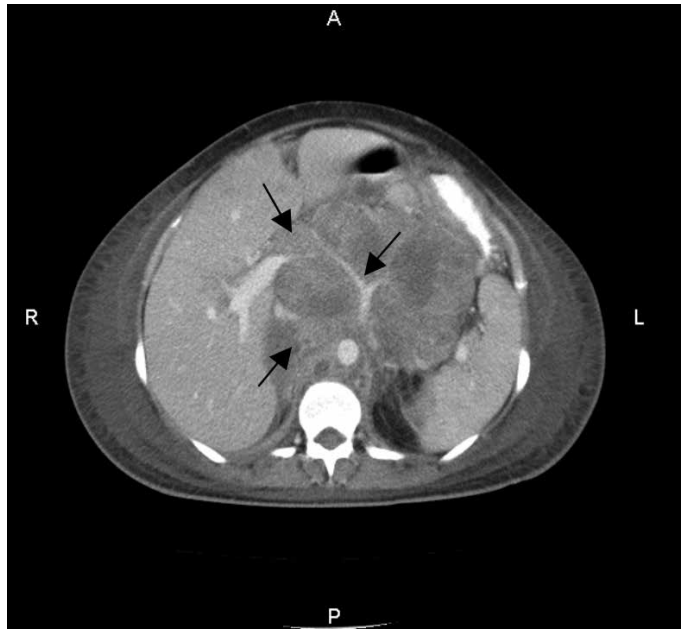

Figure 2. Axial contrast-enhanced computed tomographic image reveals a 13x11 cm mass located between the liver and para-aortic area

tumor resection[7]. Only 24 cases of pancreatic adenocarcinoma diagnosed antepartum have been described in the literature. The gestational age of the patients range from 4 to 36 weeks[8]. Khatsiev et al.[9] reported a case of pancreatic adenocarcinoma in a pregnant woman aged 29 years with situs inversus in the first trimester. Patient underwent pancreatoduodenectomy following abortion. Onuma et al.[10] described a woman at 34 weeks gestation who presented with uterine contractions and a large retroperitoneal mass. Pancreatic cancer was detected after emergency cesarean delivery, and pancreatoduodenectomy was performed. Kakoza et al.[7] described a woman who was diagnosed as having cholecystitis and gallstone pancreatitis at 24 weeks gestation. Our patient presented as having acute cholecystitis.

Vertical transmission of cancer is exceptionally rare, although maternal cells do reach the fetus. From 1866 to 1999, 58 cases of documented maternal malignancy metastatic to the placenta and fetus were reported in the English literature[11]. The most common tumor that metastasizes to the fetus or placenta is malignant melanoma, which accounts for 30% of all pregnancy-associated tumors. The second most frequently metastasizing malignancies are leukemia and lymphoma, followed by carcinoma of the breast and lung[12]. The liver and peritoneal cavities are the most common sites of metastases in pancreatic cancer. Marci et al reported a case of pancreatic carcinoma in a women at 35 weeks gestation with multiple liver metastasis[13]. Metastases to the placenta and supraclavicular lymph nodes are extremely unusual. A review of the literature revealed only six cases of supraclavicular metastases of pancreatic adenocarcinoma[14]. Al-Adnani et al.[15] reported a case of maternal pancreatic carcinoma metastatic to the placenta. In our case, placental and multiple maternal metastases were documented. Metastatic disease to the fetus is incredibly rare and has been documented only in melanoma, leukemia, and lymphoma.

To the best of our knowledge, this is the first documented case of a pancreatic adenocarcinoma to metastasize both to the placenta and multiple maternal sites (liver, supraclavicular, para-aortic lymph nodes) in a pregnant patient. Unpredictable metastases to the placenta may be encountered and may even lead to definitive diagnosis, as in our case. Therefore, the placenta in any patient with known malignancy should be sent for pathologic evaluation. Moreover, optimal care of a pregnant woman with metastatic cancer requires a prompt multidisciplinary approach, with special focus on maternal wellbeing and survival, while trying to minimize the negative impact on the fetus secondarily.

Ethics

Informed Consent: Consent form was filled out by all participants.
Peer-review: Externally peer-reviewed.

Authorship Contributions

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Case Report / Olgu Sunumu

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Unusual uterine metastasis of invasive ductal carcinoma: A case report

İnvaziv duktal karsinomlu hastada beklenmeyen uterin metastaz olgusu

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Abstract

Metastatic carcinoma of the uterus usually originates from other genital sites. Extragenital metastases such as breast are rare. A woman aged 34 years with a history of breast cancer was referred to the gynecology outpatient clinic for routine follow-up. Diagnostic tests and gynecologic examination revealed a uterine mass, which was removed with laparotomy. The pathologic investigation revealed metastasis of invasive lobular breast cancer. Chemotherapy was given and the patient has been under follow-up for 3 years with normal imaging on comput-erized tomographic examination and positron-emission tomography-computerized tomographic. It should be kept in mind that patients with breast cancer who have received tamoxifen may develop primary endometrial cancers, and may also demonstrate uterine metastases. With successful treatment these patients can obtain dis-ease-free survival.
Keywords: Uterus, ductal carcinoma, metastasis

Öz

Uterusun metastatik kanserleri genellikle diğer genital sistemlerden kaynaklanmaktadır. Meme gibi genital bölge dışı bölgelerden metastaz çok nadirdir. Hikayesinde meme kanseri olan 34 yaşındaki kadın hasta olağan kontrol için polikliniğimize başvurdu. Jinekolojik muayene ve görüntüleme yöntemleri sonucu uterusta kitle bulundu ve laparotomi yapılarak kitle çıkarıldı. Patolojik inceleme invaziv duktal karsinom metastazı olduğunu ortaya çıkardı. Hastaya kemoterapi verildi ve 3 yıl kontrolleri sırasında pozitron emisyon tomografi + bilgisayarlı tomografi görüntülemeleri normal olarak bulundu. Tamoksifen tedavisi alan meme kanserli hastalarda sadece primer endometriyal kanser değil ayrıca bazen uterusa metastazın da gelişebileceği akılda tutulmalıdır. Başarılı bir tedavi ile bu hastalar nüks hastalık olmadan hayatta kalabilirler.
Anahtar Kelimeler: Uterus, duktal karsinom, metastaz

Introduction

Breast cancer usually spreads to the lungs, bone, liver, brain, gastrointestinal (GI) tract, peritoneum or retroperitoneum. Extramammarial metastasis of breast cancer such as in the uterus is rarely seen[1-4].

Invasive lobular carcinoma (ILC) differs from infiltrating ductal carcinoma (IDC) with respect to sites of metas-tasis. IDC metastases are frequently seen in the lung, bones, and liver. However, ILC's metastatic sites are GI peritoneum and the retroperitoneum[3,4].

ILC of the breast spreads to gynecologic organs more frequently than invasive ductal carcinoma[2,3]. Recurrence of breast cancer usually occurs during the first two years. The incidence of recurrence decreases over time; however, it never disappears completely[5]. In this report, we present a patient with recurrent metastatic invasive ductal breast carcinoma in the uterus 12 years after the initial diagnosis, with 3 years survival following successful treatment.

Case Report

A woman aged 34 years with a history of ductal carcinoma of the breast was referred to the gynecology outpatient clinic for routine follow-up. She had a history of left-sided total mastectomy and

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axillary lymph node dissection due to a malignant mass in her left breast 12 years ago. The histopathologic result was reported as invasive ductal carcinoma and the patient underwent 6 courses of taxotere, adriamycin, cyclophosphamide chemotherapy and 25 days of radiotherapy (a total dose of 5000 cGy) following the operation. Hormonotherapy with tamoxifen was given for five years owing to the positive (90%) estrogen and progesterone hormone receptors.

The current diagnostic tests and gynecologic examination revealed a 4.8x3.2 cm lesion that caused diffuse thickening of the uterine wall (Figure 1). She was referred to the gynecologic oncology department for further evaluation. An endometrial biopsy was performed to eliminate any endometrial pathology caused by tamoxifen treatment, which was found negative.

The mass on the uterine wall was removed under laparotomy. The pathologic investigation revealed metastasis of invasive ductal carcinoma of the breast. Breast carcinoma metastases in the myometrium were confirmed histopathologically and immunohistochemically (Figure 2). The results of the pathologic investigation were consulted with the medical oncology department and additional chemotherapy with gemcitabine and capecitabine (1-8/28 days) was given to the patient. The chemotherapy was completed and the patient has been under follow-up for 3 years with normal imaging on computerized tomographic (CT) examination and positron-emission tomography-CT (PET/CT).

Discussion

Metastases to the female genital tract from extragenital cancers are rare. Breasts and the GI tract are the most common sites of the primary tumor. Ovaries are most frequently affected by metastases, which account for 75.8%, followed by the vagina (13.4%), uterine corpus (4.7%), cervix (3,4%), vulva (2%), and salpinx (0.7%)[6]. Uterine metastases usually occur secondary to local lymphatic spread due to ovarian involvement and thus isolated uterine metastases from the extragenital tumors are rare and probably hematogenous. The initial symptoms of uterine metastasis depend on the anatomic involvement site. If the infiltration affects only the myometrium, patients may often be asymptomatic, as seen in our case[7].

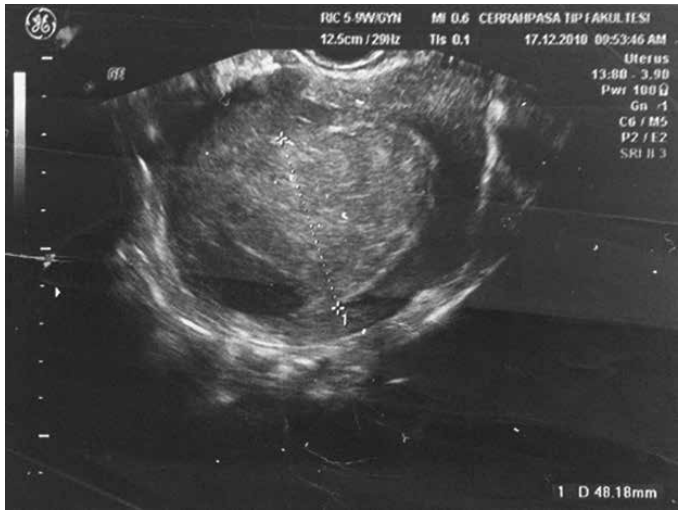

Figure 1. Ultrasound image of the uterine mass

To detect metastatic disease early, routine gynecologic follow-up examinations should always be performed, even in asymptomatic patients with breast cancer under tamoxifen therapy. Additionally, it is important to distinguish whether the uterine lesions are primary or metastatic because of the different treatment options. The uterus is an uncommon site for breast cancer metastasis. Nevertheless, most uterine metastases are found at autopsy[2].

Tamoxifen has played an essential role in the treatment of hormone receptor-positive breast cancers. Five years of treatment with tamoxifen can reduce the risk of both recurrence and mortality due to breast cancer by approximately 30%[7]. However, tamoxifen exerts a partial agonistic effect on the endometrium. Therefore, treatment with tamoxifen increases the incidence of endometrial hyperplasia, polyps, and endometrial neoplasms[8,9].

Precise diagnosis affects critical decision-making with regard to the treatment of the uterine cancer. A primary uterine tumor should be resected, whereas a metastatic uterine tumor should be treated with systemic therapy as the first choice[10,11]. In the present case, tamoxifen was used as an adjuvant hormone therapy with no additional surgical intervention.

Although there are few reports on the prognosis of patients with metastatic uterine tumors from breast cancer, most patients have been reported to have poor prognosis. However, given the limited number of reported cases, further studies are needed, along with a larger number of case reports to further

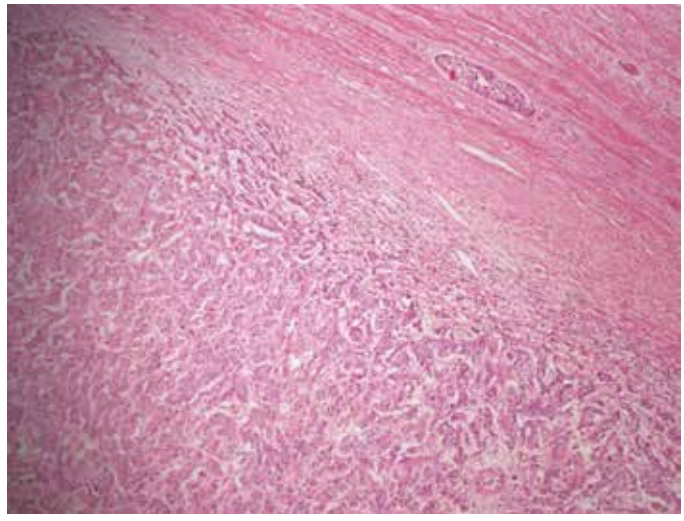

Figure 2. Pathologic examination of the excised material

Pathologic examination. Pathologic microscopic examination demonstrating malignant epithelial tumor cells; (Hematoxylin-Eosin, x100)

our understanding of the prognosis of these cancers, and to determine the best course of treatment[12]. There has been no recurrence in our patient for the last 3 years and this is the longest disease-free survival report in such cases.

Any patient with abnormal imaging should be evaluated for vaginal, cervical, and uterine pathology. As this case aptly demonstrates, negative endometrial biopsy should not reduce the concern for pathology or alter the examination of a patient with abnormal imaging.

This case demonstrates the importance of maintaining a broad differential diagnosis in patients with abnormal imaging in the setting of a history of breast cancer and tamoxifen use. While performing ultrasound examination, like with this patient, focusing on endometrial thickness, endometrial polyps or suspicion of endometrial neoplasm may cause suspicious findings to be missed, except endometrium. In addition, endometrial biopsy alone is not sufficient for a diagnosis, and may be misleading. Evaluation of symptoms with imaging remains essential in identifying the underlying pathology.

In conclusion, it should be kept in mind that patients with breast cancer who have received tamoxifen may develop primary endometrial cancers, and may also demonstrate uterine metastases.

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Ethics

Informed Consent: Consent form was filled out by all participants.
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Authorship Contributions

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