ISSN : 2149-9322
E-ISSN : 2149-9330

TURKISH JOURNAL OF OBSTETRICS AND GYNECOLOGY

September 2019 Volume: 16 Issue: 3 www.tjoddergisi.org

Clinical Investigations

TURKISH SOCIETY OF OBSTETRICS AND GYNECOLOGY

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Publisher Certificate Number:14521

Publication Date: September 2019
ISSN: 2149-9322 **E-ISSN:** 2149-9330
International scientific journal published quarterly.

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- All author name(s), institutional, corporate, or commercial affiliations, and up to two major degree(s).

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The precis is a one-sentence synopsis of no more than 30 words that describes the basic findings of the article. Precis sample can be seen below:

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· Conclusion: Directly supported by data, along with clinical implications.

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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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Describe the research methodology (the patients, experimental animals, material and controls, the methods and procedures utilized, and the statistical method(s) employed) in sufficient detail so that others could duplicate the work. Identify methods of statistical analysis and when appropriate, state the basis (including alpha and beta error estimates) for their selection. Cite any statistical software programs used in the text. Express p values to no more than two decimal places. Indicate your study's power to detect statistical difference.

Address "IRB" issues and participants informed consent as stated above, the complete name of the IRB should be provided in the manuscript. State the generic names of the drugs with the name and country of the manufactures.

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Present the detailed findings supported with statistical methods. Figures and tables should supplement, not duplicate the text; presentation of data in either one or the other will suffice. Authors should report

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outcome data as both absolute and relative effects since information presented this way is much more useful for clinicians. Actual numbers and percentages should be given in addition to odds ratios or relative risk. When appropriate, number needed to treat for benefits (NNTb) or harm (NNTh) should be supplied. Emphasize only your important observations; do not compare your observations with those of others. Such comparisons and comments are reserved for the discussion section.

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Case Reports

Clinical Investigation / Araştırma

DOI: 10.4274/tjod.galenos.2019.46244

Turk J Obstet Gynecol 2019;16:143-50

Effects of vitamin D supplementation on follicular development, gonadotropins and sex hormone concentrations, and insulin resistance in induced polycystic ovary syndrome

İndüklenmiş polikistik over sendromunda, D vitamin desteğinin, folliküler gelişim, gonadotropinler ve seks hormonu konsantrasyonları ve insülin direnci üzerindeki etkileri

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Abstract

Objective: Polycystic ovary syndrome (PCOS) as a reproductive disorder disturbs ovarian follicular development, vitamin D stimulated insulin activity, and sex hormone concentrations. This study aimed to examine the effects of vitamin D on ovarian follicular development, insulin resistance, and sex hormone changes in rats with induced PCOS.

Materials and Methods: Forty female Wistar rats were randomly divided into four groups: (1) control, (2) induced PCOS, (3) vitamin D-treated non-PCOS (sham group), (4) vitamin D treated PCOS groups. All rats were then sacrificed under anesthesia and ovarian tissue samples were evaluated histomorphometrically. Blood samples were collected for analyzing the serum concentrations of sex hormones and insulin resistance.

Results: The number of atretic follicles at different stages of development increased in the PCOS ovaries ($p<0.001$). Vitamin D treatment significantly increased the normality of follicles in rats with PCOS ($p<0.001$). The serum concentration of follicle stimulating hormone and the estradiol significantly increased in rats with PCOS, whereas the testosterone and luteinizing hormone concentrations, glucose, insulin, and insulin resistance concentrations significantly decreased during vitamin D treatment ($p<0.001$).

Conclusion: This study indicated that vitamin D treatment may protect ovarian tissue from the negative effect of PCOS by improving insulin activity and gonadotropin concentrations.

Keywords: Vitamin D, polycystic, ovary, gonadotropin

Öz

Amaç: Polikistik over sendromu (PKOS), bir üreme bozukluğu olarak, overlerde follikül gelişimini, D vitamin tarafından stimüle edilen insülin aktivitesini ve seks hormonu konsantrasyonlarını bozar. Bu çalışma, D vitamin'nin overlerde follikül gelişimi, insülin direnci ve seks hormonu değişiklikleri üzerindeki etkilerini, indüklenmiş PKOS'li sıçanlarda incelemektir.

Gereç ve Yöntemler: Kırk dişi Wistar sıçanı rastgele olarak 4 gruba ayrılmıştır: (1) kontrol, (2) indüklenmiş PKOS, (3) D vitamin-uygulanmış non-PKOS (sahte grup), (4) D vitamin uygulanmış PKOS grubu. Sonrasında, tüm sıçanlar anestezi altında sakrifiye edilmiş ve over doku örnekleri histomorfometrik olarak değerlendirilmiştir. Kan örnekleri, seks hormonlarının konsantrasyonlarının ve insülin direncinin analizi için toplanmıştır.

Bulgular: PKOS overlerinde çeşitli gelişim evrelerindeki atretik follikül sayısı artmıştır ($p<0,001$). Vitamin D verilmesi PKOS'li sıçanlardaki folliküllerin normalitesini önemli oranda artırmıştır ($p<0,001$). PKOS'li sıçanlarda, D vitamin uygulaması sırasında, follikül stimüle edici hormon ve östradiolün serum konsantrasyonları anlamlı oranda artarken, testesteron ve luteinizan hormon konsantrasyonları, glukoz, insülin ve insülin direnci konsantrasyonları anlamlı şekilde azalmıştır ($p<0,001$).

Sonuç: Bu çalışma, D vitamin uygulamasının insülin aktivitesini ve gonadotropin konsantrasyonlarını iyileştirerek, over dokusunu PKOS'nin negatif etkilerinden koruyabileceğini göstermiştir.

Anahtar Kelimeler: D Vitamin, polikistik, over, gonadotropin

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Received/Geliş Tarihi: 06.09.2018 **Accepted/Kabul Tarihi:** 09.06.2019

PRECIS: We have found that daily intake or injection vitamin D improves the symptoms of Polycystic ovary syndrome and also decreases body mass index and ultimately regulates and balances the sex hormones.

Introduction

Polycystic ovary syndrome (PCOS) is a type of endocrine disorder, characterized by disturbances of androgen secretion, which can result in the disruption of cyclicity and the induction of polycystic ovaries[1-3]. These conditions can disturb and block the follicular development and induce oligo/anovulation and infertility[3]. The majority of the available studies show that testosterone and luteinizing hormone (LH) concentrations are higher in patients with PCOS[4]. Aromatase activity stimulates granulosa cells to convert androgens to estrogens, resulting in a balance between androgens and estrogen productions. In contrast, the inhibition of aromatase activity in granulosa cells suppresses the conversion of testosterone to estrogen and reduces estradiol concentrations, leading to anovulation[5-7]. Moreover, the majority of patients with PCOS are at a higher risk of obesity and insulin resistance (IR)[8]. Some studies have established an association between vitamin D deficiency (concentration <50 nmoL/L), obesity, IR, and infertility in patients with PCOS and have identified vitamin D deficiency as the main factor contributing to hyperandrogenism[9-11]. Vitamin D entering the body is either in the ergocalciferol (D2) or cholecalciferol (D3) form. D2 is obtained from plants, and D3 is made in the cells of the epidermis. Vitamin D is then converted to 25-hydroxyvitamin D in the liver and 1.25 dihydroxyvitamin D (calcitriol) as the active form in the kidney[12]. Vitamin D is a steroid hormone that regulates numerous actions, including calcium, insulin, and phosphorus metabolism in different tissues of the body[13]. The vitamin D receptor is expressed in the ovary, endometrium, placenta and testis, suggesting that vitamin D plays a critical role in these tissues[14]. Previous studies have highlighted the role of vitamin D in female reproductive functions such as steroidogenesis, which can enhance granulosa cell proliferation, oocyte activation, ovulation, and follicular development[15-17]. Parikh et al.[18] demonstrated that vitamin D induced the production of progesterone, estrogen, and insulin-like growth factor-binding protein 1 in human ovarian cells. However, vitamin D deficiency is commonly found in women with PCOS, but the role of vitamin D deficiency in ovarian tissue structure and patients with PCOS is not yet entirely clear. Therefore, the aim of the current study was to investigate the effect of vitamin D on ovarian follicular morphology, follicular development, androgen concentrations, IR, and insulin activity in rats with PCOS.

Materials and Methods

Chemicals and experimental animals

All chemicals were purchased from Sigma-Aldrich, unless otherwise indicated. All methods and experiments were approved by The research protocol of this study was approved by Vice Chancellor for Research of Tabriz University of Medical Sciences and Ethics in Research Committee of Tabriz University of Medical Sciences, (under code number: TBZMED.REC.94/2-5/7). In this study, 40 healthy adult Wistar albino female rats aged 8 weeks and weighing 200±20 g were obtained from the Animal Care Center of Tabriz University of Medical Sciences. Rats were housed in a controlled cycle of 12 hours' light and 12 hours' darkness at temperatures of 24-24 °C with free access to water and food.

Experimental design

Forty female rats were randomly assigned to the following 4 treatment groups (n=10 for each group):

-Group 1: control group, rats were not injected,

-Group 2: induced PCOS groups, rats received estradiol valerate,

-Group 3: sham groups, rats received vitamin D (vitamin D treated non-PCOS group),

-Group 4: vitamin D treated PCOS group, rats were induced by estradiol valerate and then treated with vitamin D.

Evaluation of the sexual cycle

Estrous cycles were evaluated 1 week before the experiment and during the treatment between 8:00 a.m. and 10:00 a.m. The samples in the experimental group were examined daily[19]. The vaginal smears were dried and monitored under a light microscope at magnification of 400x, and then the relative frequencies of leukocytes, and cornified epithelial cells were calculated. The mice were evaluated regularly for 4-5 days for both control and experimental groups and all the study rats had a regular period before performing the experiment.

Polycystic ovary syndrome induction model

The injection site was sterilized and 2 mg/kg body weight (BW) single dose of E.V. (Aburaihan, Iran) was injected subcutaneously for 60 days. The induction of PCOS was verified by vaginal smears and histologic and serologic examination was performed for a period of 60 days[20].

Preparation and administration of vitamin D

Vitamin D was purchased from Abu Ravihan Company (Iran) and about 2 mg of vitamin D was dissolved in dimethyl sulfoxide solution under standard conditions (away from sunlight, humidity, and microbial conditions), and stored at -20 °C. The sham group and PCOS-induced rats were injected using 1 mg/kg of vitamin D subcutaneously for 14 days at 10:00 a.m. At the end of the treatment, the ovary and BWs of the rats were measured, and then 5 mL blood was withdrawn directly from the heart of the anesthetized rats. Blood samples were placed

into centrifuge tubes of 3000× g for 10 minutes and the plasma was collected and stored at -70 °C until required for hormonal analysis

Histopathologic observations

For histopathologic assessment, all rats were sacrificed by anesthesia and the ovaries were excised and immediately fixed in 4% (w/v) paraformaldehyde solution, dehydrated in concentrations of alcohol, cleared with xylene, embedded in paraffin wax, and tissue blocks were serially sectioned at 5 µm. The serial ovarian sections were stained with hematoxylin and eosin and viewed under a light microscope (Olympus, Japan). All follicles were classified as normal and atretic. The follicles were classified as normal if they had intact oocytes and a complete layer of granulosa cells or atretic if vacuolization and pyknotic nuclei were present in the granulosa cells and occasional shrinkage of oocytes was observed[21].

Histomorphometric analysis

The follicles were divided into the following four groups based on their developmental stages: (1) primordial follicles (oocytes of follicles surrounded by a layer of squamous or flattened granulosa cells); (2) primary follicles (oocytes surrounded by a single layer of cuboidal granulosa cells); (3) preantral follicles (oocytes surrounded by more than one layer of cuboidal granulosa cells with no antrum); and (4) antral follicles (oocytes surrounded by more than one layer of cuboidal granulosa cells with a visible antrum). The percentage of follicles at every stage per ovary was determined by counting the total number of follicles in sections. All follicles were counted when the nuclei of the oocytes were visualized and counting was repeated three times and averaged[22]. The number of corpora lutea (CL) and thickness of the granulosa cells, as well as the thecal cell in the ovaries of control and treated rats were evaluated.

Ovarian follicular viability

Different stages of ovarian follicles were mechanically isolated under a stereomicroscope (SZ-STS, Olympus, Tokyo, Japan) and were assessed through membrane-enclosed granulosa cells and central oocytes. Ovarian follicles were stained using 0.4% Trypan blue and detected using an inverted microscope (Olympus, Japan). The follicles were scored as viable if the oocytes and surrounding granulosa cells were stained and were assessed as degenerate follicles if the central oocytes and surrounding granulosa cells were not stained (Figure 1)[23].

Follicle stimulating hormone and luteinizing hormone and steroidal hormone measurement

The blood samples of anesthetized rats were collected and centrifuged at 3000 g for 10 min, and then the plasma of both the control and experimental groups was separated and stored at -70 °C for the measurement of follicle stimulating hormone (FSH) and LH concentrations and sex steroid hormones (such as testosterone, estrogen, and progesterone). The gonadotropin and sex hormones were measured using an enzyme-linked immunosorbent assay kit (Monobind Inc., USA) according to the manufacturer's instructions.

Glucose, insulin, lipid marker, and insulin resistance assays

The stored serum was used to measure glucose, insulin, and IR in the control and experimental groups. Plasma glucose and lipids concentrations were assayed using the Siemens Dimension MAX (Siemens Healthcare Diagnostics Inc.). Plasma insulin was evaluated using a magnetic affinity immunoassay (Insulin MPAIA Kit) according to the manufacturer's instructions. The homeostasis model assessment-IR (HOMA-IR) was calculated using the formula described by Matthews et al.[24].

Statistical Analysis

To determine the effects of vitamin D supplementation on ovarian structures and androgen concentrations, we used mean ± standard deviation and one-way analysis of variance. All statistical analyses were performed using the SPSS version 16 software package. P values <0.05 were considered statistically significant.

Results

Body and ovary weights

The BW of rats with induced PCOS and treatment rats are shown in Table 1. In the PCOS group, both the BW and ovary weight were significantly increased by elevating abdominal fat tissue and increasing follicular fluid and ovarian stroma, respectively ($p<0.001$). Treatment with vitamin D in rats with PCOS for 14 days induced weight loss and significantly decreased ovarian weight compared with the non-treatment rats with PCOS ($p<0.001$).

Histopathologic observations of ovarian tissue

Histologic observation in the control and vitamin D-treated non-PCOS rats indicated that ovarian follicles at different stages of development were normal and intact. In contrast, the preantral

Table 1. Effect of vitamin D supplementation on body weight and ovary weight in rats with polycystic ovary syndrome

Groups	Control	PCOS	Vitamin D	PCOS + Vitamin D
Ovarian weight (mg)	14.60±1.20	19.78±0.52^{a***}	12.23±0.81	13.41±0.70
Body weight (g)	197.52±11.35	223.45±7.12^{a***}	190.92±8.35	195.81±11.55

PCOS: Polycystic ovary syndrome, Vitamin D, ^{a}shows a significant difference between PCOS and other groups, $^{***}p<0.001$
Comparisons among groups were performed using one-way ANOVA. All data are presented as mean ± standard deviation

(Figure 2a) and antral follicles (Figure 2b) showed more signs of degeneration, including granulosa cell pyknosis (Figure 2b), thin granulosa cells layer (Figure 2c), numerous atretic follicles, thickened theca layer, and absence of CL in PCOS rats (estradiol valerate-administrated group). The ovarian follicles were well developed in vitamin D-treated rats and normal granulosa cells and theca cells layer were observed (Figure 3a, b), and CL were defined (Figure 3c), indicating that the ovarian follicles were matured (folliculogenesis) and ovulated in rats treated with vitamin D.

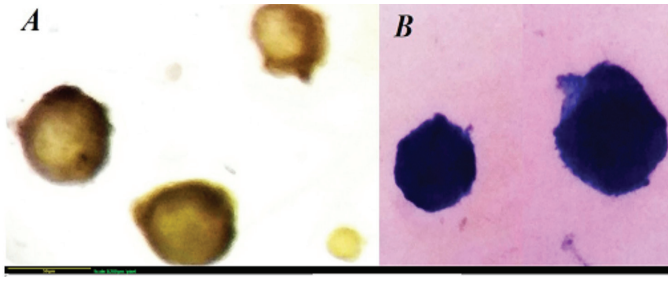

Figure 1. (A-B) Trypan blue staining, the follicles categorized as viable if the oocyte and surrounding granulosa cells were not stained and as degenerated follicles if stained blue

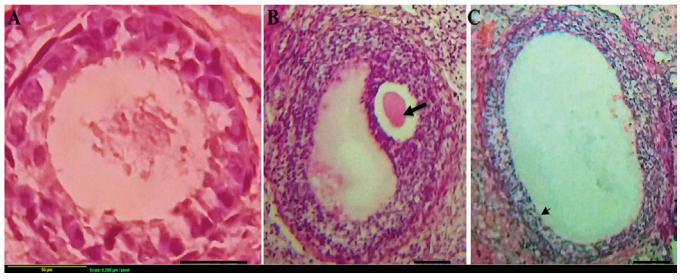

Figure 2. Various stages of ovarian follicles in the polycystic ovary syndrome group. a) Preantral follicles, b) antral follicles, c) atretic follicles. The number of degenerated oocytes (arrow head) increased and the thickness of granulosa cells layer decreased in the polycystic ovary syndrome group (black arrow)

Histomorphometric assay of ovarian tissue

The histomorphometric analysis of ovarian follicles in the control and experimental groups is presented in Table 2. In PCOS ovaries, a significant decrease was observed in the number of follicles at the different stages of development. In PCOS rats, the percentage of normal follicles at the different stages of development was significantly decreased compared with the controls ($p<0.001$), whereas the number of atretic follicles in rats with PCOS was higher than in the other

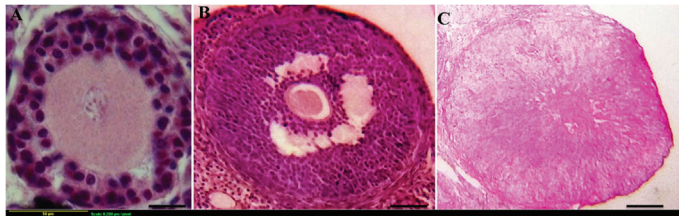

Figure 3. Various stages of ovarian follicles in the vitamin D-treated/polycystic ovary syndrome group (vitamin D + polycystic ovary syndrome). a) Preantral follicles, b) Antral follicles, c) Corpus luteum. The morphology of follicles and corpora lutea were normal in vitamin D-treated rats

Table 2. Histomorphometric assay of follicles at the various stages of development after hematoxylin-eosin staining

Group	Primary follicles (%)			Preantral follicle (%)			Antral follicle (%)		
	Total	Int	Atr	Total	Int	Atr	Total	Int	Atr
Control	126	124 (98)	2 (2)	101	99 (98)	2 (2)	85	82 (96)	3 (4)
Vitamin D	120	117 (97)	3 (3)	99	95 (96)	4 (4)	78	72 (92)	6 (8)
PCOS	97	81 (83)^{a***}	16 (17)^{a***}	81	66 (81)^{a***}	15 (19)^{a***}	67	47 (70)^{a***}	20 (30)^{a***}
Vitamin D + PCOS	119	115 (97)	4 (3)	109	103 (94)	6 (6)	79	74 (93)	5 (7)

PCOS: Polycystic ovary syndrome
^{a}shows significant difference between PCOS and other groups, $^{***}p<0.001$

Table 3. The viability of follicles at the various stages of development after Trypan blue staining

Group	Primary follicles (%)			Preantral follicle (%)			Antral follicle (%)		
	Total	Int	Deg	Total	Int	Deg	Total	Int	Deg
Control	60	57 (95)	3 (5)	53	51 (96)	2 (4)	63	60 (95)	3 (5)
Vitamin D	62	60 (97)	2 (3)	57	53 (93)	4 (7)	55	53 (96)	2 (4)
PCOS	55	46 (84)^{a**}	9 (16)^{a**}	48	40 (83)^{a**}	8 (17)^{a**}	55	45 (82)^{a**}	10 (18)^{a**}
Vitamin D + PCOS	65	62 (95)	3 (5)	57	53 (93)	4 (7)	59	56 (95)	3 (5)

PCOS: Polycystic ovary syndrome
^{a}shows a significant difference between PCOS and other groups, $^{**}p<0.01$

groups (p<0.001). In the rats with PCOS treated with vitamin D, the number of ovarian follicles at the different stages of development significantly increased and the number of normal follicles reversed as compared with the PCOS group (p<0.001). Data analysis showed that the percentage of atretic follicles at the different stages of development was significantly lower in the vitamin D-treated PCOS rats in comparison with the PCOS group (p<0.001).

The viability of ovarian follicles

The viability of ovarian follicles isolated from the control and experimental groups is presented in Table 3. The viability of ovarian follicles at the different stages of development was significantly decreased in the PCOS group compared with the controls (p<0.001). In rats with PCOS treated with vitamin D, the viability of follicles at the different stages of development was significantly increased in comparison with the PCOS groups with no treatment (p<0.001), whereas the degenerated follicles at the different stages of development were significantly decreased (p<0.001)

Effects of vitamin D supplementation on corpora lutea, granulosa cells, and theca layers

The number of CL, and theca and granulosa layer diameters in the control and experimental groups is presented in Table 4. The thickness of the theca layer was significantly increased in the PCOS group compared with the controls (p<0.001), whereas the thickness of granulosa layers and the number of CL were significantly decreased (p<0.001). Treatment with vitamin D significantly increased the number of CL and granulosa cells (p<0.01) but decreased the thickness of the theca layer (p<0.001).

Effects of vitamin D supplementation on hormone concentrations in the serum of rats with polycystic ovary syndrome

The serum concentrations of gonadotropin and sex hormones in the control and experimental groups are presented in Table 4. The serum concentration of LH was significantly increased in rats with PCOS compared with the controls (p<0.05), whereas the FSH concentration was significantly decreased (p<0.05). In rats with PCOS treated with vitamin D, there was a significant decrease in LH concentration, but the FSH concentration was significantly increased (p<0.05). In rats with PCOS, testosterone concentrations were significantly increased within a few days of the end of the study (p<0.001), whereas the serum concentrations of estradiol and progesterone were significantly decreased compared with the controls (p<0.001). Treatment with vitamin D in rats with PCOS significantly decreased the testosterone concentration and increased the estradiol and progesterone concentrations (p<0.001).

Table 4. The number of corpora lutea in the ovaries, the thickness of the granulosa layer (mm), the theca layer (mm) in the antral follicles, the serum concentrations of sex steroids and lipid markers, glucose, insulin concentrations, and insulin resistance (mean ± standard deviation) in the control and experimental groups

Groups	Control	Vitamin D	PCOS	PCOS + vitamin D
Granulosa layer	31.83±1.15^{b**}	33.14±0.79	19.25±0.86^{a***}	31.08±1.42
Theca layer	24.81±1.15^{b**}	22.36±1.43	30.08±1.28^{a***}	19.82±1.20
Corpus luteum	2.7±0.41	2.3±0.56	0.0±0.00^{a***}	2.3±0.45
FSH (IU/L)	4.46±0.02	3.42±0.02	0.50±0.08$^{\alpha**}$	4.38±0.04
LH (IU/L)	0.45±0.02	0.43±0.01	1.21±0.01$^{\alpha**}$	0.36±0.04
Testosterone (ng/mL)	4.42±0.01	4.35±0.03	10.07±0.02$^{\alpha***}$	3.01±0.04
Progesterone (ng/mL)	11.30±0.02	12.18±0.05	4.66±0.02$^{\alpha***}$	11.01±0.02
Estradiol (ng/mL)	3.18±0.02	4.20±0.01	2.22±0.06$^{\alpha**}$	4.22±0.02
Triglycerides (mg/dL)	81.15±7.83	75.15±6.21	135.22±8.63^{a***}	65.39±6.18
Cholesterol (mg/mL)	74.23±6.01	73.11±6.22	128.27±7.28^{a***}	73.15±5.34
HDL (mg/mL)	34.86±1.11	35.75±0.95	17.18±1.12^{a***}	24.04±0.87
LDL (mg/mL)	24.26±1.02	24.45±1.02	84.24±1.11^{a***}	25.03±0.98
Glucose (mM/L)	10.13±0.10	10.01±0.80	19.10±0.70^{a**}	13.22±0.09
Insulin (MU/L)	40.31±0.12	36.41±0.09	65.10±0.18^{a**}	42.21±0.10
HOMA-IR	21.17±0.09	19.21±0.08	51.20±0.13^{a***}	23.02±0.11

PCOS: Polycystic ovary syndrome, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, HOMA-IR: Homeostasis model assessment-insulin resistance
[a]Represents a significant difference between polycystic ovary syndrome and other groups,
[b]Represents a significant difference between control and other groups, **p<0.01, ***p<0.001

Effects of vitamin D supplementation on the serum concentrations of glucose and insulin, and insulin resistance in rats with polycystic ovary syndrome

The data of insulin, glucose, and IR (HOMA-IR) are presented in Table 4. The serum concentrations of insulin, glucose, and IR in rats PCOS were significantly higher than those in controls ($p<0.001$), and the insulin, glucose, and IR concentrations in vitamin D-treated PCOS group were significantly lower than those in the non-treated PCOS group ($p<0.001$).

Effects of vitamin D supplementation on lipid concentrations in rats with polycystic ovary syndrome

The serum concentrations of triglyceride, cloistral, and low-density lipoprotein (LDL) in rats with PCOS were significantly higher than those in controls, whereas the concentration of high-density lipoprotein (HDL) was significantly lower (Table 4, $p<0.001$). In vitamin D-treated rats, a significant reduction was observed in the triglyceride, cloistral, and LDL concentrations, but there was a higher significant in the concentration of HDL compared with non-treated rats with PCOS ($p<0.001$).

Discussion

The present study demonstrated that an imbalance gonadotropin hormone as a negative effect of PCOS could affect follicular development. Treatment with vitamin D decreased the adverse effects of PCOS, which is one of the most important hormone disorders, resulting in infertility for unknown reasons. The histologic observations of ovarian tissue of rats with induced PCOS demonstrated a large number of cysts and damaged follicles at the different stages of development with atrophy granulosa cells and hypertrophy theca layer. In this study, the percentage of the atretic follicles at the various stages of development decreased in rats with PCOS, and then growing follicles and folliculogenesis were impaired, and ovulation did not occur during development. Some studies found that vitamin D deficiency was associated with various PCOS symptoms, including IR , infertility, and hirsutism by gene transcription and hormonal modulation[25-27]. Wehr et al.[26] reported that the patients with PCOS with hirsutism had lower vitamin D concentrations as compared with those without hirsutism (21.4 ng/mL vs. 26.8 ng/mL, respectively). Selimoglu et al.[28] demonstrated that 300.000 units of vitamin D3 oral supplementation in patients with PCOS significantly decreased the HOMA-IR, but no significant changes were observed in glucose or insulin concentrations. However, in this study, vitamin D3 supplementation decreased the glucose or insulin concentrations in rats with PCOS. Our results confirmed that all rats with PCOS had higher concentrations of HOMA-IR or insulin resistant. Moreover, vitamin D was negatively correlated with IR in rats with PCOS treated with vitamin D. An increasing number of studies have found that IR is common in women with PCOS and also vitamin D deficiency is associated with IR[29,30]. Recent evidence suggests that vitamin D may decrease IR by stimulating the expression of insulin receptors in ovarian tissues, the renin-angiotensin-aldosterone system, and the calcium regulatory system, thereby increasing insulin sensitivity[31-33]. The results of the study of Kotsa et al.[34] indicated that the majority of women with PCOS had vitamin D deficiency and abnormalities in the PTH-vitamin D axis. Many studies demonstrated that IR and obesity were associated with vitamin D deficiency and a reduction in gonadotropin hormone secretion in women with PCOS[25,35,36]. In the present study, the lipid profile was evaluated as an indirect index of insulin sensitivity. The analysis indicated a decrease in HOMA-IR, glucose, total cholesterol and LDL concentrations, and an increase in HDL concentrations after treatment with vitamin D in rats with PCOS. The present study highlighted the fact that vitamin D might be associated with an improvement in both insulin sensitivity and effectiveness, and with a decrease in fat mass and obesity in rats with PCOS. Treatment with vitamin D decreased the body and ovary weight in rats with induced PCOS. This could be associated with the reduction of testosterone concentrations under the influence of vitamin D. Vitamin D deficiency and hyperandrogenism are common symptoms in the initiation and development of PCOS, suggesting that inverse associations exist among vitamin D concentrations and testosterone concentrations, and vitamin D deficiency induces hyperandrogenism[37,38]. Our study, in agreement with Pal et al.[39] demonstrated a significant decrease in testosterone concentrations in patients with PCOS after vitamin D supplementation[39]. Karadağ et al.[40] suggested that decreased androgen concentrations might have been associated with the elevation of insulin sensitivity, and a decrease in insulin concentrations might have increased sex hormone-binding globulin concentrations and decreased the circulation of androgen concentrations. Thys-Jacobs et al.[41] revealed that vitamin D deficiency induced follicular arrest and impaired folliculogenesis through calcium dysregulation, which resulted in menstrual irregularity, ovulatory, and fertility dysfunction. Another study indicated that calcium-vitamin D regulated the menstrual cycle and treated anovulation and oligomenorrhea in patients with PCOS[42]. In the present study, the menstrual irregularity in rats with PCOS returned to normal and regular conditions after vitamin D treatment. These results highlight the critical role of vitamin D in oogenesis and oocyte maturation. Vitamin D deficiency could be responsible for disorders of oocyte development in PCOS. First, the results of a study conducted by Patra et al.[43] demonstrated a positive correlation between vitamin D deficiency and IR in PCOS. Moreover, our results showed the highest IR (HOMA-IR values) in rats with PCOS as compared with controls. Finally, vitamin D may enhance insulin activity by stimulating the expression of insulin receptors and thereby improving insulin responsiveness for glucose transport. Our results indicated that vitamin D decreased high concentrations of insulin and glucose in rats with PCOS. These results show that rats with PCOS have insufficient vitamin D

and supplementation of vitamin D plays a critical role in the treatment of PCOS in rats. Studies have shown that vitamin D also has a role in gonadal steroidogenesis in both cellular and serum concentrations[18]. In this study, vitamin D increased estrogen concentrations by improving aromatase activity and progesterone concentrations through corpus luteum formation in rats with PCOS.

In the present study, the FSH concentrations decreased and LH concentrations increased in rats with PCOS, thus the maturation of follicles was impaired and multi-sized cystic follicles were formed. Vitamin D may induce granulosa cell differentiation by inhibiting anti-mullerian hormone expression, thereby allowing follicles to reach terminal maturation. Our results showed that the thickness of granulosa cells increased in vitamin D-treated rats with PCOS. Moreover, in luteinized granulosa cells, vitamin D resulted in granulosa cells being less dependent on FSH and more dependent on LH, thereby the matured follicles ovulated[44]. In addition, vitamin D induced follicular development by antiapoptotic functions and the regulation of Bcl-family and Bax[45,46]. Vitamin D plays an important role in estrogen and progesterone biosynthesis in the ovary. Our results were consistent with those of Kinuta et al.[45], demonstrating that vitamin D promoted folliculogenesis and follicular development in rats with PCOS by increasing estrogen and progesterone concentrations and regulating the FSH and LH ratio.Vitamin D deficiency increases PTH secretion (a decrease in serum calcium concentration) because insulin plays a role in calcium absorption[47]. Many studies have demonstrated that the number of follicles larger than 14 mm in the calcium-vitamin D-treated group was higher than in those who received vitamin D, and this has been associated to the presence of calcium, which can increase the effect Vitamin D when used with calcium. It also regulates sex cycles and syndrome symptoms, including decreased insulin concentrations and reduced blood pressure. Calcium-vitamin D intake, which can help increase calcium and lower blood glucose concentrations, reveals the effect of calcium on the alteration of insulin secretion disorders and the increased efficacy of vitamin D[11,3,32,41]. Therefore, the measurement of the serum calcium concentrations and its use during treatment with vitamin D can be effective.

Conclusion

Vitamin D supplementation in rats with PCOS regularized the androgen hormones ratio, increased insulin sensitivity, and thereby stimulated the development of the dominant follicles and the ovulation of matured follicles. Therefore, our study provides further support for the idea that vitamin D supplementation can protect ovarian tissue from the negative effects of PCOS. However, further attempts and longitudinal intervention studies are needed to evaluate the effect of vitamin D in treating PCOS models.

Acknowledgments

The present study was financially supported by Tabriz University of Medical Sciences.

Ethics

Ethics Committee Approval: The research protocol of this study was approved by Vice Chancellor for Research of Tabriz University of Medical Sciences and Ethics in Research Committee of Tabriz University of Medical Sciences, (under code number: TBZMED.REC.94/2-5/7).

Informed Consent: Not applicable.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.A., N.B., Concept: A.A., N.B., A.A., Design: A.A., N.B., A.A., Data Collection or Processing: A.A., N.B., H.N.C., Analysis or Interpretation: A.A., N.B., A.A., H.N.C., Literature Search: A.A., N.B., A.A., Writing: A.A., N.B., A.A.

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

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Balen A. The pathophysiology of polycystic ovary syndrome: trying to understand PCOS and its endocrinology. Best Pract Res Clin Obstet Gynaecol 2004;18:685-706.
2. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril 2004;81:19-25.
3. Walters KA, Allan CM, Handelsman DJ. Rodent models for human polycystic ovary syndrome. Biol Reprod 2012;86:149.
4. Vosnakis C, Georgopoulos NA, Rousso D, Mavromatidis G, Katsikis I, Roupas ND, et al. Diet, physical exercise and Orlistat administration increase serum anti-Müllerian hormone (AMH) levels in women with polycystic ovary syndrome (PCOS). Gynecol Endocrinol 2013;29:242-5.
5. Hillier SG, Whitelaw PF, Smyth CD. Follicular oestrogen synthesis: the 'two-cell, two-gonadotrophin' model revisited. Mol Cell Endocrinol 1994;100:51-4.
6. Kafali H, Iriadam M, Ozardali I, Demir N. Letrozole-induced polycystic ovaries in the rat: a new model for cystic ovarian disease. Arch Med Res 2004;35:103-8.
7. Zurvarra FM, Salvetti NR, Mason JI, Velazquez MM, Alfaro NS, Ortega HH. Disruption in the expression and immunolocalisation of steroid receptors and steroidogenic enzymes in letrozole-induced polycystic ovaries in rat. Reprod Fertil Dev 2009;21:827-39.
8. Hahn S, Fingerhut A, Khomtsiv U, Khomtsiv L, Tan S, Quadbeck B, et al. The peroxisome proliferator activated receptor gamma Pro12Ala polymorphism is associated with a lower hirsutism score and increased insulin sensitivity in women with polycystic ovary syndrome. Clin Endocrinol (Oxf) 2005;62:573-9.
9. Hyppönen E, Power C. Hypovitaminosis D in British adults at age 45 y: nationwide cohort study of dietary and lifestyle predictors. Am J Clin Nutr 2007;85:860-8.
10. Belenchia AM, Tosh AK, Hillman LS, Peterson CA. Correcting vitamin D insufficiency improves insulin sensitivity in obese adolescents: a randomized controlled trial. Am J Clin Nutr 2013;97:774-81. 11. Mahmoudi T, Gourabi H, Ashrafi M, Yazdi RS, Ezabadi Z. Calciotropic hormones, insulin resistance, and the polycystic ovary syndrome. Fertil Steril 2010;93:1208-14.

12. Lips P. Vitamin D physiology. Prog Biophys Mol Biol 2006;92:4-8.
13. Lieben L, Carmeliet G, Masuyama R. Calcemic actions of vitamin D: effects on the intestine, kidney and bone. Best Pract Res Clin Endocrinol Metab 2011;25:561-72.
14. Lerchbaum E, Obermayer-Pietsch B. Vitamin D and fertility: a systematic review. Eur J Endocrinol 2012;166:765-78.
15. Anagnostis P, Karras S, Goulis DG. Vitamin D in human reproduction: a narrative review. Int J Clin Pract 2013;67:225-35.
16. Wojtusik J, Johnson PA. Vitamin D regulates anti-Mullerian hormone expression in granulosa cells of the hen. Biol Reprod 2012;86:91.
17. Wehr E, Trummer O, Giuliani A, Gruber HJ, Pieber TR, Obermayer-Pietsch B. Vitamin D-associated polymorphisms are related to insulin resistance and vitamin D deficiency in polycystic ovary syndrome. Eur J Endocrinol 2011;164:741-9.
18. Parikh G, Varadinova M, Suwandhi P, Araki T, Rosenwaks Z, Poretsky L, et al. Vitamin D regulates steroidogenesis and insulin-like growth factor binding protein-1 (IGFBP-1) production in human ovarian cells. Horm Metab Res 2010;42:754-7.
19. Rajan RK, M SS, Balaji B. Soy isoflavones exert beneficial effects on letrozole-induced rat polycystic ovary syndrome (PCOS) model through anti-androgenic mechanism. Pharm Biol 2017;55:242-51.
20. Brawer JR, Munoz M, Farookhi R. Development of the polycystic ovarian condition (PCO) in the estradiol valerate-treated rat. Biol Reprod.1986;35:647-55.
21. Radavelli-Bagatini S, Blair AR, Proietto J, Spritzer PM, Andrikopoulos S. The New Zealand obese mouse model of obesity insulin resistance and poor breeding performance: evaluation of ovarian structure and function. J Endocrinol 2011;209:307-15.
22. Tayefi Nasrabadi H, Gavami M, Akbarzadeh A, Beheshti R, Mohammadnejad D, Abedelahi A. Preservation of mouse ovarian tissue follicle morphology and ultra-structure after vitrifying in biotechnological protocols. J Ovarian Res 2015;8:7.
23. Ghavami M, Mohammadnejad D, Beheshti R, Solmani-Rad J, Abedelahi A. Ultrastructural and Morphalogical Changes of Mouse Ovarian Tissues Following Direct Cover Vitrification with Different Cryoprotectants. J Reprod Infertil 2015;16:138-47.
24. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412-9.
25. Hahn S, Haselhorst U, Tan S, Quadbeck B, Schmidt M, Roesler S, et al. Low serum 25-hydroxyvitamin D concentrations are associated with insulin resistance and obesity in women with polycystic ovary syndrome. Exp Clin Endocrinol Diabetes 2006;114:577-83.
26. Wehr E, Pilz S, Schweighofer N, Giuliani A, Kopera D, Pieber TR, et al. Association of hypovitaminosis D with metabolic disturbances in polycystic ovary syndrome. Eur J Endocrinol 2009;161:575-82.
27. Mahmoudi T. Genetic variation in the vitamin D receptor and polycystic ovary syndrome risk. Fertil Steril 2009;92:1381-3.
28. Selimoglu H, Duran C, Kiyici S, Ersoy C, Guclu M, Ozkaya G, et al. The effect of vitamin D replacement therapy on insulin resistance and androgen levels in women with polycystic ovary syndrome. J Endocrinol Invest 2010;33:234-8.
29. Li HW, Brereton RE, Anderson RA, Wallace AM, Ho CK. Vitamin D deficiency is common and associated with metabolic risk factors in patients with polycystic ovary syndrome. Metabolism 2011;60:1475-81.
30. Moran L, Teede H. Metabolic features of the reproductive phenotypes of polycystic ovary syndrome. Hum Reprod Update 2009;15:477-88.
31. Maestro B, Campión J, Dávila N, Calle C. Stimulation by 1,25-dihydroxyvitamin D3 of insulin receptor expression and insulin responsiveness for glucose transport in U-937 human promonocytic cells. Endocr J 2000;47:383-91.
32. Pittas AG, Lau J, Hu FB, Dawson-Hughes B. The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis. J Clin Endocrinol Metab 2007;92:2017-29.
33. Rammos G, Tseke P, Ziakka S. Vitamin D, the renin-angiotensin system, and insulin resistance. Int Urol Nephrol 2008;40:419-26.
34. Kotsa K, Yavropoulou MP, Anastasiou O, Yovos JG. Role of vitamin D treatment in glucose metabolism in polycystic ovary syndrome. Fertil Steril 2009;92:1053-8.
35. Panidis D, Balaris C, Farmakiotis D, Rousso D, Kourtis A, Balaris V, et al. Serum parathyroid hormone concentrations are increased in women with polycystic ovary syndrome. Clin Chem 2005;51:1691-7.
36. Premoli AC, Santana LF, Ferriani RA, Moura MD, De Sá MF, Reis RM. Growth hormone secretion and insulin-like growth factor-1 are related to hyperandrogenism in nonobese patients with polycystic ovary syndrome. Fertil Steril 2005;83:1852-5.
37. Thomson RL, Spedding S, Buckley JD. Vitamin D in the aetiology and management of polycystic ovary syndrome. Clin Endocrinol (Oxf) 2012;77:343-50.
38. Velija-Ašimi Z. Evaluation of the association of vitamin D deficiency with gonadotropins and sex hormone in obese and non-obese women with polycystic ovary syndrome. Med Glas (Zenica) 2014;11:170-6.
39. Pal L, Berry A, Coraluzzi L, Kustan E, Danton C, Shaw J, et al. Therapeutic implications of vitamin D and calcium in overweight women with polycystic ovary syndrome. Gynecol Endocrinol 2012;28:965-8.
40. Karadağ C, Yoldemir T, Yavuz DG. Effects of vitamin D supplementation on insulin sensitivity and androgen levels in vitamin-D-deficient polycystic ovary syndrome patients. J Obstet Gynaecol Res 2018;44:270-277.
41. Thys-Jacobs S, Donovan D, Papadopoulos A, Sarrel P, Bilezikian JP. Vitamin D and calcium dysregulation in the polycystic ovarian syndrome. Steroids 1999;64:430-5.
42. Rashidi B, Haghollahi F, Shariat M, Zayerii F. The effects of calcium-vitamin D and metformin on polycystic ovary syndrome: a pilot study. Taiwan J Obstet Gynecol 2009;48:142-7.
43. Patra SK, Nasrat H, Goswami B, Jain A. Vitamin D as a predictor of insulin resistance in polycystic ovarian syndrome. Diabetes Metab Syndr 2012 ;6:146-9.
44. Durlinger AL, Kramer P, Karels B, de Jong FH, Uilenbroek JT, Grootegoed JA, et al. Control of primordial follicle recruitment by anti-Müllerian hormone in the mouse ovary. Endocrinology 1999;140:5789-96.
45. Kinuta K, Tanaka H, Moriwake T, Aya K, Kato S, Seino Y. Vitamin D is an important factor in estrogen biosynthesis of both female and male gonads. Endocrinology 2000;141:1317-24.
46. Tilly JL. The molecular basis of ovarian cell death during germ cell attrition, follicular atresia, and luteolysis. Front Biosci 1996;1:d1-11.
47. Savastano S, Valentino R, Di Somma C, Orio F, Pivonello C, Passaretti F, et al. Serum 25-Hydroxyvitamin D Levels, phosphoprotein enriched in diabetes gene product (PED/PEA-15) and leptin-to-adiponectin ratio in women with PCOS. Nutr Metab (Lond) 2011;8:84.

Clinical Investigation / Araştırma

DOI: 10.4274/tjod.galenos.2019.88899

Turk J Obstet Gynecol 2019;16:151-7

Psychological distress in women with recurrent spontaneous abortion: A case-control study

Rekürren spontan abortus yapan kadınlarda psikolojik sıkıntı: Bir olgu kontrol çalışması

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Abstract

Objective: The aim of the present study was to evaluate psychological problems in women with recurrent spontaneous abortion (RSA).

Materials and Methods: In this case-control study, 115 women with RSA were assigned to the case group and 240 non-pregnant women comprised the control group. The revised version of the Symptom Checklist-90 (SCL-90-R) and the Intolerance of Uncertainty scale (IUS) were used for assessing mental health problems.

Results: The results showed that the mean Global Severity Index (GSI) of the SCL-90-R and the IUS scores in the case and control groups were 109.10±59.85 and 68.91±22.17, and 82.98±52.99 and 59.19±23.01, respectively. GSI was the strongest predictor of RSA [odds ratio (OR)=6.43; 95% confidence interval (CI): 3.52-11.72]. The chance estimate of RSA was approximately 2.1 times higher in women in rural areas (OR=2.07; 95% CI: 1.16-3.69), and 2 times higher at 12 months after the last pregnancy (OR=1.99; 95% CI: 1.42-2.78).

Conclusion: Psychological problems are greater after RSA. Therefore, it is suggested that the treatment of RSA emphasizes psychological counseling and psychological management.

Keywords: Recurrent spontaneous abortion, anxiety, depression, intolerance of uncertainty

Öz

Amaç: Mevcut çalışmanın amacı, rekkürren spontan abortus (RSA) yapan kadınlardaki psikolojik problemleri değerlendirmektir.

Gereç ve Yöntemler: Bu olgu kontrol çalışmasında, 115 RSA'lı kadın olgu grubuna ve 240 gebe olmayan kadın da kontrol grubuna dahil edilmiştir. Semptom Kontrol Listesi'nin revize edilmiş versiyonu (SCL-90-R) ve Belirsizlik İntoleransı ölçeği (IUS) mental sağlık problemlerinin değerlendirilmesi için kullanılmıştır.

Bulgular: Sonuçlar, SCL-90-R ve IUS skorları ortalama Global Şiddetlilik İndeksinin (GSI), olgu ve kontrol grupları için sırası ile 109,10±59,85 ve 68,91±22,17 ile 82,98±52,99 ve 59,19±23,01 olduğunu göstermiştir. GSI, RSA'nın en güçlü ön göstergesidir [olasılık oranı (OO)=6,43; %95 güven aralığı (GA): 3,52-11,72]. RSA'nın şans tahmini kırsal kesimdeki kadınlarda yaklaşık 2,1 kat daha yüksektir (OO=2,07; %95 GA=1,16-3,69) ve en son gebelikten 12 ay sonra da 2 kat daha yüksektir (OO=1,99; %95 GA=1,42-2,78).

Sonuç: RSA sonrasında psikolojik problemler daha büyüktür. Bu nedenle, RSA tedavisinin psikolojik danışmayı ve psikolojik yönetimi vurgulaması önerilir.

Anahtar Kelimeler: Rekürren spontan abortus, anksiyete, depresyon, belirsizlik intoleransı

Introduction

Infertility and recurrent spontaneous abortion (RSA) are two challenging issues in the field of obstetrics and gynecology[1,2]. The perception of infertility has received great attention as a psychological problem[3,4]. It is considered as one of the numerous difficulties that patients should receive the best services in the diagnosis, treatment, and psychological support[5]. RSA is one of the most important problems related to infertility. It is defined as two or more consecutive pregnancy losses[6]. According to the American Society for Reproductive Medicine Practice Committee, RSA includes clinical abortion that is ascertained by

PRECIS: The loss of a desired pregnancy is a considerable negative life occurrence, and this problem may cause important physical and psychological distress.

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Received/Geliş Tarihi: 13.02.2019 **Accepted/Kabul Tarihi:** 09.06.2019

ultrasound or histology[7]. RSA occurs due to genetic or uterine problems, thrombophilia, autoimmune endocrine diseases, infections, and several environmental factors[8]. Further, all cases of unknown infertility are often imputed to psychological causes[9]. The loss of a desired pregnancy is a considerable negative life occurrence, and this problem may cause notable physical and psychological distress[10]. Pregnancy loss is related with anxiety and distress, especially in women who experience RSA[11]. The prevalence of depression in abortion ranges from 15% to 33%[12,13]. In one study, researchers surveyed psychological adjustment to abortion and found that 50% of women with a history of abortion experienced depression and anxiety for several months[14]. Abortion may cause intolerance of uncertainty (IU) in women, which is a cognitive bias from a series of negative beliefs about uncertainty and its implications. In IU, a person perceives information in unclear circumstances and responds to it with a set of cognitive, emotional, and behavioral reactions[15]. Anxiety symptoms start immediately after abortion and continue until nearly 4-6 months later[16]. Additionally, while waiting for the next pregnancy, there is usually a high level of uncertainty and anxiety, which reduces the person's ability to tackle problems[17]. According to the recommendations of the World Health Organization, women should wait for 6 months after an abortion and before attempting to become pregnant again[18]. However, about 50 to 80% of women become pregnant again soon after the abortion, and the next pregnancy is at risk of causing anxiety and depression[19]. Therefore, it is unclear if past RSA may be associated with depression or anxiety experienced by women. Thus, the future consequences of an RSA are unknown. Sham et al.[20] reported no enhanced risk of psychiatric symptoms in subsequent abortion. Nevertheless, another study revealed that depression and anxiety after an abortion were significant predictors of symbolic anxiety and depression in the first trimester of the subsequent pregnancy[21]. Additionally, pregnancy loss may cause women to be concerned about the success of the next pregnancy[22]. Thus, owing to the impact of RSA, the diagnosis and management of anxiety and depression during the pregnancy after an abortion is as crucial as that of psychological distress during pregnancy[23]. Psychological support, also known as "tender loving care", is considered essential for women who experience unexplained RSA[24]. Women without social support are at a higher risk of exhibiting psychological morbidity or symptoms after a pregnancy loss or infertility[25,26]. RSA is a distressing situation for infertile couples and frustrating for physicians. Accordingly, the European Society of Human Reproduction and Embryology and the Royal College of Obstetricians and Gynaecologists recommended offering supportive care during future pregnancies for women with unexplained RSA[27]. Many studies have been performed on depression in infertility but there are few studies on distress in RSA. Also, studies on the impact of psychological issues in RSA have reported conflicting findings. Therefore, the present study was conducted in Babol University of Medical Sciences in northern Iran to determine the impact of psychological problems on RSA.

Materials and Methods

Participants and procedure

This study was approved by the Research Ethics Committee of the Babol University of Medical Sciences (ID: MUBABOL.REC.2015.42). This case-control study was conducted from May 2015 to February 2017 in Babol, Iran. All patients signed the free and informed consent form. In total, 120 women with RSA were referred to the research center because of infertility. The women in the RSA group had primary infertility and had no children. RSA was defined as having two or more consecutive abortions in the first trimester of pregnancy. Out of those referred, 5 women were excluded owing to incomplete questionnaires, and the final case sample comprised 115 women. All women with known probable etiologies for RSA and known mental illnesses were excluded from the study. The inclusion criteria for the patients with RSA included having experienced at least two consecutive idiopathic abortions of a desired pregnancy with a sexual partner; regular menstruation; no history of polycystic ovary syndrome; normal gynecologic status; anatomy, and karyotype; normal levels of the anti-phospholipid antibody, anti-nuclear antibody, anti-cardiolipin antibody, anti-thrombin 3, lupus anti-coagulant, homocysteine, protein S, protein C, factor V Leiden, anti-thyroid peroxidase, thyroid hormones, and prolactin; and normal spermogram and karyotype of the sexual partner. Women without RSA who were referred to primary healthcare centers were selected as control subjects. These 265 healthy, non-pregnant women with at least one living child had no history of infertility, previous abortion, preterm deliveries, or stillbirths. Among them, 25 women were excluded from the study due to failure to complete the questionnaire, and a final sample of 240 women was used as the control group. The case and control groups were evaluated from three months to one year after abortion or childbirth, respectively.

Demographics and questionnaires

All participants completed the sociodemographic information questionnaire, the revised version of the Symptom Checklist-90 (SCL-90-R), and the Intolerance of Uncertainty scale (IUS). For both groups, we collected information on the couple's age, level of education, body mass index (BMI), occupation, residence, home ownership status, satisfaction with income, and gravidity and time passed since the last pregnancy. The SCL-90-R is one of the most widely used symptom questionnaires in the field of psychiatry. This self-reported questionnaire evaluates the following 9 symptoms: somatization, sensitivity, obsessive-compulsive disorder, aggression, phobic anxiety, paranoia, depression, anxiety, and psychotic tendency. The total score is evaluated as the Global Severity İndex (GSI). This checklist comprises 90 questions with 5 response options (0=not at all,

1=a little bit, 2=moderately, 3=quite a bit, 4=extremely)[28,29]. The IUS assesses cognitive bias that changes perceptions, interpretations, and individual reactions in uncertain situations based on the levels of cognitive, emotional, and behavioral responses in such situations. IU is defined as the predisposition to react negatively to an uncertain event or situation, independent of its probability of occurrence and of its associated consequences. IU reflects beliefs about the necessity of being certain, the capacity to cope with unpredictable change, and about adequate functioning in situations that are inherently ambiguous[30]. IUS is correlated with psychological problems such as anxiety and depression, but infertility and abortion, especially recurrent abortion, is a specific situation with high frequency of uncertainty events. Infertility is uncertainty as a diagnosis, uncertainty as successful treatments and uncertainty as future outcomes. Also, recurrent abortion is full of uncertainty conditions, such as uncertainty as to the cause and if related with disease, uncertainty regarding future pregnancy and future outcomes. The IUS is a 27-item questionnaire that assesses incompatible beliefs that lead to IU . Responses to items are made using a 5 point Likert scale (not at all, somewhat, medium, high, very high). The internal consistency of the scale was α=0.91, and its reliability was 78% in a previous study[15]. This scale classifies the nature of worry experienced by healthy into the following four categories: bearing down on ambiguous situations, positive beliefs about worry, cognitive avoidance, and negative problem orientation[31].

Statistical Analysis

Data analyses were performed using the Statistical Package for the Social Sciences (SPSS) 22.0 software package. The differences in sociodemographic characteristics and psychological distress between women with and without RSA were determined using the t-test and chi-square test. Analysis of variance (ANOVA) and the Tukey's test were used to examine differences in psychological distress at 1-6, 7-12, and >12 months after abortion and delivery. Additionally, the predictive factors of RSA (age, GSI, education, time passed since last pregnancy, occupation, residence, and income) were examined using multiple logistic regression analysis. Also, Pearson correlation analysis was used to identify the significant relationship of IUS and SCL-90-R. A p value of less than 0.05 was considered significant.

Results

The sociodemographic characteristics of the participants are presented in Table 1. There was no significant difference between the case and control groups regarding BMI, occupation, level of education, husband's age and level of education, satisfaction with income, and home ownership status (Table 1). The mean global GSI on the SCL-90-R score in women with and without RSA were 109.10±59.85, and 82.98±52.99, respectively (p=0.0001). Also, the mean IUS score in women with and without RSA was 68.91±22.17, and 59.19±23.01, respectively (p=0.0001). There was a significant difference in location between the two groups. Therefore, we examined if their psychological distress varied based on location. Table 2 shows the mean and standard deviation on all subscales of the SCL-90-R and the IUS for the recognition of prior learning and control groups. It was observed that in the case group, the scores were higher in rural populations as compared with those in urban populations. In contrast, in the control group, the scores in rural populations were lower than those in urban populations (p=0.0001). ANOVA and Tukey's test were used to assess differences in psychological distress at 1-6, 7-12, and >12 months after pregnancy loss and birth. In the group without RSA (control group), scores on all psychological distress subscales reduced significantly between 1-6 months to >12 months after birth (p=0.0001). However, in the RSA group, mental health problems remained stable even after 12 months since abortion. The Tukey's test results for the different time periods since the last pregnancy are summarized in Table 3. Table 4 shows the predictive factors of RSA based on the findings of multiple logistic regression analysis in the first stage. Seven factors including age, GSI, education, time passed since last pregnancy, occupation, residence, and satisfaction with income were included in the analysis. The odds ratio (OR) of the GSI was good for RSA before the adjustment [OR=3.48; 95% confidence interval (CI)=(2.10-5.77), p<0.001] and this association was strengthened by considering other factors. The adjusted ORs for factors that were significantly associated with the chance of RSA are summarized in Table 4. Using this method, we excluded the variable of having age over 30 years in the second stage, jobs in the third stage, and satisfaction with income in the fourth stage, and only GSI [OR=6.43; 95% CI=(3.52-11.72)], time passed since last pregnancy (OR=1.99; 95% CI=1.42-2.78), education (OR=0.49; 95% CI=0.50-1.84), and residence (OR=2.07; 95% CI=1.16-3.69) remained in the model. After adjusting for other variables, the multiple logistic regression analysis showed that the chance of RSA was higher in women living in rural areas as compared with those living in urban areas (p=0.013), and in people with an educational level of high school diploma or less as compared with their counterparts (p=0.026). Also, Pearson correlation analysis showed a significant relationship of IUS with SCL-90-R (r=0.650, p<0.001).

Discussion

Recurrent abortion and the postpartum period are serious time points for women[32,33]. In this study, we found that the incidence of psychological disorders was higher in women with recurrent abortions, as evident from their higher scores on the SCL-90-R and IUS as compared with those of the control group. These results are in agreement with those of the Kolte et al.[34] who revealed that 8.6% of women with RSA, versus 2.2% of healthy women had moderate or severe

depression. In another study that examined the psychological adjustment in couples with a history of recurrent miscarriage, the results showed that, according to Beck Depression index scores, women presented significantly higher levels of anxiety and depression as compared with men. Further, 25% of the women, versus 3.9% of the men, exhibited a high level of state anxiety as assessed using the State-Trait Anxiety Inventory (STAI-S ≥ 55), and 23.7% of the women, versus 5.3% of the men, exhibited a high level of trait anxiety (STAI-T ≥55)[35]. In Sugiura-Ogasawara et al.'s[29] study, 305 women with a history of recurrent abortion first completed a set of questionnaires including the K6 (a new screening instrument for anxiety and mood disorders) and the SCL-90-R. Subsequently, 170 women received a description about a successful live birth, after which they answered the questionnaires again. The results showed that, in the first survey, 15.4% of the women exhibited anxiety or depression. Additionally, high scores on the K6 were correlated with high scores on all the subscales of the SCL-90-R. Further, in the 170 women who received a description of a successful live birth, all scores in the second survey were significantly lower as compared with the first survey, indicating an improvement in their depression levels[29]. In another study, results showed that a high score on the IUS were associated with an increased risk of opposing behaviors[36]. In addition, Carleton et al.[37] reported that IUS scores in women with social anxiety disorder were higher than those in women with panic disorder (p<0.01). Furthermore, in one study on 151 members with primary social anxiety disorder, their IUS scores were evaluated before and after 12 weeks of cognitive behavioral therapy. The findings showed significantly lower scores after treatment[38]. These findings indicate that anxiety is higher in infertile women. Infertility and recurrent abortion can lead to a substantial amount of pressure on women. These women do not recover spontaneously, and they need appropriate diagnostic services, care, and psychological intervention. In our study, the control group exhibited a significant reduction in

Table 1. Sociodemographic characteristics in population study

Characteristic	With RSA (n=115)	Without RSA (n=240)	p value†
Age (mean ± SD, year)	30.66±5.30	29.29±4.85	0.020
Husband's age (mean ± SD, year)	33.99±5.83	33.62±5.22	0.552
BMI (kg/m²)	26.85±4.05	26.72±4.17	0.782
Occupation (n, %)			
Employed	12 (46.2)	14 (53.8)	0.119
Housewife	103 (31.3)	226 (68.7)	
Level of education (n, %)			
Under the diploma	35 (38.9)	55 (61.1)	
Diploma	37 (25.7)	107 (74.3)	0.073
College	43 (35.5)	78 (64.5)	
Husband's education (n, %)			
Under the diploma	48 (35.6)	87 (64.4)	
Diploma	30 (27.5)	79 (72.5)	0.398
College	37 (33.3)	74 (66.7)	
Residence (n, %)			
Urban	63 (27.6)	165 (72.4)	0.010
Rural	52 (40.9)	75 (59.1)	
Satisfaction with income (n, %)			
Good (very satisfactory)	31 (26.1)	88 (73.9)	
Moderate (satisfactory)	70 (37.2)	118 (62.8)	0.109
Weak (unsatisfactory)	14 (29.2)	34 (70.8)	
Home ownership status (n, %)			
Private	64 (31.7)	138 (68.3)	0.742
Rental	51 (33.3)	102 (66.7)	
Gravidity (mean ± SD)	2.64±0.92	1.52±0.50	0.0001
Time passed since last pregnancy (n, %)			
1-6 months	33 (21.9)	118 (78.1)	
7-12 months	38 (41.8)	53 (58.2)	
>12 months	44 (38.9)	69 (61.1)	0.001

SD: Standard deviation, BMI: Body mass index, RSA: Recurrent spontaneous abortion, †The data were assessed using chi-square and t-tests,

their scores on all subscales in psychology from 1-6 months to >12 months after birth; however, the same women with RSA remained stable even 12 months after abortion. Broen et al.[39] showed that women who experienced a spontaneous abortion exhibited more distress between 10 days and 6 months after the miscarriage. Kagami et al.[35] reported that depression increased from 8.9% in the ≤3 month period after miscarriage, and to 9.1% in the >3 month period; whereas, anxiety decreased after 3 months. In contrast to our study, Kolte et al.[34] stated that, in 44.4% of women whose last pregnancy loss was six months ago, the time since abortion was not related to psychological factors. In another study, the effect of duration since last recurrent abortion was not evaluated with regard to mental health[12]. The above results indicate that abortion and mental health problems resulting from RSA may sustain even after one year. Therefore, psychological counseling and intervention are necessary for patients with RSA. In our study, the predictors of RSA included GSI, time passed since last pregnancy, education, and

Table 2. Psychological distress according to the residence in two groups

Psychological scores	With RSA		p value†	Without RSA		p value†
	Urban (n=63)	Rural (n=52)		Urban (n=165)	Rural (n=75)	
SCL-90-R (mean ± SD)						
Somatization	1.03±0.60	1.25±0.84	0.104	1.08±0.68	0.56±0.33	0.0001
OCD	1.34±0.62	1.53±0.76	0.138	1.38±0.72	0.59±0.38	0.0001
Interpersonal sensitivity	1.18±0.61	1.53±0.81	0.014	1.19±0.68	0.52±0.34	0.0001
Depression	1.29±0.73	1.55±0.92	0.099	1.17±0.75	0.54±0.34	0.0001
Anxiety	1.02±0.56	1.39±0.98	0.017	1.04±0.75	0.70±0.50	0.0001
Hostility*	1.08±0.69	1.45±0.92	0.021	1.11±0.72	0.57±0.51	0.0001
Phobic anxiety	0.60±0.56	1.03±0.83	0.002	0.72±0.59	0.41±0.31	0.0001
Paranoid ideation	1.27±0.69	1.50±0.86	0.121	1.33±0.73	0.66±0.48	0.0001
Psychoticism	0.69±0.52	1.13±0.98	0.005	0.77±0.63	0.35±0.30	0.0001
GSI	96.88±44.39	123.90±72.14	0.021	98.27±54.93	49.34±26.73	0.0001
IUS (mean ± SD)	67.12±21.70	71.03±22.76	0.349	67.61±21.88	40.66±11.96	0.00001

SD: Standard deviation, SCL-90-R: Symptom Checklist-90-Revised, RSA: Recurrent spontaneous abortion, OCD: Obsessive-compulsive disorder, GSI: Global severity index, IUS: Intolerance of Uncertainty Scale, *Aggression and irritability, †The data were assessed using t-tests

Table 3. Trend of psychological distress after pregnancy loss/birth

Psychological scores†	With RSA			p††	Without RSA			p††
	1-6 months after loss (n=33)	7-12 months after loss (n=38)	>12 months after loss (n=44)		1-6 months after birth (n=118)	7-12 months after birth (n=53)	>12 months after birth (n=69)	
Somatization	1.20±0.69	1.14±0.80	1.07±0.68	0.716	1.10±0.70[b]	1.04±0.59[c]	0.51±0.31b[c]	0.0001
OCD	1.46±0.64	1.51±0.76	1.33±0.67	0.480	1.39±0.71[b]	1.32±0.71[c]	0.55±0.36b[c]	0.0001
Interpersonal sensitivity	1.31±0.64	1.46±0.71	1.26±0.80	0.456	1.21±0.67[b]	1.16±0.66[c]	0.46±0.30b[c]	0.0001
Depression	1.38±0.78	1.56±0.93	1.29±0.77	0.358	1.19±0.74[b]	1.16±0.72[c]	0.46±0.30b[c]	0.0001
Anxiety	1.19±0.71	1.26±0.85	1.13±0.83	0.765	1.12±0.72[b]	1.13±0.69[c]	0.46±0.35b[c]	0.0001
Hostility*	1.37±0.82	1.27±0.84	1.14±0.79	0.445	1.12±0.72[b]	1.14±0.73[c]	0.48±0.38b[c]	0.0001
Phobic anxiety	0.84±0.76	0.83±0.67	0.74±0.75	0.787	0.74±0.61[b]	0.70±0.54[c]	0.37±0.29b[c]	0.0001
Paranoid ideation	1.57±0.81[b]	1.54±0.72[c]	1.09±0.72b[c]	0.007	1.35±0.70[b]	1.27±0.76[c]	0.63±0.49b[c]	0.0001
Psychoticism	0.90±0.71	0.95±0.80	0.82±0.85	0.761	0.80±0.63[b]	0.73±0.59[c]	0.31±0.25b[c]	0.0001
GSI	112.63±52.80	115.68±63.41	100.77±61.99	0.784	100.11±54.02[b]	97.47±50.49[c]	42.56±23.83b[c]	0.0001
IUS	71.6±21.96	72.07±22.44	64.06±21.74	0.494	68.85±20.80[b]	65.49±21.90[c]	37.84±9.71b[c]	0.0001

RSA: Recurrent spontaneous abortion, OCD: Obsessive-compulsive disorder, GSI: Global severity index, IUS: Intolerance of Uncertainty scale, [a]Tukey test significantly in 1-6 months and 7-12 months after loss/birth, [b]Tukey test results 1-6 months and >12 months after loss/birth, [c]Tukey test results 7-12 months and >12 months after loss/birth, *Aggression and irritability, †Data are presented as mean ± standard deviation, ††The data were assessed using t-tests

Table 4. Predictive factors of recurrent spontaneous abortion in the multiple logistic regression analysis in the first stage

Variable	OR	95% CI	p value†
Age >30 years	1.27	0.75-2.24	0.398
GSI >63	6.05	3.27-11.18	0.0001
Time passed since last pregnancy >12 months	1.87	1.29-2.70	0.001
Education			
Under the diploma (R)			0.033
Diploma	0.47	0.25-0.89	0.022
College	0.95	0.47-1.90	0.894
Occupation	0.63	0.23-1.73	0.379
Residence	2.13	1.19-3.81	0.011
Satisfaction with income			
High (R)			0.250
Middle	1.60	0.88-2.90	0.118
Low	1.11	0.48-2.61	0.795

OR: Odds ratio, CI: Confidence interval, GSI: Global severity index, R: Reference, †The data were assessed using multiple logistic regression

place of residence. Similarly, in a previous study, researchers reported that depression rates increased after adjusting for the level of education, income, age, and number of pregnancies [unadjusted OR=4.19, 95% CI=(2.52-6.98), adjusted OR: 5.53, 95% CI=(2.09-14.61)][34]. How can we explain the higher distress in women living in rural areas? Rural and urban areas exhibit differences in terms of social culture. For instance, in rural areas, infertility is considered a stigma. Therefore, rural couples without children may feel more pressurized about being childless than those who live in cites. Supportive care from healthcare professionals can be effective in avoiding distress after pregnancy loss and during a new pregnancy[40]. One of the strengths of our study was the assessment of psychological problems in the two groups at 12 months and more after an abortion and normal delivery. In this period, psychological problems persisted in those with RSA, which provided proof of the need for social support and psychological counseling in this group. The other strong point of our study was the evaluation of psychological distress using the IUS scale, which has never been used in any study in this field.

Study Limitation

The limitation of our study is that the case sample only included women who had experienced RSA in the first trimester due to the absence of cases of abortion in the second trimester. Therefore, it is suggested that future studies include psychiatric evaluations of women who experience abortion in the second trimester.

Conclusion

In conclusion, the findings of our study showed that the psychological distress in women with RSA was higher after abortion, it persisted even after one year since the abortion, and it was of greater intensity in women from rural areas. Therefore, it is suggested that women with RSA be provided with psychological counseling to handle the distress they experience. Thus, the psychological management of distress in women with miscarriage must be included in the treatment of RSA.

Acknowledgments

The authors would like to thank Babol University of Medical Sciences and the participants in this study for their support.

Ethics

Ethics Committee Approval: This study was approved by the Research Ethics Committee of the Babol University of Medical Sciences (ID: MUBABOL.REC.2015.42).
Informed Consent: All patients signed the free and informed consent form.
Peer-review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Z.B., H.A-R., Concept: H.A-R., Z.B., M.F., A.M., Design: H.A-R., Z.B., M.F., A.M., Data Collection or Processing: H.A-R., Analysis or Interpretation: A.B., Literature Search: H.AR., Writing: H.A-R.
Conflict of Interest: No conflict of interest was declared by the authors.
Financial Disclosure: The authors declared that this study received no financial support.

References

1. Basirat Z, Adib Rad H, Esmailzadeh S, Jorsaraei SG, Hajian-Tilaki K, Pasha H, Ghofrani F. Comparison of pregnancy rate between fresh embryo transfers and frozen-thawed embryo transfers following ICSI treatment. Int J Reprod Biomed (Yazd) 2016;14:39-46.
2. Adib Rad H, Basirat Z, Mostafazadeh A, Faramarzi M, Bijani A, Nouri HR, Soleimani Amiri S. Evaluation of peripheral blood NK cell subsets and cytokines in unexplained recurrent miscarriage. J Chin Med Assoc 2018;81:1065-70.
3. Pasha H, Basirat Z, Esmailzadeh S, Faramarzi M, Adibrad H. Marital Intimacy and Predictive Factors Among Infertile Women in Northern Iran. J Clin Diagn Res 2017;11:QC13-QC17.
4. Volmer L, Rösner S, Toth B, Strowitzki T, Wischmann T. Infertile Partners' Coping Strategies Are Interrelated–Implications for Targeted Psychological Counseling. Geburtshilfe Frauenheilkd 2017;77:52-8.
5. Pasha H, Faramarzi M, Esmailzadeh S, Kheirkhah F, Salmalian H. Comparison of pharmacological and nonpharmacological treatment strategies in promotion of infertility self-efficacy scale in infertile women: A randomized controlled trial. Iran J Reprod Med 2013;11:495-502.
6. Sugiura-Ogasawara M, Ozaki Y, Suzumori N. Management of recurrent miscarriage. J Obstet Gynaecol Res 2014;40:1174-9.
7. Practice Committee of the American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss: a committee opinion. Fertil Steril 2013; 99:63. 2012/10/26. DOI: 10.1016/j.fertnstert.2012.09.023.

8. Comba C, Bastu E, Dural O, Yasa C, Keskin G, Ozsurmeli M, et al. Role of inflammatory mediators in patients with recurrent pregnancy loss. Fertil Steril 2015;104:1467-1474.e1.
9. Aisenberg Romano G, Ravid H, Zaig I, Schreiber S, Azem F, Shachar I, Bloch M. The psychological profile and affective response of women diagnosed with unexplained infertility undergoing in vitro fertilization. Arch Womens Ment Health 2012;15:403-11.
10. Toffol E, Koponen P, Partonen T. Miscarriage and mental health: results of two population-based studies. Psychiatry Res 2013;205:151-58.
11. Mevorach-Zussman N, Bolotin A, Shalev H, Bilenko N, Mazor M, Bashiri A. Anxiety and deterioration of quality of life factors associated with recurrent miscarriage in an observational study. J Perinat Med 2012;40:495-501.
12. Craig M, Tata P, Regan L. Psychiatric morbidity among patients with recurrent miscarriage. J Psychosom Obstet Gynaecol 2002;23:157-64.
13. Sugiura-Ogasawara M, Suzuki S, Ozaki Y, Katano K, Suzumori N, Kitaori T. Frequency of recurrent spontaneous abortion and its influence on further marital relationship and illness: the Okazaki Cohort Study in Japan. J Obstet Gynaecol Res 2013;39:126-131.
14. Lok IH, Neugebauer R. Psychological morbidity following miscarriage. Best Pract Res Clin Obstet Gynaecol 2007;21:229-47.
15. Ladouceur R, Gosselin P, Dugas MJ. Experimental manipulation of intolerance of uncertainty: A study of a theoretical model of worry. Behav Res Ther 2000;38:933-41.
16. Geller PA, Kerns D, Klier CM. Anxiety following miscarriage and the subsequent pregnancy: a review of the literature and future directions. J Psychosom Res 2004;56:35-45.
17. Boivin J, Lancastle D. Medical waiting periods: imminence, emotions and coping. Womens Health (Lond) 2010;6:59-69.
18. Report of a WHO Technical Consultation on Birth Spacing Geneva Switzerland 13-15 June 2005. 2007.
19. Nynas J, Narang P, Kolikonda MK, Lippmann S. Depression and anxiety following early pregnancy loss: recommendations for primary care providers. Prim Care Companion CNS Disord 2015;17(1).
20. Sham Ak, Yiu Mg, Ho Wy. Psychiatric morbidity following miscarriage in Hong Kong. Gen Hosp Psychiatry 2010;32:284-93.
21. Bergner A, Beyer R, Klapp BF, Rauchfuss M. Pregnancy after early pregnancy loss: a prospective study of anxiety, depressive symptomatology and coping. J Psychosom Obstet Gynaecol 2008;29:105-113.
22. Fertl KI, Bergner A, Beyer R, Klapp BF, Rauchfuss M. Levels and effects of different forms of anxiety during pregnancy after a prior miscarriage. Eur J Obstet Gynecol Reprod Biol 2009;142:23-9.
23. Grote NK, Bridge JA, Gavin AR, Melville JL, Iyengar S, Katon WJ. A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. Arch Gen Psychiatry 2010;67:1012-24.
24. Lachmi-Epstein A, Mazor M, Bashiri A. Psychological and mental aspects and" tender loving care" among women with recurrent pregnancy losses. Harefuah 2012;151:633-7, 54.
25. Bhat A, Byatt N. Infertility and perinatal loss: when the bough breaks. Curr Psychiatry Rep 2016;18:31.
26. Li J, Liu B, Li M. Coping with infertility: a transcultural perspective. Curr Opin Psychiatry 2014;27:320-5.
27. Musters AM, Taminiau-Bloem EF, van den Boogaard E, van der Veen F, Goddijn M. Supportive care for women with unexplained recurrent miscarriage: patients' perspectives. Hum Reprod 2011;26:873-7.
28. Rentz AM, Kahrilas P, Stanghellini V, Tack J, Talley NJ, de la Loge C, et al. Development and psychometric evaluation of the patient assessment of upper gastrointestinal symptom severity index (PAGI-SYM) in patients with upper gastrointestinal disorders. Qual Life Res 2004;13:1737-49.
29. Sugiura-Ogasawara M, Nakano Y, Ozaki Y, Furukawa TA. Possible improvement of depression after systematic examination and explanation of live birth rates among women with recurrent miscarriage. J Obstet Gynaecol 2013;33:171-4.
30. Francis K, Dugas MJ, Ricard NC. An exploration of Intolerance of Uncertainty and memory bias. J Behav Ther Exp Psychiatry 2016;52:68-74.
31. Buhr K, Dugas MJ. Investigating the construct validity of intolerance of uncertainty and its unique relationship with worry. J Anxiety Disord 2006;20:222-36.
32. Haghparast E, Faramarzi M, Hassanzadeh R. Psychiatric symptoms and pregnancy distress in subsequent pregnancy after spontaneous abortion history. Pak J Med Sci 2016;32:1097-101.
33. Salmalian H, Nasiri Amiri F, Kheyrkhah F. Prevalence of pre and postpartum depression symptoms and some related factors (Babol; 2006-2007). Journal Of Babol University Of Medical Sciences (Jbums) 2008;10:67-75.
34. Kolte AM, Olsen LR, Mikkelsen EM, Christiansen OB, Nielsen HS. Depression and emotional stress is highly prevalent among women with recurrent pregnancy loss. Hum Reprod 2015;30:777-82.
35. Kagami M, Maruyama T, Koizumi T, Miyazaki K, Nishikawa-Uchida S, Oda H, et al. Psychological adjustment and psychosocial stress among Japanese couples with a history of recurrent pregnancy loss. Hum Reprod 2012;27:787-94.
36. Carleton RN, Duranceau S, Shulman EP, Zerff M, Gonzales J, Mishra S. Self-reported intolerance of uncertainty and behavioural decisions. J Behav Ther Exp Psychiatry 2016;51:58-65.
37. Carleton RN, Mulvogue MK, Thibodeau MA, McCabe RE, Antony MM, Asmundson GJ. Increasingly certain about uncertainty: Intolerance of uncertainty across anxiety and depression. J Anxiety Disord 2012;26:468-79.
38. Talkovsky AM, Norton PJ. Intolerance of uncertainty and transdiagnostic group cognitive behavioral therapy for anxiety. J Anxiety Disord 2016;41:108-14.
39. Broen AN, Moum T, Bødtker AS, Ekeberg O. The course of mental health after miscarriage and induced abortion: a longitudinal, five-year follow-up study. BMC Med 2005;3:18.
40. Musters AM, Koot YE, van den Boogaard NM, Kaaijk E, Macklon NS, van der Veen F, et al. Supportive care for women with recurrent miscarriage: a survey to quantify women's preferences. Hum Reprod 2013;28:398-405.

Clinical Investigation / Araştırma

DOI: 10.4274/tjod.galenos.2019.93584

Turk J Obstet Gynecol 2019;16:158-63

Surgical risk assessment for gynecological oncologic patients

Jinekolojik onkoloji hastalarda cerrahi risk değerlendirmesi

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Abstract

Objective: Preoperative surgical risk assessment is important in terms of postoperative morbidity and mortality. Therefore, it is necessary to evaluate the efficacy and safety of these surgeries via an ideal risk assessment model, and reduce risks via applying some findings (for instance, perioperative beta-blockers). There are some risk assessment systems, but these have generally not been verified for patients with gynecologic cancer. The aim of this study was to assess the risk of surgery for gynecological oncologic patients and suggest an easy risk assessment model and risk reduction by applying our findings.

Materials and Methods: We retrospectively analyzed 258 gynecologic patients with cancer. Age, diagnosis, staging, performance scale, metoprolol use, heart, renal diabetes, Chronic Obstructive Pulmonary disease, diabetes, operation type and length, carcinoma antigen 125, ascites, albumin, surgical procedure, hospitalization length, and complications were recorded.

Results: Of the 258 patients, 173 patients (67.1%) had no complications, 43 patients (16.7%) had one and 42 patients (16.3%) had two or more complications. The most common complication was the acid-base imbalance (14%), followed by urinary tract infection (9.7%). Parameters associated with complications were performance status, ascites, operating length, metoprolol use, and upper abdominal surgery. In our proposed scoring model with a total score range 0-23, cut-off value points for both the presence and rate of complications was found as >5.

Conclusion: In gynecological patients with cancer, the addition of metoprolol use and upper abdominal surgery within preoperative risk assessment evaluation parameters are significantly effective in predicting the rate and severity of complications. Moreover, we have suggested a simple, practical, and convenient scoring model for this evaluation.

Keywords: Gynecological oncology, metoprolol, upper abdominal surgery, surgical risk assessment

Öz

Amaç: Cerrahi risk değerlendirilmesi, cerrahi işlem sırasında ve sonrasında morbidite ve mortalite açısından önem taşımaktadır. Risk değerlendirmeleriyle cerrahi tedavinin etkinliği ve güvenliği belirlenerek, gerektiğinde risk azaltıcı prosedürler uygulanabilir (örneğin beta bloker kullanımı).

Günümüzde kullanılan bazı risk değerlendirme sistemleri bulunsa da jinekolojik kanser hastalarında kabul edilmiş bir sistem bulunmamaktadır. Bu çalışmanın amacı jinekolojik onkoloji hastalarında kolay uygulanacak risk değerlendirme modeli ile cerrahi riskini değerlendirerek, ön görülen riskler için risk azaltıcı yöntemlerin uygulanmasını sağlamaktır.

Gereç ve Yöntemler: Jinekolojik kanser tanısı alan 258 hasta retrospektif olarak analiz edildi. Yaş, hastalığın tipi ve evresi, karsinoma antijen 125 seviyesi, asit varlığı, albümin düzeyi, cerrahi prosedür ve süresi, hastanede yatış süresi ve komplikasyonlar kaydedildi. Hastaların özgeçmişinde; performans ölçeği, metoprolol kullanımı, diabetes mellitus, kalp, böbrek ve Kronik Obstrüktif Akciğer hastalıkları değerlendirildi.

Bulgular: Toplam 258 hastadan 173 (%67,1) hastada hiçbir komplikasyon bulunmazken, 43 (%16,7) hastada yalnızca bir komplikasyon ve 42 (%16,3) hastada ≥2 komplikasyon saptandı. En yaygın komplikasyon-baz dengesizliği (%14) ve ikinci sırada idrar yolları enfeksiyonu izlendi.

Hastanın performans durumunun, asit varlığının, operasyon süresinin ve metoprolol kullanımının komplikasyon gelişmesi ile ilişkili olduğu saptandı. Çalışmada kullanılan 0-23 puan aralığına sahip skorlama modelinde, skorun 5'in üzerinde olması artmış komplikasyon sayısı ve komplikasyon gelişme riski açısından anlamlı bulunmuştur.

Sonuç: Jinekolojik kanser hastalarının preoperatif risk değerlendirmesine, metoprolol kullanılıp kullanılmadığının ve üst batın cerrahisinin planlanıp planlanmadığının eklenmesi, komplikasyon gelişme ve sayısını tahmin etmede yarar sağlamaktadır. Bunlara ek olarak çalışmada kolay uygulanabilecek bir skorlama modeli önerilmektedir.

Anahtar Kelimeler: Jinekolojik onkoloji, metoprolol, üst batın cerrahisi, cerrahi risk değerlendirmesi

PRECIS: For preoperative risk assessment in gynecologic cancers, a simple and practical scoring model is recommendable. Moreover, the addition of metoprolol use and upper abdominal surgery improve the accuracy of these programs.

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Received/Geliş Tarihi: 09.03.2019 **Accepted/Kabul Tarihi:** 09.06.2019

Introduction

In 2016, approximately 105.000 new cases of gynecologic malignancies were estimated in the United States of America[1]. Two-thirds of these cases will undergo surgery[2]. Usually, complete tumor resection is a goal, and these surgeries may be expanded as upper abdominal surgery such as diaphragmatic peritoneal resection, splenectomy, and segmental liver resection according to the patients' condition and diagnosis[3]. It is necessary to evaluate the efficacy and safety of these surgeries because of the association between extensive surgical procedures and postoperative morbidity and mortality[4]. Furthermore, the initiation of postoperative chemotherapy may lag due to these complications[4]. For example, extensive debulking ovarian cancer surgery to no gross residual tumor may be accompanied by major complications in about 50% of these patients, especially in older patients, the risks of mortality and morbidity are greater[5]. There are some risk assessment systems for surgical risk assessment; however, generally, the predictive value of these systems has not been verified for patients with gynecologic cancer[6,7]. Therefore, a risk scoring model study was performed to predict major complications in patients with ovarian cancer who underwent laparoscopic interventions before primary debulking surgery. In the validation population, observed risk and predicted risks were 16.7% and 17.8%, respectively. The major contribution of this study was to provide a preoperative tool to predict outcomes[5]. An ideal risk assessment model would be simple, reproducible, authentic and correct, objective, and accessible to all patients, and especially able to perform personalized assessments of patients according to the use of patient-specific characteristics[5,8]. Furthermore, ideally, it should be low-cost and feasible to perform at the bedside[8]. Thus, as physicians, our endeavor is to perform a simple and practical risk assessment to prevent complications and assure decreased peri-operative healthcare costs and postoperative morbidity and mortality. Notably, when compared with other elections, conservative treatment or neoadjuvant chemotherapy can be performed instead of upfront surgical treatment[5,9]. Several studies have shown that the use of perioperative beta-blockers (metoprolol was shown as more suitable), reduces mortality in both cardiologically high and low-risk operations[10-13]. The aim of this study was to assess the risk of surgery for gynecological oncologic patients and to suggest an easy risk assessment model that was feasible to perform at the bedside, and reduce risk of postoperative complications by applying our data and findings.

Materials and Methods

Study design

We retrospectively analyzed 258 patients with gynecologic cancer who underwent surgery between 2008 and 2017, and whose complete data were available. In our center, Eastern Cooperative Oncology Group (ECOG) performance status (PS) score findings and presence of systemic diseases are routinely determined and noted in patient files during the hospitalization of the patients. Additionally, we measure electrolytes and draw blood gases for all patients before and after surgery; we analyzed these data.

Study variables

The evaluated parameters were stage of primary disease according to the International Federation of Gynecology and Obstetrics (FIGO) (stage 1-2: non-disseminated, stage 3-4: disseminated), age (<65 or ≥65 years),[14] PS scale (ECOG),[15] carcinoma antigen 125 (CA-125) (<500, 500-1000, >1000 IU/dL), amount of ascites (<500, 500-1000, >1000 mL), diabetes (no, <10 years, >10 years,) according to a few studies about duration-related diabetes morbidity,[16,17] Chronic Obstructive Pulmonary disease (COPD), heart disease (arrhythmia, heart failure), renal disease (renal failure, others), preoperative albumin (<3 or >3 g/dL),[7] surgical procedures including major pelvic surgery,[18] and upper abdominal surgery,[3] the total surgical time[2] (<4 or ≥4 hours), metoprolol use,[10,13] operation intent (primary, recurrent), and the length of hospital stay (Table 1). We categorized these parameters as the above-mentioned references[2,3,10-18]. Complications were electrolyte imbalance (hypernatremia, hyponatremia, hypokalemia hyperkalemia, hypocalcemia, hypercalcemia, hypermagnesemia, hypomagnesemia), acid-base imbalance, pneumonia, venous thromboembolism, death, surgical site infection, renal failure, postoperative transfusion, and urinary tract infection (UTI) (Table 2). Diagnosis was made histopathologically. The patient

Table 1. Scoring parameters and model

Scoring parameters	0 points	1 point	2 points
Stage	Early	Advanced	
Age	<65	≥65	
ECOG	0-1	2	3-4
CA-125	<500	500-1000	>1000
Ascites	<500	500-1000	>1000
Diabetes	No	<10 years	>10 years
COPD	No		Yes
Heart disease	No	Arrhythmia	Failure
Renal disease	No	The others	Failure
Albumin	≥3	<3	
Upper abdominal surgery	No		Yes
Major pelvic surgery	No		Yes
Total surgical time	<4 hours	≥4 hours	
Metoprolol use	Yes	No	

CA-125: Carcinoma antigen 125, ECOG: Eastern Cooperative Oncology Group, COPD: Chronic Obstructive Pulmonary Disease

who underwent the first surgery was recorded as primary and the others were as recurrent. We recorded scoring system parameters using specific criteria. The stage was determined according to the FIGO criteria. PS was recorded according to the ECOG score, which is classified from 0 to 4. Patents who are ECOG 0 have no limitations, ECOG 1 has mild limitation in exhausting activity, ECOG 2 is partially dependent, and ECOG 3 is capable of limited self-care. Patients wo are ECOG 4 cannot resume self-care without continuous support[15]. Upper abdominal surgery includes diaphragmatic peritoneal resection, splenectomy, pancreatectomy, gastrectomy, segmental liver resection, and biliary surgery. Major pelvic surgery encompasses radical hysterectomy, pelvic lymph node dissection, pelvic exenteration, and debulking surgery[3,18]. In our center, within a certain time period, based on previous studies,[10-13] 8.5% of patients received metoprolol two days prior to surgery and continued one week after surgery. Postoperative complications including acid-base imbalance, electrolyte imbalance, pneumonia, surgical site infection, and renal failure were defined and recorded according to the Common Terminology Criteria for Adverse Events[19]. Additionally, we recorded the presence of complications, number of complications, and total score. The study was approved by the Süleyman Demirel University Local Ethics Committee (approval number: 164, date: 28.09.2016). Additionally, consent forms were routinely completed by patients at the time of hospitalization.

Statistical Analysis

Statistical analyses were performed using the Medcalc Software (version 16.8). Forward regression analysis was used to identify the predictive scoring parameters. P values of 0.05 or less were regarded as statistically significant. We used multiple regression analysis to predict the number of complications, presence of complications, and length of hospital stay. We assessed the area under the curves (AUC) of the receiver operating characteristic (ROC) curve for predicting models of risk scoring. To assess the optimal cut-off point, Youden's index (sensitivity + specificity-1) was used.

Results

The mean age of the entire population was 58.8±10.9 years, where 77 patients (29.8%) were aged ≥65 years. The median total surgical time was 4 (range, 0.5-13) hours. The number of patients who underwent surgery for primary disease was 214 (82.9%) and for the recurrent disease it was 44 (17.1%). The majority of the patients were early stage (61.2%). In our study, 157 patients (60.9%), 85 patients (32.9%) and 16 patients (6.2%) underwent surgery for uterine cancer, ovarian cancer, and cervical cancer, respectively. We follow up the patients according to enhanced recovery after surgery protocols[20,21] and the median length of hospital stay was 9 (range, 1-65) days. Our center is a reference center and accepts complicated patients; for instance, 201 patients (77.9%) underwent major pelvic surgery, so the median length of hospital stay was found as 9 days. When PS was evaluated, there were 183 patients (70.9%) with ECOG PS <2, 43 patients (16.7%) with an ECOG PS of 2, and 32 patients (12.4%) with ECOG PS ≥3 (the majority of them were under ECOG 2). In the analysis of complications, the majority of patients (173 patients, 67.1%) had no complications, 43 patients (16.7%) had one complication, and 42 patients (16.3%) had ≥2 complications. The most common complication was acid-base imbalance (14%), followed by UTI (9.7%) (Table 2). In multiple regression analysis, ECOG (p=0.02), ascites (p<0.01), total surgical time (p<0.0001), metoprolol use (p<0.0001), and upper abdominal surgery (p<0.0001) were found to be significantly effective for predicting complications (Table 3). ECOG score (p<0.001), presence of ascites (p<0.01), diabetes (p<0.01), major pelvic surgery (p<0.04), total surgical time (p<0.0004), metoprolol use (p<0.001), and upper abdominal surgery (p<0.001) were also found to be significantly correlated with the number of complications (Table 4). We assessed the performance of the scoring system using the ROC curve for estimating the presence of complications (Figure 1A). Finally, we evaluated the estimated count of complications (>1) using the ROC curve according to the scoring system (Figure 1B). In our scoring model, the total score range was between 0-23.

Table 2. Complications and their distributions

Complication	Rate
Electrolyte imbalance	5%
Acid-base imbalance	14%
Pneumonia	1.6%
VTE	3.9%
Death	2.3%
Surgical site infection	5.4%
Renal failure	8.9%
Postoperative transfusion	8.9%
UTI	9.7%

UTI: Urinary tract infection, VTE: Venous thromboembolism

Table 3. Multiple regression analysis results for the correlation between parameters and presence of complication (parameters with p<0.05 were included)

Efficient parameters	p	r partial	Coefficient
ECOG	0.02	0.14	0.09
Ascites	0.01	0.16	0.13
Length of total operation time	0.0001	0.24	0.23
Metoprolol using	0.0001	-0.23	-0.38
Upper abdominal surgery	0.0001	-0.22	-0.13

ECOG: Eastern Cooperative Oncology Group
For multiple regression analysis, p=0.001

For the presence of complications, the AUC was found as 0.60 with 95% confidence interval (CI) 0.54-0.66 and the Youden's index was 0.18; the cut-off value in the model was >5, p=0.005. For the complications count, the AUC was found as 0.70 with 95% CI 0.64-0.75, and the Youden's index was 0.35; the cut-off value in the model was >5, p<0.001.

Discussion

Main findings

Our study demonstrates that preoperative metoprolol use decreases and upper abdominal surgery increases the risk and number of postoperative complications in gynecological cancers. Additionally, other parameters that showed an association with postoperative complications and significance in our scoring system were the stage of the disease, ECOG, ascites, major pelvic surgery, total surgical time, and diabetes.

Table 4. Multiple regression analysis results for the correlation between parameters and count of complications (parameters with p<0.05 were included)

Efficient parameters	p value	r partial	coefficient
ECOG	0.001	0.20	0..20
Ascites	0.01	0.15	0.20
Diabetes	0.01	0.14	0.18
Major pelvic surgery	0.04	0.12	0.11
Total surgical time	0.0004	0.22	0.33
Metoprolol use	0.001	-0.20	-0.51
Upper abdominal surgery	0.001	-0.20	-0.19

ECOG: Eastern Cooperative Oncology Group
For multiple regression analysis, p=0.001

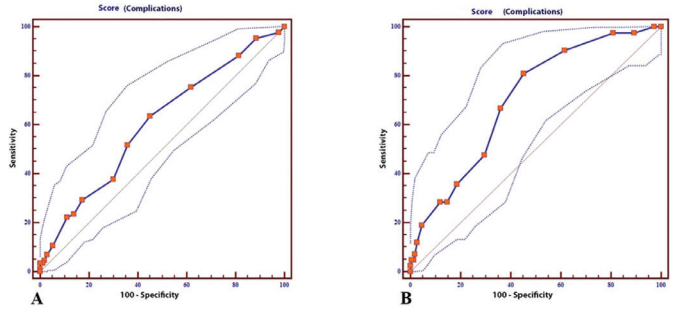

Figure 1. Performance assessment of the scoring system to predict the complications using the receiver operating characteristic curve. A) For the presence of complications, the area under curve (AUC) was found as 0.60 (thick and quadratic curve) with 95% confidence interval (CI) 0.54-0.66 (dotted curves for lower and upper bound of 95% CI). Youden's index was 0.18 (cut-off value for the count of points in the model >5), p=0.005, B) For the count of complication, the AUC was found as 0.70 (thick and quadratic curve) with 95% CI: 0.64-0.75 (dotted curves for lower and upper bound of 95% CI). Youden's index was 0.35 (cut-off value for the count of points in the model >5), p<0.0001

Results of the study in the context of other observations

Similar to previous studies, the most common type of gynecologic cancer was uterine cancer, followed by ovarian and cervical cancer in this study[1]. In gynecologic cancers, prediction of postoperative complications is important because the incidence of these diseases is progressively increasing[2,4]. As a consequence, postoperative morbidity, mortality, and healthcare costs can be reduced through the prevention of postoperative complications. Previous studies have depicted that several parameters such as age, advanced stage, poor performance, ascites ≥1000, hypoalbuminemia, extended surgical time, and extensive surgery were associated with a higher risk of postoperative complications[4-6,22-27]. There are several studies about surgical risk assessment. Although some studies have been evaluated for gynecological cancers,[2] generally they are non-specific in terms of gynecologic cancers or validated only for ovarian cancer[25-29]. On the other hand, several studies have shown that peri-operative beta-blockers use (metoprolol being more suitable and beneficial) was associated with reduced mortality among patients with high and low cardiac risk[10-13]. In our study, we evaluated the effect of metoprolol use on postoperative mortality and morbidity and it was significantly correlated with the prediction of complications (p<0.0001). Some studies investigated the role of extended surgery on postoperative mortality and morbidity. Patankar et al.[26] reported that extended cytoreductive procedures were the strongest risk factor for complications in ovarian cancers. Conversely, Phillips et al.[27] found that the number of surgical procedures was significantly correlated with an increased risk of major morbidity, and was a better predictor of major postoperative morbidity than the high-risk performance alone. Also, in the prediction of major complications, they found that ultra-radical surgery was less useful than any solitary gastrointestinal resection. They identified standard surgery as "total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, pelvic and/or para-aortic lymphadenectomy, and bowel surgery outside the definition of 'ultra-radical' (localized colonic resection, non-multiple bowel resection)" and ultra-radical surgery as "diaphragmatic stripping, extensive peritoneal stripping, multiple resections of the bowel (excluding localized colonic resection), liver resection, partial gastrectomy, cholecystectomy, splenectomy"[27]. In this study, upper abdominal surgery was found as a risk factor for postoperative complications. Other parameters that showed significance in our scoring system were the stage, ECOG, ascites, major pelvic surgery, total surgical time, and diabetes. Preoperative albumin levels, CA-125 levels, COPD, and heart and renal disease were parameters that were assessed in prior studies[4,6,7]. These parameters have been found

to be correlated significantly with postoperative complications. According to a study designed by Ataseven et al.[23] preoperative hypoalbuminemia had been found as an independent predictive parameter for severe postoperative complications in epithelial ovarian cancer. Conversely, in our study, no significant correlation was found between hypoalbuminemia and postoperative complications in gynecologic cancers. CA-125 levels had no significant correlation with postoperative complications, which was probably influenced by our study design with the inclusion of all gynecologic cancers. Also, there were not many patients with COPD, renal disease, and heart disease in the study population, and thus these parameters were not found eligible for predicting complications. In our study, after estimating the risk assessment with ROC analysis, we found the AUC as 0.60 for the presence of complications and 0.70 for the number of complications, respectively. We have arranged a simple, practical and convenient model for preoperative risk assessment in patients with gynecological cancer.

Study Limitations

The main strength of this study is the recommendation of a simple, practical, and convenient scoring model for preoperative risk assessment in patients with gynecologic cancer, also the addition of metoprolol use and upper abdominal surgery to preoperative risk assessment parameters.

Our study covered all gynecologic cancers and this is the main limitation of this study, Thus, to develop more effective scoring systems, further studies with specific patients and diagnostic groups are needed.

Preclinical/clinical implications

In this research study we investigated if any preclinical/clinical implications would forebode postoperative complications. As a result, the evaluation and prediction of metoprolol use, upper abdominal surgery, stage of disease, ECOG, ascites, major pelvic surgery, total surgical time, and diabetes status were found as effective parameters; thus, preoperative improvement of these parameters could be beneficial in terms of reducing postoperative complications in gynecologic cancers.

Conclusion

Several studies have shown that the use of perioperative metoprolol reduces mortality and morbidity in patients with both high and low cardiac risk. We added metoprolol use and upper abdominal surgery into the parameters of the evaluation system and as a result, metoprolol use decreased and upper abdominal surgery increased the risk and number of complications in gynecological cancers; therefore, these two parameters can also be used for predicting risk in patients with gynecologic cancer. Moreover, we have suggested a simple, practical and convenient scoring model for preoperative risk assessment in patients with gynecologic cancer.

Ethics

Ethics Committee Approval: The study was approved by the Süleyman Demirel University Local Ethics Committee (approval number: 164, date: 28.09.2016).

Informed Consent: Consent form routinely has filled out by patients at the hospitalization time.

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.E., Concept: E.E., Ç.B., Design: E.E., Ç.B., Data Collection or Processing: Ç.B., M.G., Analysis or Interpretation: E.E., J.R., S.C.İ., Literature Search: E.E., Ç.B., J.R., Writing: E.E., J.R., S.C.İ.

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

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66:7-30.
2. Uppal S, Igwe E, Rice LW, Spencer RJ, Rose SL. Frailty index predicts severe complications in gynecologic oncology patients. Gynecol Oncol 2015;137:98-101.
3. Benedetti Panici P, Di Donato V, Fischetti M, Casorelli A, Perniola G, Musella A, et al. Predictors of postoperative morbidity after cytoreduction for advanced ovarian cancer: Analysis and management of complications in upper abdominal surgery. Gynecol Oncol 2015;137:406-11.
4. Vizzielli G, Costantini B, Tortorella L, Pitruzzella I, Gallotta V, Fanfani F, et al. A laparoscopic risk-adjusted model to predict major complications after primary debulking surgery in ovarian cancer: A single-institution assessment. Gynecol Oncol 2016;142:19-24.
5. Barber EL, Rutstein S, Miller WC, Gehrig PA. A preoperative personalized risk assessment calculator for elderly ovarian cancer patients undergoing primary cytoreductive surgery. Gynecol Oncol 2015;139:401-6.
6. Szender JB, Frederick PJ, Eng KH, Akers SN, Lele SB, Odunsi K. Evaluation of the National Surgical Quality Improvement Program Universal Surgical Risk Calculator for a gynecologic oncology service. Int J Gynecol Cancer 2015;25:512-20.
7. Uppal S, Al-Niaimi A, Rice LW, Rose SL, Kushner DM, Spencer RJ, et al. Preoperative hypoalbuminemia is an independent predictor of poor perioperative outcomes in women undergoing open surgery for gynecologic malignancies. Gynecol Oncol 2013;131:416-22.
8. Barnett S, Moonesinghe SR. Clinical risk scores to guide perioperative management. Postgrad Med J 2011;87:535-41.
9. Chand M, Armstrong T, Britton G, Nash GF. How and why do we measure surgical risk? J R Soc Med 2007;100:508-12.
10. Wiesbauer F, Schlager O, Domanovits H, Wildner B, Maurer G, Muellner M, et al. Perioperative beta-blockers for preventing surgery-related mortality and morbidity: a systematic review and meta-analysis. Anesth Analg 2007;104:27-41.
11. Angeli F, Verdecchia P, Karthikeyan G, Mazzotta G, Gentile G, Reboldi G. ß-Blockers reduce mortality in patients undergoing high-risk non-cardiac surgery. Am J Cardiovasc Drugs 2010;10:247-59.
12. POISE Study Group, Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, et al. Effects of extended-release metoprolol succinate

in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. Lancet 2008;371:1839-47.
13. Devereaux PJ, Beattie WS, Choi PT, Badner NH, Guyatt GH, Villar JC, et al. How strong is the evidence for the use of perioperative beta blockers in non-cardiac surgery? Systematic review and meta-analysis of randomised controlled trials. BMJ 2005;331:313-21.
14. Mistry PK, Gaunay GS, Hoenig DM. Prediction of surgical complications in the elderly: Can we improve outcomes? Asian J Urol 2017;4:44-9.
15. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-55.
16. Bethel MA, Sloan FA, Belsky D, Feinglos MN. Longitudinal incidence and prevalence of adverse outcomes of diabetes mellitus in elderly patients. Arch Intern Med 2007;167:921-7.
17. Huang ES, Laiteerapong N, Liu JY, John PM, Moffet HH, Karter AJ. Rates of complications and mortality in older patients with diabetes mellitus: the diabetes and aging study. JAMA Intern Med 2014;174:251-8.
18. Cardosi RJ, Cox CS, Hoffman MS. Postoperative neuropathies after major pelvic surgery. Obstet Gynecol 2002;100:240-4.
19. National Institutes of Health (NIH), National Cancer Institute, Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0, 2009-2010, NIH Publication No. 09-5410, https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
20. Nelson G, Altman AD, Nick A, Meyer LA, Ramirez PT, Achtari C, et al. Guidelines for pre- and intra-operative care in gynecologic/oncology surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations--Part I. Gynecol Oncol 2016;140:313-22.
21. Nelson G, Altman AD, Nick A, Meyer LA, Ramirez PT, Achtari C, et al. Guidelines for postoperative care in gynecologic/oncology surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations--Part II. Gynecol Oncol 2016;140:323-32.
22. Clark RM, Lee MS, Alejandro Rauh-Hain J, Hall T, Boruta DM, del Carmen MG, et al. Surgical Apgar Score and prediction of morbidity in women undergoing hysterectomy for malignancy. Gynecol Oncol 2015;136:516-20.
23. Ataseven B, du Bois A, Reinthaller A, Traut A, Heitz F, Aust S, et al. Pre-operative serum albumin is associated with post-operative complication rate and overall survival in patients with epithelial ovarian cancer undergoing cytoreductive surgery. Gynecol Oncol 2015;138:560-5.
24. Melamed A, Bercow AS, Bunnell K, Rauh-Hain JA, Wright JD, Rice LW, et al. Age-Associated Risk of 90-Day Postoperative Mortality After Cytoreductive Surgery for Advanced Ovarian Cancer. JAMA Surg 2019;154:669-71.
25. Zighelboim I, Kizer N, Taylor NP, Case AS, Gao F, Thaker PH, et al. "Surgical Apgar Score" predicts postoperative complications after cytoreduction for advanced ovarian cancer. Gynecol Oncol 2010;116:370-3.
26. Patankar S, Burke WM, Hou JY, Tergas AI, Huang Y, Ananth CV, et al. Risk stratification and outcomes of women undergoing surgery for ovarian cancer. Gynecol Oncol 2015;138:62-9.
27. Phillips A, Sundar S, Singh K, Pounds R, Nevin J, Kehoe S, et al. The NICE classification for 'Ultra-radical (extensive) surgery for advanced ovarian cancer' guidance does not meaningfully predict postoperative complications: a cohort study. BJOG 2019;126:96-104.
28. Cham S, Chen L, St Clair CM, Hou JY, Tergas AI, Melamed A, et al. Development and validation of a risk-calculator for adverse perioperative outcomes for women with ovarian cancer. Am J Obstet Gynecol 2019;220:571.e1-571.e8.
29. Jering MZ, Marolen KN, Shotwell MS, Denton JN, Sandberg WS, Ehrenfeld JM .Combining the ASA Physical Classification System and Continuous Intraoperative Surgical Apgar Score Measurement in Predicting Postoperative Risk. J Med Syst 2015;39:147.

Clinical Investigation / Araştırma

DOI: 10.4274/tjod.galenos.2019.62558

Turk J Obstet Gynecol 2019;16:164-8

Visceral adiposity indicators as predictors of metabolic syndrome in postmenopausal women

Postmenapozal kadınlarda metabolik sendromun belirleyicisi olarak viseral adipozite indikatörleri

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Abstract

Objective: The aim of the present study was to evaluate the importance of visceral adiposity indicators on metabolic parameters in postmenopausal women.
Materials and Methods: This cross-sectional study included 200 postmenopausal subjects. Postmenopausal women were divided into two groups based on the presence of metabolic syndrome (MetS) as MetS+ and MetS-. Comparisons of clinical and metabolic characteristics were performed between the groups.
Results: The current study included 200 postmenopausal women and 63 subjects were diagnosed as having MetS. Postmenopausal women with MetS demonstrated significantly higher values with respect to systolic and diastolic blood pressures, body mass index (BMI), waist-hip ratio (WHR), triglyceride (TG), lipid ratios, Homeostasis Model Assessment Insulin Resistance (HOMA) index, TG glucose (TyG), Visceral Adiposity Index (VAI), and lipid accumulation product (LAP) when compared with women without MetS. Correlation analyses showed that LAP and VAI were positively correlated with waist circumference, WHR, BMI, TG, lipid ratios, TyG and HOMA index, and with each other. LAP was also positively correlated with blood pressures.
Conclusion: Visceral adiposity indicators may be useful as predictors of MetS in postmenopausal women.
Keywords: Menopause, metabolic syndrome, lipid accumulation product, visceral obesity

Öz

Amaç: Bu çalışmanın amacı postmenapozal kadınlarda viseral adipozite indikatörlerinin metabolik parametreler üzerine etkisini araştırmaktır.
Gereç ve Yöntemler: Bu kesitsel çalışmaya 200 postmenapozal kadın dahil edildi. Postmenopozal kadınlar metabolik sendromun (MetS) varlığına göre MetS+ ve MetS- olmak üzere iki gruba ayrıldı. Gruplar arasında klinik ve metabolik parametrelerin karşılaştırılması gerçekleştirildi.
Bulgular: Bu çalışmaya 200 postmenapozal kadın dahil edildi ve 63 olguda MetS saptandı. MetS saptandığı postmenapozal kadınlarda, MetS saptanmayanlara göre kan basınçları, vücut kitle indeksi (VKİ), bel-kalça oranı (BKO), trigliserit (TG), lipit oranları, insülin direnci testi (HOMA) indeksi, TG-glukoz (TyG), Viseral Adipozite İndeksi (VAİ), lipid birikim ürünü (LBÜ) değerleri anlamlı olarak daha yüksek bulunmuştur. Korelasyon analizlerinde VAİ ve LBÜ, bel çevresi, BKO, VKİ, TG, lipit oranları, TyG ve HOMA indeksi ve birbirleri ile pozitif korelasyon gösterdiği tespit edilmiştir. LBÜ ayrıca kan basıncı ile pozitif korelasyon göstermiştir.
Sonuç: Viseral adipozite indikatörleri postmenapozal kadınlarda MetS prediksiyonunda yararlı olabilir.
Anahtar Kelimeler: Menapoz, metabolik sendrom, lipit birikim ürünü, viseral obezite

Introduction

Obesity is a major risk factor for many conditions including metabolic syndrome (MetS) and cardiovascular disease (CVD), and also is a leading avoidable cause of death worldwide[1,2]. MetS, a cluster of conditions including abdominal obesity, hypertension, hyperglycemia, and dyslipidemia, serves as a risk factor for type 2 diabetes mellitus (T2DM) and CVD, and is becoming a serious health problem due to the rising trend in the prevalence of obesity worldwide[1,3]. Insulin resistance (IR) is also determined as a hallmark feature and a major underlying mechanism of the syndrome[4-6]. Abdominal obesity, rather than general obesity, is linked to IR with higher risks of MetS and CVD in postmenopausal women[7]. Lipid accumulation product (LAP) and Visceral Adiposity Index (VAI) are clinical markers of visceral obesity and have been proposed as simple, novel

PRECIS: Visceral adiposity indicators may be useful in the early detection of metabolic syndrome in postmenopausal women.

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Received/Geliş Tarihi: 24.06.2019 **Accepted/Kabul Tarihi:** 18.07.2019

metabolic indices, that combine anthropometric parameters and metabolic variables as effective markers that have reliable accurracy for predicting MetS[8,9]. The triglyceride glucose (TyG) index, a simple measure that combines fasting plasma glucose and triglyceride (TG), is also determined as a good marker for identifying individuals with IR and MetS[9,10]. A recent study emphasized the importance of menopausal status on the predictive value of LAP and VAI for MetS, and further studies are recommended; special attention is suggested while applying these markers in women of menopausal transition[11]. In another study, LAP and VAI were also found to be effective markers for identifying the metabolically obese, normal-weight individuals who are predisposed to diabetes and CVD development[12]. In a recent meta-analysis, the pooled prevalence of MetS was found as 37.17% among postmenopausal women[13]. MetS was also found to be more prevalent in postmenopausal women compared with premenopausal women[13]. Additionally, in another meta-analysis, it was also suggested that almost all MetS-associated components except high-density lipoprotein cholesterol (HDL-C) were unfavorably changed after menopause[14]. Early recognition of high-risk individuals is important because MetS is a cluster of risk factors for CVD and diabetes, and menopause is associated with an increased risk for MetS[13,14]. Simple and reliable indicators for the early detection of metabolic disturbances in postmenopausal women may be beneficial in clinical practice. The current study evaluated the importance of visceral adiposity indicators on metabolic parameters in postmenopausal women.

Materials and Methods

Two hundred postmenopausal women who attended Marmara University Outpatient Clinics were included in this study after obtaining written informed consent. The study protocol was approved by the Ethics Committee of Marmara University (approval number: 09.2018.039). Subjects with systemic disease, malignancy or those using any medications were excluded from the study. Body mass index (BMI) was calculated after obtaining the weight and height measurements of the subjects. Waist (WC) and hip circumferences were measured and WC-to-hip ratios (WHR) were recorded. This cross-sectional study was approved by the ethics committee of the university and conducted in accordance with the Helsinki Declaration. Participants were grouped according to the absence or presence of MetS diagnosed according to the National Cholesterol Education Program Adult Treatment Panel III criteria[15]. The diagnosis of MetS was made depending on the presence of at least 3 of the following parameters: abdominal obesity (WC ≥88 cm), elevated TG (≥150 mg/dL), reduced HDL-C (<50 mg/dL) elevated blood pressure (≥130/≥85 mmHg), and elevated fasting plasma glucose (≥110 mg/dL)[15]. In addition to the clinical and biochemical evaluation of the postmenopausal subjects, by using fasting insulin and glucose results, the Quantitative Insulin Sensitivity Check index (QUICKI), Homeostasis Model Assessment IR index (HOMA-IR) and fasting glucose-insulin ratio (FGIR) were calculated by using the following formula: HOMA-IR=fasting insulin (μU/L) x fasting glucose (mmoL/L)/22.5 and QUICKI=1/[log fasting insulin (μU/mL) + log fasting glucose (mg/dL)] and (FGIR)= fasting glucose (mg/dL)/fasting insulin (mIU/mL). TyG indices were calculated based on the formula: ln [fasting TG (mg/dL) x fasting plasma glucose (mg/dL)/2][16]. In addition to traditional lipid ratios [TG/HDL-C, total cholesterol (TC)/HDL-C, low density lipoprotein (LDL)-C/HDL-C], calculations of VAI and LAP were also determined by using established formulae from previous studies:

$VAI = [WC/36.58 + (1.89 \times BMI)] \times (TG/0.81) \times (1.52/HDL\text{-}C)$[17]

$LAP = [WC\ (cm) - 58] \times [TG\ (mmol/L)]$[18].

Statistical Analysis

Statistical analyses were performed using the SPSS version 20.0 software package and comparisons of baseline demographic, biochemical, and metabolic characteristics were performed between the groups using Student's t-test. Continuous variables are described as mean and standard deviation (SD) (Table 1). $P<0.05$ was considered statistically significant. Pearson correlation analyses were performed between VAI and LAP and cardiometabolic features in postmenopausal women (Table 2). Receiver operating curve (ROC) analysis of VAI, LAP, and TyG was performed for the prediction of MetS.

Results

The baseline demographic, biochemical, and metabolic characteristics of the groups are described in Table 1. The current study included 200 postmenopausal women and 63 subjects were diagnosed as having MetS. Age, LDL-C, and TC levels were similar between the groups. Postmenopausal women with MetS demonstrated significantly higher values with respect to systolic and diastolic blood pressures, BMI, WHR, TG, lipid ratios, HOMA index, TyG, VAI, and LAP when compared with those without MetS. HDL-C, FGIR, and QUICKI were found to be lower in the MetS+ group (Table 1). Correlation analyses showed that LAP and VAI were positively correlated with WC, WHR, BMI, TG, lipid ratios, TyG, and HOMA index, and with each other. LAP was also positively correlated with blood pressures. Correlation analyses also showed that LAP and VAI were negatively correlated with HDL-C, FGIR, and QUICKI in postmenopausal women (Table 2). ROC analysis of visceral adiposity indicators in predicting MetS was performed, which demonstrated 89% sensitivity and 80% specificity of VAI at an optimal cut-off level of 2.04 [area under the curve (AUC) 0.88; 95% confidence interval (CI)=0.83-0.94]. The sensitivity and specificity for LAP was 84% and 78% at a cut-off level of 54.09 (AUC=0.88; 95% CI=0.82-0.93). The TyG index showed 81% sensitivity and 69% specificity at the optimal cut-off level of 8.56 (AUC=0.87; 95% CI=0.81-0.93) in predicting MetS in postmenopausal women.

Discussion

Modern lifestyle changes, decreased physical activities, and concomitant increase in obesity subsequently result in a rise in the prevalence of MetS, a condition that affects the morbidity and mortality of older women, with an increased risk for CVD and T2DM[11,19]. Postmenopausal women merit special attention because they have an increase in central adiposity that contributes to the development of IR and dyslipidemia, which are also components of a cluster of metabolic abnormalities that increases the risk of T2DM and CVD[11,20,21]. The detection of postmenopausal women with a high cardiometabolic risk may aid in the implementation of early lifestyle changes and treatment strategies for future CVD risks. Two novel markers of visceral obesity, VAI and LAP, have been regarded as reliable, simple clinical markers and indicators of MetS in the older people[8,9]. In a recent study, the AUC of these markers were found to be different in postmenopausal women than in premenopausal women, and it was suggested that studies evaluating the predictive value of these clinical indicators in postmenopausal women were needed because most studies evaluating these indices were performed in the general population[11]. In our study, the AUC of both LAP and VAI was 0.88, in accordance with the study by Lee et al.,[11] which stated that the AUC of both LAP and VAI was 0.89 in postmenopausal women. In a recent meta-analysis, it was reported that the pooled prevalence of MetS among postmenopausal women was 37.17%, ranging from 13.60% to 46% with an overall odds ratio 3.54 times higher than in premenopausal women[13]. In our study, the prevalence of MetS was 31.5% in postmenopausal women. Considering the increase in life expectancy and high prevalence of MetS among postmenopausal women, simple and reliable clinical markers to predict metabolic disturbances may be helpful to allow early

Table 1. Demographic, biochemical and metabolic characteristics of groups

Variable	MetS+	MetS-	p
	n=63	n=137	
Age (years)	53.14±6.22	51.56±5.58	0.075
BMI (kg/m^2)	30.51±4.09	28.21±4.51	0.001[a]
WHR	0.91±0.06	0.86±0.07	<0.001[a]
Systolic blood pressure (mmHg)	137.42±16.23	122.69±17.33	<0.001[a]
Diastolic blood pressure (mmHg)	84±10.04	75.69±11.03	<0.001[a]
LDL-C (mg/dL)	137.90±29.24	145.13±33.07	0.139
HDL-C (mg/dL)	49.07±11.06	61.21±12.63	<0.001[a]
TC (mg/dL)	219.96±36.90	226.39±39.19	0.274
TG (mg/dL)	166.28±54.28	99.68±37.07	<0.001[a]
Glucose/insulin	9.71±5.39	13.73±9.47	0.002[a]
HOMA-IR	3.29±1.62	2.28±2.38	0.002[a]
QUICKI	0.32±0.02	0.35±0.03	<0.001[a]
TC/HDL-C	4.59±0.86	3.79±0.76	<0.01[a]
LDL-C/HDL-C	2.88±0.68	2.44±0.66	<0.001[a]
TG/HDL-C	3.58±1.48	1.73±0.82	<0.001[a]
TyG index	8.95±0.40	8.34±0.36	<0.001[a]
VAI	3.20±1.32	1.49±0.71	<0.001[a]
LAP	83.52±30.03	41.05±19.89	<0.001[a]

HOMA-IR: Homeostasis Model Assessment-Insulin Resistance, QUICKI: Quantitative Insulin Sensitivity Check index, VAI: Visceral Adiposity index, TyG: Triglyceride-glucose, LAP: Lipid accumulation product, BMI: Body mass index, WHR: Waist to hip ratio, LDL-C: Low density lipoprotein cholesterol, HDL-C: High density lipoprotein cholesterol, TG: Triglyceride, TC: Total cholesterol, [a]p<0.01
Values are expressed as mean ± standard deviation

Table 2. The correlations between lipid accumulation product and Visceral Adiposity Index and cardiometabolic variables in postmenopausal women

	LAP r	VAI r
Age	0.027	0.022
Waist circumference	0.659**	0.331**
BMI	0.466**	0.158*
WHR	0.500**	0.293**
Diastolic blood pressure	0.164*	0.103
Systolic blood pressure	0.165*	0.082
TG	0.843**	0.904**
LDL-C	0.019	-0.057
TC	0.084	-0.037
HDL-C	-0.467**	-0.677**
Glucose/insulin	-0.236**	-0.223**
QUICKI	-0.320**	-0.261**
HOMA-IR	0.190**	0.141*
TC/HDL-C	0.583**	0.737**
LDL-C/HDL-C	0.415**	0.548**
TG/HDL-C	0.822**	0.983**
LAP	-	0.861**
TyG index	0.819**	0.821**
VAI	0.861**	-

HOMA-IR: Homeostasis Model Assessment-insulin resistance, QUICKI: Quantitative Insulin Sensitivity Check index, VAI: Visceral Adiposity index, TyG: Triglyceride glucose, LAP: Lipid accumulation product, BMI: Body mass index, WHR: Waist to hip ratio, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, TG: Triglyceride, TC: Total cholesterol, **p<0.01, *p<0.05

intervention and to reduce future related complications such as CVD and T2DM. Won et al.[22] found that the TyG index was associated with arterial stiffness in the healthy population and also reported that the prevalence of MetS and diabetes significantly increased with increasing TyG indeces. In a recent study, both MetS as an entity per se and its individual features were found to be significantly associated with subclinical atherosclerosis in postmenopausal women independently of traditional cardiovascular risk factors[23]. The TyG index was found to be associated with carotid atherosclerosis and was suggested as a useful marker for identifying high-risk women in the normal-weight postmenopausal population. Additionally, the TyG index was also found to be strongly correlated with HOMA-IR and was suggested as a surrogate index of IR in postmenopausal women[24]. Maturana et al.[25] reported LAP as a suitable method to screen for cardiovascular risk in postmenopausal women. Wehr et al.[26] demonstrated an association of LAP levels with T2DM and suggested that high LAP levels were associated with increased mortality in postmenopausal women. A recent study showed that LAP, VAI, and TyG were reliable surrogate markers in identifying MetS in a population aged ≥40 years[9]. LAP and VAI were both determined as significant markers to predict the presence and severity of MetS; however, further studies were recommended to apply these markers in clinical practice and to determine appropriate cut-off values for each index in the postmenopausal group[11]. In our study, we found significantly higher values for lipid ratios, HOMA-IR, TyG, LAP, and VAI indexes in postmenopausal women with MetS. LAP and VAI were both found to be positively correlated with each other and with BMI, WHR, TG, TyG index, HOMA index, and lipid ratios, and negatively correlated with HDL-C, FGIR, and QUICKI. LAP and VAI were both found to have strong and reliable accuracy for the prediction of MetS in postmenopausal women.

Study Limitations

Considering the small sample size as a limitation of our study, further studies with larger samples are needed to assess the predictive value of visceral adiposity indicators in identifying MetS in the postmenopausal group. A premenopausal group was not included, which is also a limitation of our study.

Conclusion

The present study showed that visceral adiposity indicators might be promising in the early detection of MetS in postmenopausal women. Early detection of subjects that are candidates for high cardiometabolic risk is essential, and with regard to the difficulties in assessing cardiovascular risk using traditional measures in postmenopausal women[27], visceral adiposity indicators may be effective for critical primary prevention strategies for subsequent cardiometabolic risks in a woman's life span.

Ethics

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of Marmara University (approval number: 09.2018.039).

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.Y., G.A.İ., Concept: G.A.İ., Design: G.A.İ., Data Collection or Processing: B.Y., G.A.İ, Analysis or Interpretation: G.A.İ., Literature Search: G.A.İ., Writing: G.A.İ.

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

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Sherling DH, Perumareddi P, Hennekens CH. Metabolic syndrome. J Cardiovasc Pharmacol Ther 2017;22:365-7.
2. Hennekens CH, Andreotti F. Leading avoidable cause of premature deaths worldwide: case for obesity. Am J Med 2013;126:97-8.
3. Xu H, Li X, Adams H, Kubena K, Guo S. Etiology of metabolic syndrome and dietary intervention. Int J Mol Sci 2018;20:128.
4. Alberti, KG, Zimmet P, Shaw J, IDF Epidemiology Task Force Consensus Group. The metabolic syndrome-a new worldwide definition. Lancet 2005;366:1059-62.
5. Guo S. Insulin signaling, resistance, and metabolic syndrome: Insights from mouse models into disease mechanisms. J Endocrinol 2014;220:T1-T23.
6. Bonora BM, Marescotti M, Marcuzzo G, Avogaro A, Fadini GP. Synergistic interactions among metabolic syndrome components and homeostasis model assessment of insulin resistance in a middle-aged general population over time. Metab Syndr Relat Disord 2015;13:171-8.
7. Goh VHH, Hart WG. Excess fat in the abdomen but not general obesity is associated with poorer metabolic and cardiovascular health in premenopausal and postmenopausal Asian women. Maturitas 2018;107:33-8.
8. Gu Z, Zhu P, Wang Q, He H, Xu J, Zhang L, et al. Obesity and lipid-related parameters for predicting metabolic syndrome in Chinese elderly population. Lipids Health Dis2018;17:289.
9. Li R, Li Q, Cui M, Yin Z, Li L, Zhong T, et al. Clinical surrogate markers for predicting metabolic syndrome in middle-aged and elderly Chinese. J Diabetes Investig 2018;9:411-8.
10. Du T, Yuan G, Zhang M, Zhou X, Sun X, Yu X. Clinical usefulness of lipid ratios, visceral adiposity indicators, and the triglycerides and glucose index as risk markers of insulin resistance. Cardiovasc Diabetol 2014;13:146.
11. Lee HJ, Jo HN, Kim YH, Kim SC, Joo JK, Lee KS. Predictive value of lipid accumulation product, fatty liver index, visceral adiposity index for metabolic syndrome according to menopausal status. Metab Syndr Relat Disord 2018;16:477-82.
12. Du T, Yu X, Zhang J, Sun X. Lipid accumulation product and visceral adiposity index are effective markers for identifying the metabolically obese normal-weight phenotype. Acta Diabetol 2015;52:855-63.

13. Hallajzadeh J, Khoramdad M, Izadi N, Karamzad N, Almasi-Hashiani A, Ayubi E, et al. Metabolic syndrome and its components in premenopausal and postmenopausal women: a comprehensive systematic review and meta-analysis on observational studies. Menopause 2018;25:1155-64.
14. Pu D, Tan R, Yu Q, Wu J. Metabolic syndrome in menopause and associated factors: a meta-analysis. Climacteric 2017;20:583-91.
15. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005;112:2735-52.
16. Simental-Mendia LE, Rodriguez-Moran M, Guerrero-Romero F. The product of fasting glucose and triglycerides as surrogate for identifying insulin resistance in apparently healthy subjects. Metab Syndr Relat Disord 2008;6:299-304.
17. Amato MC, Giordano C, Galia M, Criscimanna A, Vitabile S, Midiri M, et al. Visceral Adiposity Index: a reliable indicator of visceral fat function associated with cardiometabolic risk. Diabetes Care. 2010;33:920-2.
18. Kahn HS. The "lipid accumulation product" performs better than the body mass index for recognizing cardiovascular risk: a population-based comparison. BMC Cardiovasc Disord 2005;5:26.
19. Wilson PW, D'Agostino RB, Parise H, Sullivan L, Meigs JB. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. Circulation 2005;112:3066-72.
20. Carr MC. The emergence of the metabolic syndrome with menopause. J Clin Endocrinol Metab 2003;88:2404-11.
21. Rodrigues MH, Bruno AS, Nahas-Neto J, Santos ME, Nahas EA. Nonalcoholic fatty liver disease and metabolic syndrome in postmenopausal women. Gynecol Endocrinol 2014;30:325-9.
22. Won KB, Park GM, Lee SE, Cho IJ, Kim HC, Lee BK, et al. Relationship of insulin resistance estimated by triglyceride glucose index to arterial stiffness. Lipids Health Dis 2018;17:268.
23. Lambrinoudaki I, Kazani A, Armeni E, Rizos D, Augoulea A, Kaparos G, et al. The metabolic syndrome is associated with carotid atherosclerosis and arterial stiffness in asymptomatic, nondiabetic postmenopausal women. Gynecol Endocrinol 2018;34:78-82.
24. Lambrinoudaki I, Kazani MV, Armeni E, Georgiopoulos G, Tampakis K, Rizos D, et al. The TyG Index as a Marker of Subclinical Atherosclerosis and Arterial Stiffness in Lean and Overweight Postmenopausal Women. Heart Lung Circ 2018;27:716-24.
25. Maturana MA, Moreira RM, Spritzer PM. Lipid accumulation product (LAP) is related to androgenicity and cardiovascular risk factors in postmenopausal women. Maturitas 2011;70:395-9.
26. Wehr E, Pilz S, Boehm BO, März W, Obermayer-Pietsch B. The lipid accumulation product is associated with increased mortality in normal weight postmenopausal women. Obesity (Silver Spring) 2011;19:1873-80.
27. Lambrinoudaki I, Armeni E, Georgiopoulos G, Kazani M, Kouskouni E, Creatsa M, et al. Subclinical atherosclerosis in menopausal women with low to medium calculated cardiovascular risk. Int J Cardiol 2013;164:70-6.

Clinical Investigation / Araştırma

DOI: 10.4274/tjod.galenos.2019.89137

Turk J Obstet Gynecol 2019;16:169-73

The impact of vaginal cone therapy on stress urinary incontinence compared with transobturator tape

Stres üriner inkontinans tedavisinde vajinal koni terapisinin etkinliğinin transobturator tape ile karşılaştırılması

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Abstract

Objective: To emphasize the efficiency of vaginal cone (VC) therapy in stress urinary incontinence (SUI) through a comparison with transobturator tape (TOT).

Materials and Methods: A prospective randomized controlled study was conducted at the Etlik Zübeyde Hanım Maternity and Women Hospital during a one year study period. Forty women were allocated into two equal groups; those treated with VCs for a 3 month period, and women who underwent TOT procedures. These women were followed up at 6 weeks and 6 months after the treatments. Subjective cure was assessed using Wagner's Quality of Life Questionnaire. Objective cure was evaluated through a cough stress and pad test results.

Results: Maternal demographic features were comparable among groups. We observed improvement in pad weight test among groups when compared with the pretreatment state (p=0.015, p=0.005). Although the subjective cure rate was similar in both groups at the 6th week and 6th month follow up (65% vs. 75%; 75% vs. 80%) (p>0.05), the objective cure rate was significantly higher in the TOT group than in the VC group, as expected (10% vs. 80%; 30% vs. 75%) (p<0.05).

Conclusion: The main treatment of SUI is surgery; however, VC could be offered as an alternative treatment for women who refuse surgery, those at high risk for surgery or it could be used temporarily before surgery.

Keywords: Stress urinary incontinence, vaginal cone therapy, transobturator tape, conservative treatment

Öz

Amaç: Stres üriner inkontinans (SUİ) tedavisinde vajinal koni (VK) terapisinin etkinliğinin transobturator tape (TOT) ile karşılaştırılmasıdır.

Gereç ve Yöntemler: Bir yıllık dönemde, Etlik Zübeyde Hanım Kadın Hastalıkları Hastanesi'nde prospektif randomize kontrollü bir çalışma yapıldı. Kırk kadın iki gruba ayrıldı; bunların yirmisi vajinal koni ile üç ay boyunca tedavi edilirken, kalan 20 kişi transboturator tape operasyonu ile tedavi edildi. Bu kadınlar tedaviden sonra 6. hafta ve 6. ay kontrolleri ile takip edildi. Subjektif iyileşme, Wagner'in Yaşam Kalitesi Anketi ile değerlendirildi. Objektif iyileşme ise öksürük stres ve ped testi sonuçları ile değerlendirildi

Bulgular: Maternal demografik özellikler açısından gruplar arasında fark yoktu. Gruplar arasında ped testinde, tedavi öncesi durumla karşılaştırıldığında iyileşme gözlendi (p=0,015 p=0,005). Her iki grupta subjektif iyileşme oranı, 6. hafta ve 6. ay kontrolünde benzer olmasına ragmen (%65 vs %75; %75 vs %80) (p>0,05), objektif iyileşme oranı, beklendiği gibi, TOT grubunda VK grubundan anlamlı derecede yüksekti (%10 vs %80; %30 vs %75) (p<0,05).

Sonuç: SUİ'nin ana tedavisi cerrahidir; bununla birlikte VK, cerrahiyi reddeden veya ameliyat riski yüksek olan kadınlar için alternatif bir tedavi olarak sunulabilir ya da cerrahi öncesi geçici olarak kullanılabilir.

Anahtar Kelimeler: Stres üriner inkontinans, vajinal koni tedavisi, transobturator tape, konservatif tedavi

PRECIS: Vaginal cone (VC) should not be considered as one of the alternatives to surgical treatment in stress urinary incontinence but VCs may be considered temporarily or in combination with other surgical procedures.

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Received/Geliş Tarihi: 17.04.2019 **Accepted/Kabul Tarihi:** 22.07.2019

Introduction

Stress urinary incontinence (SUI) is an involuntary leakage of urine during an exerted effort, exertion, sneezing, or coughing[1]. Approximately 50% of patients diagnosed with urinary incontinence have SUI[2]. SUI may occur in 4% to 35% of women[3]. SUI is the most common type of urinary incontinence in young women and is more common between the age of 45 and 49 years[4]. It is associated with serious economic, social, and psychological problems that affect women's health[1]. There are several treatment options for SUI. Depending on the clinical findings and on the severity of symptoms, SUI can be managed both with conservative methods including pelvic floor exercises, vaginal cones (VC) and general lifestyle modifications, and surgery. It can be treated surgically with procedures such as Burch colposuspension, vaginal slings or tension-free tapes, and injection of bulking agents alongside the urethra. Techniques aimed to strengthen pelvic floor muscles are considered as the first-choice treatment due to the low risk of adverse effects and the low-to-moderate costs[3]. Midurethral slings or tapes are widely used as a surgical procedure in SUI, first described by Herbison and Dean[4] in 1995. The rationale of transobturator passage is the restoration of hammock-like support and the avoidance of rare but serious bladder complications such as injury to major vessels or the bowel. Pelvic floor muscle exercises should be encompassed in the first-line of conservative management of women with SUI[5]. VC were initially proposed in 1985 by Plevnik[6] to strengthen pelvic floor muscles. Non-surgical treatment of SUI is not the definitive choice; however, it improves the quality of life of women with SUI. The present study aimed to compare the effectiveness of VC therapy and transobturator tape (TOT) in women with SUI, which has not been thoroughly addressed in the literature[6,7].

Materials and Methods

Women with urodynamic SUI were enrolled in this, controlled, randomized trial at the department of urogynecology and reconstructive pelvic surgery, a division of the gynecology department at a tertiary research and training hospital, Ankara, during a one-year study period. The study was approved by the Hospital's Institutional Review Board, and informed consent was obtained from each participant. Forty patients were allocated into two groups; patients treated with VC (n=20, group 1) and patients who underwent TOT (n=20, group 2). Women who had urodynamic stress incontinence were confirmed through a positive cough stress test, and >3 g leakage as measured using a pad test with a standardized bladder volume (200 mL) without detrusor overactivity[8]. Exclusion criteria were considered as chronic degenerative diseases, advanced genital prolapses, pregnancy, active or recurrent urinary tract infections, vulvovaginitis, atrophic vaginitis, and continence surgery within one year (Figure 1). VC (StepFree VC, SRS Medical, USA) were implemented per the original definition of Plevnik[9], and additionally by a gynecologist at the urogynecology clinic. Patients applied the cones weighted at 20-70 g for 15 minutes twice a day. At the initial visit, patients were guided as to their use. After the first weight was successfully implemented for 15 minutes twice a day, the weight would be prolonged for a week. Afterwards, the VC weight gradually increases and ends within a 3 month treatment period at 70 g. TOT (polypropylene; Dowmedics Co. Ltd., Wonju, Korea) was performed by the same surgeon under spinal anesthesia as described by Delorme[10]. Patients were invited for postoperative follow up at six weeks and six months. At each visit, urinary symptoms and other problems were recorded, and a cough stress test was performed, after filling the bladder with 200 mL of water and provoking the patient in a 45° upright sitting position. All patients were also asked to complete the validated Wagner's Quality of Life Questionnaire before and after treatment as adapted for Turkish women[11]. The results are classified as follows: 1-28 points were recorded for minimal incontinence, 29-56 points recorded for moderate incontinence, and 57-84 points for severe incontinence. Treatment outcome was assessed with respect to overall complication and treatment rates. Complications were intraoperative bladder injury, voiding dysfunction lasting more than 1 month after surgery or requiring surgical intervention such as urethral dilation, tape release, or urethrolysis, de novo urgency, recurrent urinary tract infection, and mesh erosion. Women without subjective symptoms of leakage and/or objective leakage on a cough stress test (cure/dry) were defined as completely treated.

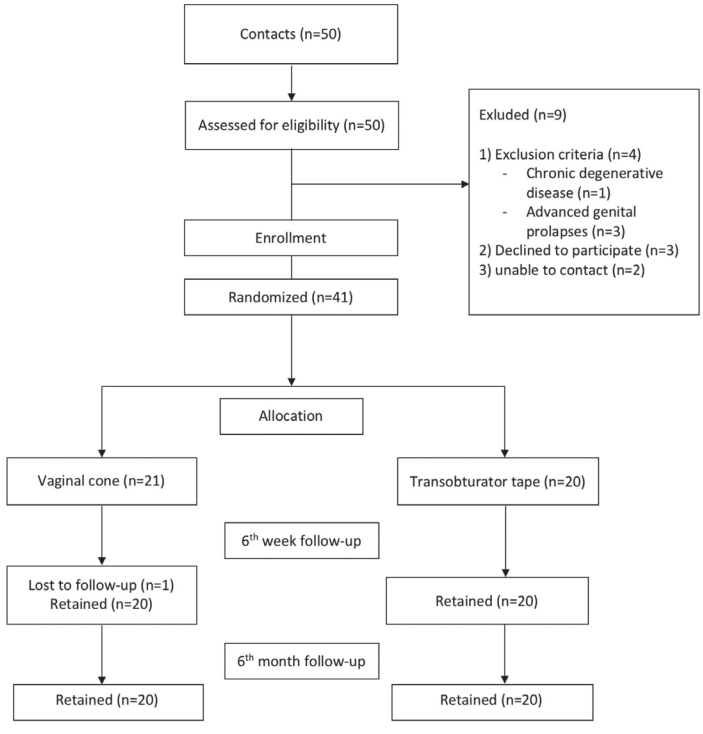

Figure 1. Flow diagram of the study

Statistical Analysis

Data were analyzed using the SPSS version 12.0 software package (2004; SPSS Inc., Chicago, IL, USA). Descriptive statistics of the data were determined in the form of mean ± standard deviations and range. Using our data, which represent categorical data, we used the chi-square test to determine the significance of the study with p<0.05 being accepted as significance.

Results

A total of 40 patients were involved to our study. Table 1 shows the clinical and demographic features of the patients in each group. The mean surgical time and intraoperative blood loss were 14±2 minutes and 35 mL, respectively. There were no intraoperative or postoperative complications in the TOT group. Although we observed a significant decrease in pad weights in the two groups, the TOT group was superior to the VC group at both the 6th week and 6th month follow ups (Table 2). The rate of negative stress test was higher in the TOT group than in the VC group (85% vs. 50% at 6 weeks and 75% vs. 50% at 6 months, respectively) (p<0.05). The results of the quality of life questionnaire are shown in Table 3 and Table 4. There was significant recovery in both groups at the end of the 6th week when compared with pretreatment scores (p<0.05). We observed complete healing in two patients, mild incontinence in 14 patients, and severe incontinence in one women in the TOT group at the 6th week follow-up. By contrast, one patient had no symptoms, mild incontinence was present in nine patients, and severe incontinence was observed in four patients in the VC group. Moreover, we determined complete healing in one patient, mild incontinence in 12 patients, and severe incontinence in two patients at the 6th month follow up in the VC group. On the other hand, 8 patients had no symptoms, seven women had mild incontinence, and three patients had severe incontinence in the TOT group at the 6th month follow up. According to the survey, the subjective cure rate of women in the VC group and TOT group was 65% and 75% at the 6th week follow up, respectively (p>0.05). The objective cure rate in group 1 (n=2) was significantly lower than in group 2 (n=16) at the sixth week follow up (10% vs. 80 %). At the sixth month follow up, the subjective cure rate was similar between the groups (75% vs. 80%) (p>0.05). However, objective cure rates were significantly lower in the VC group (30% vs. 75%) (p<0.05).

Discussion

Although SUI is not a life-threatening health concern, it affects approximately 200 million women and it influences the patients' social, psychological, occupational, domestic, physical, and sexual well-being[1]. In 1982, Ulmsten hypothesized that urinary continence is related 1/3 of mid-urethra with the highest pressure[12]. TOT aims to provide urethral support tissue via a minimally invasive procedure as defined by Delorme in 2001. According to the literature, vaginal slings seem to be the best option in SUI treatment with lower complication rates and better short- and long-term outcomes than other surgical procedures[13-16]. Pelvic floor muscle training (PFMT) is a conservative treatment for SUI, which aims to strengthen pelvic floor muscles, described in 1948 by Arnold Kegel. On the other hand, women may have difficulties in identifying and controlling this group of muscles[17]. Plevnik[6] developed VCs to solve this dilemma. According to the Cochrane database in 2013, there was a statistically significant difference between a VC and no treatment group regarding pelvic muscle strength and pad test. In this review, cones had no additional benefit over PFMT and electrostimulation therapy[4]. In our study, we

Table 1. Clinical and demographic characteristics of study groups

	Vaginal cones (n=20)	TOT (n=20)	p
Mean age (years)	47.2±10.6	50.1±5	>0.05
BMI (kg/m^2)	30.3±5.6	32.1±4.9	>0.05
Parity	3.1	3.5	>0.05

BMI: Body mass index, TOT: Transobturator tape, demographic characteristics of both groups were similar (p>0.05)

Table 2. Outcome measure and multiple comparisons of all groups at 6 weeks and 6 months

	Group 1 pad test (gr)	Group 2 pad test (g)	p
Pretreatment	33.41±41.6	63±41.2	0.062
Post-treatment 6th week	25.8±35.8	11.8±30.3	0.015
Post-treatment 6th month	23.4±39.5	11.6±28.6	0.005
p	<0.05	<0.05	

We observed a statistically significant decrease in pad weights in the two groups (p<0.05), transobturator tape group was superior to the vaginal cone group at both the 6th week and 6th month follow-ups (p<0.05)

Table 3. The results of quality of life questionnaire in all groups at 6th weeks

	Vaginal cones (n=20)		TOT (n=20)		TOT vs. VC
	Bt	At	Bt	At	
No symptoms	-	1	-	2	p>0.05
Mild	9	9	5	14	
Moderate	3	6	9	3	
Severe	8	4	6	1	
	20		20		40
p	p<0.05		p<0.05		

Bt: Before treatment, At: After treatment, VC: Vaginal cone, TOT: Transobturator tape, There was significant recovery in both groups at the end of the 6th week when compared with pretreatment scores (p<0.05)

Table 4. The results of quality of life questionnaire in all groups at 6 months

	Vaginal cones (n=20)		TOT (n=20)		TOT vs. VC
	Bt	At	Bt	At	
No symptoms	-	1	-	8	p<0.05
Mild	9	12	5	7	
Moderate	3	5	9	2	
Severe	8	2	6	3	
	20		20		40
p	p<0.05		p<0.05		

Bt: Before treatment, At: After treatment
At the sixth month follow up the subjective cure rate was similar between the groups (75% vs. 80%) (p>0.05)

compared the effectiveness of VC therapy with TOT. To the best of our knowledge, this is the first randomized study to compare surgical and conservative treatment of SUI. In our trial, all women were multiparous (the rate of parities are 3.5 for TOT and 3.1 for VC) and all women's body mass indexs were over 30 kg/m^2; the SUI for both groups showed a strong association with the parity and obesity (Table 1)[18,19]. The duration of TOT procedures (14±2 minutes) and intraoperative median blood loss (35 mL) were compatible with previous studies[10,20,21]. There were no intraoperative complications in our study. VCs are treatment options that have some advantages including the ease of learning how to implement them, which reduces patient visits, and ease of use at home[22]. In our study, treatment adherence was high with a reported integration of 100% of the participants. At the 6th week and 6th month follow ups, slightly varying subjective cure rates were observed between the two groups (group 1, 65% vs. group 2, 90%) (group 1, 75% vs. group 2, 80%), respectively, but there were no significant differences in their subjective cure rates (p>0.05). However, the objective cure rates were significantly different between the two groups at the 6th week (VC, vs. 10% vs. TOT, 80%) and 6th month follow ups (VC 30% vs. TOT 75%). After the 6 weeks and also 6 months of follow up, the rates were statistically different in the two groups (p<0.05). All patients were analyzed using a quality of life questionnaire before and after treatment. Although the subjective cure rates were similar, the objective cure rate was higher in the TOT group, as expected (p<0.05). Our study is the first randomized control study to compare TOT and VC treatment; however, it is not without limitations. One of the main limitations of this study is the limited number of patients in the study group. Also, we were not be able to compare various VC weights. In our study, we used fixed weights (20-70 g), which may have affected the subjective and objective cure rates.

Conclusion

TOT is highly efficient minimally invasive surgical procedure with high success rates and low complication rates. VC should not be considered as one of the alternatives to surgical treatment. VCs are cheap and simple conservative methods. VCs may be considered temporarily or in combination with other surgical procedures. Cones could be offered as a treatment option for women who are scheduled for surgery or in those at high risk for surgery if they find them acceptable.

Ethics

Ethics Committee Approval: The study was approved by Hospital's Ethics Committee (2007/92).
Informed Consent: Informed consent was obtained from Training and Research Hospital participant.
Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: R.D., A.A.S., Concept: G.D., Design: R.D., A.A.S., Data Collection or Processing: R.D., Analysis or Interpretation: G.D., A.A.S., R.D., Literature Search: B.C., R.D., M.Ü., Writing: İ.A., B.C., R.D.
Conflict of Interest: None of the authors has any conflict of interest relative to this work.
Financial Disclosure: Financial support was not received.

References

1. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Am J Obstet Gynecol 2002;187:116-26.
2. Reigota RB, Pedro AO, de Souza Santos Machado V, Costa-Paiva L, Pinto-Neto AM. Prevalence of urinary incontinence and its association with multimorbidity in women aged 50 years or older: A population-based study. Neurourol Urodyn 2016;35:62-8.
3. Malallah MA, Al-Shaiji TF. Pharmacological treatment of pure stress urinary incontinence: a narrative review. Int Urogynecol J 2015;26:477-85.
4. Herbison GP, Dean N. Weighted vaginal cones for urinary incontinence. Cochrane Database Syst Rev 2013;CD002114.
5. Dumoulin C, Hay-Smith EJ, Mac Habée-Séguin G. Pelvic floor muscle training versus no treatment, or inactive control treatments, for urinary incontinence in women. Cochrane Database Syst Rev 2014;CD005654.
6. Plevnik S. New method for testing and strengthening of pelvic floor muscles. Proceedings of the 15th annua. 1985:267-8.
7. Faiena I, Patel N, Parihar JS, Calabrese M, Tunuguntla H. Conservative Management of Urinary Incontinence in Women. Rev Urol 2015;17:129-39.
8. Lose G, Rosenkilde P, Gammelgaard J, Schroeder T. Pad-weighing test performed with standardized bladder volume. Urology 1988;32:78-80.
9. Plevnik S. Vaginal cones. In: Baessler, K., Schüssler, B., Burgio, K.L., Moore, K., Stanton, S.L. editors. Pelvic floor re-education principles and practice. London, United Kingdom. Springer; 1994.p.139-42.

10. Delorme E. [Transobturator urethral suspension: mini-invasive procedure in the treatment of stress urinary incontinence in women]. Prog Urol 2001;11:1306-13.
11. Wagner TH, Patrick DL, Bavendam TG, Martin ML, Buesching DP. Quality of life of persons with urinary incontinence: development of a new measure. Urology 1996;47:67-71
12. Westby M, Asmussen M, Ulmsten U. Location of maximum intraurethral pressure related to urogenital diaphragm in the female subject as studied by simultaneous urethrocystometry and voiding urethrocystography. Am J Obstet Gynecol 1982;144:408-12.
13. Delorme E, Droupy S, de Tayrac R, Delmas V. Transobturator tape (Uratape): a new minimally-invasive procedure to treat female urinary incontinence. Eur Urol 2004;45:203-7.
14. Aygül C, Özyurt R, Şık BA, Kumbasar S. Evaluation of the efficacy of transobturator tape surgery in the treatment of stress urinary incontinence using urodynamics and questionnaires. Turk J Obstet Gynecol 2016;13:172-7.
15. Natale F, Illiano E, Marchesi A, La Penna C, Costantini E. Transobturator Tape: Over 10 Years Follow-up. Urology 2019;129:48-53.
16. Sivaslioglu AA, Caliskan E, Dolen I, Haberal A. A randomized comparison of transobturator tape and Burch colposuspension in the treatment of female stress urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct 2007;18:1015-9.
17. [Bump RC, Hurt WG, Fantl JA, Wyman JF. Assessment of Kegel pelvic muscle exercise performance after brief verbal instruction. Am J Obstet Gynecol 1991;165:322-7
18. Juliato CR, Baccaro LF, Pedro AO, Gabiatti JR, Lui-Filho JF, Costa-Paiva L. Factors associated with urinary incontinence in middle-aged women: a population-based household survey. Int Urogynecol J 2017;28:423-9.
19. Alling Møller L, Lose G, Jørgensen T. Risk factors for lower urinary tract symptoms in women 40 to 60 years of age. Obstet Gynecol 2000;96:446-51.
20. Naidu A, Lim YN, Barry C, Goodwin S, Corstiaans A, Rane A. Transobturator tape for stress incontinence: the North Queensland experience. Aust N Z J Obstet Gynaecol 2005;45:446-9.
21. Taner CE, Okay G. Early Complications Of The Transobturator Tape And Mini Sling Procedure. Turk J Obstet Gynecol. 2014;11:14-20
22. Baessler K, Schüssler B, Burgio KL, Moore KH, Norton PA, Stanton S. Pelvic floor re-education. In: Baessler, K., Schüssler, B., Burgio, K.L., Moore, K., Stanton, S.L. (eds). London: Springer; 2008.

Clinical Investigation / Araştırma

DOI: 10.4274/tjod.galenos.2019.98752

Turk J Obstet Gynecol 2019;16:174-9

Predictors of adverse maternal and perinatal outcomes in a refugee population from an active conflict country, Syria

Suriyeli mülteci gebelerde maternal ve perinatal komplikasyonların belirleyicileri

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Abstract

Objective: To elucidate predictors of adverse maternal and perinatal outcomes in refugees emigrating from an active conflict region (Syria).

Materials and Methods: This study included Syrian pregnant women who gave birth in Etlik Zübeyde Hanım Training and Research Hospital between 2013 and 2016. Adverse perinatal outcomes were defined as preterm labor, premature rupture of membranes, early membrane rupture, intrauterine growth retardation, hypertension, perinatal excites, and erythrocyte-transfused cases. Factors associated with those adverse outcomes were assessed using multiple logistic regression analysis.

Results: Having an active smoking habit [odds ratio (OR): 2.647, 95% confidence interval (CI): 1.767-3.965; p<0.001], obesity (OR: 2.272, 95% CI: 1.396-3.699; p=0.001), and adolescent age (OR: 1.732, 95% CI: 1.204-2.491; p=0.003) were found to be the most important predictors of adverse maternal and perinatal outcomes. Eighty of 129 (62%) smokers, 45 of 81 (55.65%) obese individuals, and 91 of 169 adolescents (53.8%) had adverse maternal and perinatal outcomes.

Conclusion: Prevention strategies for obesity, smoking, and adolescent pregnancies should be implemented primarily to reduce maternal and antenatal adverse outcomes. Pregnant women with these risk factors in a refugee community emigrating from a conflict-zone nation should be followed up closely.

Keywords: Refugees, Syrian, immigrants, pregnancy, perinatal outcome, maternal outcome

Öz

Amaç: Suriyeli mülteci gebelerde maternal ve perinatal komplikasyonlara etki eden faktörleri belirlemeyi amaçladık.

Gereç ve Yöntemler: Etlik Zübeyde Hanım Kadın Hastalıkları Eğitim ve Araştırma Hastanesi'nde 2013-2016 yıllarında doğum yapmış Suriyeli gebeler çalışma kapsamında değerlendirilmiştir. Maternal ve perinatal komplikasyonlar; preterm eylem, preterm erken membrane rüptürü, erken membrane rüptürü, intrauterin büyüme kısıtlılığı, hipertansiyon, perinatal ölüm ve kan transfüzyonu yapılması olarak tanımlanmıştır. Bu komplikasyonlara etki eden faktörler çoklu regresyon analizi ile değerlendirilmişlerdir.

Bulgular: Sigara kullanmak [olasılık oranı (OR): 2,647, %95 güven aralığı (CI): 1,767-3,965; p<0,001], obezite (OR: 2,272, 95% CI: 1,396-3,699; p=0,001), adölesan gebelik (OR: 1,732, 95% CI: 1,204-2,491; p=0,003) maternal ve perinatal komplikasyonların en önemli belirleyicileridir. Sigara kullanan gebelerin %62'si (80/129), obez gebelerin %55,65'i (45/81), adölesan gebelerin %53,8'i (53,8%) maternal ve perinatal komplikasyonlar ile birliktedir.

Sonuç: Maternal ve perinatal komplikasyonların önlenmesi amacıyla gebelikte obezite, sigara kullanımı ve adolesan gebeliklerin önlenmesi amaçlanmalıdır. Bu belirleyicilerle birlikte olan mülteci kadınlar düzenli takip edilmelidir.

Anahtar Kelimeler: Mülteci, Suriyeli, göçmen, gebelik, perinatal sonuç, maternal sonuç

Introduction

Refugees, especially those emigrating from their home country due to war or other hardships, face many difficulties in their new host countries. Changes in food consumption, economic difficulties, language barriers, and limitations in accessing healthcare may disturb their health-related conditions[1-3]. Being a vulnerable group, immigrant pregnant women in particular experience more difficulties and perhaps may have more adverse outcomes. Since March 2011, the Turkish government has begun hosting millions of Syrian refugees, preparing refugee

PRECIS: Smoking, obesity, and adolescence are the most important predictors for adverse maternal and perinatal outcomes in pregnant refugees.

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Received/Geliş Tarihi: 31.05.2019 **Accepted/Kabul Tarihi:** 23.07.2019

camps and giving them the opportunity to travel to all cities of the country. At present, more than 3.5 million Syrian refugees are scattered all around Turkey[4]. According to the United Nations Refugee Agency, Turkey is the most accessed hosting country for refugees worldwide[4]. Previous studies have shown an increased risk of adverse maternal and perinatal outcomes for emigrating pregnant women including maternal anemia, preterm birth, low birth weight, bleeding during delivery, psychological distress, perineal laceration, and postpartum hemorrhage[1-3,5-7]. Besides these data, pregnant women leaving conflict regions have increased adverse perinatal complications as compared with pregnant women from non-conflict regions[8,9]. A pregnant refugee's country of origin is found to be an important predictor of pregnancy outcomes. Moreover, immigration itself has a negative impact on pregnancy outcomes in the same nation[10,11].

Predictors of adverse events in pregnancy in among women emigrating from a nation in an active conflict region have not been well studied to date. Therefore, in the present study, we sought to identify predictors of adverse maternal and perinatal outcomes in refugees coming from an active conflict region, specifically Syria.

Materials and Methods

Study design

The maternity clinic at Etlik Zübeyde Hanım Training and Research Hospital is a tertiary maternity unit with a neonatal intensive care unit (NICU). Most patients seen here, including both refugees and Turkish people, are referred from other clinics when gestational and fetal complications are suspected. For this study, we employed a Syrian interpreter to communicate with the refugees. After approval of the study protocol by our institutional review board, the files and birth records of Syrian refugees concerning the period 2013 through 2016 were retrospectively analyzed. As the Turkish government provided a translator, hospital staff and medical team communicated with the patients with the help of a translator or relatives speaking Turkish. To establish a high-quality dataset, only parameters of singleton pregnancies with complete data were included. Parameters including gestational diabetes mellitus and systemic disorders were not included in the analysis because the refugee population had poor antenatal care. All patients were evaluated using ultrasonography at the time of delivery and according to need at each other visit. Demographic data including maternal age, gravidity, parity, smoking habits, history of abortion, route of delivery in previous births, gestational age at delivery, number of antenatal follow-ups, mode of delivery, and maternal hemoglobin (Hb) levels were extracted. Patients' body mass index (BMIs) were calculated based on their height and body weight at the time of admission to hospital for delivery. Obese patients were defined as those with BMI values equal to or greater than 30 kg/m^2. Adverse perinatal outcomes were defined as preterm labor, premature rupture of membranes (PPROM), early membrane rupture (EMR), intrauterine growth retardation (IUGR), hypertension, perinatal exitus, and erythrocyte-transfused cases. The newborn's birth weight, one and five-minute Apgar scores, heart pulse rates, grimace response, activity, respiration scores, admission to the NICU were recorded. Gestational age was determined based on the first day of the last menstruation period (LMP) of the mother. For patients who did not know their LMP, gestational age was calculated based on their earliest obstetric ultrasound. Hypertension during pregnancy was defined as a blood pressure of more than 140/90 mmHg measured on two occasions. Preterm delivery was defined as birth before 37 weeks, and IUGR was determined based on clinical evaluation and ultrasonographic parameters. Adolescent pregnancy was noted when the patient was younger than 20 years of age at the time of delivery.

Statistical Analysis

The Statistical Package for the Social Sciences version 23.0 for Windows (IBM Corp., Armonk, NY, USA) software package was used and p values less than 0.05 were defined as statistically significant. Variables with p values less than 0.1 on univariate analysis were included in binominal logistic regression analysis.

Results

A total of 747 pregnant Syrian refugees had deliveries between 2013 and 2016. Eight twin pregnancies and 35 patients with incomplete data were excluded from this study. Therefore, a total of 698 Syrian refugees were included in the present study, including 167 adolescents (23.9%) aged between 12 and 19 years. The clinical characteristics of the study population are presented in Table 1. The median age of the study participants was 24 years, and the majority (67.2%) were multigravida. Most patients (n=370) had visits only during the third trimester (53.0%), and only 220 (31.5%) patients had four or more antenatal visits. Adverse maternal and perinatal outcomes were present in 306 (43.8%) cases. In 83 patients, multiple adverse maternal and/or perinatal outcomes were recorded as follows: preterm labor was observed in 134, IUGR in 86, and PPROM or EMR in 81, respectively. Additionally, gestational hypertension in two out of 11 women resulted in ablatio placenta, intrauterine exitus was seen in seven, neonatal exitus was observed in eight, and severe maternal anemia requiring erythrocyte transfusion was present in 45 women (Table 2). Table 3 demonstrates the relationship between adverse maternal-fetal outcomes and possible risk factors. Adolescent pregnancy (p=0.003), being a smoker (p<0.001), obesity (p=0.024), and a number of antenatal visits of less than four (p<0.001) were related with adverse maternal and fetal outcomes.

Results of logistic regression analysis

The probability of adverse maternal and perinatal outcomes increased 2.647 times [95% confidence interval (CI) for odds

ratio (OR): 1.767-3.965] in smokers when compared with nonsmokers (p<0.001). Obesity (BMI >30 kg/m^2) increased the probability of adverse maternal-fetal outcomes 2.272 times (95% CI for OR: 1.396-3.699) relative to patients with BMIs of 30 k/m^2 or less (p=0.001). Also, the probability of adverse maternal-fetal outcomes increased 1.732 times (95% CI for OR: 1.204-2.491) in adolescent pregnant women in comparison with adult pregnant women (p=0.03). In the regression analysis, gravidity of more than two and less than four antenatal visits were not significant indicators of adverse maternal-fetal outcomes (Table 4). Correlations between the detected risk factors and each adverse maternal or perinatal outcome are presented in Table 5. Maternal anemia requiring erythrocyte transfusion was found as a more common feature of nonsmoking pregnant women versus those with an active smoking habit (p=0.008). Preterm birth (p=0.022), PPROM or EMR (p<0.001), IUGR (p<0.001), and perinatal exitus (p<0.001) were more commonly observed in smokers than in nonsmokers. PPROM or EMR (p=0.039) and hypertension (p=0.009) were additionally found more

Table 1. Characteristics of study population

Characteristic	Parameters	Values (%)
Age (years)	Median 25th-75th percentiles	24 20-28.25
Gravidity	Median 25th-75th percentiles	2 1-3
Parity	Median 25th-75th percentiles Nullipar ≥1	1 0-2 283 (41.1) 406 (58.9)
Age group	Adolescent Adult	167 (23.9) 531 (76.1)
Smoking habitus	Non-smoker Smoker	565 (80.9) 133 (19.1)
Abortus history	+ -	94 (13.5) 604 (86.5)
Previous cesarean	+ -	104 (14.9) 594 (85.1)
BMI	Median 25th-75th percentiles	26.6 24.3-28.3
Maternal Hb	Median 25th-75th percentiles	11.15 10.10-12.10
Birth week	Median 25th-75th percentiles	37 36-39
Fetal body weight	Median 25th-75th percentiles	3060 2720-3380
Apgar score (1st m)	Median 25th-75th percentiles	9 9-9
Apgar score (5th m)	Median 25th-75th percentiles	10 9-10
Antenatal follow-up	≥4 <4	217 (31.1) 481 (68.9)
Mode of delivery	Vaginal birth Cesarean	439 (62.9) 259 (37.1)
Maternal transfusion	+ -	80 (11.5) 618 (88.5)
Neonatal intensive care	+ -	83 (11.9) 615 (88.1)
Adverse maternal fetal outcome	+ -	306 (43.8) 392 (56.2)

BMI: Body mass index, Hb: Hemoglobin

Table 2. Number of adverse maternal and perinatal outcomes

Adverse perinatal outcomes	n
Preterm labor	134
IUGR	86
PPROM/EMR	81
Hypertension	17
Perinatal exitus	15
Maternal transfusion	56
Total	389

PPROM: Premature rupture of membranes, EMR: Early membrane rupture, IUGR: Intrauterine growth retardation

Table 3. Relationship between adverse maternal perinatal outcome and possible risk factors

Characteristics	Parameters	Adverse maternal fetal outcome		Univariate analysis
		+	-	p value
Age (years)	≤24 >24	177 (46.6) 129 (40.6)	203 (53.4) 189 (59.4)	0.111
Gravidity	≤2 >2	202 (47.5) 169 (61.9)	223 (52.5) 104 (38.1)	0.014
Parity	Nullipar ≥1	146 (50.0) 160 (39.4)	146 (50.0) 246 (60.6)	0.005
Adolescent	+ -	91 (53.8) 215 (40.6)	78 (46.2) 314 (59.4)	0.003
Previous cesarean	+ -	41 (39.8) 265 (44.5)	62 (60.2) 330 (55.5)	0.372
Smoking habitus	Smoker Non-smoker	80 (62.0) 226 (39.7)	49 (38.0) 343 (60.3)	<0.001
Abortus history	+ -	36 (38.7) 270 (44.6)	57 (61.3) 335 (55.4)	0.284
BMI	Obese Non-obese	45 (55.6) 261 (42.3)	36 (44.4) 356 (57.7)	0.024
Antenatal visits	<4 ≥4	229 (48.6) 77 (33.9)	242 (51.4) 105 (46.3)	<0.001

BMI: Body mass index

commonly in obese patients versus non-obese patients. Lastly, preterm birth (p=0.018) and IUGR (p<0.001) were more commonly observed in adolescent pregnant women than in adult pregnant women.

Discussion

This study showed that an active smoking habit [OR: 2.647, 95% CI: (1.767-3.965 9); p<0.001], obesity [OR: 2.272, 95% CI: (1.396-3.699); p=0.001], and adolescence [OR: 1.732, 95% CI: (1.204-2.491); p=0.003] were the most important predictors for adverse perinatal outcomes of pregnant women emigrating from an active war region. Eighty of 129 (62%) smokers, 45 of 81 (55.65%) obese individuals (BMI >30 kg/m^2), and 91 of 169 (53.8%) adolescent pregnant women had any one of the following adverse maternal and perinatal outcomes: preterm birth, PPROM, EMR, IUGR, hypertension, a need for erythrocyte transfusion or perinatal exitus. As compared with nonsmokers, smoking during pregnancy increased the risks of preterm birth [OR: 2.6, 95% CI: (1.1-1.6) for >10 cigarettes/day], and PPROM [OR: 1.97, 95% CI: (1.32-2.94) for >10 cigarettes/day] depending on the pack/years of smoking[12,13]. A meta-analysis of 46 studies documented that any amount of smoking increased the risk of perinatal death (OR: 1.33, 95% CI: 1.25-1.41)[14]. Besides, smoking had a negative impact on fetal growth and increased the risk of IUGR (OR: 2.07, 95% CI: 1.69±2.53)[15]. In accordance with previous studies, we found that, even in a migrant population, smoking increased the risks of preterm birth, PPROM, IUGR, and perinatal death (Table 4). It was reported that anemia is not a generalized sign, and elevated Hb levels were detected in smokers[16]. Accordingly, we found that a need for blood transfusion for anemia was more frequent among nonsmokers in the refugee population. Obesity is the principle health problem that causes adverse effects in pregnancy[17]. Obesity is related with various adverse obstetric complications such as gestational diabetes mellitus, hypertension, venous thromboembolism, shoulder dystocia, prematurity, stillbirth, neonatal death, postpartum hemorrhage, and urinary, uterine, and wound infections[18]. A prevalence rate of 46.4% was reported in a study among Syrian women in 2006[19]. In the present study of refugee women, we found obesity at a rate of 11.6%, which is significantly lower than that reported in the literature. This may be explained by the negative impact of war on adequate nutrition and its related factors (e.g., difficulty in reaching food, low socioeconomic levels, and

Table 4. Logistic regression results of the risk factors for adverse maternal and fetal outcomes

	Coefficient	SE	Wald	df	p	OR	95% CI for OR	
							Lower	Upper
Smoking	0.973	0.206	22.277	1	<0.001	2.647	1.767	3.965
BMI	0.821	0.249	10.899	1	0.001	2.272	1.396	3.699
Adolescent pregnancy	0.549	0.185	8.768	1	0.003	1.732	1.204	2.491

SE: Standard error, df: Degrees of freedom, OR: Odds ratio, CI: Confidence interval, BMI: Body mass index
Hosmer and Lemeshow test value: 0.998, Nagelkerke R square test value: 0.096, Sensitivity: 46%, specificity: 74%

Table 5. Relationship between risk factors and adverse maternal-perinatal outcomes

Adverse maternal-fetal outcomes		Smoking		p	BMI		p	Adolescent pregnancy		p
		+	-		≤30	>30		+	-	
Preterm birth	+	34 (26.4)	100 (17.6)	0.022	14 (17.3)	120 (19.4)	0.642	43 (25.4)	91 (17.2)	0.018
	-	95 (73.6)	469 (82.4)		67 (82.7)	497 (80.6)		126 (74.6)	438 (82.8)	
PPROM, EMR	+	42 (32.6)	39 (6.9)	<0.001	15 (18.5)	66 (10.7)	0.039	23 (13.6)	58 (11.0)	0.350
	-	87 (67.4)	530 (93.1)		66 (81.5)	551 (89.3)		146 (86.4)	471 (89.0)	
IUGR	+	37 (28.7)	49 (8.6)	<0.001	6 (7.4)	80 (13.0)	0.152	37 (21.9)	49 (9.3)	<0.001
	-	92 (71.3)	520 (91.4)		75 (92.6)	537 (80.0)		132 (78.1)	480 (90.7)	
Hypertension	+	2 (1.6)	15 (2.6)	0.751	6 (7.4)	11 (1.8)	0.009	6 (3.6)	11 (2.1)	0.264
	-	127 (98.4)	554 (97.4)		75 (92.6)	606 (98.2)		163 (96.4)	518 (97.9)	
Maternal transfusion	+	3 (2.3)	53 (9.3)	0.008	10 (12.3)	46 (7.5)	0.128	16 (9.5)	40 (7.6)	0.427
	-	126 (97.7)	516 (90.7)		71 (87.7)	571 (92.5)		153 (90.5)	489 (92.4)	
Perinatal exitus	+	11 (8.5)	4 (0.7)	<0.001	0	15 (2.4)	0.239	4 (2.4)	11 (2.1)	0.766
	-	1180 (91.5)	565 (99.3)		81 (100)	602 (97.6)		165 (97.6)	518 (97.9)	

PPROM: Premature rupture of membranes, EMR: Early membrane rupture, IUGR: Intrauterine growth retardation, BMI: Body mass index

increased psychological problems such as depression). In the present study, we found that obesity was not associated with idiopathic preterm birth; this finding was in accordance with the outcomes of a study of nearly 1.600.000 deliveries in a population-based cohort study of women with live singleton births in Sweden[20]. Cnattingius et al. [20] showed that obesity increased the incidence of preterm births, especially in the context of deliveries happening between 22 and 27 gestational weeks. In their study, the authors stated that obesity was related with preterm delivery because of PPROM and other obesity-related diseases such as hypertension and diabetes; when these conditions were excluded, the preterm delivery risk was unchanged in obese patients[20]. Similarly, in a series of 4653 preterm births among more than 55.000 births, Madan et al. [21] also stated the adverse impact of diabetes and hypertension on the relationship between obesity and premature birth. In accordance with these prior studies, we found that obesity was not related with idiopathic preterm birth but was with hypertension and PPROM (Table 4). Indeed, Zhong et al.[22] showed that obesity was associated with a decreased risk of spontaneous preterm birth without PPROM at less than 37 weeks' gestation (OR: 0.8, 95% CI: 0.7-0.9) and increased risks of PPROM before 37 and 34 weeks' gestation [OR: 1.3, 95% CI: (1.1-1.6) and OR: 1.4, 95% CI: (1.0-2.0), respectively]. Adolescent pregnancy is one of the major health problems in refugee populations, resulting in adverse maternal-fetal outcomes. In a multinational study organized by the World Health Organization, Ganchimeg et al.[23] documented more adverse maternal and adverse fetal outcomes among adolescent mothers (aged ≤20 years) than among mothers aged 20 to 24 years. It is suggested that significantly younger adolescent mothers carry an especially higher risk of preterm delivery. In other words, mothers aged 15 years or younger are 1.6 times more likely to experience preterm delivery as compared with mothers aged 20 to 24 years (OR: 1.60, 95% CI: 1.37-1.87). In the study by Ganchimeg et al.[23] 11.2% of mothers aged 10 to 15 years, but only 7% of mothers aged 20 to 24 years had a risk of preterm delivery ($p<0.001$). In our study, we found that 25.4% of adolescent and 17.2% of adult mothers had a risk of preterm delivery[23]. Besides this, we also documented a higher risk of IUGR in the adolescent group (21.9%) as compared with the adult group (9.3%) ($p<0.001$). Although we did not have the opportunity to compare the adult refugee population with an adolescent control group, we estimated higher risks of adverse maternal and perinatal outcomes in an adolescent refugee population as a result of the insufficient food supply, higher workloads, and malnutrition.

Study Limitations

There are some limitations to our study. Regression analysis results revealed 46% sensitivity and 74% specificity rates for the estimation of the risk of adverse maternal and perinatal outcomes. To increase the sensitivity and specificity of calculations, some other possible risk factors could be added to the study. However, this was a retrospective study, making it impossible to adequately evaluate all possible factors related to adverse outcomes in pregnancy. Additionally, our sample size was not large enough to be sufficiently powered to examine the relationship between possible risk factors and rates of pregnancy complications due to the low prevalence rates of stillbirth, preeclampsia, congenital anomalies, venous thromboembolism, and maternal death. Secondly, most of the patients in our series were referred from other clinics when a high-risk pregnancy complication was suspected, potentially introducing bias into the patient selection scheme for this study. Despite these limitations, our study is unique due to its evaluation of risk factors for adverse maternal and perinatal outcomes in a refugee population coming from an active conflict country. We believe that taking the results of this study into account could help in reducing adverse outcomes in pregnant refugee populations.

Conclusion

This study showed that smoking, obesity, and adolescence were the most important predictors for adverse maternal and perinatal outcomes in pregnant refugees coming from an active conflict region. Prevention strategies for obesity, smoking, and adolescent pregnancies should be implemented, primarily to reduce maternal and antenatal adverse outcomes. Additionally, pregnant women with these risk factors in a refugee communities emigrating from nations in conflict zones should be followed up closely.

Ethics

Ethics Committee Approval: Retrospective study.
Informed Consent: Retrospective study.
Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.S.Y.., S.F.T., B.T., L.M., Concept: E.S.Y.., S.F.T., B.T., L.M., Design: E.S.Y.., S.F.T., B.T., L.M., Data Collection or Processing: S.F.T., B.T., Analysis or Interpretation: E.S.Y.., S.F.T., B.T., L.M., Literature Search: S.F.T., Writing: S.F.T.

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

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Mangrio E, Sjögren Forss K. Refugees' experiences of healthcare in the host country: a scoping review. BMC Health Serv Res 2017;17:814.
2. Alder J, Fink N, Lapaire O, Urech C, Meyer A, Bitzer J, et al. The effect of migration background on obstetric performance in Switzerland. Eur J Contracept Reprod Health Care 2008;13:103-8.
3. Lansakara N, Brown SJ, Gartland D. Birth outcomes, postpartum health and primary care contacts of immigrant mothers in an Australian nulliparous pregnancy cohort study. Matern Child Health J 2010;14:807-16.

4. 4.The UN Refugee Agency (UNHCR). Figures at a glance. 2018. http://unhcr.org/figures-at-a-glance.html. Accessed 25.06.2018
5. Wanigaratne S, Cole DC, Bassil K, Hyman I, Moineddin R, Urquia ML. The influence of refugee status and secondary migration on preterm birth. J Epidemiol Community Health 2016;70:622-8.
6. Johnson EB, Reed SD, Hitti J, Batra M. Increased risk of adverse pregnancy outcome among Somali immigrants in Washington state. Am J Obstet Gynecol 2005;193:475-82.
7. Philibert M, Deneux-Tharaux C, Bouvier-Colle MH. Can excess maternal mortality among women of foreign nationality be explained by suboptimal obstetric care? BJOG 2008;115:1411-8.
8. Jamieson DJ, Meikle SF, Hillis SD, Mtsuko D, Mawji S, Duerr A. An evaluation of poor pregnancy outcomes among Burundian refugees in Tanzania. JAMA 2000;283:397-402.
9. Abu Hamad Kh, Abed Y, Abu Hamad B. Risk factors associated with preterm birth in the Gaza Strip: hospital-based case-control study. East Mediterr Health J 2007;13:1132-41.
10. Malin M, Gissler M. Maternal care and birth outcomes among ethnic minority women in Finland. BMC Public Health 2009;9:84.
11. Badshah S, Mason L, McKelvie K, Payne R, Lisboa PJ. Risk factors for low birthweight in the public-hospitals at Peshawar, NWFP-Pakistan. BMC Public Health 2008;8:197.
12. Kyrklund-Blomberg NB, Granath F, Cnattingius S. Maternal smoking and causes of very preterm birth. Acta Obstet Gynecol Scand 2005;84:572-77.
13. England MC, Benjamin A, Abenhaim HA. Increased risk of preterm premature rupture of membranes at early gestational ages among maternal cigarette smokers. Am J Perinatol 2013;30:821-6.
14. Pineles BL, Hsu S, Park E, Samet JM. Systematic Review and Meta-Analyses of Perinatal Death and Maternal Exposure to Tobacco Smoke During Pregnancy. Am J Epidemiol 2016; 184:87-97.
15. Horta BL, Victora CG, Menezes AM, Halpern R, Barros FC. Low birthweight, preterm births and intrauterine growth retardation in relation to maternal smoking. Paediatr Perinat Epidemiol 1997;11:140-51.
16. Nordenberg D, Yip R, Binkin NJ. The effect of cigarette smoking on hemoglobin levels and anemia screening. JAMA 1990;264:1556-9.
17. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. JAMA 2012;307:491-7.
18. Fitzsimons KJ, Modder J, Greer IA. Obesity in pregnancy: risks and management. Obstet Med 2009;2:52-62.
19. Fouad M, Rastam S, Ward K, Maziak W. Prevalence of obesity and its associated factors in Aleppo, Syria. Prev Control 2006;2:85-94.
20. Cnattingius S, Villamor E, Johansson S, Edstedt Bonamy AK, Persson M, Wikström AK, et al. Maternal obesity and risk of preterm delivery. JAMA 2013;309:2362-70.
21. Madan J, Chen M, Goodman E, Davis J, Allan W, Dammann O. Maternal obesity, gestational hypertension, and preterm delivery. J Matern Fetal Neonatal Med 2010;23:82-8.
22. Zhong Y, Cahill AG, Macones GA, Zhu F, Odibo AO. The association between prepregnancy maternal body mass index and preterm delivery. Am J Perinatol 2010;27:293-8.
23. Ganchimeg T, Ota E, Morisaki N, Laopaiboon M, Lumbiganon P, Zhang J, et al. Pregnancy and childbirth outcomes among adolescent mothers: a World Health Organization multicountry study. BJOG 2014; 121 Suppl 1:40-8.

Clinical Investigation / Araştırma

DOI: 10.4274/tjod.galenos.2019.04578

Turk J Obstet Gynecol 2019;16:180-6

High-grade uterine corpus-confined endometrial cancer with lymphadenectomy: does adjuvant therapy improve survival?

Erken evre yüksek riskli ve lenfadenektomi yapılmış endometrium kanserinde adjuvan tedavi sağkalımı iyileştirir mi?

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Abstract

Objective: To evaluate the necessity of adjuvant therapy and other prognostic factors in high-grade uterine corpus-confined endometrial cancer (EC) with lymphadenectomy performed.

Materials and Methods: This study included 120 patients who had endometrioid-type grade 3, serous-type, clear cell-type, and undifferentiated-type EC and underwent lymphadenectomy.

Results: Patients with high-grade uterine corpus-confined EC who underwent lymphadenectomy were evaluated. The modality of adjuvant therapy performed was not a predictor for the site of recurrence. The loco-regional recurrence rate decreased from 9.5% to 3.8% in patients who received radiotherapy. However, this difference was not statistically significant (p=0.206). In addition, performing adjuvant chemotherapy did not alter the risk of extrapelvic recurrence. Only International Federation of Gynecology and Obstetrics 2009 stage was significant in the univariate analysis. On the other hand, age, tumor type, number of removed lymph nodes, presence of myometrial and lymphovascular space invasion, tumor size and adjuvant therapy modality were not related with disease-free survival.

Conclusion: Performing adjuvant therapy and therapy modality does not improve oncologic outcomes in intermediate and high-risk patients. However, radiotherapy reduced the risk of local recurrence by more than 50%. Vaginal brachytherapy was efficient as external beam radiotherapy. Therefore, vaginal brachytherapy should be used for these patients in order to reduce loco-regional recurrence even if it is not reported to be effective on disease-free survival.

Keywords: Adjuvant therapy, endometrial cancer, high risk

Öz

Amaç: Uterusa sınırlı endometrium kanserinde adjuvant tedavinin yeri tartışmalıdır. Çalışmamızda uterusa sınırlı erken evre EK'inde lenfadenektomi yapılmış hasta grubunda adjuvant tedavinin gerekliliğinin ve diğer prognostik faktörlerin yerinin araştırılması amaçlandı.

Gereç ve Yöntemler: Lenfadenektomi yapılmış endometrioid tip grade 3, seröz tip, berrak hücreli tip ve andifferansiye tip EK olan 120 hasta incelendi.

Bulgular: Adjuvan tedavi modalitesinin rekürrens yeri ile ilşkisiz olduğu tespit edildi. Radyoterapi alan hastalarda lokal rekürrens oranı %9,5'ten %3,8'e düşmekteydi. Bu fark istatistiksel olarak anlamlı değildi (p=0,206). Ayrıca, adjuvant kemoterapi uygulanması ekstrapelvik rekürrens riskini artırmamaktaydı. Uluslararası Jinekoloji ve Obstetri Federasyonu evre univaryant analizde hastalıksız sağkalım ile ilişkili iken; yaş, tümör tipi, çıkarılan lenf nodu sayısı, myometrial ve lenfovasküler alan invazyonu varlığı, tümör çapı ve adjuvant tedavi modalitesi ilişkisiz bulundu.

Sonuç: Orta ve yüksek riskli hastalarda adjuvant tedavi uygulanması ve tedavi tipi onkolojik sonuçları iyileştirmemekteydi. Fakat radyoterapi lokal rekürrens riskini %50'den fazla azaltmaktaydı. Vajinal brakiterapi, eksternal beam radyoterapi kadar etkili bulundu. Bu yüzden bu hasta grubuna hastalıksız sağkalıma etkisi olmasa da lokal rekürrensi azaltmak için vajinal brakiterapi uygulanabilir.

Anahtar Kelimeler: Adjuvan tedavi, endometrium kanseri, yüksek risk

PRECIS: In this study, we aimed to evaluate the use of adjuvant therapy in patients with high-grade uterine corpus-confined endometrial cancer who underwent lymphadenectomy.

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Received/Geliş Tarihi: 26.03.2019 **Accepted/Kabul Tarihi:** 28.08.2019

Introduction

Endometrial cancer (EC) is the most frequent cancer of the female genital tract and the fourth cancer among all cancer types[1]. According to GLOBOCAN 2012 data, 320.000 new cases are diagnosed each year[2]. EC is mostly diagnosed at the early stage and the main treatment is surgery[3]. Five-year overall survival (OS) is over 80% for low-grade tumors in early-stage EC[4]. Surgery consisting of total hysterectomy + bilateral salpingo-oophorectomy and evaluation of the extent of the disease is the standard initial therapy. EC has been staged surgically according to the International Federation of Gynecology and Obstetrics (FIGO) since 1988[5]. FIGO revised the staging system in 2009[6].

The use of adjuvant therapy in uterine corpus-confined EC is controversial. Reports revealed that external beam radiotherapy (EBRT) decreased loco-regional recurrence in patients with deep myometrial invasion, tumor with poor differentiation, and advanced age, but EBRT did not improve OS[7,8]. Other trials that investigated the difference between adjuvant therapy modalities revealed that EBRT had serious adverse effects. Vaginal brachytherapy (VBT) could be a type of adjuvant radiotherapy (RT) given in patients with EC because of its tolerability[9,10]. This study was designed to evaluate the necessity of adjuvant therapy and other prognostic factors in patients with high-grade uterine corpus-confined EC who underwent lymphadenectomy.

Materials and Methods

This study included 120 patients whose staging surgeries (total hysterectomy and bilateral salpingo-oophorectomy and pelvic and paraaortic lymphadenectomy) were performed in our oncology clinic between January 1993 and December 2017 and who had uterine corpus- confined endometrioid-type grade 3, serous-type, clear cell-type, and undifferentiated-type EC according to the final pathology results. Data of the patients were obtained from the hospital's electronic database, and the patients' files and pathology results were analyzed, retrospectively. Patients whose surgeries had not been performed in our clinic, with endometrioid-type grade 1 and 2 or mixed-type adenocarcinoma, whose tumors had a sarcoma component, with synchronized primary tumor, whose surgeries had not included lymphadenectomy, who were lost during follow-up, who died in the first month after surgery, and those who underwent neo-adjuvant treatment were excluded. Ethical board approval exists for this study. Staging was performed according to the FIGO 2009 criteria. Tumor size was measured as the longest tumor diameter in the uterine corpus after fixation in a paraffin block. Lymphovascular space invasion (LVSI) was defined as the tumoral cells or cell clusters held on vessel walls that were stained with hematoxylin and eosin in the pathologic sections, containing both tumor and the surrounding healthy tissue. The omentum was pathologically examined through 2-3 sections taken from the macroscopic tumor and suspicious areas, or through 3-5 sections taken from healthy looking omentum tissue. Pathologic examinations of the hysterectomy material were performed with at least 4 cut-out sections. Lymph node examinations were performed as follows: the material was embedded in a paraffin block (i) directly, if the size was less than 1 cm; (ii) with horizontally cutting at least into two pieces according to size, if it was more than 1 cm. In the presence of the macroscopic tumor, only that part was directly taken into the paraffin block. The sections were evaluated after hematoxylin and eosin staining. Standard staging surgery included cytologic sampling, total abdominal hysterectomy, bilateral salpingo-oophorectomy, systematic pelvic and paraaortic lymphadenectomy, and omentectomy. During the intra-operative observation, cytoreductive surgical techniques were performed in addition to staging surgery in the presence of a macroscopic tumor. Lymphadenectomy was performed in most patients by skeletonizing the pelvic and paraaortic regions. Bilateral pelvic lymphadenectomy was performed to complete skeletonization with all lymphatic tissue of the common, external, and internal iliac vessels, and the obturator fossa, which was removed after visualization of the obturator nerve. The superior surgical dissection margin for the pelvic nodes was the aortic bifurcation, and the anterior distal surgical dissection margin was the circumflex iliac vein. Presacral lymphatic tissue was removed separately. The upper limit of the paraaortic lymphadenectomy was the left renal vein. All lymphatic tissue was then removed from the precaval, laterocaval, interaortacaval, preaortic and lateroaortic regions up to the left renal vein. All surgeries were performed using open surgical techniques, and pathologic findings were examined and interpreted at a single institution. The use and type of adjuvant therapy was decided by a gynecologic oncology council and senior surgeons. Adjuvant RT was administered as EBRT and/or VBT. Low-dose cisplatin used within concurrent chemoradiotherapy was not accepted as systemic therapy due to it being non-curative. Recurrence following surgery used as the initial therapy for a period of one month or progression during adjuvant therapy was regarded as refractory disease. One month after the completion of adjuvant therapy, a follow-up examination was performed and the non-appearance of disease had to be documented. From this point, any abnormal finding was evaluated as recurrent disease. Loco-regional recurrence was defined as relapses located in the vagina, vaginal vault, and pelvic side wall below the level of the linea terminalis. The recurrence region between the level of the linea terminalis and diaphragm was called "upper abdominal" and all other regions were called extra-abdominal. Recurrence in the liver parenchyma and bone was accepted as extra-abdominal; ascites proven with cytologic evaluation and peritoneal carcinomatosis was accepted as upper abdominal. Recurrence was defined after the evaluation of the patient's clinical, radiologic, and pathologic findings by performing pelvic and systematic examinations, abdominal X-ray, abdominopelvic and thoracic

computed tomography (CT) or magnetic resonance imaging. The decision of recurrence-related therapy was made by a gynecologic oncology council. The patients were followed-up quarterly in the first two years, semi-annually up to five years, and annually thereafter. Pelvic examination, abdominopelvic ultrasonography, complete blood count, and blood chemistry were performed. Chest X-ray was performed yearly unless there was clinical suspicion. Thoracic and/or abdominal CT was used when needed. Canser antigen 125 levels were used in the follow-up, even though they were not used routinely. The time period from initial surgery to recurrence or the last visit was accepted as disease-free survival (DFS), and the time period from the initial surgery to disease-related death or the last visit was accepted as disease-specific survival (DSS). Time to recurrence (TTR) was defined as the period of time from the initial surgery to relapse in patients with recurrence. Categorical variables were analyzed using Kaplan-Meier survival analysis using the log-rank test to determine whether they had statistically significant effects on DFS or DSS.

Statistical Analysis

Whether the continuous and discrete numeric variables had statistically significant effects were calculated using univariate Cox proportional hazard regression analysis. Multivariate backward stepwise Cox proportional hazard regression analysis was used to determine the effects of variables effective on survival after the univariate statistical analysis. Factors with a p value of <0.25 in univariate analyses were included as candidate variables in multivariate analyses. P values <0.05 were considered statistically significant for the results. Data analyses were performed using the SPSS for Windows 11.5 package program.

Results

The mean age of the patients was 60 (range, 38-79) years. The tumor type was grade 3 endometrioid in 76 patients, clear cell in 24, serous in 18, and undifferentiated in two. Sixty-seven (55.8%) patients were stage 1A and 53 (44.2%) patients were stage 1B according to the FIGO 2009 criteria. Myometrial invasion was not detected in 18 patients. The median tumor size was 35 (range, 5-150) mm. The median number of removed lymph nodes was 51 (range, 3-118). Lymphadenectomy was performed with ≥21 lymph nodes in 91% of the patients. LVSI was positive in 38 patients, cervical glandular invasion was positive in four, and peritoneal cytology was positive in one patient. Data related to surgico-pathologic factors are summarized in Table 1. Adjuvant therapy was performed in 90 (75%) of the patients. The most frequent adjuvant therapy was RT and 78 (65%) patients received RT with/without chemotherapy. Thirty-six (30%) patients received VBT only, 28 (23.3%) patients received EBRT only, and five (4.2%) patients received VBT + EBRT. Information about the type of RT could not be found in nine patients' files. Adjuvant systemic therapy was applied to 21 (17.5%) patients, 12 (10%) of whom received only chemotherapy. Data related to adjuvant therapy are shown in Table 2. Tumor type was a significant predictor for determining the modality of adjuvant therapy. Adjuvant RT rates were 73% in patients with grade 3 endometrioid-type tumors and 50% in patients with non-endometrioid-type tumors (p=0.009). Similar rates were found for systemic therapy between the same groups of patients. Chemotherapy was performed in 6.6% of patients in the endometrioid group and 36.4% of patients in the non-endometrioid group (p<0.001). In spite of this, tumor type, FIGO 2009 stage, and presence of myometrial invasion did not determine the adjuvant therapy modality in patients receiving RT only (p=0.068, p=0.883, and p=0.504, respectively). The modality of adjuvant therapy performed was not a predictor for the site of recurrence. The loco-regional recurrence rate decreased from 9.5% to 3.8% in patients who received RT (VBT and/or EBRT with/without chemotherapy). However, this difference was not statistically significant (p=0.206). In addition, performing adjuvant chemotherapy did not alter the risk of extrapelvic recurrence.

Table 1. Clinical, surgical and pathological characteristics of patients

Characteristics		n/mean	%/median (range)
Age at initial diagnosis		60	60 (38-79)
Tumor size (mm)		38	35 (5-150)
Number of removed lymph node		51.8	51 (3-118)
Tumor type	Endometrioid type grade 3	76	63.3
	Clear cell type	24	20
	Serous type	18	15
	Undifferentiated type	2	1.7
FIGO 2009 stage	1A	67	55.8
	1B	53	44.2
Depth of myometrial invasion	No invasion	18	15
	<½	49	40.8
	≥½*	53	44.2
Lymphovascular space invasion	Negative	63	52.5
	Positive	38	31.7
	Not reported	19	15.8
Cervical invasion	Negative	116	96.7
	Glandular	4	3.3
Peritoneal cytology	Negative	111	92.5
	Positive	1	0.8
	Not reported	8	6.7

*Except for patient with uterine serosal invasion, FIGO: International Federation of Gynecology and Obstetrics

The extrapelvic recurrence rates were 4.8% and 6.1% in the chemotherapy group and non-chemotherapy group, respectively (p=0.818). The median follow-up period was 33 (range, 2-152) months. It was observed that during this period, 11 (9.2%) patients had recurrence and three (2.5%) patients died of the disease. In the entire cohort, none of the patients had refractory disease. The median TTR was 15 (range, 2-54) months in patients who developed recurrence. Four (3.3%) patients had recurrence only in the pelvic region and seven (5.8%) patients had extrapelvic recurrence; six (5%) of which were in extra-abdominal regions (Table 3). In our study, the 5-year DFS was 87% and the 5-year DSS was 97%. The factors affecting the prognosis were determined by using DFS because there were only three disease-related deaths. Accordingly, only the FIGO 2009 stage was significant in the univariate analysis. The 5-year DFS was 92% in stage 1A and 81% in stage 1B (p=0.023) (Figure 1). On the other hand, age, tumor type, number of removed lymph nodes, presence of myometrial and LVSI , tumor size, and adjuvant therapy modality were not related with DFS (Table 4). Stage (2009 FIGO stage 1A vs. 1B), presence of myometrial invasion (noninvasive vs. myoinvasive), LVSI (negative vs. positive), and adjuvant RT type (VBT vs. EBRT ± VBT) whose p values were found below 0.25 on univariate analysis, were evaluated using multivariate analysis. However, a model could not be developed because of the correlation within these factors. Also, a multivariate analysis defining recurrence risk could not be obtained. The efficacy of prognostic factors was assessed through subgroup analysis in patients with stage 1B disease (n=53). The median follow-up period of this group was 36 (range, 2-121) months. In the follow-up, eight (15.1%) patients had recurrence and three (5.7%) patients died of the disease. It was considered that prognostic factors were ineffective for determining DFS using univariate analysis. Age (≤60 year vs. >60 year; p=0.522), tumor type (endometrioid vs. non-endometrioid; p=0.377), number of removed lymph nodes (≤48 vs. >48; p=0.072), LVSI (negative vs. positive; p=0.507), tumor size (≤40 mm vs. >40 mm; p=0.671), adjuvant therapy (received vs. not received; p=0.457), adjuvant RT (received vs.

Table 2. Adjuvant treatment

Characteristics		Frequency	Percent
Adjuvant treatment	Not received	30	25
	Received	90	75
Type of adjuvant therapy	Radiotherapy only	68	56.7
	Chemotherapy only	12	10
	Sandwich treatment	5	4.2
	Radiotherapy followed by chemotherapy	1	0.8
	Chemotherapy followed by radiotherapy	3	2.5
	Concurrent chemoradiotherapy	1	0.8
Adjuvant radiotherapy	Not received	42	35
	Received*	78	65
Type of adjuvant radiotherapy	VBT only	36	30
	EBRT only	28	23.3
	EBRT + VBT	5	4.2
	Not reported	9	7.5
Adjuvant systemic chemotherapy	Not received	99	82.5
	Received**	21	17.5

Sandwich treatment: 3 cycles paclitaxel and carboplatin followed by radiotherapy followed by 3 cycles paclitaxel and carboplatin, VBT: Vaginal brachytherapy, EBRT: External beam radiotherapy, *Radiotherapy only + sandwich treatment + radiotherapy followed by chemotherapy + chemotherapy followed by radiotherapy + concurrent chemoradiotherapy, **Chemotherapy only + sandwich treatment + radiotherapy followed by chemotherapy + chemotherapy followed by radiotherapy

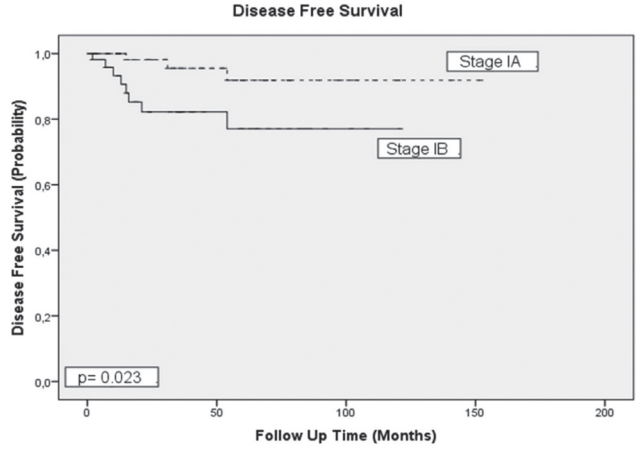

Figure 1. Relationship between disease free survival and stage

Table 3. Recurrence, recurrence site and death

Recurrence and death		Frequency	Percent
Recurrence	Negative	109	90.8
	Positive	11	9.2
Recurrence site	Only pelvic	4	3.3
	Only upper abdominal	1	0.8
	Only extra abdominal	3	2.5
	Pelvic + upper abdominal	-	-
	Pelvic + extra abdominal	1	0.8
	Pelvic + upper abdominal + extra abdominal	2	0.17
Death	No death	116	96.7
	Because of endometrial cancer	3	2.5
	Because of other disease	1	0.8

not received; p=0.693), type of adjuvant RT (VBT vs. EBRT ± VBT; p=0.114), adjuvant chemotherapy (received vs. not received; p=0.869), and RT+ chemotherapy therapy (received vs. not received; p=0.858) showed no statistical significance.

Table 4. The factors predicting disease-free survival, univariate analysis

Factors		5-year disease-free survival, (%)	p value
Age at initial diagnosis*	≤60 years	89	0.503
	>60 years	84	
Tumor type	Endometrioid type grade 3	89	0.600
	Clear cell type	78	
	Serous type	100	
	Undifferentiated type	100	
Tumor type	Endometrioid	89	0.921
	Non-endometrioid	85	
Number of lymph node*	≤51	87	0.384
	>51	90	
2009 FIGO stage	1A	92	0.025
	1B	81	
Myometrial invasion	Noninvasive	100	0.137
	Myoinvasive	85	
Tumor size*	≤35 mm	88	0.625
	>35 mm	92	
Lymphovascular space invasion	Negative	92	0.124
	Positive	82	
Adjuvant therapy**	Not received	80	0.307
	Received	90	
Adjuvant radiotherapy***	Not received	84	0.619
	Received	90	
Type of adjuvant radiotherapy***	VBT only	96	0.076
	EBRT ± VBT	83	
Adjuvant chemotherapy****	Not received	93	0.568
	Received	86	
Multimodal therapy*****	Not received******	87	0.997
	Received	88	

*Median value, **Radiotherapy and/or chemotherapy, ***Radiotherapy ± chemotherapy, ****Chemotherapy ± radiotherapy, *****Radiotherapy and chemotherapy (sandwich treatment + radiotherapy followed by chemotherapy + chemotherapy followed by radiotherapy), ******Chemotherapy only + radiotherapy only + concurrent chemoradiotherapy, FIGO: International Federation of Gynecology and Obstetrics

Discussion

This study suggested that clinical, surgical, and pathologic factors, except for stage, had no prognostic value in high-grade uterine corpus-confined EC with lymphadenectomy performed. The 5-year DFS decreased from 92% to 81% in patients with deep myometrial invasion (stage 1B). The entire cohort of patients had recurrence, 63% (n=7/11) in the extrapelvic region and 55% (n=6/11) in the abdominal region. However, local (RT) or systemic (chemotherapy) therapy had no beneficial effect or did not change the recurrence site. Despite that, RT decreased pelvic recurrence rates from 9.5% to 3.8% with no statistical significance. In addition, the type of RT had no effect on oncologic outcomes. There have been opposing studies in the literature offering the utility of adjuvant therapy and discussing the modality types of the therapy. Gupta et al.[11] evaluated 33.600 patients by using the National Cancer Database to examine the impact of adjuvant radiation therapy on OS in patients with high-intermediate risk stage 1 EC. They accepted stage 1B and/or grade 3 patients as the high-intermediate risk group. Approximately three-quarters of the patients underwent lymphadenectomy. The average number of removed lymph nodes was not obvious. The study showed a statistically significant difference in OS rates between the surgery alone vs. surgery + adjuvant RT groups. According to this study, loco-regional control with adjuvant RT causes an improvement in 5-year OS (respectively, 79.2% vs. 83.3%, p<0.0001)[11]. Postoperative Radiation Therapy in Endometrial Carcinoma (PORTEC-1) was a study that included patients with grade 1 EC and ≥50% invasion, grade 2 with any invasion, or grade 3 with <50% invasion. In this study, 715 patients were randomized to the surgery alone vs. surgery + EBRT arms. Surgery was performed without lymphadenectomy. This study suggested that postoperative radiation therapy in stage 1 EC decreased loco-regional recurrence rates, but did not change OS (85% vs. 81%, p=0.31). For the prevention of loco-regional recurrence (5% vs. 18%), radiation therapy should be used for patients with high-intermediate risk who have two of these factors; age ≥60 years, grade 3 and deep myometrial invasion[7]. After 15 years of follow-up, 426 patients from the PORTEC-1 trial were re-evaluated. Loco-regional recurrence rates were 6% for EBRT vs. 15.5% for the surgery alone group (p<0.0001). The 15-year OS was 52% vs. 60%, and the failure-free survival was 50% vs. 54%. These rates showed no statistical significance[12]. The Gynecologic Oncology Group 99 trial[8] was designed to determine the effect of adjunctive whole pelvic radiation therapy (EBRT) on loco-regional recurrence and OS rates. The entire cohort consisting 447 patients with FIGO stage IB, IC and II disease with intermediate risk factors were accepted as the high-intermediate and low-intermediate risk groups. High-intermediate risk factors were defined as moderate, poorly differentiated tumor, presence of lymphovascular invasion, outer third myometrial invasion, age 50 years or older with any two risk factors or 70 years or older with any of the risk factors. All

patients underwent lymphadenectomy. For patients in the low-intermediate risk group, adjuvant RT was not recommended. After 2 years of follow-up, no additional therapy group had an estimated cumulative incidence of recurrence rate of 12%, and the RT group had 3% (p=0.007). The OS rates showed no statistically significant difference (p=0.557). This study suggested that additional RT in uterine corpus-confined EC should be given to patients with high-intermediate risk factors. In the PORTEC-2 trial, 427 patients with stage 1 or 2A disease who had high-intermediate risk factors and underwent EBRT or VBT were compared for recurrence, survival, and toxicity. High-intermediate risk factors include age more than 60 years, FIGO 1988 stage 1C grade 1 or 2 disease, or stage 1B grade 3 disease and stage 2A disease at any age. However, routine lymphadenectomy was not performed; only suspicious lymph nodes were removed. The 5-year loco-regional recurrence rates were 2.1% for the EBRT group and 5.1% for the VBT group (p=0.17). No difference was found in OS (respectively, 79.6% vs. 84.8%, p=0.57) and disease free survival (respectively, 78.1% vs. 82.7%, p=0.74) rates. Grade 1-2 gastrointestinal toxicity was lower in the VBT group than in the EBRT group (12.6% vs. 53.8%) at the completion of adjuvant therapy. However, after 2-years of follow-up, the difference between the reported toxic effects decreased and showed no statistical significance. In this study, it was suggested that VBT should be the choice of treatment as adjuvant therapy because of the gastrointestinal adverse effects[9]. PORTEC-3 was a multicenter, open-label, randomized, international trial investigating the survival rates and adverse effects of adjuvant therapy modalities in patients with EC[10]. Women with high-risk EC were randomized to radiation therapy alone or concurrent chemoradiotherapy arms to evaluate the difference between the two adjuvant therapy modalities. Lymphadenectomy was not performed for all patients. The 5-year OS was 81% in the chemoradiotherapy group vs. 76% in the RT group (p=0.11). The 5-year DFS was 75% vs. 68%, respectively (p=0.022). Grade 2 or higher sensory neuropathy was found to have a statistically significant difference between the two groups at 36 months (8% vs. 1%, respectively, p<0.0001). For patients with stage 1 and 2 disease, chemoradiotherapy did not improve OS and should not be recommended as a standard procedure.

Study Limitations

The retrospective nature of the study is its most important limitation. The small sample size of the study group is another disadvantage. However, the entire cohort consists of patients who underwent lymphadenectomy. The median number of removed lymph nodes was 51, and 90% of patients had 21 or more lymph nodes removed. This allowed us to create a study group consisting of uterine corpus-confined disease in which nodal spread was common. Thus, a homogenized cohort was obtained. This is the most remarkable advantage of this study. In addition, the other inclusion and exclusion criteria strengthened the study homogenization.

Conclusion

Performing adjuvant therapy and therapy modality do not improve oncologic outcomes in patients at intermediate and high risk. However, RT reduced the local recurrence risk by more than 50%. VBT was efficient as EBRT. Therefore, VBT should be used for these patients in order to reduce loco-regional recurrence, even if it is not reported to be effective on DFS. For more accurate results, more randomized controlled trails should be performed in patients with uterine corpus-confined EC who have undergone systematic lymphadenectomy.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences, Etlik Zübeyde Hanım Women's Diseases Training and Research Hospital Ethics Committee (approval number: 963).
Informed Consent: Retrospective study design.
Peer-review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.T., N.B., A.K., G.B., Concept: Ç.K., T.T., Design: Ç.K., G.B., Data Collection or Processing: Ç.K., D.Y., Y.D., G.K.C., Analysis or Interpretation: Ç.K., A.K., T.T., N.B., Literature Search: Ç.K., D.Y., C.Ç., G.K.C., Y.D., Writing: Ç.K., T.T.
Conflict of Interest: No conflict of interest was declared by the authors.
Financial Disclosure: The authors declared that this study received no financial support.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61:69-90.
2. Richman DM, Tirumani SH, Hornick JL, Fuchs CS, Howard S, Krajewski K, et al. Beyond gastric adenocarcinoma: Multimodality assessment of common and uncommon gastric neoplasms. Abdom Radiol (NY) 2017;42:124-140.
3. Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study. Cancer 1987;60(8 Suppl):2035-41.
4. Lewin SN, Herzog TJ, Barrena Medel NI, Deutsch I, Burke WM, Sun X, et al. Comparative performance of the 2009 international Federation of gynecology and obstetrics' staging system for uterine corpus cancer. Obstet Gynecol 2010;116:1141-9.
5. Announcements: FIGO (the International Federation of Obstetricians and Gynecologists) stages: 1988 revision. Gynecol Oncol 1989;35:125-6.
6. Meeting Report. The new FIGO staging system for cancers of the vulva, cervix, endometrium and sarcomas. Gynecol Oncol 2009;115:325-8.
7. Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsen JJ, Wárlám-Rodenhuis CC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC

Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet 2000;355:1404-11.
8. Keys HM, Roberts JA, Brunetto VL, Zaino RJ, Spirtos NM, Bloss JD, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2004;92:744-51.
9. Nout RA, Smit VT, Putter H, Jürgenliemk-Schulz IM, Jobsen JJ, Lutgens LC, et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. Lancet 2010;375:816-23.
10. de Boer SM, Powell ME, Mileshkin L, Katsaros D, Bessette P, Haie-Meder C, et al. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial. Lancet Oncol 2018;19:295-309.
11. Gupta V, McGunigal M, Prasad-Hayes M, Kalir T, Liu J. Adjuvant radiation therapy is associated with improved overall survival in high-intermediate risk stage I endometrial cancer: A national cancer data base analysis. Gynecol Oncol 2017;144:119-24.
12. Creutzberg CL, Nout RA, Lybeert ML, Wárlám-Rodenhuis CC, Jobsen JJ, Mens JW, et al., Fifteen-year radiotherapy outcomes of the randomized PORTEC-1 trial for endometrial carcinoma. Int J Radiat Oncol Biol Phys 2011;81:e631-8.

Clinical Investigation / Araştırma

DOI: 10.4274/tjod.galenos.2019.75428

Turk J Obstet Gynecol 2019;16:187-92

Major problems, current characteristics and future career plans of obstetrics and gynecology residents in Turkey

Türkiye'de kadın hastalıkları ve doğum asistanlığı mevcut durum, karşılaşılan başlıca sorunlar ve kariyer planları

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Abstract

Objective: To evaluate the current problems and future career plans of obstetrics and gynecology residents in Turkey.

Materials and Methods: In this cross-sectional study, a survey was conducted with 143 trainees from 25 cities in different regions of Turkey. The questionnaire, which was sent via e-mail to all available trainees, consisted of four parts: information on hospitals, number and variety of surgical interventions, scientific activities, and current problems. Descriptive statistics were used to analyze participants' responses.

Results: The mean number of trainees in each hospital was 24 in education and research hospitals and 15 in university hospitals ($p<0.001$). Perinatology, oncology, and infertility clinics were present in about 70% of the hospitals, and there was no difference in this regard between public and university hospitals. Most trainees (68.5%) complained about being alone in an outpatient clinic. Third-year trainees from training and research hospitals performed a significantly higher number of vaginal births than those at universities ($p=0.035$). Most trainees complained about their workload during their residency in both training and research hospitals (74.4%) and university hospitals (66%). The three most common plans for the future were to attend a subspecialty program in the field of obstetrics and gynecology (28%), to pursue an academic career (23.1%), and to work in a private hospital (21%).

Conclusion: Extremely long work hours, excessive workload, many monthly duties, and lack of supervision at outpatient clinics were found to be the major problems of the obstetrics and gynecology residents in Turkey. The most common future plan of the residents was to attend a subspecialty program in the field of obstetrics and gynecology.

Keywords: Obstetrics and gynecology department, hospital, residency, training

Öz

Amaç: Türkiye'de kadın hastalıkları ve doğum asistanlığının güncel sorunlarını ve özelliklerini değerlendirmektir.

Gereç ve Yöntemler: Bu anket, Türkiye'nin her bölgesinden, 25 ilden araştırma görevlisi üzerinde yapıldı. Tüm katılımcılara e-posta ile bir anket gönderildi. Bu anket hastane bilgileri, çeşitli cerrahi müdahalelerin sayısı, bilimsel aktiviteler ve güncel problemler olmak üzere dört bölümden oluşmaktaydı. Katılımcı yanıtları analiz etmek için tanımlayıcı istatistikler kullanıldı.

Bulgular: Ortalama asistan sayısı eğitim ve araştırma hastanelerinde 24 iken üniversite hastanelerinde 15 olarak saptandı ($p<0,001$). Perinatoloji, onkoloji ve infertilite klinikleri tüm hastanelerin %70'inde mevcut olup gruplar arasında anlamlı bir fark izlenmedi. Katılımcıların çoğu (%68,5) poliklinikte yalnız kaldıklarından şikayetçiydi. Eğitim ve araştırma hastanelerinde 3. yıl araştırma görevlilerinin üniversite hastanelerindekilere oranla daha fazla sayıda vajinal doğum yaptırdıkları gözlendi ve bu sonuç istatistiksel olarak anlamlıydı ($p=0,035$). Katılımcılar en fazla iş yoğunluğundan şikayetçi olup eğitim ve araştırma hastanelerinde ve üniversite hastanelerinde bu oran sırasıyla %74,4 ve %66 idi. Gelecek için en çok tercih edilen planlar kadın hastalıkları ve doğum yan dal programına katılmak, akademik kariyer yapmak ve özel bir hastanede çalışmak olup bu oranlar sırasıyla %28, %23,1, %21 saptanmıştır.

PRECIS: In this study, the current problems and future expectations of obstetrics and gynecology residents across the nation were evaluated.

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Received/Geliş Tarihi: 18.11.2018 **Accepted/Kabul Tarihi:** 02.09.2019

Sonuç: Anket sonuçlarına göre kadın hastalıkları ve doğum asistanlarının en önemli problemleri; uzun çalışma saatleri, fazla iş yükü, aylık nöbet sayısının fazlalığı, polikliniklerde denetimsiz çalışmak olarak saptandı. Asistanların en yaygın gelecek planı, kadın hastalıkları ve doğum alanında bir yan dal programına katılmak olarak tespit edildi.
Anahtar Kelimeler: Kadın hastalıkları ve doğum bölümü, hastane, tıp asistanlığı, eğitim

Introduction

Turkish Trainees of Obstetrics and Gynecology is an organization that has collaborated with the European Board College for Obstetrics and Gynecology and European Network Trainees of Obstetrics and Gynecology (ENTOG) since 2010[1]. This collaboration facilitated a mutual understanding of educational models across Europe. There are advantages and disadvantages of training in obstetrics and gynecology (OBGYN) specialism in Turkey. The population of Turkey is about 80 million[2] and the annual number of trainees in OBGYN is about 1200. The low trainee to population ratio results in long working hours and fatigue. On the other hand, the upside of this low ratio is the high number of operations per trainee[3]. Training in OBGYN takes place in two types of hospitals in Turkey. Training and research hospitals are public hospitals that are affiliated to the ministry of health and render most of the healthcare service to the general population[4]. University hospitals are self-governing hospitals that deal with more complex cases and their work load is lower than public hospitals. Despite some technical limitations, these two types of hospitals have nationwide coverage, even in rural areas. There are no operational national mobilization and external rotation programs, so trainees have to complete all of their rotations in the same hospital. To the best of our knowledge, there is no study evaluating current problems and characteristics of OBGYN training in Turkey. This survey evaluates the current conditions and issues regarding OBGYN residency. We believe that identifying the issues is the first step to developing the relevant solutions.

Materials and Methods

The study was conducted in cross-sectional design. The OBGYN training institutions in Turkey were determined relying on the information from Measuring, Selection and Placement Center's web page[5]. Fifty-six institutions were identified. The names of trainees were collected from the webpages of the 44 of the institutions that provided this information. The contact information of the trainees was collected through social networks (Facebook/tjodasistan). A survey was sent via e-mail to 568 trainees whose contact information was available. One hundred forty-three of the 568 trainees (25.3%) responded to the survey. These 143 trainees were from 25 cities from all the different regions of Turkey. Informed consent was obtained from these trainees. The survey was an online multiple choice questionnaire. The questionnaire consisted of four parts, concerning information on hospitals, number and variety of surgical interventions, scientific activities and problems. More specifically, the questions asked for the city, year of training, presence of departments of gynecologic oncology, perinatology, infertility, whether the hospital was public or university, the number of trainees at the hospital, number of deliveries per day, number of night shifts, supervision at outpatient clinics and operations, time of first deliveries and cesarean section, number of operations in gynecology, perinatology, infertility and oncology, utility of rotations to other specialties, number of scientific meetings, and number of international meetings. The questions on the problems of trainees included day-after duties, workload, working hours, mobbing, lack of support for scientific activities, lack of supervision in outpatient clinics, vacations, satisfaction with salary, and future plans. The data were collected using Google documents and analyzed with the IBM SPSS statistics ver. 21.0 (IBM Corp., Armonk, NY) software package. Continuous data are presented as mean ± standard deviation or median (minimum-maximum), and categorical data are reported as number and percentage. Continuous data were compared using the Independent Sample t-test or Mann-Whitney U tests. Categorical data were compared using the chi-square test.

Results

One hundred forty-three trainees from 56 institutions, 27 university hospitals and 29 education and research hospitals (a type of public hospital that provides training to residents), were included in the study. The percentage of trainees with 1, 2, 3, and 4 years of training were 16%, 35%, 37%, and 55%, respectively. The mean number of trainees in training and research hospitals and university hospitals was 24 and 15 respectively. Although the median number of births per day was higher in public hospitals than in university hospitals, there was no significant difference between university and public hospitals (20 vs. 10; $p>0.05$). Perinatology, oncology and infertility clinics were present in about 70% of the hospitals and the difference between public and university hospitals was not significant. Only about 7% of the trainees could do post-call off. The trainees preferred to be a trainee in OBGYN as a first choice with a rate of 61%. Most of the trainees complained about being alone in outpatient clinics, with 68.5% reporting no supervision. The first labor during training was performed in the first month by 70% of the trainees. The comparison of the data between public and university hospitals is shown in Table 1. The number of operations performed by the trainees under supervision is shown in Table 2. All operation rates were found to be similar between the two types of hospitals except for vaginal births for 3rd year trainees. Trainees at public hospitals in the 3rd year performed a significantly higher number of vaginal births than those at university hospitals. About half of the trainees assessed the utility of rotations with the lowest

score. The trainees ranked pathology as the branch with the least utility during training. The utility rates of the other rotations from the point of view of the trainees are given in Figure 1. The trainees in training and research hospitals and university hospitals complained about the workload at rates of 74.4% and 66%, respectively. Excessive numbers of nightshifts bothered 46% and 39% of trainees in public hospitals and university hospitals, respectively. Trainees also identified mobbing as a problem at 30% and 22% in public and university hospitals, respectively. Working alone in an outpatient clinic without a supervisor was identified as a problem by 61% and 58.5% of the trainees in public and university hospitals. Problems related to work and their review by the trainees are given in Table 3. If given the chance to choose their specialty again, OBGYN remained the most popular choice of the trainee at 25.2%. Dermatology, urology, and pathology specialties were chosen by 7.2%, 4.2%, and 4.2% of the trainees, respectively. The least popular specialties were cardiovascular surgery, infectious diseases, and emergency medicine (0.7% for each) as demonstrated in Figure 2. After completing the residency, the three most common preferences for the future career plans were to attend a subspecialty fellowship program in the field of OBGYN, to pursue an academic career, and to work in a private hospital (28%, 23.1%, and 21%, respectively). Seven percent of the trainees, on the other hand, planned to pursue a career in another specialty. With regard to future places of work, 15.4% of the residents were planning to work in a public hospital, and 5.6% were planning to have their own private clinic, as demonstrated in Figure 3.

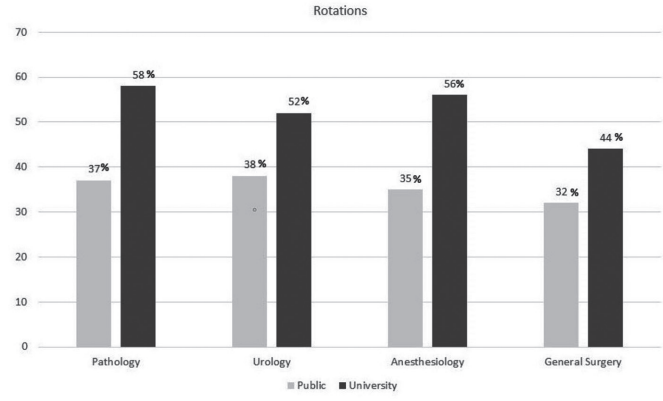

Figure 1. Percentage of trainees scoring rotations as inefficient

Discussion

This study highlights the main problems of OBGYN residents in Turkey by providing objective baseline data that can be compared with other European countries. The evidence points to an excessive workload on OBGYN residents with the benefit of an early start to vaginal/cesarean births and performing a large number of gynecologic surgeries. Half of the (54.6%) trainees planned to work in the private sector, and 7% planned to switch to another specialty. The number of residents in OBGYN training programs is inadequate to meet demands of the growing adult female population, and the current shortage of OBGYNN residents is projected to worsen in the future[6]. Residents were found to experience significantly more burnout, have a higher risk for psychological morbidity, and lower career satisfaction rates relative to attending surgeons[7]. Becker et al.[8] assessed burnout and depression rates in 118 residents from 23 different randomly selected OBGYN residency programs in the

Table 1. Demographic data of hospitals and residents in obstetrics and gynecology in Turkey

	Whole group	Training and research hospitals (n=90)	University hospitals (n=53)	P value
Number of trainees (mean ± SD)	19 (1-90)	24 (1-90)	15 (1-30)	<0.001
Number of faculty	6 (1-25)	7 (1-30)	6 (1-30)	0.188
Perinatology	92 (64)	60 (66)	32 (60)	0.474
Gynecologic oncology	110 (76)	78.8 (71)	39 (73)	0.467
Infertility/family planning	86 (60)	55 (61)	31 (58)	0.860
Labor (per day)	15 (0-100)	20 (1-100)	10 (1-40)	0.261
Shifts (per month)	7 (0-15)	7 (0-12)	8 (0-15)	0.097
Every other day duty	85 (59)	63.3 (57)	28 (52)	0.224
Post-duty off	8 (5)	4 (4.4)	4 (7.5)	0.336
Supervision at outpatient clinic	45 (31)	28 (31)	17 (32)	0.905
Supervision at surgery	112 (78)	72 (80)	40 (75)	0.526
First normal labor at 1st month of training	99 (69)	65 (72)	34 (64)	0.312
First CS at 1st month of training	46 (32)	31 (34)	15 (28)	0.448

CS: Cesarean section, data are presented as median (minimum-maximum) or number (percentage), SD: Standard deviation

United States. Almost 90% of the residents were found to have moderate burnout and one-third showed signs of depression. Working hours are known to be a powerful predictor of burnout, psychiatric morbidity, and decreased work-life balance[7]. Alston et al.[9] interviewed 226 medical students who stood up for an OBGYN residency position. The greatest concern about

Table 2. Number of operations performed by trainees under supervision

	Entire group	Training and research hospital	University	P value
Normal labor				
1st year	5 (2-40)	100 (4-500)	100 (30-500)	0.999
2nd year	20 (0-100)	400 (20-1500)	200 (20-1900)	0.780
3rd year	15 (1-70)	500 (10-2500)	250 (50-1500)	0.035
4th year	13 (1-100)	600 (50-1500)	250 (80-1600)	0.062
CS				
1st year	45 (1-300)	24 (3-200)	100 (1-300)	0.408
2nd year	200 (50-1000)	250 (50-1000)	120 (50-600)	0.831
3rd year	400 (12-1000)	400 (50-1000)	300 (12-500)	0.063
4th year	500 (35-2500)	500 (35-2000)	450 (80-2500)	0.205
Operative labor				
1st year	0 (0-10)	0 (0-2)	3 (0-10)	0.113
2nd year	5 (0-45)	5 (0-45)	5 (0-17)	0.479
3rd year	7 (0-50)	8 (0-50)	6 (0-10)	0.216
4th year	10 (0-25)	10 (0-100)	8 (0-125)	0.214
Amniocentesis				
1st year	0 (0-10)	0 (0-10)	0 (0-5)	0.918
2nd year	5 (0-50)	3 (0-30)	5 (0-50)	0.705
3rd year	10 (0-50)	10 (0-50)	10 (0-20)	0.460
4th year	20 (0-60)	20 (0-60)	18 (0-50)	0.758
Abdominal hysterectomy				
1st year	1 (0-50)	1 (0-50)	1 (0-6)	0.837
2nd year	5 (0-100)	3 (0-70)	8 (0-100)	0.610
3rd year	20 (0-150)	14 (1-150)	20 (0-25)	0.781
4th year	50 (1-200)	50 (5-200)	50 (1-200)	0.642
Laparoscopic hysterectomy				
1st year	0 (0-3)	0 (0-3)	0 (0-3)	0.837
2nd year	1 (0-30)	1 (0-20)	0 (0-30)	0.805
3rd year	3 (0-90)	3 (0-90)	6 (0-10)	0.192
4th year	5 (0-95)	5 (0-95)	7 (0-90)	0.641
Vaginal hysterectomy				
1st year	0 (0-2)	0 (0-2)	0 (0-2)	0.758
2nd year	1 (0-30)	1 (0-30)	1 (0-10)	0.780
3rd year	4 (0-40)	2 (0-25)	10 (0-40)	0.141
4th year	10 (1-150)	10 (1-150)	10 (1-50)	0.758

CS: Cesarean section

OBGYN was the long work hours for 65% of the students. The current study revealed that 59.4% of the residents had night-shifts every other day in their first half of the residency. Only 5.6% of the residents had the chance to return home after the in-hospital call. One-third of the residents claimed that they had no chance for a yearly vacation. An observational, descriptive, and cross-sectional study conducted in 25 different ENTOG member countries found the average number of weekly working hours for 6056 OBGYN trainees as 51.6 hours, with an average night-shift number of 5 (range, 2-9) per month[10]. The burnout effects, physiologic morbidities, and potential safety concerns caused by these extreme working hours are still unknown and need to be investigated. Impaired surgeon performance due to sleep deficiency has been associated with serious medical errors. However, it was hypothesized that home call design may compromise resident clinical experience and satisfaction, although it has allowed for compliance with duty hour requirements[11]. We believe that extending the duration of OBGYN residency may be better for training and work-life balance than transforming in-hospital calls into house calls. In this vein, ENTOG has officially suggested that the minimum duration of training should be at least five years to improve harmonization[10]. In an interview study, it was found that the most important factor in selecting an OBGYN residency among medical students was the overall surgical training, particularly training in laparoscopic surgery[12]. Cadish and Muffly[13] conducted a retrospective cohort study of recent OBGYN residency graduates to estimate the average simple hysterectomy volume performed in the United States. It was found that recent graduates performed an average of 4 hysterectomies annually in their first five years after residency. The most common route was the abdominal route with 41.6%, and the second common route was laparoscopy with 32.4%. In the current study, a trainee primarily performed an average of 50 abdominal hysterectomies, 5 laparoscopic hysterectomies, and 10 vaginal hysterectomies in the last year before graduation. The number of performed surgeries during the residency is the main upside of the excessive work hours and night shifts. A recent study conducted in six different university in the United States revealed that 43% of residents were planning to enter private practice and only 19.4% of those were planning to pursue an academic career[14]. In the current study, comparable findings were observed with 44.6% of the residents planning to work in the private sector and 23.1% planning an academic career. The obstacles in the way of pursuing an academic career should be investigated further. In the present study, medicolegal issues were found to worry 31% and 22.6% of the residents in public and university hospitals, respectively. Current data suggest that medico-legal training during OBGYN residency is inadequate[15]. A large survey study showed that more than 20% of the fourth-year OBGYN residents had already been in a lawsuit[16] and more than half of those indicated that they had not received adequate training on legal matters. In a prospective survey study, 35% of residents stated that they had been planning for a fellowship program only because of malpractice concerns. In Turkey, all procedures are under a specialist's

Table 3. Percentage of trainees who scored problems as most annoying

	Public	University	P value
Too many duties	42 (46.7)	21 (39.6)	0.413
Working hours	56 (62.2)	30 (56.6)	0.507
Workload	66 (74.4)	35 (66)	0.355
Number of faculty	17 (18.9)	7 (13.2)	0.380
Mobbing	27 (30)	12 (22.6)	0.340
Operations	7 (13.2)	18 (20)	0.860
No supervision at outpatients clinic	55 (61)	31 (58.5)	0.757
Medicolegal issues	28 (31)	12 (22.6)	0.355
No vacation	33 (36.7)	17 (32.1)	0.578

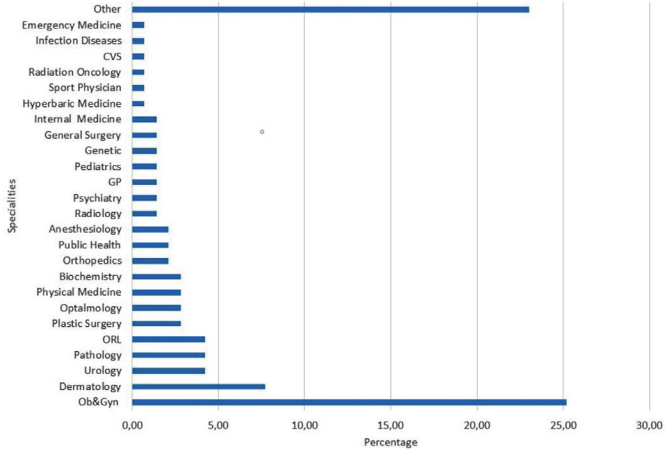

Figure 2. What would you choose if you had a chance to change your specialty?

Ob&Gyn: Obstetrics gynecology, ORL: Otorhinolaryngology, CVS: Cardiovascular surgery

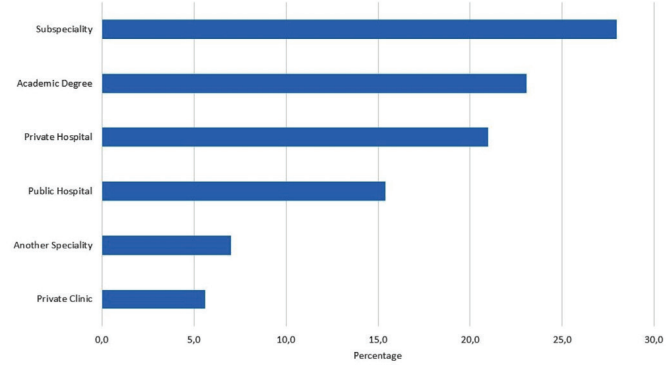

Figure 3. Future plans of residents in Turkey

responsibility. However, malpractice insurance is still a crucial support for the residents. In Turkey, malpractice insurances are semi-subsidized, and should be encouraged more. This study is the first to objectively assess the problems and career plans of OBGYN residents in Turkey. Its major limitations are the lack of subgroup analysis for sex distribution and the low response rate. At the same time, the respondents were from 25 cities from all the different regions of Turkey, which bodes well for the representativeness of the sample.

Based on the analysis of the survey results, one-to-one interviews and concilium with the ENTOG, the following suggestions were identified in order to improve the job satisfaction, quality of training, burnout and depression levels, and liability and medicolegal preparedness:

- Minimum duration of OBGYN residency should be five years to improve harmonization with Europe and reduce long working hours,
- Post-call leaves should be well balanced,
- Supervision in outpatient clinics should be provided,
- Generalized national qualification exams should be compatible with ENTOG member countries,
- A standardized national logbook should be formed to standardize training,
- Rotations should be functional, and external rotations should be implemented in university hospitals.

Conclusion

OBGYN has been the top preferred residency position in Turkey in the past. OBGYN trainees' career expectations and future plans appear to be changing. Extremely long work hours, excessive workload, high number of duties per month, and no supervision in outpatient clinics were found to be the major issues. Identifying these issues is critical to improve the quality of training and demand/supply balance for residency.

Ethics

Ethics Committee Approval: Not applicable.
Informed Consent: Informed consent was obtained from these trainees.
Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.K., S.E., Design: S.E., M.Y., B.C., Data Collection or Processing: M.Y., B.C., Analysis or Interpretation: S.E., O.İ., iterature Search: S.E., O.İ., Writing: S.E., M.Y., O.İ.

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

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Nunes F, Bevan R. The implementation of a European Network of Trainees in Obstetrics and Gynaecology (ENTOG). Eur J Obstet Gynecol Reprod Biol 1999;87:199-201.
2. Barber MD, Maher C. Apical prolapse. Int Urogynecol J 2013;24:1815-33.
3. Kafadar YT, Gode F, Demir C, Baloglu A. Current challenges of the gynecology assistants ın Turkey. Turk J Obstet Gynecol 2013;10:37-41.
4. Tuncer AM, Tatar M, Şahin İ. University hospitals in Turkey: Structural crisis in financing or consequence of mismanagement? Journal of Hospital Administration 2017;6:52.
5. www.osym.gov.tr.
6. Stonehocker J, Muruthi J, Rayburn WF. Is There a Shortage of Obstetrician-Gynecologists? Obstet Gynecol Clin North Am 2017;44:121-32.
7. Pulcrano M, Evans SR, Sosin M. Quality of Life and Burnout Rates Across Surgical Specialties: A Systematic Review. JAMA Surg 2016;151:970-8.
8. Becker JL, Milad MP, Klock SC. Burnout, depression, and career satisfaction: cross-sectional study of obstetrics and gynecology residents. Am J Obstet Gynecol 2006;195:1444-9.
9. Alston MJ, Autry AM, Wagner SA, Winkel A, Allshouse AA, Stephenson-Famy A. Obstetricians and Gynecologists of the Future: A Survey of Medical Students Applying to Residency. Obstet Gynecol 2017;130:1-7.
10. Rodríguez D, Christopoulos P, Martins N, Pärgmäe P, Werner HM. Working conditions survey and trainees situation: new approach to auditing the situation of European trainees in obstetrics and gynaecology ten years later. Eur J Obstet Gynecol Reprod Biol 2009;147:130-4.
11. Prabhu AM, Chiang S, Schiff MA, Landis CA, Lee K, Reed SD. Effects of home call on obstetrics and gynecology resident sleep patterns. Am J Obstet Gynecol 2016;214:409-10.
12. Alston MJ, Metz TD, Fothergill R, Meg Autry A, Wagner SA, Allshouse AA, et al. Factors Influencing Residency Program Selection by Medical Students Pursuing Obstetrics and Gynecology. J Grad Med Educ 2017;9:123-7.
13. Cadish LA, Muffly TM. Recent Ob/Gyn Residency Graduates' Experience With Hysterectomy. Obstetrics & Gynecology 2018;132:46S.
14. Alston MJ, Ehrig J, Autry AM, Wagner SA, Kohl-Thomas BM, Allshouse AA, et al. Career Expectations of Obstetrics and Gynecology Residents and Future Residents. Obstet Gynecol 2018;132:1-7.
15. Glaser LM, Alvi FA, Milad MP. Trends in malpractice claims for obstetric and gynecologic procedures, 2005 through 2014. Am J Obstet Gynecol 2017;217:340.e1-340.e6.
16. Blanchard MH, Ramsey PS, Gala RB, Gyamfi Bannerman C, Srinivas SK, Hernandez-Rey AE. Impact of the medical liability crisis on postresidency training and practice decisions in obstetrics-gynecology. J Grad Med Educ 2012;4:190-5.

Clinical Investigation / Araştırma

DOI: 10.4274/tjod.galenos.2019.29795

Turk J Obstet Gynecol 2019;16:193-8

Awareness of women about cervical smear, human papilloma virus and human papilloma virus vaccine

Kadınların servikal smear, insan papilloma virüsü ve insan papilloma virüsü aşısı hakkındaki farkındalığı

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Abstract

Objective: The aim of this study was to assess the awareness level of women about cervical smears, human papilloma virus (HPV), and HPV vaccine in a rural city in the central part of Anatolia.

Materials and Methods: A total of 553 patients were included in the study. A 16 item questionnaire developed by our group was completed by all participants. The first part of the questionnaire collected the demographic and socioeconomic information of the participants. In the second part, it was questioned whether this information had a relationship with HPV, HPV vaccine awareness, and cervical screening tests. In the third part, the participants were asked questions related to the acceptance of an HPV vaccine for themselves and their willingness to give consent to have their children vaccinated.

Results: In our study, it was found that HPV awareness significantly increased with the level of education, occupational status and total monthly family income ($p<0.001$). There was a significant increase in HPV vaccine awareness as the parity ($p=0.016$), level of education ($p=0.025$), and occupational status ($p=0.001$) increased. Having a Pap smear significantly increased with age, income, and number of parity ($p<0.001$).

Conclusion: Our study revealed that only 9.8% of the women had knowledge about HPV, the majority of the women reported that they would accept vaccination for themselves and for their children. These results indicate that physicians should pay attention to increasing the awareness about HPV.

Keywords: Human papilloma virus, vaccine, cervical smear, cervical cancer

Öz

Amaç: Bu çalışmanın amacı, Anadolu'nun orta kesiminde yer alan kırsal bir şehirde kadınların servikal smear, insan papilloma virüsü (HPV) ve HPV aşısı konusundaki farkındalık seviyelerini değerlendirmektir.

Gereç ve Yöntemler: Çalışmaya toplam 553 hasta dahil edildi. Grubumuz tarafından geliştirilen 16 maddelik bir anket tüm katılımcılar tarafından doldurduldu. Anketin birinci bölümünde katılımcıların demografik ve sosyo-ekonomik bilgileri toplanmıştır. İkinci bölümde, bu bilgilerin HPV, HPV aşı farkındalığı ve servikal tarama testleri ile ilişkisi olup olmadığı sorgulanmıştır. Üçüncü bölümde katılımcılara HPV aşısının kendileri için kabulü ve çocuklarının aşılanması için rıza göstermeye istekli olmaları ile ilgili sorular sorulmuştur.

Bulgular: Çalışmamızda HPV farkındalığının eğitim düzeyi, meslek durumu ve toplam aylık geliri ile anlamlı olarak arttığı tespit edilmiştir ($p<0,001$). Parite ($p=0,016$), eğitim seviyesi ($p=0,025$) ve mesleki durum ($p=0,001$) arttıkça HPV aşısı farkındalığında önemli bir artış olmuştur. Pap smear yaptırılması yaş, gelir ve parite sayısı ile birlikte anlamlı olarak arttığı saptanmıştır ($p<0,001$).

Sonuç: Çalışmamız, kadınların sadece %9,8'inin HPV hakkında bilgisine sahip olduğunu, örneklenen kadınların büyük çoğunluğunun kendileri ve çocukları için aşı kabul edeceğini bildirdi. Bu sonuçlar klinisyenin kadınlara HPV hakkında bilgi ve eğitim vermeye dikkat etmesi gerektiğini göstermektedir.

Anahtar Kelimeler: İnsan papilloma virüsü, aşı, servikal smear, servikal kanser

Introduction

The incidence of cervical cancer is 9 per 100.000 for women in developing countries[1]. The rate of cervical cancer has declined dramatically in recent years[1]. The most important reason for this is the regular cervical smear screening programs. Although some developed countries have taken these screening programs

PRECIS: The importance of awareness about cervical smear, HPV and HPV vaccine.

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Received/Geliş Tarihi: 22.06.2019 **Accepted/Kabul Tarihi:** 02.09.2019

into routine practice, others have not done so yet; cervical cancer screening rates are much higher in developed countries. For example, the incidence of cervical cancer in the United States was 15 per 100.000 women in 1975, and this incidence was reduced to six per 100.000 women in 2008[2]. In Turkey, the rate of cervical cancer has also decreased dramatically after screening programs became widespread. The incidence of cervical cancer was reported as 4.0 per 100.000 in 2014[3]. Human papilloma virus (HPV) is the most common sexually transmitted disease agent in the world[4]. It causes infections and cancers in many parts of the body. The most common area that is affected by HPV is the cervix. HPV is isolated in 99% of cervical cancers[5,6]. Most infections seen in young age are spontaneously cleared by the immune system. Those that are not spontaneously cleansed primarily lead to pre-invasive lesions. Disease that is detected at this stage can be terminated with treatment without conversion to invasive lesions. In addition, HPV vaccination prevents infection with HPV. HPV vaccines have shown an efficacy of 90% in preventing cervical intraepithelial neoplasia 2/3[7,8]. The HPV vaccination and smear screening test are highly valuable in the prevention of cervical cancer development. Thus, the most important thing that needs to done is to increase patient awareness. The aim of this study was to assess the awareness level of women about cervical smears, HPV, and HPV vaccines in a rural city in the central part of Anatolia.

Materials and Methods

This cross-sectional, observational study was conducted at Bozok University Faculty of Medicine, Department of Obstetrics and Gynecology, Turkey. The study protocol was performed according to the principles of the Declaration of Helsinki. After gaining the approval of the Bozok University Ethics Committee, questionnaires were administered through face-to-face interviews to 553 participants in the gynecology clinic. Patients who had a history of HPV infection, had abnormal smear tests or underwent gynecologic surgery were excluded from the study.

A 16 item questionnaire developed by our group was completed by all participants (Table 1). The first part of the questionnaire collected demographic and socioeconomic information of participants, such as age, educational status, educational status of their husbands, total monthly family incomes, occupational status, and number of births (Table 2). In the second part, it was examined whether this information had a relationship with HPV, HPV vaccine awareness, and having cervical screening tests (Tables 3 and 4). In the third part, the participants were asked questions related to the acceptance of HPV vaccination.

Statistical Analysis

Statistical analysis was performed using the SPSS 20.00 software package (SPSS Inc., Chicago). Descriptive statistics were used to assess patients' responses. The chi-square test or Fisher's exact

Table 1. Questionnaire*

1	Age
2	Marital status
3	Educational status
4	Educational status of the husband
5	Occupational status
6	Monthly family income
7	Number of parity
8	Have you ever heard of HPV?
9	Have you heard of a vaccine for HPV?
10	Have you ever had a Pap smear test?
11	Did your children receive all their vaccines?
12	Vaccination status of children (if any)
13	If HPV vaccines were free, are you willing to vaccinate yourself?
14	If HPV vaccines were free, are you willing to vaccinate your daughter?
15	If HPV vaccines were free, are you willing to vaccinate your son?
16	Who should pay the fee for the vaccine?

*Modified from references 6 and 11, HPV: Human papilloma virus

Table 2. Characteristics of study respondents

Characteristics	n	%
Age (years) (n=553)		
<20	150	27.1
20-30	119	21.5
>30	284	51.4
Educational status (n=553)		
Illiterate	26	4.7
Primary school	221	40.0
Secondary-high school	217	39.2
University	89	16.1
Educational status of the husband (n=553)		
Primary school	145	26.2
Secondary-high school	289	52.3
University	119	21.5
Occupational status (n=553)		
Working	479	86.6
Not working	74	13.4
Monthly family income (TL) (n=553)		
<2000	233	42.1
>2000	320	57.9
Parity (n=553)		
0	179	32.4
1	155	28.0
>1	219	39.6

TL: Turkish lira

test was applied for categorical variables. P values <0.05 were accepted as significant. The reliability of the questionnaire was assessed by using Cronbach's alpha coefficients (α). Cronbach's coefficients range between 0 (weak reliability) and 1 (perfect reliability). We considered 0.7 as the cut-off value indicating acceptable internal consistency for research purposes. An α≥0.8 shows good internal consistency and high reliability.

Results

The rate of the women aged over 30 years was 51.4%. Educational status was lower in women than men. Although 40% of the women had graduated from primary school, 52% of the men (spouses of the women) had graduated from a middle or high school. When the employment status was investigated, the vast majority of the women were not working (86.6%). The demographic characteristics of the participants are shown in Table 2. HPV awareness was not associated with age and parity (p=0.272 and p=0.299 respectively, and the difference was not statistically significant). However, it was found that HPV awareness significantly increased with levels of education, occupational status, and total monthly family incomes (p<0.050). The awareness of HPV vaccination was significantly higher in women with high parity (p=0.016), but there was no significant difference between the awareness of HPV vaccination and income level (p=0.611). Awareness of HPV and awareness of HPV vaccination were distributed similarly according to occupational status and education level. Both parameters were found to be significantly higher in women with high education level and those with a job (p<0.050). Information associated with HPV and HPV vaccine awareness was shown in Table 3. Two hundred twenty-three participants had a cervical Pap smear at least once before. Having a Pap smear significantly increased with age, income level, and parity (p<0.001, p=0.001,

Table 3. Comparison between the groups regarding knowledge of human papillomavirus and human papillomavirus vaccine

Characteristics	Total n=553	Have you ever heard of HPV?		p value	Have you heard of a vaccine for HPV ?		p value
		Yes n (%)	No n (%)		Yes n (%)	No n (%)	
Age (years)				0.272			0.220
<20	150	16 (10.7)	134 (89.3)		18 (12.0)	132 (88.0)	
20-30	119	7 (5.9)	112 (94.1)		15 (12.6)	104 (887.4)	
>30	284	31 (10.9)	253 (89.1)		21 (7.4)	263 (92.6)	
Educational status (n=553)				<0.001			0.025
Illiterate	26	0 (0.0)	26 (100.0)		0 (0.0)	26 (100.0)	
Primary school	221	8 (3.6)	213 (96.4)		15 (6.8)	206 (93.2)	
Secondary-high school	217	13 (6.0)	204 (94.0)		25 (11.5)	192 (88.5)	
University	89	33 (37.1)	56 (62.9)		14 (15.7)	75 (84.3)	
Educational status of the husband (n=553)				<0.001			0.028
Primary school	145	4 (2.8)	141 (97.2)		6 (4.1)	139 (95.9)	
Secondary-high school	289	26 (9.0)	263 (91.0)		34 (11.8)	255 (88.2)	
University	116	24 (20.7)	92 (79.3)		14 (12.1)	102 (87.9)	
Monthly family income (TL)				<0.001			0.611
<2000	233	6 (2.6)	227 (97.4)		21 (9.0)	212 (91.0)	
>2000	320	48 (15.0)	272 (85.0)		33 (10.3)	287 (89.7)	
Occupational status				0.001			0.001
Working	479	39 (8.1)	440 (91.9)		39 (8.1)	440 (91.9)	
Not working	74	15 (20.3)	59 (79.7)		15 (20.3)	59 (79.7)	
Parity				0.299			0.016
0	179	15 (8.4)	164 (91.6)		15 (8.4)	164 (91.6)	
1	155	20 (12.9)	135 (87.1)		24 (15.5)	131 (84.5)	
>1	219	19 (8.7)	200 (90.2)		15 (6.8)	204 (93.2)	

p<0.05 was statistically significant, TL: Turkish lira, HPV: Human papilloma virus

and p<0.001, respectively). However, having a Pap smear was not significantly distributed in relation with educational and occupational status. The previous Pap smear status is shown in detail in Table 4. Only 9.8% of the women had knowledge about HPV. The majority of the women reported that they would accept vaccination for themselves and for their children (Table 5). In addition, HPV awareness was significantly higher in women who had Pap smears (p=0.001). Given that HPV vaccines are not free in Turkey, the women who participated in this study were asked: "If HPV vaccines were free, would you agree to vaccinate yourself, your daughter or your son?" and 56% of the women stated that they would accept the vaccine for themselves, 58% for their daughter, and 59% for their son (Table 5).

Table 4. Comparison between the groups regarding status of cervical screening tests

Characteristics	Total n=553	Have you ever heard of HPV?		p value
		Yes n (%)	No n (%)	
Age (years)				**0.272**
<20	150	27 (18.0)	134 (89.3)	
20-30	119	39 (32.8)	112 (94.1)	
>30	284	157 (55.3)	253 (89.1)	
Educational status (n=553)				**<0.001**
Illiterate	26	10 (38.5)	26 (100.0)	
Primary school	221	87 (39.4)	213 (96.4)	
Secondary-high school	217	82 (37.8)	204 (94.0)	
University	89	44 (49.4)	56 (62.9)	
Educational status of the husband (n=553)				**<0.001**
Primary school	145	55 (37.9)	90 (62.1)	
Secondary-high school	289	111 (38.4)	178 (61.6)	
University	116	54 (46.6)	62 (53.4)	
Monthly family income (TL)				**0.001**
<2000	233	76 (32.6)	157 (67.4)	
>2000	320	147 (45.9)	173 (54.1)	
Occupational status				**0.248**
Working	479	190 (39.7)	289 (60.3)	
Not working	74	33 (44.6)	41 (55.4)	
Parity				**<0.001**
0	179	42 (23.5)	137 (76.5)	
1	155	63 (40.6)	92 (59.4)	
>1	219	118 (53.9)	101 (46.1)	

p<0.05 was statistically significant, TL: Turkish lira, HPV: Human papilloma virus

Discussion

Approximately 528.000 women in the world were diagnosed as having cervical cancer in 2012, and about 266.000 patients died of cervical cancer[9]. The most important cause of this disease is known to be HPV infection. In the 1970s, the association of HPV with cervical cancer was first detected by Professor Harald zur Hausen. Subsequently, important molecular studies related to HPV have been conducted and its structure described in detail. As a result, prophylactic HPV vaccines have been developed. Prophylactic HPV vaccines were licensed in Europe in the second half of 2006. Quadrivalent and bivalent vaccines have long been marketed in Turkey as well. Although there has been extensive intense debate within the medical community and the media regarding HPV vaccination, it is known that the level of knowledge about HPV in the Turkish community is still very low. Many studies reported that most women were unaware of associated genital lesions such as condyloma and cervical cancer. Unfortunately, no studies have been conducted in recent years to improve awareness of HPV. In a study investigating the knowledge and awareness of the HPV test in the United States, the United Kingdom, and Australia,

Table 5. Other results of the survey

Characteristics	n	% of the respondents
Have you heard of HPV? (n=553)		
Yes	54	9.8
No	499	90.2
Have you ever had a Pap smear test? (n=553)		
Yes	223	40.3
No	330	29.7
If HPV vaccines were free. Are you willing to vaccinate yourself? (n=553)		
Yes	313	56.6
No	240	43.4
If HPV vaccines were free. Are you willing to vaccinate your daughter? (n=553)		
Yes	324	58.6
No	229	41.4
If HPV vaccines were free. Are you willing to vaccinate your son? (n=553)		
Yes	238	59.3
No	225	40.7
Who should pay the fee for the vaccine? (n=553)		
Government	536	96.9
Patient	17	3.1

HPV: Human papilloma virus

50% of all participants reported that they had never heard of HPV[10]. In a Serbian study, this rate was reported at about 40%[11]. In Turkey, a study conducted in an area of patients with higher socio-economic level found that 45% of women had knowledge about HPV and 40% had knowledge about the causal relationship between HPV and cervical cancer[12]. In our study, this rate was found to be much lower (the rate of having information about HPV was 9%). The reason for this difference can be explained by the fact that our study consisted mostly of people living in rural areas. In another study on patients living in rural areas of China, the awareness of HPV was 9.3%[13]. This result also supports our opinion. Other than this, this difference is thought to be due to many reasons, such as age, educational status, and religious beliefs.

As age increases, women are less likely to take preventative measures against HPV infection[14]. In previous studies among populations of Asian origin, results were found to be similar[15,16]. The incidence of cervical cancer screening in general is significantly higher among young women, especially between the ages of 20-35 years[15,16]. Although women aged 40 years and over have an increased risk of developing cervical cancer, there is a greater tendency to perceive the cervical examination as taboo in this age group, as well as having more misleading health beliefs and less knowledge about cervical cancer[17,18]. In our study, contrary to this information, the rate of having a cervical cancer screening test was found to increase significantly as the age increased. We think the reason for this situation is that as age increases, the fear of gynecologic examination diminishes in relation to the increase in the number of births. As the parity increases, the frequency of referral to the hospital increases. Gynecologists routinely perform cervical screening tests on admission, which increases this rate. We found that the rate of having cervical cancer screening tests in our study was increased with parity ($p<0.001$), which supports this situation. In a study investigating the relationship between HPV awareness and age, there was no significant difference between women aged under 45 years and women aged over 45 years[19]. In our study, no significant relationship was found between age and HPV awareness. This is because the levels of education are at different rates in each age group. According to the World Health Organization's opinion on HPV vaccination, the recommended primary target population is girls aged 9-14 years, and the secondary target population is older girls or boys. There is no defined age limit for vaccination[20]. Due to religious beliefs and social oppression in our country, women may be uncomfortable with talking about sexually transmitted diseases. Therefore, it is important to choose the best words to describe HPV, the HPV vaccine, and cervical cancer screening. The rate of HPV vaccines acceptance is approximately 80-90% worldwide[21-23]. In studies performed in Turkey, this rate is lower. For example, in a study conducted by Dursun et al.[12] 70% of women stated that they would accept HPV vaccination for themselves, 64% for their daughters, and 59% for their sons. In our study, 56% of the women stated that they would accept the HPV vaccine for themselves, 58% for their daughters, and 59% for their sons. We think that the most important reason why these rates are low is the concerns about religious and social beliefs, and complications of vaccination. In addition, having one sexual partner and practicing safe sex are the main reasons for women's desire not to have HPV vaccination. Apart from this, an important detail of our study is that no participants had HPV vaccines. We think that the most important reasons for this is the lack of free vaccinations, the lack of adequate information, and the low socio-cultural level of those surveyed. One of the most important factors in health protection is the level of education. For example, in a study conducted among women who have received university education, HPV and HPV vaccine awareness was found to be significantly higher[12]. In our study, as the level of education increased, it was found that HPV and HPV vaccine awareness increased significantly. This is supported by a study that found that HPV knowledge was more accessible for women in higher education and metropolitan areas[13]. In addition, they reported a higher HPV awareness in women who had previously undergone a Pap smear test in the same study[13]. In our study, a similarly high prevalence of HPV awareness was found in women who had previously received a Pap smear. As a result, the importance of the routine application of the Pap smear test arises.

Conclusion

In conclusion, it is necessary to educate the rural and low-educated population in order to increase the awareness of HPV and the acceptability of the HPV vaccine. In particular, individuals in our society neither take enough care of their own health nor make any attempt to protect their health until disease occurs. However, after disease has occurred, more awareness is created by the information gained in hospitals. Therefore, the most appropriate approach is to make it easier for patients to reach healthcare services.

Ethics

Ethics Committee Approval: This study was approved by the Research Ethics Committee of the Bozok University Faculty of Medicine (decision no: 1/16 of 09.01.2013).

Informed Consent: It has been taken.

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Concept: E.B., M.K., E.S.Y., Design: E.B., M.K., E.S.Y., Data Collection or Processing: E.B., D.A.K., M.D.Ç., T.O., Analysis or Interpretation: E.B., Literature Search: E.B., M.D.Ç., D.A.K., Writing: E.B., M.K.

Conflict of Interest: There is no conflict of interest in our study.

Financial Disclosure: No financial support was received for this study.

References

1. Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Dicker D, Pain A, Hamavid H, Moradi-Lakeh M, et al. The Global Burden of Cancer 2013. JAMA Oncol 2015;1:505-27.
2. Howlader N, Noone A, Krapcho M, Neyman N, Aminou R, Waldron W, et al. SEER Cancer Statistics Review, 1975-2008. Bethesda, MD: National Cancer Institute 2011:140-3.
3. Sencan I, Bekir K. Cancer statistics 2014 Turkish Public Health Foundation 2014:9.
4. Koutsky L. Epidemiology of genital human papillomavirus infection. Am J Med 1997;102:3-8.
5. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol 1999;189:12-9.
6. Slomovitz BM, Sun CC, Frumovitz M, Soliman PT, Schmeler KM, Pearson HC, et al. Are women ready for the HPV vaccine? Gynecol Oncol 2006;103:151-4.
7. Castellsagué X, Muñoz N, Pitisuttithum P, Ferris D, Monsonego J, Ault K,et al. End-of-study safety, immunogenicity, and efficacy of quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in adult women 24-45 years of age. Br J Cancer 2011;105:28-37.
8. Lehtinen M, Paavonen J, Wheeler CM, Jaisamrarn U, Garland SM, Castellsagué X, et al. Overall efficacy of HPV-16/18 AS04-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. Lancet Oncol 2012;13:89-99.
9. Cancer IAfRo. Cervical cancer estimated incidence, mortality and prevalence worldwide in 2012. World Health Organization 2012.
10. Dodd RH, McCaffery KJ, Marlow LA, Ostini R, Zimet GD, Waller J. Knowledge of human papillomavirus (HPV) testing in the USA, the UK and Australia: an international survey. Sex Transm Infect 2014;90:201-7.
11. Markovic-Denic L, Djuric O, Maksimovic N, Popovac S, Kesic V. Effects of Human Papillomavirus Awareness and Knowledge on Psychological State of Women Referred to Cervical Cancer Screening. J Low Genit Tract Dis 2018;22:178-83.
12. Dursun P, Altuntas B, Kuscu E, Ayhan AWomen's knowledge about human papillomavirus and their acceptance of HPV vaccine. Aust N Z J Obstet Gynaecol 2009;49:202-6.
13. Li J, Li LK, Ma JF, Wei LH, Niyazi M, Li CQ, et al. Knowledge and attitudes about human papillomavirus (HPV) and HPV vaccines among women living in metropolitan and rural regions of China. Vaccine 2009;27:1210-5.
14. Larasati L, Afiyanti Y, Rahmah H, Milanti A. Women's knowledge, beliefs, and behaviors toward the prevention of human papillomavirus transmission. Enferm Clin 2018;28 Suppl 1:191-4.
15. Lee EE, Eun Y, Lee SY, Nandy K. Age-related differences in health beliefs regarding cervical cancer screening among Korean American women. J Transcult Nurs 2012;23:237-45.
16. Iskandar FN, Puspitaningrum D, Mulyanti L. Hubungan antara sikap wanita usia subur (usia 20-35 tahun) terhadap perilaku pencegahan servisitis dengan pemeriksaan skrining di kelurahan kalibanteng kulon lebdosari semarang tahun 2013. Jurnal Kebidanan 2013;2:66-71.
17. Montgomery K, Bloch JR, Bhattacharya A, Montgomery O. Human papillomavirus and cervical cancer knowledge, health beliefs, and preventative practices in older women. J Obstet Gynecol Neonatal Nurs 2010;39:238-49.
18. Herrero R, Castle PE, Schiffman M, Bratti MC, Hildesheim A, Morales J, et al. Epidemiologic profile of type-specific human papillomavirus infection and cervical neoplasia in Guanacaste, Costa Rica. J Infect Dis 2005;191:1796-807.
19. Li J, Kang LN, Li B, Pang Y, Huang R, Qiao YL.Effect of a group educational intervention on rural Chinese women's knowledge and attitudes about human papillomavirus (HPV) and HPV vaccines. BMC Cancer 2015;15:691.
20. World Health Organization. Human papillomavirus vaccines: WHO position paper, May 2017-Recommendations. Vaccine 2017;35:5753-5.
21. Watts LA, Joseph N, Wallace M, Rauh-Hain JA, Muzikansky A, Growdon WB,et al. HPV vaccine: A comparison of attitudes and behavioral perspectives between Latino and non-Latino women. Gynecol Oncol 2009;112:577-82.
22. Sauvageau C, Duval B, Gilca V, Lavoie F, Ouakki M. Human papilloma virus vaccine and cervical cancer screening acceptability among adults in Quebec, Canada. BMC Public Health 2007 25;7:304.
23. Kara M, Balci M, Yilmaz N. The Past, Today, and the Future of Human Papilloma Virus Vaccines. Int J Hematol 2011;21:1-9.

Clinical Investigation / Araştırma

DOI: 10.4274/tjod.galenos.2019.03266

Turk J Obstet Gynecol 2019;16:199-204

The predictive value of weight gain and waist circumference for gestational diabetes mellitus

Gestasyonel diabetes mellitus için kilo alımının ve bel çevresinin prediktif değeri

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Abstract

Objective: The first objective of this study was to investigate the relationship between gestational diabetes mellitus (GDM) and gestational weight gain (WG), waist circumference (WC), prepregnancy, and gestational body mass index (BMI). The second aim of our study was to assess the ability of WG, WC, prepregnancy, and gestational BMI with special reference to their cut-off points on predicting the risk of GDM in pregnant women in Turkey.

Materials and Methods: A total of 261 women who underwent screening for GDM with the 75-g glucose tolerance test (GTT) between 24th and 28th gestational weeks were included. According to the 75-g oral GTT results, women were classified into two groups: the GDM group and non-GDM group. The data collected included age, parity, plasma glucose level for fasting, 1- and 2-h tests, WC, prepregnancy and gestational BMI, prepregnancy weight, WG during pregnancy, gestational age at birth, and birth weight.

Results: WC at 20-24 weeks of gestation, prepregnancy BMI, and gestational BMI had a predictive capacity for GDM. According to our results, optimal cut-off points for the best predictive value of GDM were WC of 100 cm with a sensitivity of 84% and specificity of 70%, prepregnancy BMI of 25 kg/m^2 with a sensitivity of 81.8% and specificity of 76%, and gestational BMI of 28.3 kg/m^2 with a sensitivity of 75% and specificity of 77.4%.

Conclusion: The measurement of prepregnancy BMI, gestational BMI, and WC may be useful in predicting the risk of GDM. Pregnant women with increased prepregnancy BMI, gestational BMI, and WC measurements may be susceptible to the development of GDM.

Keywords: Gestational diabetes mellitus, waist circumference, body mass index, weight gain, pregnancy

Öz

Amaç: Bu çalışmada birincil amaç gestasyonel diabetes melitus (GDM) gestasyonel kilo alımı (WG), karın çevresi (WC), pregestasyonel ve gestasyonel vücut kitle indeksi (VKİ) ile olan ilişkisini araştırmak, ikincil amaç ise WG, WC, pregestasyonel ve gestasyonel VKİ'nin Türkiye'deki hamile kadınlarda GDM riskini öngörebilmesi açısından sınır değerleri belirlemektir.

Gereç ve Yöntemler: Çalışmaya 24. ve 28. gebelik haftaları arasında 75 gr glukoz tolerans testi (GTT) ile GDM taraması yapılan toplam 261 kadın dahil edildi. Yetmiş beş g oral GTT sonuçlarına göre, kadınlar iki grup olarak sınıflandırıldı: GDM grubu ve GDM olmayan grup. Yaş, parite, açlık plazma glukoz düzeyi, 1. ve 2. saat plazma glukoz düzeyi, WC, pregestasyonel ve gestasyonel VKİ, pregestasyonel kilo, doğumdaki gebelik haftası ve bebeğin doğum ağırlığı kaydedildi.

Bulgular: Yirmi dördüncü. haftalardaki WC, pregestasyonel VKİ ve gestasyonel VKİ GDM'yi öngörebilmektedir. Elde ettiğimiz sonuçlara göre, GDM'yi predikte eden optimal değer WC için 100 (%84 duyarlılık ve %70 özgüllük), pregestasyonel VKİ 25 kg/m^2 (%81,8 duyarlılık ve %76 özgüllük) ve gestasyonel VKİ 28,3 kg/m^2'dir (%75 duyarlılık ve %77,4 özgüllük).

Sonuç: Pregestasyonel VKİ, gestasyonel VKİ ve WC ölçümü GDM riskini öngörmede faydalı olabilir. Artmış pregestasyonel VKİ, gestasyonel VKİ ve WC ölçümleri olan gebeler GDM gelişimi açısından risk grubundadır.

Anahtar Kelimeler: Gestasyonel diabetes mellitus, karın çevresi, vücut kitle indeksi, kilo alımı, gebelik

PRECIS: The objective of this study was to investigate the relationship between gestational diabetes mellitus and gestational weight gain, waist circumference, prepregnancy and gestational Body moss index in pregnant women in Turkey.

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Received/Geliş Tarihi: 10.07.2019 **Accepted/Kabul Tarihi:** 15.09.2019

Introduction

Gestational diabetes mellitus (GDM) complicates 2-10% of all pregnancies. It is defined as varying degrees of glucose intolerance first diagnosed during pregnancy[1,2]. The diagnosis and management of GDM is extremely important because of the strong relationship between GDM and increased maternal and neonatal risks[3,4]. However, maternal and fetal outcomes in pregnancies complicated by GDM are strongly related to metabolic control[5-7]. GDM is probably a combination of genetic predisposition, metabolic factors, environmental factors, and lifestyle such as dietary habits and physical activity. There are several predictive markers for GDM including maternal obesity, gestational weight gain (WG), waist circumference (WC), and prepregnancy and gestational body mass index (BMI)[8,9]. Obesity is responsible for the central role in the pathogenesis of DM, a metabolic syndrome. WC and BMI seem to be more strongly linked to obesity. Increased BMI, a measure of general obesity, is a well-established risk factor for GDM. Increased WC, a simple and valid index of abdominal obesity, is an independent predictor for diabetes[3]. Maternal obesity is considered as an important predictive and modifiable marker in the short term for both maternal and fetal complications, including miscarriages, GDM, pregnancy-induced hypertensive disorders, macrosomia, maternal and fetal mortality, and cesarean sections, and in long-term risk factors for obesity and the metabolic syndrome in the child[10-14]. Moreover, maternal obesity, a major public health problem, has recently become more prevalent in line with the increase in the global prevalence of obesity. Maternal lifestyle is important for the reduction of GDM risk and the improvement of the total well-being of pregnant women and adverse pregnancy-related outcomes because pregnant women complicated with GDM have a higher prepregnancy and gestational BMI, a higher gestational WG, and a higher WC in general[15,16]. Thus, it should be an intervention focus. Turkish women may genotypically differ from other races and have different diet and lifestyle habits, which make them more vulnerable to obesity and GDM. However, body fat distribution is influenced by ethnicity. The first objective of this study was to investigate the relationship between GDM and gestational WG, WC, and prepregnancy and gestational BMI. The second aim of our study was to assess the ability of gestational WG, WC, and prepregnancy and gestational BMI, with special reference to their cut-off points, to predict the risk of GDM in pregnant women in Turkey.

Material and Methods

Study design and study population

The prospective cohort study was conducted at Department of Obstetrics and Gynecology of Etlik Zubeyde Hanim Women's Health Teaching and Research Hospital between March 2015 and June 2015. The study protocol was approved by the institutional local ethics committee and institutional education and planning committee. It was based on the analysis of the results of 261 pregnant women who attended our outpatient department. A total of 261 women who underwent screening for GDM with the 75-g glucose tolerance test (2-h GTT) between the 24th and 28th gestational weeks as recommended by International Association of Diabetes and Pregnancy Study Groups (IADPSG) were included[17]. An abnormal GTT was defined as a single abnormal value that established the diagnosis (abnormal values defined by IADPSG: fasting ≥92, 1 h ≥180, and 2 h ≥153 mg/dL). According to the 75-g oral GTT (OGTT) results, women were classified into two groups: the GDM group (abnormal response, confirmed disease) and the non-GDM group (normal response, disease free). The inclusion criteria consisted of age 18-41 years with a single pregnancy. Exclusion criteria were maternal diabetes mellitus diagnosed before pregnancy, multiple gestations, preterm or postterm pregnancies, congenital malformation, the use of hyperglycemic agents (corticosteroids and thyroid hormones), a history of systemic medical conditions, a history of GDM or macrosomia, and pregnancy-induced hypertensive disorders. The data collected included age, parity, plasma glucose level for fasting, 1- and 2-h tests, WC, prepregnancy and gestational BMI, prepregnancy weight, WG during pregnancy, gestational age at birth, and birth weight.

Measurements

WC was measured in the standing position, at the end of a normal expiration by using an inelastic tape (0.5 cm x200 cm) placed at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest at the time of screening of GDM[18,19]. Prepregnancy and gestational BMI [(weight/height^2 (kg/m^2)] was calculated using the World Health Organization criteria as the most useful epidemiologic measure of obesity. Women were allocated into low weight (BMI <18.5 kg/m^2), normal weight (BMI=18.5-24.9 kg/m^2), overweight (BMI=25-29.9 kg/m^2) and obese (BMI ≥30 kg/m^2)[20]. Prepregnancy BMI was estimated based on self-reported prepregnancy weight. When prepregnancy weight was unknown, the weight measurement taken at the first prenatal clinic visit was used. Gestational BMI was determined based on the weight measurement taken at enrollment at the time of screening of GDM. WG was defined as the weight at enrollment (gestational weight) minus prepregnancy weight. WG percentage (WG%) was calculated as (gestational weight-prepregnancy weight/gestational weight) x100[10].

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences, version 22 software package. Data were reported as mean ± standard deviation or number and percentage. P≤0.05 was considered significant. Normaly distributed continuous variables were assessed using independent Samples t-tests. Non-normally distributed metric variables were analysed using the Mann-Whitney U test.

Spearman's correlation was used to evaluate the associations of GDM with the variables of interest (WC, prepegnancy and gestational, BMI, WG). A multivariate logistic regression model was used to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) for the likelihood of the prediction of GDM for WC, and prepegnancy and gestational BMI. Receiver operating characteristic (ROC) curves were constructed to calculate the sensitivity and specificity for different measures of prepegnancy and gestational BMI and WC in predicting GDM.

Results

Two hundred sixty-one women who underwent GDM screening with the 75-g OGTT were included in this study. The demographic and baseline obstetric characteristics of the women are shown in Table 1. There were 18 (6.9%) women with low weight (BMI <18.5 kg/m^2), 155 (59.3%) women with normal weight (BMI=18.5-24.9 kg/m^2), 52 (19.9%) women were overweight (BMI=25-29.9 kg/m^2), and 36 (13.7%) women were obese (BMI ≥30 kg/m^2). The mean ages of the women were 30.57±5.78 years in the GDM group and 26.34±5.58 years in the non-GDM group. Of the 261 women, 44 (16.85%) who had abnormal 75-g OGTT were allocated to the GDM group. There were statistically significant differences in age, WC, fasting plasma glucose concentrations, 1- and 2-h tests, prepregnancy and gestational BMI, prepregnancy weight, WG during pregnancy, and gestational age at birth (weeks) between the GDM group and the non-GDM group (Table 1) (p<0.01). In women with GDM, age, fasting plasma glucose concentration, 1- and 2-h tests, prepregnancy and gestational BMI, prepregnancy weight, WG during pregnancy, and WC were significantly higher, and gestational age at birth was significantly lower compared with women in the non-GDM group (Table 1). The GDM and non-GDM groups were similar with regard to birth weight. Multivariate logistic regression analysis revealed that there was a positive correlation between GDM and WC, and prepregnancy and gestational BMI. WC ≥100 cm [OR=8.36; 95% CI: (0.74-0.84); p<0.01], prepregnancy BMI ≥25 kg/m^2 [OR=7.05; 95% CI: (0.72-0.82); p<0.01], and gestational BMI ≥28.3 kg/m^2 [OR=7.2; 95% CI: (0.73-0.83); p<0.01] increased the incidence of GDM (Table 2). ROC curve analysis showed that prepregnancy BMI ≥25 kg/m^2 predicted GDM with a sensitivity of 81.8% and specificity of 76% (AUC=0.78); gestational BMI ≥28.3 kg/m^2 predicted GDM with sensitivity of 75% and specificity of 77.4% (AUC=0.78); and WC measurements ≥100 cm predicted GDM with a sensitivity of 84% and specificity of 70% (AUC=0.79) (Figure 1).

Discussion

The results of our study demonstrated that the prevalence of GDM in our study population was 16.8%, and WC, prepregnancy, and gestational BMI, prepregnancy weight, and WG during pregnancy were significantly higher in women with GDM. Therefore, these markers may independently predict the risk of developing GDM. Moreover, there was a positive correlation between GDM and WC, and prepregnancy and gestational BMI; finally, our results may suggest new cut-off points for WC (≥100 cm), prepregnancy BMI (≥25 kg/m^2) and gestational BMI (≥28.3 kg/m^2) for the prediction of GDM.

GDM is undoubtedly associated with increased adverse maternal and neonatal outcomes[21,22]. The diagnosis and treatment of GDM absolutely results in decreased risks of maternal and neonatal adverse effects related to GDM[23]. Screening is important for the diagnosis of GDM because affected women are often asymptomatic. The screening of GDM may consist of either a one or a two-step approach. The IADPSG promoted the one-step approach (75 g, 2-h GTT at 24-28 weeks' gestation) for the screening of GDM primarily based on the hyperglycemia and adverse pregnancy outcome trial data conducted to evaluate the association between mild hyperglycemia and adverse pregnancy outcomes in 2010[24]. The one-step approach was subsequently adopted by the American Diabetes Association in 2011[25]. We also adopted the one-step approach for the screening of GDM because of the cost-effectiveness and ease of application, and a relatively inexpensive future type 2 DM follow-up of the one-step approach. A retrospective study from Turkey demonstrated the prevalence of GDM as 4.8%, 8%, and 13.4% using the National Diabetes Data Group, Carpenter-Coustan and O'Sullivan two-step approach, respectively, and 22.3% with the IADPSG single-step approach. The study also reported that the prevalence of GDM increased with increasing age[26]. The pre-pregnancy or antenatally prediction of the risk of GDM with different strategies allows to reduce the incidence of GDM and improve maternal and infant health through the prevention of GDM (dietary, physical activity, behavior modification) or accurate diagnosis and appropriate treatment[27,28]. Overweight or obese, maternal age older than 35 years, excessive gestational WG, chronic hypertension, a history of GDM, strong family history of diabetes, polycystic ovarian syndrome, macrosomia, and stillbirth in a previous pregnancy, and high-risk racial/ethnic group are well-known risk factors for GDM[29,30].

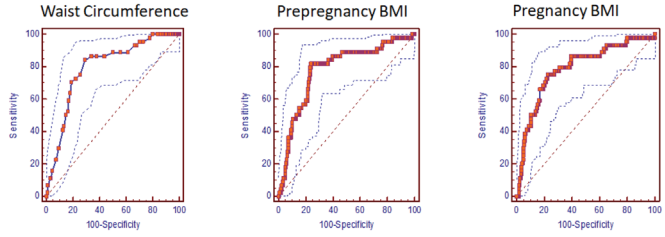

Figure 1. Receiver operating characteristic curve-sensitivity and specificity of waist circumference at 20-24 gestational weeks of pregnancy, prepregnancy and gestational body mass index to predict gestational diabetes mellitus

BMI: Body mass index

Table 1. Demographic and baseline obstetric characteristics of groups

Variables	GDM group (n=44)	Non-GDM group (n=217)	P value
Age	30.57±5.78 (18-40)	26.34±5.58 (18-39)	<0.01*
Parity	1.14±1.11 (0-4)	0.94±0.94 (0-4)	0.21
Glucose level/75-g OGTT fasting	94.30±22.37 (69-103)	77.59±8.57 (63-92)	<0.01*
1 h test	177.82±38.00 (100-252)	115.65±23.52 (55-180)	<0.01*
2 h test	145.86±29.58 (77-207)	98.53±20.75 (46-148)	<0.01*
Waist circumference	103.91±14.13 (63-122)	96.07±10.64 (56-120)	<0.01*
Prepregnancy BMI	28.25±4.84 (19.1-37.3)	23.4±4.69 (15.8-46.9)	<0.01*
Gestational BMI	30.61±4.62 (22.6-39)	26.13±4.37 (19.5-52)	<0.01*
Weight gain during pregnancy	10.71±5.94 (0-32.39)	7.92±4.28 (0-16.07)	<0.01*
Gestational age at birth (weeks)	38.18±0.97 (37-40)	38.66±1.16 (37-41)	<0.01*
Birth weight (g)	3287.50±565.80 (2280-4500)	3229.56±420.93 (2180-4400)	<0.01*
Prepregnancy weight (kg)	72±14.63 (47-98)	60.52±12.76 (42-120)	<0.01*

All values are expressed as mean ± standard deviation or percentage. *p<0.05, significant difference, BMI: Body mass index, OGTT: Oral glucose tolarence test, GDM: Gestational diabetes mellitus

Table 2. Multivariable analysis to predict to the presence of gestational diabetes mellitus

Variables	OR	P value	95% CI
WC	8.36	<0.01*	0.74-0.84
Prepregnancy BMI	7.05	<0.01*	0.72-0.82
Gestational BMI	7.2	<0.01*	0.73-0.83

Waist circumference <100 vs. ≥100 cm, prepregnancy body mass index <25 vs. ≥25 kg/m² and gestational body mass index <28.3 vs. ≥28.3 kg/m², *p<0.05, significant difference, BMI: Body mass index, CI: Confidence interval, OR: Odds ratio, WC: Waist circumference

Maternal obesity is potentially a well-established risk factor for GDM and it is associated with some adverse maternal and neonatal outcomes such as preeclampsia, GDM, preterm birth, large-for-gestational-age babies or macrosomia[31-33]. Maternal obesity is principally defined based on the basis of WC and pre-pregnancy BMI. BMI is the most widely used method to determine total body fat and WC is a more practical measure for abdominal fat mass. A recent systematic review indicated that the risk of GDM was positively correlated with prepregnancy BMI, and the prevalence of GDM increased by 0.92% with every 1 kg/m² increase in BMI [95% CI: (0.73-1.10)][8]. A population-based study including 6795 women with GDM evaluated singleton pregnancies complicated by GDM in underweight and normal weight women. The authors reported 301 underweight women and 6494 women with normal BMI of 6795 women with GDM. According to their results, underweight women were younger, more often nulliparous, and had a lower incidence of birthweight >4000 g[34].

However, several studies demonstrated that excessive gestational WG and gestational BMI might increase the risk of GDM[35,36]. Studies that assess cut-off points for prepregnancy and gestational BMI and WC based on race/ethnicity to predict GDM really important because body fat distribution is influenced by race/ethnicity. Madhavan et al.[37] clearly demonstrated that there was a strong correlation between maternal obesity and obstetric complications. This pilot study conducted on Asian and Indian patients found that WC of 85.5 cm and a BMI of 24.3 kg/m² had the best predictive value for GDM[37]. A cross-sectional study that included 240 women from Brazil showed that prepregnancy BMI (OR=4.21), gestational BMI (OR=3.17), and WC at 20-24 weeks (OR=4.02) were associated with developing GDM. According to the results of this study, WC at 20-24 weeks' gestation is an important risk factor for GDM, and the range of 86-88 cm of WC has the best predictive performance for GDM[38]. Our results suggested that WC at 20-24 weeks' gestation, prepregnancy BMI, and gestational BMI had predictive capacity for GDM. According to our results, the optimal cut-off points for the best predictive value of GDM are WC of 100 cm with a sensitivity of 84% and specificity of 70.9%, prepregnancy BMI of 25 kg/m² with a sensitivity of 81.8% and specificity of 76%, and gestational BMI of 28.3 kg/m² with a sensitivity of 75% and specificity of 77.4%.

Study Limitations

The main strength of our study was its population-based and prospective nature with adjustment for the predictive capacity of traditional GDM risk factors and the selection of best predictive value of the cut-off points of prepregnancy and gestational BMI and WC for our country. The limitations of our study was the relatively small sample size.

Conclusion

Our results confirm that the measurement of prepregnancy BMI, gestational BMI, and WC may be useful in predicting the risk for GDM. Pregnant women with increased prepregnancy BMI, gestational BMI, and WC measurements may be susceptible to the development of GDM. The cut-off points of prepregnancy BMI ≥25 kg/m², gestational BMI ≥28.3 kg/m² for being generally overweight, and WC ≥100 cm for central obesity were associated with increased risks of GDM. Determining these threshold points for prepregnancy BMI, gestational BMI, and WC measurements may be helpful in defining risky pregnant women in early pregnancy. Further well-designed randomized

controlled trials are required to evaluate the use of these simple indicators of obesity for predicting GDM in pregnant women before these values can be used in clinical practice.

Ethics

Ethics Committee Approval: This study was approved by the Research Ethics Committee of the Zübeyde Hanım Women's Health Training and Research Hospital Clinical Research Hospital (approval number: 196 23/06/2015).

Informed Consent: Written informed consent was obtained from all patients

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.T., Concept: E.S.Y., T.T., Design: E.S.Y., Data Collection or Processing: T.T., M.Ü., Analysis or Interpretation: A.F.G.K., Literature Search: U.Ç., Writing: P.Ö.

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

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Hunt KJ, Schuller KL. The increasing prevalence of diabetes in pregnancy. Obstet Gynecol Clin North Am 2007;34:173-99, vii.
2. American Diabetes Association (ADA). Diagnosis and classification of diabetes mellitus. Diabetes Care 2009;32:62-7.
3. Schmidt MI, Duncan BB, Reichelt AJ, Branchtein L, Matos MC, Costa e Forti A, et al. Brazilian Gestational Diabetes Study group. Gestational diabetes mellitus diagnosed with a 2-h 75-g oral glucose tolerance test and adverse pregnancy outcomes. Diabetes Care 2001;24:1151-5.
4. Khandelwal M, Homko C, Reece EA. Gestational diabetes mellitus: controversies and current opinions. Curr Opin Obstet Gynecol 1999;11:157-65.
5. Casey BM, Lucas MJ, Mcintire DD, Leveno KJ. Pregnancy outcomes in women with gestational diabetes compared with the general obstetric population. Obstet Gynecol 1997;90:869-73.
6. de Veciana M, Major CA, Morgan MA, Asrat T, Toohey JS, Lien JM, et al. Postprandial versus preprandial blood glucose monitoring in women with gestational diabetes mellitus requiring insulin therapy. N Engl J Med 1995;333:1237-41.
7. Langer O, Rodriguez DA, Xenakis EM, McFarland MB, Berkus MD, Arrendondo F. Intensified versus conventional management of gestational diabetes. Am J Obstet Gynecol 1994;170:1036-46
8. Torloni MR, Betrán AP, Horta BL, Nakamura MU, Atallah AN, Moron AF, et al. Prepregnancy BMI and the risk of gestational diabetes: a systematic review of the literature with meta-analysis. Obes Rev 2009;10:194-203.
9. Qiao Q, Nyamdorj R. Is the association of type II diabetes with waist circumference or waist-to-hip ratio stronger than that with body mass index? Eur J Clin Nutr 2010;64:30-4.
10. Guelinckx I, Devlieger R, Beckers K, Vansant G. Maternal obesity: pregnancy complications, gestational weight gain and nutrition. Obes Rev 2008;9:140-50.
11. The National Academies Press. National Research Council, Institute of Medicine. Influence of pregnancy weight on maternal and child health. Workshop report. Committee on the Impact of Pregnancy Weight on Maternal and Child Health. Board on Children, Youth, and Families, Division of Behavioral and Social Sciences and Education and Food and Nutrition Board, Institute of Medicine. Washington, DC: The National Academies Press; 2007.
12. Boney CM, Verma A, Tucker R, Vohr BR. Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. Pediatrics 2005;115:e290-6.
13. Scifres C, Feghali M, Althouse AD, Caritis S, Catov J. Adverse Outcomes and Potential Targets for Intervention in Gestational Diabetes and Obesity. Obstet Gynecol 2015;126:316-25.
14. Ferraro ZM, Contador F, Tawfiq A, Adamo KB, Gaudet L. Gestational weight gain and medical outcomes of pregnancy. Obstet Med 2015;8:133-7.
15. Harizopoulou VC, Kritikos A, Papanikolaou Z, Saranti E, Vavilis D, Klonos E, et al. Maternal physical activity before and during early pregnancy as a risk factor for gestational diabetes mellitus. Acta Diabetol 2010;47:83-9.
16. Blum JW, Beaudoin CM, Caton-Lemos L. Physical activity patterns and maternal well-being in postpartum women. Matern Child Health J 2004;8:163-9.
17. International Association of Diabetes and Pregnancy Study Groups Consensus Panel, Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care 2010;33:676-82.
18. Wendland EM, Duncan BB, Mengue SS, Nucci LB, Schmidt MI. Waist circumference in the prediction of obesity-related adverse pregnancy outcomes. Cad Saude Publica 2007;23:391-8.
19. WHO STEPS. Section 3: guide to physical measurements (Step 2). Geneva. 2008. Disponı´vel em:http://www.who.int/chp/steps/Part3_Section3.pdf [Acessado em 28 June 2011.
20. WHO, 2000. The Asia-Pacific perspective: redefining obesity and its treatment. IASO International Association for the Study of Obesity, International Obesity Taskforce. World Health Organization, Regional Office for the Western Pacific, Manila, 2000.
21. Ferrara A, Weiss NS, Hedderson MM, Quesenberry CP Jr, Selby JV, Ergas IJ, et al. Pregnancy plasma glucose levels exceeding the American Diabetes Association thresholds, but below the National Diabetes Data Group thresholds for gestational diabetes mellitus, are related to the risk of neonatal macrosomia, hypoglycaemia and hyperbilirubinaemia. Diabetologia 2007;50:298-306.
22. Moses RG, Morris GJ, Petocz P, San Gil F, Garg D. The impact of potential new diagnostic criteria on the prevalence of gestational diabetes mellitus in Australia. Med J Aust 2011;194:338-40.
23. Landon MB, Spong CY, Thom E, Carpenter MW, Ramin SM, Casey B, et al. A multicenter, randomized trial of treatment for mild gestational diabetes. N Engl J Med 2009;361:1339-48.
24. Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, Damm P et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care 2010;33, 676-82.
25. Basevi V, Di Mario S, Morciano C, Nonino F, Magrini N. Comment on: American Diabetes Association. Standards of medical care in diabetes--2011. Diabetes Care 2011;34:e53
26. Akgöl E, Abuşoğlu S, Gün FD, Ünlü A. Prevalence of gestational diabetes mellitus according to the different criterias. Turk J Obstet Gynecol 2017;14:18-22.
27. Kennelly MA, McAuliffe FM. Prediction and prevention of

Gestational Diabetes: an update of recent literature. Eur J Obstet Gynecol Reprod Biol 2016;202:92-8.
28. Aktün HL, Uyan D, Yorgunlar B, Acet M. Gestational diabetes mellitus screening and outcomes. J Turk Ger Gynecol Assoc 2015;16:25-9.
29. Garrison A. Screening, diagnosis, and management of gestational diabetes mellitus. Am Fam Physician 2015;91:460-7.
30. Solmaz Hasdemir P, Terzi H, Koyuncu FM. Recent advances in the diagnosis and management of gestational diabetes. Turk J Obstet Gynecol 2014;11:181-5.
31. Hod M. Hyperglycemia and adverse pregnancy outcome (HAPO) study: Preeclampsia. Pregnancy Hypertens 2011;1:246-7.
32. Spaight C, Gross J, Horsch A, Puder JJ. Gestational diabetes mellitus. Endocr Dev 2016;31:163-78.
33. Farrar D, Simmonds M, Bryant M, Sheldon TA, Tuffnell D, Golder S, et al. Hyperglycaemia and risk of adverse perinatal outcomes: systematic review and meta-analysis. BMJ 2016;354:i4694.
34. Košir Pogačnik R, Trojner-Bregar A, Lučovnik M, Verdenik I, Blickstein I, Tul N. Gestational diabetes mellitus in underweight women. J Matern Fetal Neonatal Med 2019:1-3.
35. Herring SJ, Oken E, Rifas-Shiman SL, Rich-Edwards JW, Stuebe AM, Kleinman KP, et al. Weight gain in pregnancy and risk of maternal hyperglycemia. Am J Obstet Gynecol 2009;201:61.e1-7.
36. Shirazian N, Emdadi R, Mahboubi M, Motevallian A, Fazel-Sarjuei Z, Sedighpour N, et al. Screening for gestational diabetes: usefulness of clinical risk factors. Arch Gynecol Obstet 2009;280:933-7.
37. Madhavan A, Beena Kumari R, Sanal MG.A pilot study on the usefulness of body mass index and waist hip ratio as a predictive tool for gestational diabetes in Asian Indians. Gynecol Endocrinol 2008;24:701-7.
38. Bolognani CV, de Sousa Moreira Reis LB, de Souza SS, Dias A, Rudge MV, de Mattos Paranhos Calderon I. Waist circumference in predicting gestational diabetes mellitus. J Matern Fetal Neonatal Med 2014;27:943-8.

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DOI: 10.4274/tjod.galenos.2019.89990

Turk J Obstet Gynecol 2019;16:205-7

Fetal fibular hemimelia with focal femoral deficiency: A case report

Fokal femoral yetmezlikli fetal fibular hemimeli: Olgu sunumu

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Abstract

Fibular hemimelia (FH) is a congenital deficiency in which a part or all of the fibular bone is hypoplastic or aplastic and associated with hypoplastic tibia and foot anomalies. The main differential diagnoses include proximal focal femoral dysplasia, Femur-Fibula-Ulna syndrome, and Femoral Hypoplasia-Unusual Facies syndrome. Proximal focal femoral dysplasia, which has a short, angulated femur with normal mineralization may be associated with FH. We report a case of unilateral FH with focal femoral deficiency detected at 18 weeks of gestation during a routine ultrasonographic anatomic screening. Sonographic findings were a unilateral short femur (1.8 cm, 3 weeks shorter than expected for gestational weeks), agenesis of ipsilateral fibula and angulation of ipsilateral tibial shaft. During a routine ultrasonographic anatomic scan, all the long bones are carefully measured and evaluated. Long bone shortness can be a part of syndrome or an isolated finding.

Keywords: Aplasia, fibula, fetal development, abnormalities

Öz

Fibular hemimeli (FH), tibia hipoplazisi ve ayak anomalileri ile birlikte olabilen fibulanın bir kısmı ya da tamamının hipoplazisi veya aplazisidir. Proksimal fokal femoral yetmezlik, Femur-Fibula-Ulna sendromu ve Femoral Hipoplazi-Yüz sendromu temel ayırıcı tanılar arasında yer almaktadır. Proksimal fokal femoral yetmezlik FH ile beraber olabilen, normal mineralizasyona sahip kısa ve açılanmış femur ile beraber olabilir. Burada, 18. gebelik haftasında rutin sonografik anatomi taraması yapılan ve fokal femoral yetmezlikli unilateral FH tanısı konulan bir olgu tartışılacaktır. Ultrasonografik incelemede, unilateral kısa femur (1,8 cm; gebelik haftasına göre beklenen uzunluktan üç hafta gerilik tespit edildi), aynı tarafta fibula yokluğu ve tibia şaftında açılanma izlendi. Rutin anatomi taramalarında bütün uzun kemikler dikkatli bir şekilde incelenmelidir. Uzun kemik kısalıkları, izole bir bulgu olabileceği gibi bir sendromun parçası da olabilir.

Anahtar Kelimeler: Aplazi, fibula, fetal gelişim, anomali

Introduction

Fibular hemimelia (FH) is a congenital deficiency in which a part or all of the fibular bone is hypoplastic or aplastic and associated with hypoplastic tibia and foot anomalies[1]. FH is one of the most common congenital deficiencies of the long bones with an estimated incidence between 5.7-20:1.000.000[2]. FH is most often sporadic and may be part of more complex syndromes. There are numerous classification systems for FH; Achtermann and Kalamchi, Coventry and Johnson, and Stanitski. The Achtermann and Kalamchi classification is more commonly used and this classification is based on the degree of fibular deficiency present[3]. In Type 1, the fibula is present but hypoplastic, whereas in Type 2, it is completely absent. Type 1 is divided into 1A, where the proximal fibular epiphysis is distal to the tibial growth plate, and the distal fibular growth plate is proximal to the talar dome, and 1B, where there is a partial absence of the fibula and there is no distal support for the ankle joint. In Type 2 deformities, bowing of the tibia is more severe than in Type 1[3]. The main differential diagnoses include proximal focal femoral dysplasia, Femur-Fibula-Ulna syndrome, and Femoral Hypoplasia-Unusual Facies syndrome. Proximal focal femoral dysplasia, which is with short, angulated femur with normal mineralization may be associated with FH[4]. We report a case of unilateral FH detected at 18 weeks of gestation during a routine ultrasonographic anatomic screening.

Case Report

A gravida 2, para 1-0-0-1, 28-year-old woman was referred to our high-risk obstetric clinic at 18 weeks 2 days of pregnancy. Detailed two-dimensional (2D) ultrasound examination was

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Received/Geliş Tarihi: 20.03.2019 **Accepted/Kabul Tarihi:** 09.06.2019

performed with a 2-7 mHz abdominal ultrasound transducer (Voluson™ 730 Pro; GE Healthcare, USA). Sonographic findings were a unilateral short femur (1.8 cm, 3 weeks shorter than expected for gestational age), agenesis of ipsilateral fibula, and angulation of ipsilateral tibial shaft (Figure 1a). The measurements of contralateral tibia, fibula, femur, and the length of the upper limbs were within the normal range according to the gestational age. No other facial morphology, cardiac, neurologic, gastrointestinal, and genitourinary system abnormalities were identified. There was no maternal history of diabetes, drug exposure, viral exposure, and trauma during this pregnancy. The patient elected for pregnancy termination. Abortion was conducted with misoprostol and a 380 g male fetus was aborted and the intact abortus material underwent pathologic and genetic examination. Post-abortal skin biopsy results indicated normal karyotype. Post-abortal X-rays of the fetus confirmed the sonographic findings (Figure 1b, 1c).

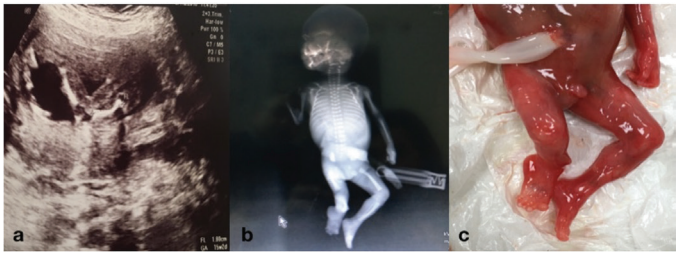

Figure 1. The right leg. a) Sonography of the right leg, showing the shortening of the right femur and abnormally angulated tibia, b) X-ray of the lower limb shows proximal focal femoral deficiency, short and angulated tibia and absence of fibula, c) post-abortus material visualization confirming the abnormalities of the right leg and right foot

Discussion

FH is defined as shortening or absence of fibula and is a rare longitudinal deficiency. It ranges from mild deficiency to complete absence of fibula. FH can also coexist with Fetus-Fibula-Ulna syndrome, intercalary hemimelia of the fibula, congenital deficiency of proximal femoral focal deficiency, and congenital short tibia with absent or dysplastic fibula. The main sonographic findings are deformed or absent fibula with normal mineralization, ossification, shortened or anteriorly curved tibia, significant shortening of the femur, and foot anomalies[2,5]. The unilateral form is approximately 60-80% of all cases and the right side is more commonly affected than the left[6]. Embryologic development and documentation by sonography of upper and lower limbs takes place nearly at the end of the eighth to tenth weeks of the pregnancy. Interconnection of complex several regulatory proteins such as bone morphogenic proteins, fibroblast growth factor, hedgehog proteins, and homeobox factors are prerequisites for limb development[7]. The definite etiology is unknown, but the proposed theory is disruption of vascular development resulting from the interruption of blood flow and muscular development[8]. When a congenital limb deficiency is diagnosed, the fetus should have a thorough anatomic scanning for other system anomalies. Longitudinal limb deficiencies can occur in isolation but sometimes may be part of a syndrome. The parents should be asked and examined for limb anomalies in order to clarify any familial transmission. A detailed pregnancy history including medications, viral exposure, drug use, trauma, diabetes mellitus, and chorion villus sampling in the early weeks of pregnancy may be helpful in identifying etiologic factors. For differential diagnosis of FH, fetal anatomic scanning can be performed by 2D and 3D ultrasonography[7,8]. When a long-bone shortness is determined, all fetal long bones should be measured. Also evaluations must be performed for the fetal face profile, cardiovascular system, neurologic, genitourinary, and gastrointestinal system to determine any co-existing syndromes. After presumptive diagnosis, early evaluation through a multidisciplinary approach with a geneticist and a pediatric orthopedic surgical team is an important component in making a management plan. Various classification systems have been made for FH and these classification systems can aid parental counseling and surgical procedure decisions. Although the Achtermann and Kalamchi classification system is more commonly used in the postnatal period,[2,3] there are mainly three types of absence of fibula: Type 1 (10% of all cases) is characterized by total or partial absence of the fibula and mild or no bowed tibia. Type 2 (35% of all cases) is characterized by unilateral absence of the fibula, anterior bowing of the tibia, and significant shortening of the leg. Type 3 (55% of all cases) includes cases with uni/bilateral absence of the fibula with same-leg and foot deformities[5,8]. According to our sonographic findings (absence of the right fibula, bowed tibia, shortening femur, and valgus deformity), our case was classified as Type 3 FH with co-existing proximal focal femoral deficiency. Its association with FH has been reported in approximately 50% of cases. The prognosis of FH depends on the severity of fibular deficiency, associated femoral malformations, and foot, ankle or knee deformities[2]. Treatment options include amputation (the preferred management of a child with absence of fibula) and orthostatic or prosthetic support (to maintain limb length equality)[2,9]. It is individualized for each case and undertaken in experienced centers with access to a multidisciplinary team including a pediatrician, physical therapists, and orthopedists. Patients with FH are not associated with mental retardation, but both treatment options for children with FH result with a lower quality of life. In the literature, several cases are reported in which the parents elected for termination of pregnancy before fetal viability, as in our case, after parental counselling. Although FH is not a definite termination indication, detailed information about the severity of limb deformity and treatment options can aid parents in decision-making regarding the continuity of pregnancy.

Ethics

Informed Consent: Informed consent was provided by the patient.

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.Y., O.A., T.Y., Concept: A.T.Ç., T.Y., Design: T.Y., B.Y., O.A., A.T.Ç., Data Collection or Processing: B.Y., T.Y., Analysis or Interpretation: B.Y., O.A., Literature Search: B.Y., O.A., Writing: B.Y.

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

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Tsai A, Kleinman PK, Laor T, Kasser JR. Lower-extremity growth patterns and skeletal maturation in children with unilateral fibular hemimelia. Pediatr Radiol 2019;49:122-7.
2. Monteagudo A, Dong R, Timor-Tritsch IE. Fetal fibular hemimelia: case report and review of the literature. J Ultrasound Med 2006;25:533-7.
3. Achterman C, Kalamchi A. Congenital deficiency of the fibula. J Bone Joint Surg Br 1979;61-B:133-7.
4. Filly AL, Robnett-Filly B, Filly RA. Syndromes with focal femoral deficiency: strengths and weaknesses of prenatal sonography. J Ultrasound Med 2004;23:1511-6.
5. Cullier F, Cartault F, Lemaire P. Absence of fibula, type II. www.fetus.net 2004-03-25-14.
6. Pallavee P, Samal R, Begum J, Ghose S. Foetal fibular hemimelia with focal femoral deficiency following prenatal misoprostol use: a case report. J Obstet Gynaecol 2016;36:760-1.
7. Wilcox WR, Coulter CP, Schmitz ML. Congenital limb deficieny disorders. Clin Perinatol 2015;42:281-300
8. Shawky R, Elkhalek H, Gad S, Mohammad SA. Unilateral proximal focal femoral deficiency, fibular aplasia, tibial campomelia and oligosyndactyly in an Egyptian child: Probable FFU syndrome. Egyptian Journal of Medical Human Genetics 2014;15:299-303.
9. Popkov A, Aranovich A, Popkov D. Prevention of recurrence of tibia and ankle deformities after bone lenghtening in children with type 2 fibular hemimelia. Int Orthop 2015;39:1365-70.

Case Report / Olgu Sunumu

DOI: 10.4274/tjod.galenos.2019.43788

Turk J Obstet Gynecol 2019;16:208-12

The rectal vaginal opacification with water and the anti-peristaltic agent in magnetic resonance scanning of the intestinal endometriosis

İntestinal endometriozis manyetik rezonans incelemesinde su ile rektal vajinal opaifikasyon ve antiperistaltik ajan kullanımı

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Abstract

The diagnosis of deep intestinal endometriosis is mandatory to plan treatment and for follow-up; however, there is no consensus worldwide in the use of rectal/vaginal opacification and anti-peristaltic agents for magnetic resonance imaging (MRI) scanning, being defined as an option for the examination. The transvaginal ultrasound images of previous MRI with the standard protocol, and recent MRI in our institution with rectal/vaginal opacification with water and the anti-peristaltic agent are presented in four cases for comparison, respectively. The technique in our institution seems to be more effective than routine pelvic MRI scans in the intestinal endometriosis.

Keywords: Endometriosis, ultrasound, magnetic resonance imaging, menstruation, painful

Öz

Derin intestinal endometriozis tanısı tedavi ve takip için zorunludur, ancak manyetik rezonans görüntülemede (MRG) rektal/vajinal opasifikasyon ve antiperistaltik ajan kullanımı açısından dünya genelinde bir uzlaşma mevcut değildir. Trans vajinal ultrason ve MRG (standart protokol ve rektal/vajinal opasifikasyon ve antiperistaltik ajan kullanarak elde edilen) karşılaştırma amacıyla sunulmuştur. Kullandığımız tekniğin standart MRG tetkiklerine göre daha efektif olduğu izlenmektedir.

Anahtar Kelimeler: Endometriozis, ultrason, manyetik rezonans görüntüleme, menstruasyon, ağrı

Introduction

Deep infiltrating endometriosis (DIE) is involvement of the retrocervical septum, rectovaginal septum, uterosacral ligaments, vaginal fornix, and bladder[(1)], and intestinal involvement occurs in 12-37% of patients with endometriosis[(2)]. Transvaginal ultrasound (TVUS) is the first-line method and magnetic resonance imaging (MRI) should be considered as a second-line technique after TVUS[(3)]. However, the MRI diagnosis of DIE is a dilemma in radiology departments because most MRI scans with suspicion of DIE are negative in spite of either an intestinal endometriotic nodule in TVUS or the clinical history being in favor of DIE. There is no universally accepted protocol for MRI in endometriosis for the use of vaginal and/or rectal opacification (RVO)[(3).] In the presented cases, which were initially diagnosed using TVUS as intestinal endometriosis, the findings of MRI scans with and without RVO with water and anti-peristaltic agent use are presented.

Case Report

The 53 patients with TVUS findings in favor of deep pelvic endometriosis were collected between 2016 and 2018. The criterion for patient selection was the presence of at least three of the following TVUS findings: [(1)] restriction of uterus mobility

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Received/Geliş Tarihi: 01.05.2019 **Accepted/Kabul Tarihi:** 02.09.2019

or pain with probe compression; [2] kissing ovaries; [3] unilateral or bilateral ovarian endometrioma; [4] intestinal wall thickening; and [5] intestinal endometriotic nodule either as the mushroom cap sign or the Indian headdress sign[4].

Twenty-nine patients who were examined using MRI due to TVUS findings and the previous MRI scans of 28 patients, performed either in our center or an external tertiary care hospital or in a private hospital, were re-examined retrospectively. All of the MRI scans were reported to be normal concerning DIE in spite of clinical information or TVUS findings. Four of the 28 patients with endometriosis with intestinal involvement considering the TVUS findings were re-scanned using MRI prospectively due to serious clinical symptoms. All of the MRI re-scans were performed according to the European Society of Urogenital Radiology DIE guideline[3]. Written informed consent was obtained from all subjects, according to the World Medical Association Declaration of Helsinki, revised in 2000, Edinburgh. The histories and the clinical information of the 4 patients are obtained as suggested by the IDEA group[4] and these were noted for each patient respectively (Table 1)

Technique

A 1.5 Tesla Magnetom_Essenza MRI system (Siemens AG Wittelsbacherplatz 2 80333 Muenchen Germany) was used for the MRI re-scans anda Toshiba Applio 500 ultrasound system was used for transvaginal examinations (TUS-A500, Toshiba Medical Systems, Europe BV, Zilverstraat 1, 2718 RP, Zoetermeer, The Netherlands). The patients were informed to use a rectal enema 12 and 2 hours before the MRI exams

Table 1. The clinical information obtained for each patient

		Case 1	Case 3	Case 2	Case 4
1	Age	26	41	39	26
2	Parity	G0 P0	G2 P1	G2 P2	G0 P0
3	Height (m)	1.68	1.50	1.64	1,78
4	Weight (kg)	75	55	68	65
5	Ethnic origin	Caucasian	Caucasian	Caucasian	Caucasian
6	Bleeding pattern (regular, irregular or absent)	Irregular	Regular, hypermenorrhea	Regular	Irregular
7	Last menstrual period	2 weeks ago	3 weeks ago	2 weeks ago	4 weeks ago
8	Previous surgery for endometriosis (type, effect)	No	No	Yes, for umbilical endometrioma	Yes
9	Previous myomectomy or cesarean delivery	No	Caesarean (once)	Caesarean (once)	No
10	Family history of endometriosis	Unknown	Unknown	Elder sister (operated)	No
11	Subfertility including duration of subfertility	Yes	Yes	No	Yes
12	Previous non-surgical treatment for endometriosis (type, duration, effect)	No	History of oral contraceptives (for 3 months)	Yes, Dienogest (Visanne-Bayer) (recently started)	Yes, transient iatrogenic menopause
13	Treatment for infertility and outcome of fertility treatment	Medical and no pregnancy	No	No	Yes, no pregnancy
14	Pain (dysmenorrhea)	Severe	Sometimes	No	No
15	Pain (dyspareunia)	Yes	Sometimes	No	No
16	Pain (dysuria)	Yes	Sometimes	No	No
17	Pain (dyschezia)	Yes	Very rare	No	No
18	Pain (chronic pelvic pain)	Sometimes	After menstruation (at intervals)	No	No
19	Hematochezia and/or hematuria	No	No	No	No
20	The onset and duration of symptoms	2-3 years	Endometrioma exists since 2005	No symptoms	8-9 years
21	The intensity of the pain with a visual analog scale(5)	7	2	1	8

for distal bowel cleansing. If the urinary bladder filling was inadequate in the survey image, 200 mL of saline infusion was administered through a Foley catheter. Isotonic saline solution was used for vaginal and RVO through the Foley or Nelatone urinary catheter. The vaginal filling with saline infusion was stopped when the patient started to feel overflow. The total amount of fluid used for rectal filling was between 500 mL and 1000 mL. After the intravenous administration of the single-dose (20 mg) American Psychological Association (APA) (Hiyosin N Butilbromur, Buscopan, Zentiva), 100-200 mL of additional fluid for bowel filling was given. The urinary bladder (if needed), vaginal and rectal saline infusions were easily performed with a simple and cheap system (Figure 1).

Magnetic Resonance Imaging Sequences

2D T2W sagittal/axial/coronal, 2D T1W sagittal/axial with and without fat saturation, T1W Dixon sagittal, and diffusion-weighted sequences were performed. Gadolinium is not used for intravenous or in saline solution for contrast opacification. If there was an interval more than 3 months between the previous and the present MRI scan, initial T2W sagittal images were obtained just before applying the RVO with water and the APA in order to exclude recent nodule growth. The findings in TVUS, the previous MRI scans, and the re-scanned MRI examinations are presented as images, respectively. The endometriotic nodules in the bowel wall are demonstrated clearly in all patient re-scans, which had been reported as normal previously (Figure 2-6).

Discussion

The MRI examinations are crucial for the proper diagnosis and for the demonstration of the extent of the lesions

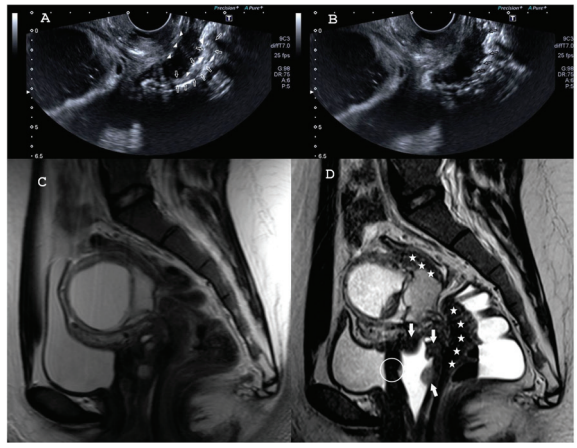

Figure 2. A) Transvaginal ultrasound (TVUS) in patient 1. The mushroom cap sign: the arrows represent the cap, which consists of the mucosa and submucosa, the arrowheads represent the base of the mushroom, which consists of fibrosis of the muscular propria. The mushroom cap sign has been described on TVUS and magnetic resonance imaging (MRI) and is accepted as a characteristic finding of severe involvement in deep infiltrating endometriosis, B) TVUS in patient 1. The Indian headdress or moose antler sign; the arrows represent the spiky extensions of the fibrosis of the muscular propria towards the bowel lumen, C) Sagittal T2W image of patient 1 in the previous MRI scan. Vaginal active bleeding and the sigmoidal chronic fibrotic lesions might be noticed only by experienced eyes, D) Sagittal T2W image of patient 1 in the present MRI scan. The vaginal and the sigmoidal lesions can be detected easily by all examiners. The white arrows represent the vaginal and the white stars represent the sigmoidal lesions. The circle indicates the invasion of the vaginal wall fibrosis into the urinary bladder. This will be shown in the following T1W Dixon image with the white arrows

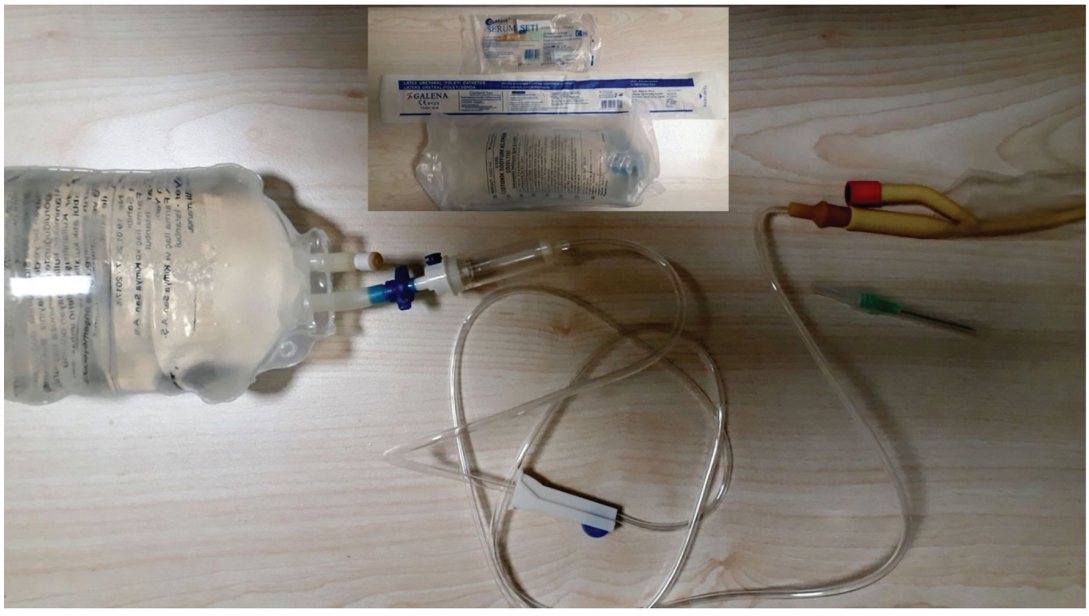

Figure 1. The simple system for administering the water into the urinary bladder (if needed), the vagina and the bowel lumen. The same system is used for the voiding cystourethrography

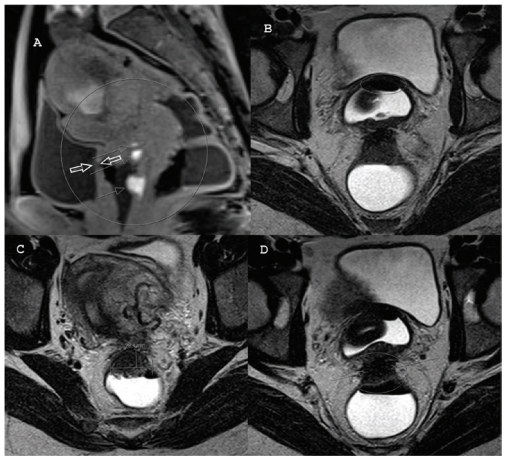

Figure 3. A) T1W Dixon image of patient 1 in the present magnetic resonance imaging (MRI) scan. The white arrows represent the invasion of the posterior wall of the urinary bladder by the vaginal anterior wall fibrosis. The thin arrows indicate the posterior vaginal wall lesions with subacute bleeding, B) Axial T2W image of patient 1 in the present MRI scan. The circle shows the fibrotic invasion between the urinary bladder and the vagina, C) Axial T2W image of patient 1 in the present MRI scan shows the measurement of transverse diameter of the anterior sigmoidal wall lesion, D) Axial T2W image of patient 1 in the present MRI scan. The circle and the thin arrows show the fibrotic invasion between the sigmoid bowel and the vagina

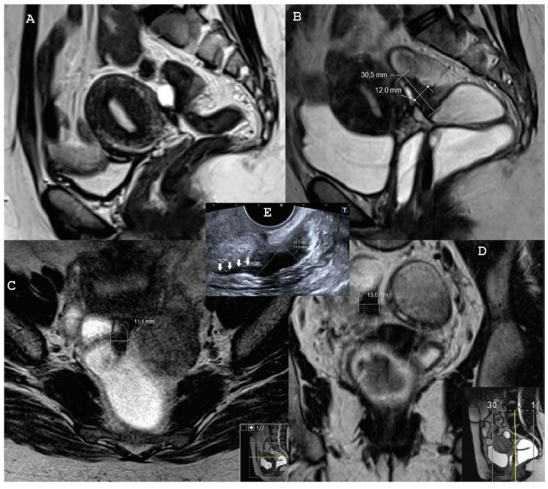

Figure 4. A) Sagittal T2W image of patient 2 in the previous magnetic resonance imaging MRI scan. It is not possible to detect the actual place of the intestinal involvement, B) Sagittal T2W image of patient 2 in the present MRI scan. The intestinal involvement of the endometriosis in the sigmoid bowel, which was measured, can be detected easily, C) Axial T2W image of patient 2 in the present MRI scan. The lesion is measured in a horizontal plane, D) Coronal T2W image of patient 2 in the present MRI scan. The lesion is measured, E) Transvaginal ultrasound in patient 2. The endometriotic intestinal nodule is measured. The nodules due to the hypertrophy and the fibrosis of the muscular propria grow into the lumen and narrowing the diameter. The nodule has a comet shape with a tail; comet sign

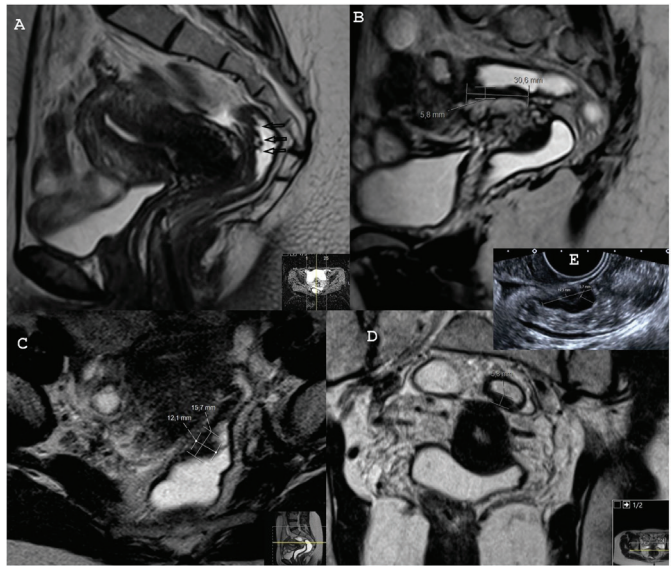

Figure 5. A) Sagittal T2W image of patient 3 in the previous magnetic resonance imaging (MRI) scan. There seems to be wall thickening with an Indian headdress sign (arrows). However, after the administration of the rectal fluid and the anti-peristaltic agent, the actual lesion is found in another segment of the sigmoid bowel, B) Sagittal T2W image of patient 3 in the present MRI scan. The actual place of the sigmoid bowel involvement was in a different segment in contrast to the previous MRI scan (Figure 5A), C) Axial T2W image of patient 3 in the present MRI scan. The lesion is measured, D) Coronal T2W image of patient 3 in the present MRI scan. The lesion is measured, E) Transvaginal ultrasound in patient 3. The endometriotic intestinal nodule is measured. There is regular thickening in the muscular propria

preoperatively, for postoperative follow-up or for the efficacy of medical treatment. The MRI findings of endometriotic nodules in the intestinal wall vary depending on the progression of the infiltration. On T1W sequences, the lesions are hyperintense in early phases due to bleeding and hypointense in the chronic phases due to fibrosis[6]. Mostly the lesions are in the chronic phase, which is why the bright intestinal lumen is mandatory in order to visualize the fibrotic nodules, especially for inexperienced examiners. However, there is no consensus for RVO with water and APA use, which is published to be an option in the medical literature[3,7]. In daily practice, MRI scans are performed without these options. Here, it is clearly seen that MRI with RVO with water and APA use is more appropriate than routine MRI scans for intestinal DIE. Administration of the optional procedures requires an extra 10 to 15 minutes, so it might be not preferred in some radiology departments. In Turkey, public hospitals are autonomized to allow them to out-source some medical services such as diagnostic imaging,[8] and the less time required for MRI scanning means more income for the out-source services. Therefore, the use of the optional technique should be restricted by choosing patients with DIE before the MRI scans using TVUS. In our experience, the

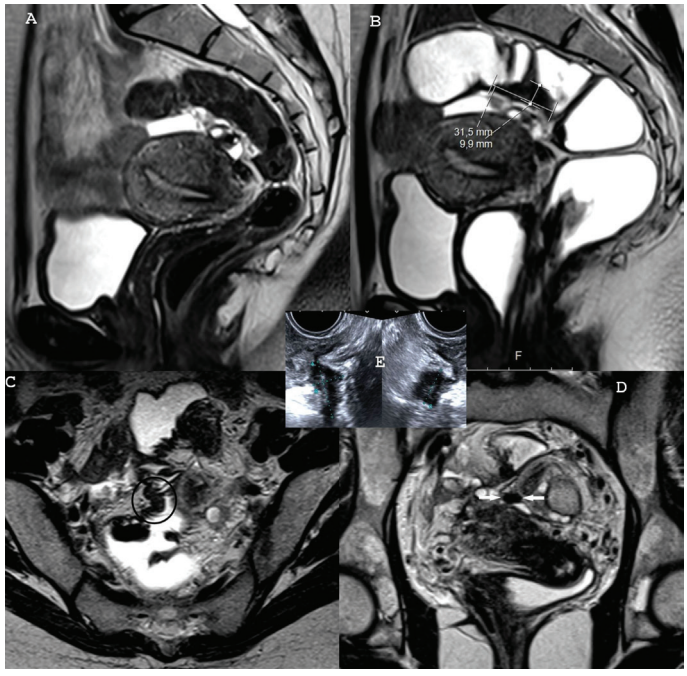

Figure 6. A) Sagittal T2W image of patient 4 in the present magnetic resonance imaging (MRI) scan obtained initially just before applying the rectal/vaginal opacification with water and the anti-peristaltic agent in our tertiary care hospital, but with the rectal cleansing enema, B) Sagittal T2W image of patient 4 in the present MRI obtained with the rectal/vaginal opacification with water and the anti-peristaltic agent use after the lesion is measured, C) Axial T2W image of patient 4 in the present MRI obtained with the rectal/vaginal opacification with water and the anti-peristaltic agent use. The lesion is in the circle, D) Coronal T2W image of patient 4 in the present MRI obtained with the rectal/vaginal opacification with water and the anti-peristaltic agent use. The lesion is between the arrows, E) Transvaginal ultrasound in patient 4. The endometriotic intestinal nodule is measured. There is irregular thickening in the muscular propria

diagnosis of intestinal involvement in endometriosis using MRI needs RVO with water and APA use; therefore, it should not be an option in MRI scans as in the guidelines, but an obligation in patients with endometriosis with intestinal involvement in order to increase the detectability.

Ethics

Informed Consent: Written informed consent was obtained from all subjects.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.M., M.Ç., Concept: C.G., Design: C.G., Data Collection or Processing: C.G., B.M., M.Ç., Analysis or Interpretation: C.G., B.M., M.Ç., Literature Search: C.G., B.M., Writing: C.G., B.M.

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

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Guerriero S, Alcázar JL, Pascual MA, Ajossa S, Perniciano M, Piras A, et al. Deep Infiltrating Endometriosis: Comparison Between 2-Dimensional Ultrasonography (US), 3-Dimensional US, and Magnetic Resonance Imaging. J Ultrasound Med 2018;37:1511-21.
2. Chamié LP, Blasbalg R, Pereira RM, Warmbrand G, Serafini PC. Findings of pelvic endometriosis at transvaginal US, MR imaging, and laparoscopy. Radiographics 2011;31:E77-100.
3. Bazot M, Bharwani N, Huchon C, Kinkel K, Cunha TM, Guerra A, et al. European society of urogenital radiology (ESUR) guidelines: MR imaging of pelvic endometriosis. Eur Radiol 2017;27:2765-75.
4. Guerriero S, Condous G, van den Bosch T, Valentin L, Leone FP, Van Schoubroeck D, et al. Systematic approach to sonographic evaluation of the pelvis in women with suspected endometriosis, including terms, definitions and measurements: a consensus opinion from the International Deep Endometriosis Analysis (IDEA) group. Ultrasound Obstet Gynecol 2016;48:318-32.
5. Bourdel N, Alves J, Pickering G, Ramilo I, Roman H, Canis M. Systematic review of endometriosis pain assessment: how to choose a scale? Hum Reprod Update 2015;21:136-52.
6. Thalluri AL, Knox S, Nguyen T. MRI findings in deep infiltrating endometriosis: A pictorial essay. J Med Imaging Radiat Oncol 2017;61:767-73.
7. Türk Radyoloji Derneği (TRD), MRG ve BT İnceleme Standartları, Pelvik MRG, TRD Standart 2018 Revizyonu, https://www.turkrad.org.tr/assets/2018/standartlar2018.pdf.
8. WHO. Successful Health System Reforms: The Case of Turkey. WHO LIS e96508. May 2012. https://dosyamerkez.saglik.gov.tr/Eklenti/2106,successful-health-system-reforms-the-case-of-turkeypdf.pdf?0.