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

TURKISH JOURNAL OF OBSTETRICS AND GYNECOLOGY

June 2020 Volume: 17 Issue: 2 www.tjoddergisi.org

Clinical Investigations

TURKISH SOCIETY OF OBSTETRICS AND GYNECOLOGY

galenos yayınevi

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Publisher Certificate Number:14521

Publication Date: March 2020

ISSN: 2149-9322 **E-ISSN:** 2149-9330
International scientific journal published quarterly.

TURKISH JOURNAL OF OBSTETRICS AND GYNECOLOGY

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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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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.

Results

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

DOI: 10.4274/tjod.galenos.2020.74152

Turk J Obstet Gynecol 2020;17:79-83

Pulmonary arterial pressure in at-term in vitro fertilization neonates: A cross-sectional study

Term in vitro fertilizasyon yenidoğanlarında pulmoner arter basıncı: Kesitsel bir çalışma

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Abstract

Objective: Hormones consumption in women who conceive through *in vitro* fertilization (IVF) as well as embryonic manipulations have raised concerns regarding the neonates' health, including the possibility of pulmonary hypertension. This study, therefore, aimed to assess the pulmonary arterial pressure in at-term IVF neonates.

Materials and Methods: This prospective cross-sectional study was conducted between March 2013 and October 2017 and compares 160 IVF neonates (group 1) with 160 naturally conceived neonates (group 2). The neonates in both groups were cesarean newborns, matched in terms of gestational and neonatal age. The neonates were three-seven days old, had a full-term gestational age of 37-39 weeks and 6 days, and a normal birth weight of 2500-4000 gr. The systolic pulmonary artery pressure (SPAP) was estimated using real-time echocardiography on the basis of peak flow velocity of tricuspid regurgitation jet.

Results: A significant difference was observed in the mean SPAPs between the two groups ($p<0.001$). Although, the effect of gestational age on reducing SPAP was greater and statistically significant in group 1, the gradual decrease in the PAP after birth appeared to be slower in this group. Moreover, in both groups, the effect of gestational age on reducing SPAP was more convincing than that of the neonatal age. Further, in both groups, a significant reverse correlation was observed between the SPAP and the neonatal weight; however, it appeared to be markedly higher in group 1.

Conclusion: Our study renders IVF as being culpable in the incidence of pulmonary hypertension among neonates. Hence, to detect the likelihood of pulmonary arterial hypertension in IVF neonates, it is recommended to monitor their PAP during the neonatal period, and thereby facilitate them with the required treatment.

Keywords: In vitro fertilization, persistent pulmonary hypertension, neonate

Öz

Amaç: *İn vitro* fertilizasyon (İVF) ve embriyonik manipülasyonlar yoluyla gebe kalan kadınlarda hormon kullanımı, pulmoner hipertansiyon olasılığı da dahil olmak üzere yenidoğanların sağlığıyla ilgili endişeleri artırmıştır. Bu nedenle bu çalışma, term İVF yenidoğanlarında pulmoner arter basıncını değerlendirmeyi amaçlamıştır.

Gereç ve Yöntemler: Bu prospektif kesitsel çalışma Mart 2013 ile Ekim 2017 arasında gerçekleştirilmiştir ve 160 İVF yenidoğanı (grup 1) 160 doğal yolla olan yenidoğanla (grup 2) karşılaştırmaktadır. Her iki gruptaki yenidoğanlar, gebelik ve yenidoğan yaşı açısından eşleştirilmiş sezaryen ile doğan yenidoğanlardı. Yenidoğanlar üç-yedi günlük idi, 37-39 hafta ve 6 günlük tam dönem gebelik yaşına sahipti ve yenidoğanların doğum ağırlığı normal sınırlarda (2500-4000 g) idi. Sistolik pulmoner arter basıncı (SPAB), triküspit yetersizlik jetinin pik akış hızını temel alan gerçek zamanlı ekokardiyografi kullanılarak tahmin edildi.

Bulgular: İki grup arasındaki ortalama SPAB açısından anlamlı bir fark gözlendi ($p<0,001$). Her ne kadar gestasyonel yaşın SPAB'yi düşürücü etkisi grup 1'de daha fazla ve istatistiksel olarak anlamlı olsa da, doğumdan sonra PAB'de kademeli azalma bu grupta daha yavaş gözlenmiştir. Ayrıca, her iki grupta da gebelik yaşının SPAB'yi düşürücü etkisi yenidoğan yaşına göre daha belirgindi. Ayrıca, her iki grupta da SPAB ile yenidoğan ağırlığı arasında anlamlı bir ters korelasyon gözlendi; ancak bu korelasyonun grup 1'de daha kuvvetli olduğu görüldü.

Sonuç: Çalışmamız, İVF'yi yenidoğanlarda pulmoner hipertansiyon insidansında artış ile ilişkili bulmuştur. Bu nedenle, İVF yenidoğanlarında pulmoner

PRECIS: The pulmonary arterial pressure in at-term in vitro fertilization neonates

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Received/Geliş Tarihi: 21.09.2019 **Accepted/Kabul Tarihi:** 19.05.2020

arteriyel hipertansiyon olasılığını tespit etmek için, yenidoğan döneminde PAB değerlerinin izlenmesi ve böylece gerekli tedavi ile bu durumun düzeltilmesi önerilir.
Anahtar Kelimeler: *İn vitro* fertilizasyon, persistan pulmoner hipertansiyon, yenidoğan

Introduction

As the fetus leaves the uterus, the pulmonary arterial pressure (PAP) starts to drop, and as a result, the vascular resistance of the lungs begins to decrease. Due to the gradual dilatation of the neonates' pulmonary arterioles lining, it usually reaches that of an adult within a week, or a maximum of six-eight weeks[1].
Pulmonary hypertension results from a lack of proper decrease in the vascular resistance of the lungs after the neonatal period[2], usually at term or later up to 34 weeks[3]. The prevalence rate of this lung condition is approximately 2 in 1,000 live births[2] with a mortality rate of about 4%-33%[3]. Arterial pulmonary hypertension is a critical and severe progressive status with weak prognosis[4], and the likelihood of the survival amounts to around 69% following the conventional treatments[5].
The method of delivery, especially, cesarean section, may also indirectly raise the risk of pulmonary hypertension as it limits the synthesis of pulmonary endogenous vasodilators, lowers the level of protective antioxidants in newborns, and exposes them to a higher risk of respiratory distress syndrome and elevated level of endothelin-1[6].
On the other end of the spectrum, *in vitro* fertilization (IVF) has been in use for three decades, so much so that assisted reproductive technology (ART) children account for about 1%-4% of births in the developed countries[7]. Although, the consumption of different hormones by women as well as the embryonic manipulations have raised many concerns regarding the neonates' health, including the possibility of pulmonary hypertension, yet, the issue remains to be further addressed. Therefore, the aim of this study was to investigate the effect of the type of pregnancy-IVF in this study-on the blood pressure of the pulmonary artery.

Materials and Methods

This study is a prospective cross-sectional study that was conducted between January 2011 and August 2019 and compares 160 neonates conceived through IVF (group 1) with 160 neonates conceived naturally (group 2). In order to control the type of delivery as a confounding factor[6], all subjects (in both groups) were selected from a cesarean section population. Moreover, to eliminate other confounding factors such as gestational and neonatal age, both groups were matched using the individual matching method. First, 160 IVF neonates born through cesarean section were admitted into the study (group 1), then, 160 others who were born through cesarean section but gestated naturally were matched with the first group for gestational and neonatal age, and all of them were included into the study.
Mothers with a history of premature rupture of the membranes, gestational infection, diabetes, or other underlying conditions were excluded from the probe[2].
The neonates were about three-seven days old, all being at term with a gestational age of 37-39 weeks and 6 days, and had a normal birth weight of 2500-4000 gr.
To estimate the systolic pulmonary artery pressure (SPAP), a real-time phased-array sector scanner echocardiography with a Color Doppler echocardiograph, the Vivid 3 expert model (GE Healthcare, USA) version 2011, was used with an integrated Color Doppler system and transducer containing crystal sets for two-dimensional image (5.0 MHz with second harmonic technology) and continuous-wave Doppler recorder (2.5 MHz). When tricuspid regurgitation was localized with color-flow Doppler, the peak flow velocity of tricuspid jet was measured using a continuous-wave Doppler. The pressure gradient between the right ventricle (RV) and the right atrium (RA) was calculated using modified Bernoulli's equation (10 and 11) at least thrice for each neonate and the mean was then recorded. Note that this approach, that is, measuring the pressure gradient between RV and RA, is a non-invasive standard method for estimating SPAP[8]. Based, on this echocardiography the neonates with a mean pulmonary arterial pressure (MPAP) >25 mmHg (SPAP > 36 mmHg) were considered as pulmonary hypertensive[1].
As a sub-target, the presence of patent ductus arteriosus (PDA) was also examined during the echocardiography using color-flow Doppler and continuous-wave Doppler.
This study was approved by the Ethical Committee of Yazd, Iran Yazd Cardiovascular Research Center (approval number: 814). Informed consent was obtained from the participants.

Statistical Analysis

Finally, data were analyzed through the SPSS software version 19 using the following tests: t-test for continuous quantitative variables, Fisher's exact test for comparing variables between ART and the control group, and analysis of variance for comparing the two groups.

Results

No significant difference was observed in the mean gestational age, neonatal age and weight, as well as the mean age of the mothers in both groups. Also, the gender proportion appeared to be similar in both groups (Table 1).
The number of boys in groups 1 and 2 were 85 (53.1%) and 75 (46.9%), respectively, therefore, no significant difference was observed between the two groups in terms of gender (p=0.15). While the mean SPAP in group 1 was 28.06+-4 mmHg, it was 22.05+-5 mmHg in group 2, thus being 27.25% higher and statistically significant (p<0.0001).

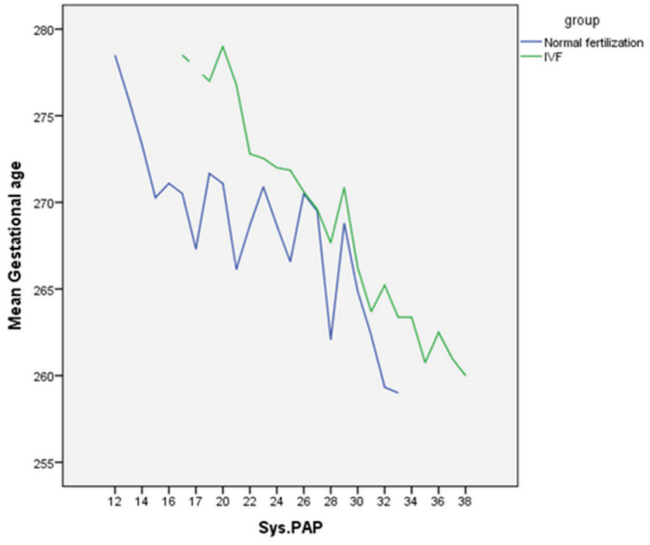
The relationship between SPAP and gestational age in group 1 was also significant but waned with growing gestational age of SPAP. In addition, while the relationship projected to be significantly higher in group 2, the relationship was more convincing in group 1. The correlation coefficient (r) turned out to be -0.74 and -0.39 in groups 1 and 2, respectively. Moreover, linear regression (B) between SPAP and gestational age performed in both groups revealed that in group 1, with a daily increment in gestational age, SPAP diminished up to 0.98 mmHg. However, in group 2, a daily rise in gestational age lowered SPAP up to 0.45 mmHg (Graph 1).

A comparison of SPAP with neonatal age in group 1 revealed an inverse and significant correlation between these two variables, that is, with a daily increase in neonatal age, SPAP dwindled up to 0.19 mmHg. This significant and inverse relationship between the two variables was also observed in group 2; with a daily increase in neonatal age, PAP reduced up to 0.25 mmHg. To put it another way, the gradual reduction of PAP in group 1 appeared to be slower than in group 2 (Graph 2).

Table 1. Demographics of mother and neonate in terms of type of fertilization

Variable	IVF	Natural pregnancy	p
Gestational age (day)	268.43±5	268.38±5	0.93
Neonatal age (day)	5.08±1.2	5.06±1.3	0.83
Neonatal weight (gram)	3044.06±383	3048.70±396	0.91
Mother's age (year)	34.76±5.03	35.32±5.80	0.35

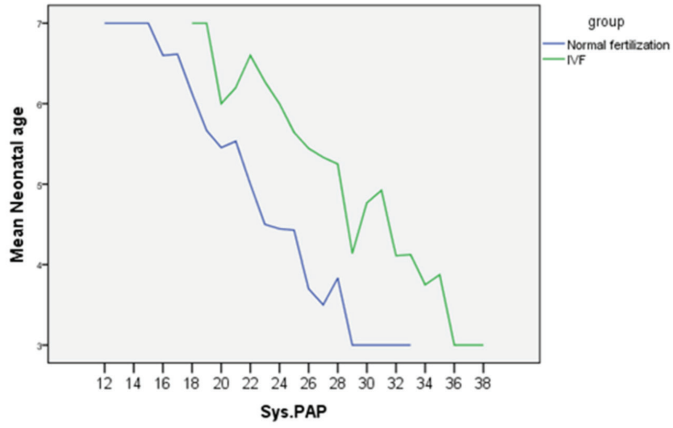
IVF: In vitro fertilization



Graph 1. Comparison of the linear regression of in vitro fertilization group and control group based on systolic pulmonary artery pressure and gestational age

IVF: In vitro fertilization, SPAP: Systolic pulmonary artery pressure

Although the effect of gestational age on SPAP reduction was seen to be greater than that of the neonatal age in both groups, the difference in group 1 was, however, more vivid and impressive (Tables 2, 3). Also, a meaningful and inverse relationship was identified between SPAP and neonatal weight in both groups; however, the relationship was markedly better in group 2 (Tables 2, 3). In group 1, with a yearly rise in the maternal age, the PAP also increased up to 0.01 mmHg, showing no significant relationship between the maternal age and SPAP. A similar observation was made in group 2, where SPAP increased by 0.04 mmHg with a daily rise in the maternal age (Tables 2, 3).



Graph 2. Comparison of the linear regression of in vitro fertilization group and control group based on systolic pulmonary artery pressure and neonatal age

IVF: In vitro fertilization, SPAP: Systolic pulmonary artery pressure

Table 2. Linear regression analysis of mother's gestational age, neonatal age and weight, and mother's age in the in vitro fertilization group

Variable	B	SD	p
Gestational age (day)	-0.98	0.07	<0.0001
Neonatal age (day)	-0.19	0.16	<0.0001
Neonatal weight (gram)	-0.008	0.001	<0.0001
Mother's age (year)	0.01	0.09	0.91

SD: Standard deviation

Table 3. Linear regression analysis of mother's gestational age, neonatal age and weight, and mother's age in the natural pregnancy group

Variable	B	SD	p
Gestational age (day)	-0.45	0.08	<0.0001
Neonatal age (day)	-0.25	0.007	<0.0001
Neonatal weight (gram)	-0.005	0.001	<0.0001
Mother's age (year)	0.04	0.09	0.16

SD: Standard deviation

In group 1, the mean SPAP proved to be 27.6+-4.4 mmhg and 28.4 + -4.1 mmhg in female and male neonates, respectively, but no significant difference was observed between the two genders (p=0.24). Similarly, in group 2, the mean SPAP appeared to be 22.4+-4.8 mmHg and 21.6+-5.4 mmHg in female and male neonates, respectively, but no significant difference was found between the two genders (p=0.34). On balance, the mean SPAP reached 24.86±1.5 mmHg and 25.24+/-5 mmHg in female and male neonates, respectively, so that no significant difference could be discerned between the two groups in terms of SPAP (p=0.54). The prevalence of PDA in both groups was 0.06% (i.e., one case in each group).

Discussion

This cross-sectional study aimed at investigating the relationship between pulmonary arterial hypertension of neonates and IVF as an ART, the PAP in IVF neonates was found to be higher than that in the control group. In addition, the gestational and the neonatal age had a positive effect on the reduction of SPAP in the neonates after birth. Our study revealed PAP in IVF neonates to be 27.25% higher than that of the control group. In a study by Scherrer et al.[9], the SPAP in the ART group was seen to be 30% higher than the control group. Although that study was conducted at an altitude of 3,450 meters and on a small population (65 ART children and 57 others in the control group) with a higher mean age (11.1 years in the ART group and 11.9 years in the control group), the ART and control groups had been matched in terms of gestational and neonatal age, hence approaching the results of ours. However, the slight difference in the result might be due to the differences in the geography of the study setting, the sample size, and the mean age differences in the investigated populations. Since all neonates were born through cesarean section and were matched on the basis of gestational and neonatal age, the only factor that brought about a significant difference in the PAP between the two groups in our study was seemingly the type of maternal pregnancy because maternal age failed to have an effect on the SPAP in both groups. Perhaps, manipulating the embryos, that appear to be very sensitive to perturbations of the environment especially in their early stages of life during ART procedure, slows down the process of thinning of the pulmonary arterioles[10]. Moreover, the arterial stiffness, which is the main cause of increased systolic pressure, and recurrent periodic stress triggering the degeneration of the arterial wall[11] seem to be more serious in ART neonates. In addition, neonates' lungs are subject to vascular dysfunction[12], which does not appear to be associated with parental factors, but to ART procedure[13]. Albeit, few human studies have been performed on ART neonates, it seems that ART induces early vascular dysfunction in lungs through epigenetic mechanisms accordingly contributing to pulmonary hypertension. This accords with what Mensah et al.[14] reported regarding the effect of ART on vascular dysfunction in mice. In our study, the gestational age was also proved to have a positive effect on SPAP reduction so that with an increase in the gestational age, SPAP subsided, as the rise in gestational age is associated with an increase in the soluble guanylate cyclase (sGC) function in the lungs[15].

This substance acts as an important receptor for nitric oxide in the pulmonary vessels and relaxes the vascular smooth muscles[14,15]. In Mensah et al.[14] study, it was demonstrated that the level of sGC mRNA, which acts as a mediating agent for the NO function on the differentiation of the smooth muscles of neonates' pulmonary vasculature, appears to be low in sheep fetus (preterm gestation of 126 days), however, it heightens significantly during the late preterm and early term gestation (137 days)[14,16]. Furthermore, in the Sprague-Dawley rats, the sGC activity in the lungs in the late gestation and the early newborn period proved to be high[14]. Gonadotropins like Gonal-F, used by the mother to induce pregnancy through the placenta, may be transmitted to the bloodstream of the fetus and trigger thrombotic events in the pulmonary vasculature. This is similar to what occurs in the mother's pulmonary arteries[17-19] and provides the underlying reason for maintaining pulmonary hypertension in the afterbirth period. Mothers' primary hormone disturbances, including polycystic ovary syndrome, which contribute to infertility and pulmonary thromboembolism in the fetus, may also engender this problem as the risk of such incidents is high in such mothers[20]. Moreover, it was identified that with an increase in the neonatal age, SPAP dwindles away. This is due to the fact that the gradual thinning of the muscular membrane, dilatation of the pulmonary arteries, the growth of the existing arteries, and the formation of new arteries all tend to occur during the postnatal pulmonary development that lasts for weeks and months, and gradually exert an influence on the reduction of PVR and, consequently, SPAP[1]. In our study, only one case affected by PDA was observed in each group. As all the subjects were at term and revealed no effective factors for their arterial duct to be kept open[17,19], the prevalence proved to be very low in at-term neonates (approximately 2,000-2,500 live births)[18]. Of interest, although in our study, SPAP appeared to be higher in the IVF group than the control and the difference was significantly higher in the former, only two neonates were affected with mild pulmonary hypertension (systolic pressure of 37 and 38 mmHg) and two with pressure leveled at 36 mmHg. Due to the low prevalence of the case (approximately 2 per 1,000 live births), more investigations are needed to diagnose neonates affected with pulmonary hypertension.

Conclusion

In the current study that was about PAP in at-term IVF neonates based on a cross-sectional study, linear regression between SPAP and gestational age in the two groups illustrates a daily boost in the gestational age, and intrauterine life significantly impinging on the reduction of SPAP in postnatal period; it

follows that it seems to be unwise to give birth to IVF neonates too early. Additionally, the comparison of linear regression between SPAP and the neonatal age in both groups indicates that gradual decrease of the PAP in group 1 proves to be slower than in group 2 (-0.19 vs -0.25). In other words, the pulmonary artery wall thinning proceeds less gradually in group 1.

Further, our study regards IVF as an predisposing factor in the incidence of pulmonary arterial hypertension in neonates. Therefore, it is recommended that IVF neonates be monitored for pulmonary hypertension during the neonatal period to receive appropriate and timely treatment. However, more studies and larger sample sizes are needed to comprehensively address and capture the causes of pulmonary hypertension in IVF neonates.

Ethics

Ethics Committee Approval: This study was approved by the Ethical Committee of Yazd, Iran Yazd Cardiovascular Research Center (approval number: 814).

Informed Consent: Informed consent was obtained from the participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: M.R.A., Design: M.R.A., Data Collection or Processing: M.S., Analysis or Interpretation: S.M.N., M.S., Literature Search: S.D., Writing: M.R.A., Z.P.

Conflict of Interest: The authors report no conflict of interest.

Financial Disclosure: Authors have no financial interests about the research.

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Clinical Investigation / Araştırma

DOI: 10.4274/tjod.galenos.2020.26032

Turk J Obstet Gynecol 2020;17:84-9

Relation between uterine morphology and severity of primary dysmenorrhea

Primer dismenorenin şiddeti ile uterin morfoloji arasındaki ilişki

Şenol Şentürk

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Abstract

Objective: This study aimed to evaluate whether uterine dimensions including uterine volume, uterine shape, uterine length, cervix length, and cervix thickness measurements have a role in the severity of primary dysmenorrhea in virgin girls.

Materials and Methods: Enrollment included 90 virgin girls suffering from primary dysmenorrhea. The girls were divided into three groups according to the severity of dysmenorrhea, which was determined by the visual analog scale (VAS). Patients with VAS scores of 8-10 comprised the severe primary dysmenorrhea group (n=30), 4-7 the moderate primary dysmenorrhea group (n=30), and 1-3 the mild primary dysmenorrhea group (n=30). Uterine characteristics including uterine volume, uterine shape, uterine length, cervix length, and cervix thickness were measured by a high-resolution four-dimensional ultrasound device with real-time capacity. They were recorded to determine if they can be predictors of dysmenorrhea severity.

Results: Girls with severe primary dysmenorrhea were more likely to complain of midline pain as opposed to mild and moderate cases with lateral or diffuse pain. None of the uterine characteristics on ultrasonography examination were significant for predicting the severity of primary dysmenorrhea. There were no significant positive correlations between the dysmenorrhea severity and uterine corpus length, cervix length, and uterine volume degree. Any combination of the measured uterine features was not predictive for determining the severity of dysmenorrhea.

Conclusion: Ultrasonographic measurements of uterine dimensions in virgins have low accuracy for predicting the severity of pain in primary dysmenorrhea.

Keywords: Primary dysmenorrhea, pain, uterine dimensions, visual analog scale score, virgin

Öz

Amaç: Bu çalışmada primer dismenoreli virjin kızlarda uterin volüm, uterin şekil, uterin uzunluk, serviks uzunluğu ve serviks kalınlığı ölçümlerini içeren uterin boyutların dismenorenin şiddetinde rol alıp almadıklarını değerlendirmek amaçlandı.

Gereç ve Yöntemler: Primer dismenore şikayeti olan 90 virjin hastanın kayıtları alındı. Hastalar primer dismenore şiddetine göre vizüyel analog skala (VAS) ile belirlenen üç gruba ayrıldı. VAS skorları 8-10 arasında olan hastalar şiddetli primer dismenore grubu (n=30), VAS skorları 4-7 arasında olan hastalar orta derece primer dismenore grubu (n=30), VAS skorları 1-3 arasında olan hastalar ise hafif primer dismenore grubu (n=30) olarak kabul edildi. Uterin volüm, uterin şekil, uterin uzunluk, serviks uzunluğu ve serviks kalınlığını içeren uterin karakteristikler high-resolution 4 boyutlu real-time capacity ultrasonografi ile ölçüldü. Bu ölçüm sonuçları dismenorenin şiddetinde prediktor olup olmadıklarını öngörebilmek için birbirleriyle karşılaştırıldı.

Bulgular: Ultrasonografi muanelerinde ölçülen uterin karakteristiklerinden hiçbirisi primer dismenorenin şiddetini öngörmede anlamlı olmadığı tespit edildi. Uterus corpusunun uzunluğu, serviks uzunluğu ve uterin volüm ile dismenorenin şiddeti arasında anlamlı pozitif korelasyon tespit edilmedi. Uterin özelliklerin ölçümlerinin herhangi bir kombinasyonu dismenorenin şiddetini belirlemede prediktif değeri saptanmadı.

Sonuç: Primer dismenoreli virjin kızlarda uterin boyutların ultrasonografik ölçümleri dismenorede ağrının şiddetini öngörmede düşük kesinliğe sahiptir.

Anahtar Kelimeler: Primer dismenore, ağrı, uterin boyutlar, vizüyel analog skala skor, virjin

Introduction

Painful menstruation that is not associated with any pelvic pathology is considered primary dysmenorrhea. Although it is a highly prevalent and multifactorial clinical disorder in adolescent girls, the etiology and risk factors of primary dysmenorrhea are unclear[1]. Patients with primary dysmenorrhea were more sensitive to other chronic pain than

PRECIS: Uterine morphology and severity of primary dysmenorrhea.

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Received/Geliş Tarihi: 28.01.2020 **Accepted/Kabul Tarihi:** 09.03.2020

those who have none[2]. Subendometrial uterine contraction, sex steroids, local and systemic prostaglandin overproduction, and pain sensitivity may contribute to the clinical background of primary dysmenorrhea. Pain in primary dysmenorrhea is believed to be caused by uterine contractions, ischemia, and prostaglandins[2-4]. Likewise, it may be influenced by low body mass index, smoking, premature menarche, family history, prolonged menstrual flow, and psychological disorders[5,6]. In addition, pelvic pain prostaglandins may increase the contractions of bronchial, intestinal, and vascular smooth muscles, and as a result, they may be related to complaints of nausea, vomiting, and diarrhea that may be seen in primary dysmenorrhea[7,8].

The shapes and dimensions of the uterine corpus and cervix may play a role on the occurrence and severity of dysmenorrhea. One possible mechanism explaining the impact of uterine corpus and cervix length on dysmenorrhea severity is that elongated and thick cervix may pose a mechanical obstruction and/or prolong the menstrual flow, which results in more uterine contractions and eventually dysmenorrhea. The second possibility is based on an opinion that "the bigger the uterus, the more endometrial surface." This may increase the volume of menstrual blood in the uterine cavity, and the menstrual blood vacuation may come late, which may cause dysmenorrhea. The third possibility is that prolonged exposure of menstrual blood within the uterine cavity and cervical canal may increase the severity of primary dysmenorrhea and could be an etiological factor.

The number of studies evaluating the relationship between dysmenorrhea and uterine shape and diameters are small[9,10]. A significant relationship was found between dysmenorrhea severity and uterus corpus and cervix measurements in most of the studies. A recent study by Li et al.[11] showed that the presence of menorrhea and large uterine volume of more than 180 cm^3 was associated with moderatetosevere dysmenorrhea and urinary tract symptoms.

However, the small number of cases, the small size of the measured parameters, and the differences in the measurement methods necessitated new studies. Therefore, this study aimed to determine whether uterine dimensions such as uterine volume, uterine corpus, and cervical length measurements have a role in the severity of primary dysmenorrhea in virgins.

Materials and Methods

The study was conducted at the Recep Tayyip Erdogan University Department of Gynecology and Obstetrics with the permission of the Non-Invasive Clinical Research Ethics Board (approval number: 97/2017) between June and October 2017. Study participants included virgin adolescents aged 17 to 25 years who were referred to the gynecology clinic for complaints of dysmenorrhea. Written informed consent was obtained for each patient after they were explained about the study in detail.

Visual Analog Scale Scores and Participant Grouping

Study participants were selected from cases with regular menstrual periods suffering from primary dysmenorrhea who had no marriage or pregnancy history. Primary dysmenorrhea was defined as suprapubic pain that starts several hours before every menstrual bleeding or on the first day of menstruation and lasts a few hours after the culmination of vaginal bleeding. Pain may spread to the waist, abdominal area, and lateral regions. It peaks with maximum blood flow and continues for 48-72 h[12]. Visual analog scale (VAS) scores were used to determine dysmenorrhea severity[13]. A study used VAS scores to classify patients with primary dysmenorrhea[14]. Participants were then divided into the following three groups based on their level of reported pain: VAS scores of 8-10 comprised the severe primary dysmenorrhea group (n=30), 4-7 the moderate primary dysmenorrhea group (n=30), and 1-3 the mild primary dysmenorrhea group (n=30). For patients in the mild pain group, menstruation is painful but seldom inhibits normal activity, and analgesics are seldom required. Meanwhile, for patients in the moderate pain group, daily activity is affected, and analgesics are required, whereas in the severe pain group, the activity is inhibited, and they are unresponsive to analgesics. In addition to uterine volume, longitudinal and transverse axes of the uterine corpus and cervix were measured. Association between primary dysmenorrhea severity and uterine measurements were calculated.

The age, height, weight, and menarche age of all participants were recorded, and their body mass indices were calculated using the (body weight)/(height)^2 formula. Each patient's history of age of menarche, duration of menstrual cycle, period of menstrual cycle, family history of dysmenorrhea, and presence of clinical symptoms accompanying dysmenorrhea (nausea, diarrhea, waist and hip pain, abdominal pain, dizziness, skin rash, fatigue, and irritability) were recorded. Patients with the following pathologies causing secondary dysmenorrhea were excluded from the study: Uterine fibroids, endometriosis, hematometra or hematocolpos, adnexal masses (abscess, ovarian cyst, or hydrosalpinges), vaginal septum or atresia, uterine shape anomalies, pelvic surgery history, pelvic inflammatory disease, urinary or other infections, oral contraceptive or alcohol use and smoking, or nonsteroidal anti-inflammatory drug use in the last 3 days. Girls with premature or late puberty, polycystic ovary syndrome, systemic diseases, and retroverted uterus were also excluded.

Measurement of Uterine Characteristics

A high-resolution four-dimensional ultrasound device with real-time capacity and a 5-MHz (multi-frequency) transducer (G.E. Voluson 730 Pro 4D Color Doppler Device, USA) were used to measure uterine and cervix lengths. Ultrasonograpy (USG) was carried out in the early follicular phase of the menstrual cycle. The uterine dimensions including corpus and uterine lengths, cervix lengths, cervix thicknesses, uterine volumes,

and uterus length/cervix length, corpus length/cervix length, and cervix length/cervix thickness ratios of each participant were calculated and recorded as follows. After bladder filling, the uterine dimensions were measured by transabdominal USG in a supine position. First, the uterine dimensions were measured in gray-scale USG on transverse, longitudinal, and anteroposterior planes. While measuring the longitudinal dimension of the uterus, the fundus and cervix were observed on the same parasagittal plane, and the distance from the top of the fundus to the end of the cervix (AC) was recorded as the uterine length. On the same plane, the distance from the top of the fundus to the beginning of the cervix (AB) was measured and recorded as the uterine corpus length. The distance from the beginning of the cervix to the end of the cervix (BC) was used as the cervix length. The transducer was rotated by 90°, and the transvers diameter of the uterus (HI) was measured on the level of the cornual component. On the same plane, the fundus anteroposterior diameter (DE) was measured from the bulgiest part of the fundus, and the cervix anteroposterior (FG) that was measured on the cervical level was used as the cervix thickness (Figures 1, 2). Uterine volume was calculated by assuming that this organ was an ellipsoid with the formula *V*=D1×D2×D3×0.52 [D1= transverse diameter (HI), D2= anteroposterior diameter (DE), and D3= longitudinal diameter (AC)][15].

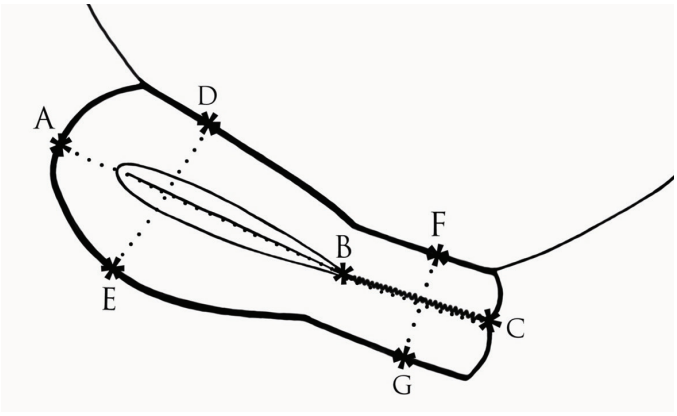

Figure 1. Longitudenal view of uterus during transabdominal ultrasound

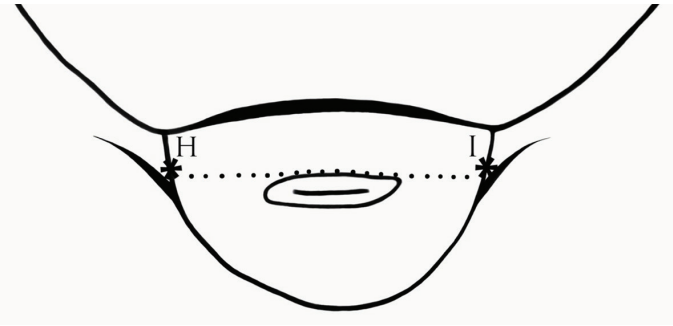

Figure 2. Transvers view of uterus during transabdominal ultrasound

Statistical Analysis

The Number Cruncher Statistical System 2007 (Kaysville, Utah, USA) software was used for the statistical analyses. While analyzing the quantitative data, in addition to descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, and maximum), One-Way analysis of variance was used to compare three or more groups that were normally distributed and the Kruskal-Wallis test for non-normally distributed groups. The qualitative data were compared using the Pearson chi-square and Fisher-Freeman-Halton tests. Significance was analyzed on the levels of $p<0.01$ and $p<0.05$.

Results

Demographic characteristics of each group are shown in Table 1. Both age and menarche age were similar in all groups ($p>0.05$). Girls with severe primary dysmenorrhea were more likely to complain of midline pain as opposed to mild and moderate cases with lateral or diffuse pain. None of the uterine characteristics on USG examination were significant for predicting primary dysmenorrhea severity. There were no significant positive correlations between primary dysmenorrhea severity and uterine corpus length, cervix length, and uterine volume. Any combination of the measured uterine features were not predictive for determining dysmenorrhea severity (Table 2). Suffering from nausea was found to be significantly higher in girls with severe pain than those in the mild and moderate pain groups ($p=0.001$ and 0.003, respectively). Significantly low waist and hip pain were noted in girls in the mild pain group compared with those in the moderate and severe pain groups ($p=0.001$ and 0.010, respectively). Likewise, fatigue and irritability in girls in the mild pain group were significantly lower than those in the severe pain group ($p=0.001$). The rates of encountering dizziness in girls in the mild pain group were significantly lower than those in the moderate and severe pain groups ($p=0.001$ and 0.001, respectively; Table 3).

Discussion

Primary dysmenorrhea is a prevalent problem accompanied by suprapubic pain without the presence of gynecological and pelvic organic diseases. The pathophysiology of primary dysmenorrhea has not yet been clearly explained. When the literature is reviewed, there is not much study investigating the effect of uterine length and volume on dysmenorrhea severity. However, a few studies have tried concluding the relation between uterine dimensions and pain severity by measuring only two markers including uterine or cervix length[9,10], although some only measured the uterocervical angle (UCA) and others evaluated the uterus and cervix length. Unlike other studies, in the current study, we evaluated many parameters, such as uterine and cervical lengths, uterine volume, and uterine and cervix thickness. Longitudinal and transverse axes of the uterine cervix were found to be higher in the severe dysmenorrhea

Table 1. Analysis of demographic characteristics based on pain scores

	All cases	Mild pain	Moderate pain	Severe pain	p
Mean ± standard deviation	20.43±4.13	21.43±4.79	19.58±2.96	20.32±4.37	
Age (years)	-	-	-	-	0.437[a]
Minimum-maximum	17-25	17-25	17-24	17-24	
Mean ± standard deviation	13.25±1.25	13.16±1.31	13.22±1.23	13.35±1.25	
Age of menarche (years)	-	-	-	-	0.838[d]
Minimum-maximum	11-16	11-16	11-16	11-16	
Mean ± standard deviation	23.42±13.32	22.13±3.75	22.09±3.19	25.99±22.45	
Body mass index (kg/m^2)	-	-	-	-	0.994[a]
Minimum-maximum	16.70-145.70	16.70–33.30	17.20–32.40	17.90-145.70	

[a]Kruskal-Wallis test, *p<0.05, **p<0.01

Table 2. Analysis of anatomic uterus dimensions based on pain score

	All cases	Mild pain	Moderate pain	Severe pain	p
Uterus lengths (mm)					
Minimum-maximum	47-96 (69.50)	47-96 (72.00)	55-95 (70.00)	54-91 (66.00)	0.338*
Mean ± standard deviation	70.93±10.33	72.63±11.55	71.41±10.36	68.80±8.93	
Cervix lengths (mm)					
Minimum-maximum	15-43 (28.50)	15-42 (28.50)	19-41 (29.00)	18-43 (27.00)	0.407*
Mean ± standard deviation	28.65±5.86	28.33±6.62	29.77±5.51	27.83±5.41	
Corpus lengths (mm)					
Minimum-maximum	28-64 (43.00)	28-62 (45.00)	29-64 (42.00)	32-57 (40.00)	0.133*
Mean ± standard deviation	42.28±6.83	44.30±6.85	41.64±7.38	40.96±5.96	
Thickness of cervix (mm)					
Minimum-maximum	13-30 (21.50)	14-30 (22.00)	13-30 (21.00)	17-29 (22.00)	0.825*
Mean ± standard deviation	21.80±3.36	21.56±3.35	22.00±3.82	22.06±2.95	
Ratio of uterus length/cervix length					
Minimum-maximum	1.91-4.13 (2.40)	2.00-4.13 (2.50)	1.91-3.47 (2.30)	2-3.44 (2.50)	0.124*
Mean ± standard deviation	2.52±0.37	2.63±0.42	2.43±0.35	2.51±0.33	
Ratio of corpus length/cervix length					
Minimum-maximum	0.91-3.13 (1.40)	1.00-3.13 (1.50)	0.91-2.47 (1.30)	1.00-2.44 (1.50)	0.124*
Mean ± standard deviation	1.52±0.37	1.63±0.42	1.43±0.35	1.51±0.33	
Ratio of cervix length/cervix thickness					
Minimum-maximum	0.86-2.15 (1.30)	0.86-2.10 (1.30)	0.86-2.15 (1.40)	0.90-2.05 (1.20)	0.256*
Mean ± standard deviation	1.32±0.26	1.31±0.25	1.38±0.29	1.27±0.24	
Volume of uterus (mm)					
Minimum-maximum	20.021-108.817 (49.085)	20.529-108.817 (49.559)	21.504-105.334 (51.018)	20.021-100.318 (45.864)	0.652*
Mean ± standard deviation	51.864.18±18.951.30	52.285.08±19.747.46	54.052.84±20.390.02	49.268.20±16.876.34	

*One-Way analysis of variance test, SD: Standard deviation, mm: millimeter

Table 3. Analysis of descriptive statistics based on pain scores

Clinical findings, n (%)	All cases	Mild pain	Moderate pain	Severe pain	p
Nausea	25 (27.20)	3 (10.00)	5 (16.10)	17 (54.80)	0.001[a**]
Diarrhea	14 (15.20)	2 (6.70)	5 (16.10)	7 (22.60)	0.240[a]
Abdominal pain	61 (66.30)	9 (30.00)	25 (80.60)	27 (87.10)	0.001[b**]
Waist-hip pain	58 (63.00)	11 (36.70)	25 (80.60)	22 (71.00)	0.001[b**]
Fatigue	52 (56.50)	10 (33.30)	18 (58.10)	24 (77.40)	0.002[b**]
İrritability	62 (67.40)	15 (50.00)	20 (64.50)	27 (87.10)	0.008[b**]
Dizziness	16 (17.40)	1 (3.30)	6 (19.40)	9 (29.00)	0.028[b*]
Skin rash	7 (7.60)	1 (3.30)	3 (9.70)	3 (9.70)	0.692[a]

[a]Fisher-Freeman-Halton test, [b]Pearson chi-square test. *p<0.05, **p<0.01

group than in the mild and moderate groups, but the difference between the groups failed to reach a statistically significant difference. In contrast to our findings, Zebitay et al.[10] showed longer cervical length and greater cervical volume in young virgin patients with dysmenorrhea. Dmitrovic et al.[16] found a positive correlation between uterine dimensions, endometrial thickness, and dysmenorrhea severity. The results of this study were not similar to those of Dmitrovic et al.[16]. This discordance may be because their control group was composed of patients without dysmenorrhea and the differences in the methods used in uterine and cervix measurements. In contrast to our study, previous studies mostly used transvaginal measurement methods.

A study conducted by Sahin et al.[9] has only tried to conclude dysmenorrheal severity by measuring the UCA. They showed that a narrow anterior UCA is associated with primary dysmenorrhea and disease severity. Contrary to this study, we did not measure UCA, although no significant correlation was found between the stenosis or width of the cervix and the severity of dysmenorrhea. Zebitay et al.[10] reported that the longitudinal and transverse axes of the uterine cervix, as well as its volume, were significantly higher in the dysmenorrhea group than the controls. They also showed a significant positive correlation between the severity of dysmenorrhea and the length of the cervical longitudinal and transverse axes and the volume of the uterine cervix. Our results are incompatible with the results of Zebitay et al.[10], and this discrepancy may result from differences in patient grouping as they only divided their sample into the severe dysmenorrhea and control groups. Their lack of mild and moderate groups may be the main cause of incompatibility. The most important limitation of our study is the absence of the control group. However, this limitation has been minimized because of the subgroup analysis.

In cases of primary dysmenorrhea, various complaints, especially complaints of abdominal, waist, or hip pain, nausea, vomiting, fatigue, irritability, dizziness, and anxiety affect quality of life. In our study, we also aimed to reveal the relationship between pain severity and these complaints in randomly selected cases. In our results, it was determined that the frequency of clinical symptoms such as nausea, fatigue, irritability, and dizziness increased in direct proportion to pain severity.

In this study, we tried to show the correlation between pain severity, clinical symptoms, and uterus dimensions. However, the results of the current study did not support the idea that the uterus dimensions affect dysmenorrheal pain severity. Although we found a positive significant relationship between severity of pain and rates of encountering clinical symptoms, we could not find any single or combined uterine parameters affecting pain severity.

Study Limitations

Our results may have been affected by the fact that the uterus dimensions of the participants in the study were within physiological limits. Measurement of uterine dimensions by abdominal USG is another important handicap, but virginity was the main reason we used this method. USG measurements combined with magnetic resonance imaging could provide more reliable results.

Conclusion

Despite several limitations, our study filled an important gap in the literature because this is the first study to evaluate the relationship between uterine dimensions and pain severity in a high number of participants.

Ethics

Ethics Committee Approval: The study was conducted at the Recep Tayyip Erdogan University Department of Gynecology and Obstetrics with the permission of the Non-Invasive Clinical Research Ethics Board (approval number: 97/2017).

Informed Consent: Written informed consent was obtained for each patient after they were explained about the study in detail.

Peer-review: Externally peer-reviewed.

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

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Clinical Investigation / Araştırma

DOI: 10.4274/tjod.galenos.2020.20727

Turk J Obstet Gynecol 2020;17:90-7

Is iodized salt efficient to overcome iodine deficiency in pregnants?

Gebelikte iyot eksikliğinin üstesinden gelmek için iyotlu tuz etkili mi?

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Abstract

Objective: Iodine is a trace element that synthesizes thyroid hormones necessary for optimal human growth and development. The relationship between dietary iodine intake and spot urinary iodine excretion in pregnant women has not been previously evaluated in Trabzon city, which is an endemic area of iodine deficiency in the Black Sea region of Turkey. This study aimed to evaluate the relationship between dietary iodine intake and urine iodine excretion in pregnant women.

Materials and Methods: This study enrolled 150 pregnant women aged between 19 and 45 years who applied to Clinic of Gynecology and Obstetrics in Trabzon. Spot urine specimens were taken, and dietary iodine intake data were collected using a food frequency questionnaire (FFQ) and 24-hours dietary recall (24-h DR) method.

Results: The median urinary iodine concentration (UIC) in the general specimen was 100.6 µg/L. Of the pregnant women, 80.0% had insufficient and 20.0% had sufficient iodine levels, according to UIC. Although total iodine-rich food intake determined by FFQ was sufficient in 20.7% (n=31) of participants, 24-h DR iodine intake was sufficient only 10.7% (n=16). A significant association between urinary iodine excretion and iodine intake was observed in both 24-h DR and FFQ intake estimates ($p<0.05$). The iodine intake values obtained in both 24-h DR and FFQ and the iodized salt effect were correlated with UIC in all models ($p<0.05$). Even though 96.0% of pregnant women used iodized salt, its effect on UIC was 15.2%.

Conclusion: Both methods indicate that the iodine intake of pregnant women might be insufficient in Trabzon area. Also, although iodized salt use is high in pregnant women in Trabzon, it is not enough to prevent iodine deficiency.

Keywords: Iodine deficiency, iodine intake, urinary iodine concentration, pregnant women

Öz

Amaç: İyot, optimal büyüme ve gelişme için gerekli olan tiroid hormonlarının sentezinde rol oynayan bir eser elementtir. Gebe kadınların diyet ile iyot alımı ve spot idrar iyot atımı arasındaki ilişki, Türkiye'nin Doğu Karadeniz Bölgesi'nde Endemik Guatr Bölgesi olarak bilinen Trabzon'da daha önce değerlendirilmemiştir. Bu nedenle çalışmanın amacı, gebe kadınların diyet iyot alımı ve idrar iyot atılımı arasındaki ilişkinin değerlendirilmesidir.

Gereç ve Yöntemler: Çalışmaya Trabzon'da Kadın Hastalıkları ve Doğum Kliniği'ne başvuran 19-45 yaş arası 150 gebe kadın alınmıştır. Spot idrar örnekleri alınmıştır ve besin tüketim sıklığı anketi (FFQ) ve 24 saatlik diyet hatırlama yöntemi (24 saatlik DR) ile diyet iyot alım verileri toplanmıştır.

Bulgular: Genel örneklemin medyan idrar atım konsantrasyonu 100,6 µg/L'dir. Gebelerin %80'i yetersiz, %20'si idrar iyot konsantrasyonuna göre yeterli iyot düzeyine sahiptir. Toplam iyot yönünden zengin besin alımı FFQ yöntemiyle katılımcıların %20,7'sinde (n=31) yeterliyken, 24 saat DR yöntemiyle sadece %10,7'sinde (n=16) yeterlidir. Hem 24 saatlik DR hem de FFQ alım tahminlerinde idrar iyot atımı ve iyot alımı arasında anlamlı bir ilişki olduğu gözlemlenmiştir ($p<0,05$). Hem 24 saatlik DR hem de FFQ ile elde edilen iyot alım değerlerinin ve iyotlu tuzun tüm modellerde idrar iyot konsantrasyonu ile korele olduğu bulunmuştur ($p<0,05$). Ayrıca, gebelerin %96'sı iyotlu tuz kullansa da iyotlu tuzun idrar iyot konsantrasyonu üzerine etkisi %15,2 olarak belirlenmiştir.

Sonuç: Her iki yöntem de gebelerde iyot alımının Trabzon Bölgesi'nde yetersiz olduğunu göstermektedir. Ayrıca, Trabzon'daki gebe kadınlarda iyotlu tuz kullanımı yüksek olmasına rağmen, iyot eksikliğini önlemek için sadece iyotlu tuz kullanmanın yeterli olmadığı saptanmıştır.

Anahtar Kelimeler: İyot eksikliği, iyot alımı, idrar iyot konsantrasyonu, gebe kadınlar

PRECIS: The use of iodized salt is high in pregnant women, but consuming iodized salt alone could not prevent iodine deficiency.

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Received/Geliş Tarihi: 15.12.2019 **Accepted/Kabul Tarihi:** 24.04.2020

Introduction

Iodine, which is a trace element of the human body (15-20 mg), ensures the optimal growth and development of a newborn. The sufficiency of thyroid hormones [thyroxine (T4) and triiodothyronine (T3)], particularly during pregnancy, is vital for the cerebral and neurological development of the fetus[1]. Therefore, iodine-rich dietary is crucial during pregnancy, and milk and fish are the leading supplies of iodine in meals. Besides, iodized salt is a strategy developed in many societies to control and prevent iodine deficiency[2].

Measuring urinary iodine concentration (UIC) is recommended to assess the dietary iodine intake during pregnancy. Concerning the urinary excretion of iodine in pregnant women, the World Health Organization (WHO) defines 150-249 µg/L as "sufficient" and <150 µg/L as "insufficient[3]." The renal clearance of iodine increases around 30-50% during pregnancy, which causes iodine deficiency, leading to an increase in the daily iodine need of pregnant women compared with normal adults. Moreover, the increased renal clearance of iodine and concurrent and continuous increase in the production of thyroid hormone stimulate the thyroid, as well. The increased level of stimulation during pregnancy is more common in areas suffering from iodine deficiency, which leads to abortion and stillbirth[1].

Turkey has been listed among the countries with sufficient amount of iodine, due to the addition of iodine to salt in recent years[4]. However, a research performed in 2011-2012 in Trabzon, a city reported having sufficient iodine intake level, assessed UIC in a large group of pregnant women (n=864) and found 77.9% iodine deficiency[5]. Most of the pregnant women who live in areas with iodine deficiency or with low iodine intake can attain the sufficient level by either taking iodine supplements or consuming iodine-rich food[6]. However, in the endemic region of Trabzon, dietary iodine intake of pregnant women has not been evaluated so far. This study distinguishes from previous reports by investigating iodine intake with both food frequency questionnaire (FFQ) and 24-hours (24-h) recalls. Therefore, this study aimed to assess the dietary iodine intake and urinary iodine excretion of pregnant women aged between 19 and 45 years in Trabzon, where there is an endemic area of iodine deficiency, and to detect the reliability of both methods by comparing UIC.

Materials and Methods

Study Design

This research is a descriptive, cross-sectional study. The number of participants recruited was calculated with reference to the study by Alvarez-Pedrerol et al.[7] According to the results of different power analyses among two independent groups (milk intake frequency and UIC), a minimum of 130 individuals were necessary to achieve a type 1 error (α)= 0.05, effect size of 0.5, and power of 80%. The study recruited 150 pregnant women between 19 and 45 years old. A central state hospital was chosen as the research place; hence, we could assess individuals from various socioeconomic degrees. Approval of the Ethics Committee was received from Ankara University Faculty of Medicine (approval number: 11-478-16, date: 23.06.2016), and the Helsinki Declaration principles were followed in the research. Before the application of the survey, each participant was informed about the contents of the research, and they were asked to sign the informed consent forms, indicating that they voluntarily agreed to participate in the research.

The research participants were selected among pregnant women aged between 19 and 45 years, with no thyroid disease history or thyroid treatment medications. Research data were collected using a questionnaire form and face-to face interviews. The intelligibility of the questions was tested with 10 women, and the survey form was finalized after the necessary corrections were made. The survey form included general information about the pregnant women (e.g., age, education level, time passed since previous delivery, and prenatal nutritional support), their iodine level intake through food, and their iodized salt consumption behaviors. In addition, spot urine specimens were taken from the women to assess the urinary iodine level.

Dietary Iodine Intake

The FFQ, which consisted of 50 semi-quantative items, was used to assess only iodine-rich and possible goitrogenic food consumption in the last 1 month. The questionnaire is an adapted version of the FFQ developed by Willett et al.[8], and it has already been used and validated in the general population in Turkey[9]. The frequency of food and iodine salt intake was evaluated per day, week, or month. The "A Photographic Atlas of Food Portion Sizes" developed for Turkey was used to correctly assess the amount of food consumed[10]. Data were collected regarding women's consumption of seafood (processed fish, lean fish, fatty fish, and shellfish), meat and poultry (processed meat, red meat, and poultry), possible goitrogenic food (cruciferous vegetables; cabbage, kale, kohlrabi, cauliflower, spinach, radish, broccoli, brussel sprouts, turnips, and sweet potatoes), egg, milk, and other dairy products (cheese, yogurt, and butter). Responses were divided into weekly categories for seafood, meat, poultry, and goitrogenic foods and daily for milk, yogurt/ayran, cheese, and egg. Milk, yogurt/ayran, meat, and poultry intakes were divided into quartiles. Other food intake was taken according to the recommended portion in the Turkey Dietary Guideline[11].

Iodine salt intake was reported based on standard referent portion sizes as pieces and spoons. The WHO[3] and TUBER[11] recommend less than 6 g (approximately 2400 mg) of iodized salt consumption per day for adults. In this study, 6 g/day was considered the cut-off value for salt intake.

Total iodine-rich food intake with FFQ and 24-h dietary recall (24-h DR) was calculated using iodine content in the food indicated in the United States Department of Agriculture (USDA) food composition database[12].Only some types of fish,

shellfish, and iodized salt were calculated from the Turkish food composition database[13]. According to the WHO, the dietary intake of iodine in pregnant women was evaluated as "≤250 µg/100 g insufficient" and "≥250 µg/100 g sufficient[3]."

Laboratory Analysis

Spot urine specimens were collected from the pregnant women who agreed to participate in the research. Urine specimens were first put into medium flow urine deionized plastic containers and then into two tubes of 2 mL deiodized capped tubes. The specimens were delivered to the biochemistry laboratory of the hospital on the same day, and all urine specimens were stored at -20 ºC for 2 weeks in a deep freezer until the day of analysis. Urine samples were centrifuged for 3 min at 1500 rpm in a Hettich Micro 200R centrifuge before the study. The resulting supernatants were collected, and the urine iodine level was measured in the biochemistry laboratory by calorimetric method, which depends on the Sandell-Kolthoff reaction using the arsenic acid solution. Urine iodine levels were given in µg/L. Urine iodine levels of the pregnant women were assessed as determined by the WHO, and the assumptions were accepted as follows: "<150 µg/L insufficient" and "≥150 µg/L sufficient."

Statistical Analysis

Statistical Package for the Social Sciences 22.0 package program was used to evaluate the data. UIC, dietary intake of most nutrients, and food groups were not normally distributed. The median and 95% reliability range values are presented. Mann-Whitney U test was used to assess the UICs and total iodine-rich food intake between the two groups that did not display a normal distribution, and Kruskal-Wallis variance analysis to evaluate the UICs and total iodine-rich food intake among the three groups. Pearson's correlation coefficients were used to examine the associations between UIC and total-iodine rich food intake with FFQ and 24-h DR. Factors that may be associated with UIC (age groups, trimester, iodized salt intake, total iodine-rich food intake, and 24-h DR iodine intake) were evaluated with linear regression analysis. In all statistical tests, the range of reliability was accepted as 95.0% and evaluated at significance level of $p<0.05$.

Results

The sociodemographic characteristics of pregnant women according to UIC and their total iodine-rich food intake are shown in Table 1. The median UIC in the general specimen was 100.6 (range: 22.7-483.0) µg/L. The mean age of the pregnant women was 28.6 (between ages 19-42) years, and the UIC and iodine-rich food intake of the pregnant women at 19-25 years of age was lower than the other age groups, but there was no significant difference ($p>0.05$). Both UIC and iodine-rich food intake were significantly higher in the first and second trimesters than in the third trimester ($p<0.05$). However, the level of education, number of pregnancies, and region of residence did not significantly differ between UIC and iodine-rich food intake ($p>0.05$).

UIC levels with food consumption of the pregnant women are provided in Table 2. While 60.7% of the pregnant women participating in the research reported that they never drank milk, the women consuming more than 190 mL of milk per day had a median UIC of 93.7 µg/L, which indicates that there is no statistically significant difference ($p>0.05$). While the women consuming more than one serving of white cheese daily had a high median UIC compared with those consuming less than one serving, the difference was not statistically significant ($p>0.05$). The difference between meat, poultry, and fish consumption and the UIC was found to be statistically insignificant. Similarly, daily yogurt/ayran and egg intakes were not significant with UIC ($p>0.05$). Of the pregnant women, 96.0% were consuming iodized salt, and those who consumed more than 6 g of iodized salt every day were found to have a significantly higher median UIC than those who did not ($p<0.01$). It was determined that the participants with sufficient iodine-rich food intake were significantly higher than those with insufficient UIC levels ($p<0.01$).

The correlation between UIC and total iodine-rich food intake of pregnant women are shown in Figure 1. According to the WHO criteria, 80.0% of the pregnant women had insufficient and 20.0% had sufficient iodine levels according to UIC (1.3% of them had high UICs of ≥250 µg/L). Although total iodine-rich food intake determined by FFQ was sufficient in 20.7% (n=31) of participants, 24-h DR iodine intake was sufficient only in 10.7% (n=16). There was a strong positive correlation between FFQ total iodine-rich food intake and UIC ($r=0.880$, $p<0.001$). Similarly, 24-h DR iodine intake had a significant positive correlation with the UIC ($r=0.560$, $p<0.001$).

When factors that could affect UIC (age group, trimester, iodized salt intake, FFQ iodine intake, and 24-h DR iodine intake) were evaluated with linear regression analysis, all models were deemed important for UIC (R^2= 0.872, 0.872, and 0.871, respectively, $p<0.05$). It was determined that age groups and trimester were not related to UIC in Model I ($p>0.05$), but total iodine-rich food determined by FFQ, iodized salt, and 24-h DR iodine intake affected all models for the UIC ($p<0.05$). When Model III was analyzed, it was found that every 1-unit increase in iodized salt consumption affects UIC by 15.2%, whereas the FFQ iodine intake affects by 77.0%. Unlike FFQ iodine intake, the effect of iodine intake on UIC was less (7.1%) with a 24-h DR (Table 3).

Discussion

UIC is deemed to be a good indicator, reflecting the recent level of iodine in pregnant women[14]. We found that pregnant women living in Trabzon province of the Black Sea region of Turkey may have insufficient amount of iodine, according to the UIC criteria. Furthermore, a significant association between urinary iodine excretion and iodine intake was observed in

Table 1. Urine iodine concentration (µg) and total iodine-rich food intake (mcg) with food frequency questionnaire according to sociodemographic characteristics

Feature	Urine iodine concentration (µg)			Iodine-rich food intake (mcg)		
	n (%)	Median (IQR)	p	n (%)	Median (IQR)	p
Age (years)						
19-25	55 (36.7)	89.7 (90.0-114.9)		55 (36.7)	201.9 (195.3-222.6)	
26-31	49 (32.7)	101.3 (92.1-119.2)	0.592	49 (32.7)	205.9 (204.5-226.7)	0.392
≥32	46 (30.7)	105.0 (98.2-143.1)		46 (30.7)	213.5 (205.9-255.0)	
Education level						
Primary	67 (44.7)	101.4 (70.0-129.4)		67 (44.7)	201.6 (206.2-227.6)	
Secondary	47 (31.3)	102.4 (74.8-156.5)	0.188	47 (31.3)	218.4 (207.2-251.1)	0.276
Higher	36 (24.0)	85.3 (56.0-128.8)		36 (24.0)	202.8 (183.5-225.0)	
Region of residence						
Village	37 (24.7)	102.4 (73.3-133.7)		37 (24.7)	201.6 (200.1-238.1)	
Country	89 (59.3)	90.1 (67.4-146.0)	0.765	89 (59.3)	205.9 (202.7-224.5)	0.810
City	24 (16.0)	105.2 (69.7-127.6)		24 (16.0)	214.2 (194.4-266.0)	
Number of pregnancies						
1	39 (26.0)	90.1 (66.5-147.5)		39 (26.0)	208.0 (198.8-247.8)	
2	59 (39.3)	105.3 (78.0-128.9)	0.788	59 (39.3)	205.9 (198.8-224.6)	0.915
≥3	52 (34.7)	100.6 (68.4-137.7)		52 (34.7)	205.8 (204.4-236.2)	
Trimester[a]						
First and second	81 (54.0)	107.8 (104.5-134.1)	**0.049***	81 (54.0)	218.6 (214.7-243.0)	**0.016***
Third	69 (46.0)	88.0 (87.4-106.8)		69 (46.0)	197.8 (192.3-216.9)	

Kruskal-Wallis test was used for statistical analysis, [a]Mann-Whitney U test, *p<0.05
IQR: Interquartile range, UIC: Urine iodine concentration

both 24-h DR and FFQ intake estimates. In this research, as reported in previous studies held in Turkey, it was determined that pregnant women failed to meet their increasing iodine need. This may have a potential negative effect on fetal brain development[5].

In studies conducted with small samples taken from pregnant women living in different areas of Turkey, the UIC level varied from 77.4 to 149.7 µg/L[15-18]. In studies conducted on iodine deficiency (80% iodine deficiency), the level was found to change between 49.6% and 100%[5,15-18], similar to this research. Previous studies indicate that in areas where iodine intake has become sufficient, iodine deficiency was still a serious problem for pregnant women.

Although Trabzon city center had previously been an endemic area, it was sufficient in terms of median UIC in school-aged children. However, UIC levels of pregnant woman in their first and second trimesters were higher than in the third trimester. Similarly, studies conducted with larger specimens also supports these results[5,15]. However, there are some other studies reporting that UIC increased as gestational weeks have passed[17,18]. As the results of this research showed lower median UIC levels in pregnant women as opposed to other studies, it is considered that as the gestational weeks pass, the amount of iodine to be transferred to the fetus will increase as well, decreasing the urinary iodine excretion. Besides, decreased iodine intake of pregnant women may lead to insufficiency as the trimester increases.

The pregnancy period is a unique process that can be affected by several factors. In this research, it was found that the level of median UIC increased as the age of the mother increased (p>0.05). This may occur due to two reasons. First, older women may consume more iodine-rich foods as in this study, or urinary creatine excretion might be decreasing as one ages, which is not evaluated in this research. Here, dietary iodine intake was shown increase with age (89.7, 205.9, and 213.5 µg/L for ages 19-25, 26-31, and ≥32 years; p>0.05). According to the findings of the Adult National Diet and Nutrition Survey, dietary iodine intake increases with age, and elder women have significantly higher iodine intake than young women[19].

The use of iodized salt is reported to be the easiest, cheapest, and most effective method in the prevention of iodine deficiency in a society. According to the findings of the Demographic and

Table 2. Urine iodine concentration (µg) according to food consumption

Food group	Urinary iodine concentration (µg/g)				
	n	%	Median	IQR	p
Daily milk intake[a] (mL)					
None	91	60.7	105.3	70.0-134.1	0.679
<120	22	14.7	76.7	56.1-154.8	
120-190	21	14.0	81.0	69.2-140.4	
>190	16	10.6	93.7	81.5-119.8	
Daily yogurt/ayran[a] (g)					
None	45	30.0	83.4	64.4-138.4	0.507
<150	44	29.3	105.3	75.8-153.3	
150-210	30	20.0	105.8	69.3-133.3	
>210	31	20.7	89.1	69.9-139.5	
Daily cheese intake[b]					
≤1 serving (30 g)	64	42.7	85.8	67.4-128.5	0.062
>1 serving (30 g)	86	57.3	105.3	72.9-151.4	
Lean fish (week)[a]					
None	76	50.7	99.0	70.0-129.2	0.313
≤1 serving (90 g)	45	30.0	104.4	68.0-149.3	
>1 serving (90 g)	29	19.3	101.3	66.5-148.3	
Fatty fish (week)[a]					
None	41	27.3	97.9	69.3-135.9	0.717
≤1 serving (150 g)	56	37.3	93.7	68.1-143.6	
>1 serving (150 g)	53	35.4	101.3	69.0-133.7	
Daily egg intake[b]					
≤1 serving (60g)	70	46.0	106.1	67.7-145.9	0.322
>1 serving (60 g)	62	42.0	87.0	68.4-127.6	
Meat and poultry intake/week[a] (g)					
<150	66	44.0	106.2	70.0-146.3	0.065
150-350	49	32.7	100.2	70.8-141.2	
>350	35	23.3	81.4	66.5-107.8	
Goitrogen intake[b]					
≤1 serving (150 g)	98	43.3	89.7	66.9-139.1	0.288
>1 serving (150 g)	52	34.7	96.4	79.0-141.8	
Iodized salt use[b]					
Yes	144	96.0	100.6	69.3-139.2	0.871
No	6	4.0	88.9	63.2-148.0	
Daily iodized salt intake[b] (g)					
≤6	60	56.0	78.1	62.1-102.1	**0.001***
>6	84	40.0	141.1	106.7-174.9	
Total iodine-rich food intake[a]					
Insufficient (≤250 mcg)	119	79.3	196.7	190.0-203.1	**0.001***
Sufficient (≥250 mcg)	31	20.7	287.5	276.1-321.9	

[a]Kruskal-Wallis test was used for statistical analysis, [b]Mann-Whitney U test, *p<0.01
IQR: Interquartile range, UIC: Urine iodine concentration

Table 3. Urine iodine concentration (µg) linear regression analysis

Variables	β	OR	t	p
Model I				
Age groups[a]	-0.032	-6.466 to 1.988	-1.047	0.297
Trimester	-0.036	-10.960 to 2.787	-1.175	0.242
Iodized salt intake (g)	0.150	1.080 to 4.848	3.110	**0.002****
FFQ iodine intake (mcg)	0.770	0.685 to 0.909	14.072	0.001**
24-hours iodine intake recall (mcg)	0.078	0.005 to 0.146	2.127	**0.035***
R^2: 0.872				
Model II				
Trimester[b]	-0.038	-11.234 to 2.472	-1.264	0.208
Iodized salt intake (g)	0.150	1.077 to 4.846	-3.107	**0.002****
FFQ iodine intake (mcg)	0.764	0.680 to 0.903	14.032	**0.001****
24-hours iodine intake recall (mcg)	0.076	0.004 to 0.145	2.090	**0.038***
R^2: 0.872				
Model III				
Iodized salt intake (g)	0.152	1.130 to 4.903	3.161	**0.002****
FFQ iodine intake (mcg)	0.770	0.685 to 0.908	14.142	**0.001****
24-hours iodine intake recall (mcg)	0.071	-0.001 to 0.140	1.959	**0.05***
R^2: 0.871				

[a]Descriptions of age status were "0", "1" and "2" for ages 19-25, 26-31, and ≥32 years, [b]Descriptions of trimester were "0" for first and second trimesters and "1" for third trimester
*p<0.05 **p<0.01
OR: Odds ratio, FFQ: Food frequency questionnaire, UIC: Urine iodine concentration

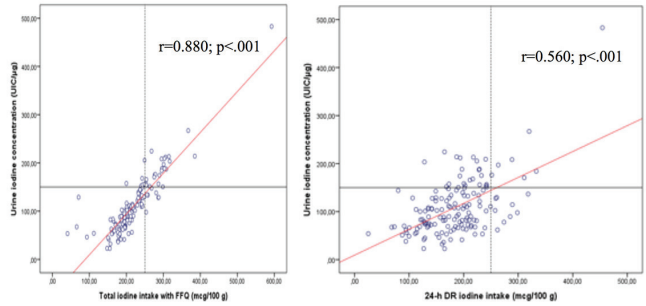

Figure 1. Correlation between urinary iodine concentration (µg/mL), total iodine intake with food frequency questionnaire, and 24-hours dietary recall iodine intake (mcg/100 g)

Health Survey in Turkey[20], although the use of iodized salt in a household was 70.2% in 2003, it increased to 85.3% in the 2008 Demographic and Health Survey[21]. In this research, 96.0% of pregnant women reported that they consume iodized salt, and the median urinary iodine excretion of pregnant

women consuming iodized salt more than 6 g was significantly higher ($p<0.05$). Therefore, sole consumption of iodized salt seems to be insufficient (79.3%) to fulfill the increased iodine need in pregnancy. A research conducted in Albania reported that eventhough 99.6% of pregnant women (n=365) had consumed iodized salt for 11 years in a prophylaxis program, the median UIC was still 85 µg/L[22]. The quality and level of iodine became more important following the extensive options of iodized salt in the market. Recently, the amount of iodine labeled on the package of salts was reported to be different from the actual amount of iodine available. This difference may arise due to iodine losses, illegal production or lack of quality control, and bad packaging or post-packaging distribution problems[23]. Furthermore, consuming more than 6 g of iodized salt to achieve the sufficient level of UIC may increase the risk of certain diseases (pre-eclampsia, edema, hypertension, etc) in pregnant women.

Although iodized salt consumption has increased in Turkey recently, iodine deficiency is still a problem for pregnant women even in metropolitan cities such as Ankara and İstanbul[17,18].

Relevant studies conducted in Europe and New Zealand have shown that women with iodine supplement intake had significantly higher UIC[24]. Here, all the participating pregnant women reported that they were not receiving iodine supplements. Iodine deficiency was detected despite the high rate of iodized salt consumption. Thus, reviewing the findings of other studies, adding a 150 µg elementary iodine containing a multivitamin tablet to the diet, in addition to iodized salt use, can be advised for pregnant women living in Turkey[25,26].

Consumption of food that are low in iodine leads to iodine deficiency in pregnancy[27]. In a study conducted in Italy, cow's milk was found to be a good source of iodine, and iodine supplements were recommended for those who did not consume milk[28]. Another study in the UK assessed the 24-h iodine excretion of those consuming more milk, eggs, and seafood and found a significantly higher iodine excretion. However, milk and iodine supplement intake in pregnant women is reported to be a more important indicator of iodine levels in pregnant women[2]. This study found a higher median UIC of pregnant women consuming more than 190 mL milk per day ($p>0.05$). As milk containers are not contaminated with iodophors in our country, unlike in other studies, it was thought that there was no relationship between milk consumption and urinary iodine excretion.

In our study, we observed restricted effect of fish intake on UIC. Similarly, it was reported that fish/seafood intake had no significant influence on 24-h urinary iodine excretion in Norway[29]. Iodine content of fish and seafood is known to be high, but their contribution to the overall dietary iodine intake is mild unless consumed every day[1,30].

Excessive intake of goitrogens in food prevents iodine from bonding with the thyroid hormone precursor, tyrosine, and suppresses T4 secretion[1]. Bath et al.[2] reported no significant relationship between goitrogenic food consumption and UIC. Also in this research, no significant difference was found between goitrogenic food and UIC levels. The amount of iodine in food may change depending on the season and the iodine level in soil. The research was conducted in summer, which was not the season for growing goitrogenic food such as black cabbage, radish, and turnips, which might have affected the UIC.

As more than 90% of dietary iodine is excreted in the urine by the kidneys, the most appropriate indicator reflecting iodine intake is urinary iodine excretion[1]. Urinary iodine excretion varies within the day and peaks after the main meals. In this study, UIC was more closely correlated with FFQ (total iodine-rich food) than with 24-h DR iodine intake estimates. Nevertheless, Brantsaeter et al.[29] reported a higher corelation between UIC and 24-h DR than FFQ iodine intake estimates.

Study Limitations

First, this was a cross-sectional study, so the study design may biased the results.

Furthermore, the small sample size may not reflect the situation in all pregnant women in the region. We are aware that there are limitations of using single-spot urine specimens. UIC alters throughout a day so that would be a more precise indicator to collect a 24-h urine specimen or multiple samples in different hours of a day[30]. However, 24-h urine specimens are inconvenient for the participants and difficult to collect accurately, and that was not possible to obtain several urine specimens. The amount of iodine in food is affected by various factors (geography and climatic conditions). Therefore, collecting the data of the study only in summer months might have caused an alteration in the results. USDA data have been used because of the unknown iodine content in food (excluding some fish types, shellfish, and iodine salt) in Turkey. The iodine content of food grown in each country is different[1]. Future studies are suggested to define iodine content of food in Turkey. To our knowledge, this study separates from the previous ones as being the first to compare UIC with two dietary iodine intake record methods (FFQ and 24-h DR).

Conclusion

In Trabzon, iodine deficiency was observed in pregnant women. Although other studies determined milk and iodine supplement intake as the best indicators to assess the iodine level in pregnant women, milk had no significant effect on the iodine level in this study. As recommended by the current world health policies, consuming two to three servings of milk per day and one to two servings of fish per week would provide a sufficient amount of iodine support. In Turkey, the amount of iodine in food can be increased by adding iodine to such food. Moreover, consuming iodized salt alone could not prevent iodine deficiency. Therefore, addition of iodine to vitamin-mineral supplements during the prenatal and pregnancy periods may improve iodine

levels. Iodine deficiency in pregnant women still seems to be a major public health problem in certain cities of Turkey, and there is no comprehensive epidemiological study comparing dietary iodine intake and urinary iodine excretion in pregnant women.

Acknowledgements: We are grateful to the pregnant women for their participation in this study and to the funders (Ankara University In Tranining Program) for the financial support.

Ethics

Ethics Committee Approval: Approval of the Ethics Committee was received from Ankara University Faculty of Medicine (approval number: 11-478-16 date: 23.06.2016), and the Helsinki Declaration principles were followed in the research.

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

Author Contributions

Concept: N.N.A.Ç., N.B.A., Design: N.N.A.Ç, A.Ö.Ö., Data Collection or Processing: Analysis or Interpretation: N.N.A.Ç., N.B.A., A.Ö.Ö., Literature Search: N.N.A.Ç., N.B.A., A.Ö.Ö., Writing: N.N.A.Ç., N.B.A., A.Ö.Ö.

Conflict of Interest: The authors declare no conflicts of interest.

Financial Disclosure: Urine samples were analyzed in the AnkaLab laboratory in Ankara, and the funding of the study was provided by Ankara University Academician Training Program Grant. The funders had no role in the design, analysis, or writing of this article.

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Clinical Investigation / Araştırma

DOI: 10.4274/tjod.galenos.2020.81592

Turk J Obstet Gynecol 2020;17:98-101

Evaluation of first-trimester neutrophil-lymphocyte ratio and platelet-lymphocyte ratio values in pregnancies complicated by intrauterine growth retardation

İntrauterin büyüme geriliği ile komplike olan gebeliklerde ilk trimester nötrofil-lenfosit oranı ve platelet-lenfosit oranının değerlendirilmesi

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Abstract

Objective: The objective of this study is to compare the first-trimester hemogram parameters [neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR)] of pregnant women complicated by intrauterine growth retardation (IUGR) and normal pregnant women.

Materials and Methods: We retrospectively evaluated the medical records of pregnant women (n=50) complicated with IUGR and pregnant women in the control group (n=50).

Results: The first-trimester NLR and PLR values of the pregnant women complicated by IUGR were 6.59±1.12 and 117.2±16.00, respectively. The first-trimester NLR and PLR values of the pregnant women in the control group were 2.84±0.55 and 112.80±13.01, respectively. There was a statistically significant difference between the two groups with respect to NLR (p<0.001).

Conclusion: Pregnancies complicated by IUGR have high neonatal mortality and morbidity rates. Therefore, the early diagnosis of disease and appropriate management are extremely crucial for both fetal and maternal prognoses. High NLR values in the first trimester may contribute to the early diagnosis of IUGR.

Keywords: Intrauterine fetal growth retardation, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio

Öz

Amaç: İntrauterin gelişme geriliği (IUGR) olan ve olmayan gebeliklerde, ilk trimester hemogram parametrelerini [nötrofil lenfosit oranı (NLR) ve platelet lenfosit oranı (PLR)] karşılaştırmayı amaçladık.

Gereç ve Yöntemler: Bu çalışmada IUGR olan (n=50) gebeler ve kontrol grubundaki gebelerin verileri (n=50) retrospektif olarak değerlendirildi.

Bulgular: IUGR ile komplike olan gebelerin ilk trimester NLO ve PLO değerleri sırasıyla 6,59±1,12 ve 117,2±16,00 olarak bulunmuştur. Kontrol grubundaki gebelerin ilk trimester NLO ve PLO değerleri sırasıyla 2,84±16,00 ve 112,80±13,01 olarak bulundu. NLO değerleri için 2 grup arasında istatistiksel olarak fark saptandı (p<0,001).

Sonuç: IUGR ile komplike olan gebeliklerde yenidoğan mortalitesi ve morbiditesi yüksektir. Bu nedenle, hastalığın erken teşhisi ve uygun tedavi hem fetal hem de maternal prognoz için son derece önemlidir. İlk trimesterdeki yüksek NLR değerleri IUGR tanısının erken dönemde konulmasına katkıda bulunabilir.

Anahtar Kelimeler: Gebelik, intrauterin gelişme geriliği, ilk trimester, nötrofil lenfosit oranı, platelet lenfosit oranı, hemogram parametreleri

PRECIS: Harun Egemen Tolunay's article, "Evaluation of first-trimester neutrophil-lymphocyte ratio and platelet-lymphocyte ratio values in pregnancies complicated by intrauterine growth retardation (2020)", analyses the predictivity of neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in intrauterine growth retardation.

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Received/Geliş Tarihi: 08.01.2020 **Accepted/Kabul Tarihi:** 05.03.2020

Introduction

Intrauterine growth retardation (IUGR) occurs when the fetus fails to reach its growth potential because of genetic and environmental factors. Sonography-based diagnosis defines IUGR as the condition in which the fetal weight is below the tenth percentile. IUGR is the most common cause of perinatal deaths after prematurity. Studies have reported that IUGR is observed in nearly 7-10% of all the pregnancies. There has been an increased risk of neonatal morbidity and mortality in pregnancies complicated by IUGR. The diagnosis of IUGR is usually based upon ultrasonographic assessment[1-3].

One of the most important objectives of obstetric follow-up is to identify the patients at risk for perinatal problems. The early recognition of this disease and early treatment interventions are very crucial in reducing the rates of morbidity and mortality in IUGR. Moreover, the diagnosis of disease and appropriate management are extremely important for both fetal and maternal prognoses[4,5].

Complete blood count [(CBC) or hemogram] is a frequently used basic laboratory test. White blood cell (WBC) count, red blood cell count, and platelet counts are some of the parameters used in this simple test. As an inexpensive and widely available marker in clinical usage, neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) have been proposed in the different areas of obstetrics and gynecology medical practice[6-9]. The purpose of this study is to evaluate the first-trimester NLR and PLR values in pregnant women complicated by IUGR and pregnant women of the control group. This study also evaluates fetal growth in both these groups.

Materials and Methods

We retrospectively reviewed the medical records of the study participants in the University of Health Sciences Turkey, Etlik Zübeyde Hanım Maternity and Women's Health Teaching and Research Hospital, Clinic of Perinatology. We included a total of 100 patients (50 pregnant women with IUGR and 50 healthy pregnant women) who were admitted to our hospital. Fetuses with an estimated fetal weight of less than tenth percentile in the ultrasonographic evaluation were diagnosed with IUGR. We randomly selected the control group from the healthy pregnant women who did not had any maternal-fetal conditions. The Local Ethics Committee University of Health Sciences Turkey, Etlik Zübeyde Hanım Maternity and Women's Health Teaching and Research Hospital granted its approval for the conduct, protocol, and procedures of the study (approval number: 01-20-1).

We examined the first-trimester routine hemogram parameters of the participating women. NLR was calculated by dividing the absolute neutrophil count with the absolute lymphocyte count, whereas PLR was determined by dividing the absolute platelet count with the absolute lymphocyte count. We compared the first-trimester hemogram parameters (NLR and PLR) of both the groups.

Statistical Analysis

We used the Statistical Package for the Social Sciences version 20.0 for Windows for all the statistical analyses of this study. Importantly, we preferred the non-parametric tests according to the tests of normality results. We used the Mann-Whitney U test to compare the continuous variables. P-value of less than 0.05 was considered as statistically significant for this study.

Results

The mean ages of the pregnant women with IUGR and pregnant women in the control group were 28±2.02 and 28.52±2.69 years, respectively. The mean numbers of gravida in the IUGR and control groups were 2.62±0.72 and 2.54±1.16, respectively. The mean parity numbers in the IUGR and control groups were 1.54±0.50 and 1.58±0.81, respectively. The mean gestational weeks in the IUGR and control groups were 36.04±1.12 and 36.08±1.38, respectively. The first-trimester NLR and PLR values of the pregnant women complicated by IUGR were 6.59±1.12 and 117.2±16.00, respectively. The first-trimester NLR and PLR values of the pregnant women in the control group were 2.84±0.55 and 112.80±13.01, respectively. There was a statistically significantly difference between the two groups with respect to NLR (p<0.001) (Table 1).

Table 1. Characteristics of the patients

Variables	IUGR (n=50)		Control (n=50)		p
	Mean	± SD	Mean	± SD	
Age (years)	28.0000	2.02031	28.5200	2.69724	p>0.05
Gravida	2.6200	0.72534	2.5400	1.16426	p>0.05
Parity	1.5400	0.50346	1.5800	0.81039	p>0.05
Gestational week	36.0400	1.12413	36.0800	1.38269	p>0.05
BMI (kg/m^2)	27.7800	1.65616	27.5660	2.12753	p>0.05
Hb	11.9380	0.73509	11.8040	0.86425	p>0.05
NLR	6.5954	1.12894	2.8488	0.55514	p<0.05
PLR	117.2000	16.00255	112.8000	13.01804	p>0.05

IUGR: Intrauterine growth retardation, SD: Standard deviation, BMI: Body mass index, Hb: Hemoglobin, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio

Discussion

This is the first study, to our knowledge, which examined the first-trimester hemogram parameters in pregnant women complicated with IUGR. We hypothesized that the inflammatory process during pregnancy can help in the diagnosis of IUGR. We showed that the first-trimester NLR and PLR values are higher in the IUGR group as compared to the control group. Importantly, the NLR values were statistically significantly higher in the IUGR group as compared to the control group.

Various causes can be attributed to the manifestation of IUGR. These causes can be fetal, maternal, and placental factors. Most of the IUGR cases (especially recurrent IUGR) occur due to placental ischemia/inflammation. These placental problems may present as IUGR, ablation, and preeclampsia. These conditions may result in preterm birth and pregnancy loss.

IUGR scanning in the general obstetric populations are based on a broader determination of risk factors and physical assessment of fetal growth. After clinical suspicion, there should be a detailed evaluation of the fetus, placenta, and amniotic fluid. Early diagnosis is very crucial in the proper management of IUGR[10,11].

NLR and PLR have been used as the inflammation markers in recent years. These parameters can be obtained quickly and cheaply from the CBC test. NLR and PLR are increasingly being used as the indicators of cancer and various systemic diseases as well as systemic inflammation. Researchers have recently studied the usage of CBC parameters in the field of obstetrics and perinatology. A recent research conducted by Örgül et al.[12] had shown that increased first-trimester WBC and neutrophil counts may be predictive of early-onset preeclampsia. Although studies have been conducted to determine whether these parameters may have predictive values in the cases such as endometrioma and tubo-ovarian abscess in gynecology and obstetrics practice, there is no study that aimed to determine the value of these parameters in IUGR[13,14].

Preterm birth, IUGR, and stillbirth have been strongly associated with antenatal inflammation. The authors reported that the maternal inflammation and organization of vascular beds, which are to be indicated by NLR, were associated with this poor pregnancy outcome and fetal development. Maternal systemic inflammation during pregnancy may restrict embryo-fetal growth. Consistent with our results, the literature data also showed that the increased maternal inflammatory response was accompanied by IUGR[15].

High NLR and PLR values in the first trimester during pregnancy may be an important and predictive biomarker of impaired intrauterine growth. High NLR and PLR values in the first trimester appear to reflect an increased inflammation. Increased placental inflammation in the etiology of IUGR may support this condition. Our study shows that increased NLR and PLR values in the first trimester may predict IUGR. The limitations of our study are as follows: The absence of placental examination, low number of pregnant women, and the lack of newborn outcomes.

Conclusion

The clinical usage of NLR and PLR in hemogram tests may facilitate the diagnostic process of IUGR pregnancies. These parameters in the first trimester of pregnancy may serve as an important biomarker in the diagnosis of IUGR.

Ethics

Ethics Committee Approval: The Local Ethics Committee University of Health Sciences Turkey, Etlik Zübeyde Hanım Maternity and Women's Health Teaching and Research Hospital granted its approval for the conduct, protocol, and procedures of the study (approval number: 01-20-1).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.E.T., D.Ş., A.Y., Design: H.E.T., Data Collection or Processing: H.E.T., E.N.V., M.A., Analysis or Interpretation: H.E.T., H.E., D.Ş., A.Y., Literature Search: H.E.T., E.N.V., M.A., Writing: H.E.T., H.E.

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

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

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Clinical Investigation / Araştırma

DOI: 10.4274/tjod.galenos.2020.23682

Turk J Obstet Gynecol 2020;17:102-7

The relationship between oxidative stress and preeclampsia. The serum ischemia-modified albumin levels and thiol/disulfide homeostasis

Preeklampsi ve oksidatif stres arasındaki ilişki. Serum iskemi modifiye albümin seviyesi ve tiyol-disülfit dengesi

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Abstract

Objective: Preeclampsia (PE) is a dangerous complication of pregnancy and still a major cause of maternal-fetal morbidity and mortality. Its etiology remains largely unknown, but researchers have suggested oxidative stress-mediated inflammation for the same. The purpose of this study is to investigate the relationship between oxidative stress and PE as well as the usability of oxidative stress indicators such as serum ischemia-modified albumin (IMA) levels and thiol/disulfide balance in the prediction of PE.

Materials and Methods: The study included 47 pregnant women with PE and 57 healthy pregnant women. We measured their serum IMA, native thiol, total thiol, and disulfide levels. Additionally, we determined the optimal cutoff values via the receiver operating characteristic curve analysis.

Results: There were no differences between the two groups with respect to the maternal age, body mass index, gravida, and parity. The native and total thiol levels were found to be low when the disulfide and IMA levels were high in the patients with PE ($p<0.05$). When the IMA level was corrected by the albumin level (IMAR), the significant difference between the two groups disappeared. We also found that the native and total thiol concentrations were correlated with the systolic and diastolic blood pressures. The optimal cut-off values calculated for the prediction of PE were as follows: 178.45 µmol/L (with sensitivity of 72% and specificity of 83%) for native thiol, 232.55 µmol/L (with a sensitivity of 75% and specificity of 85%) for total thiol, and 29.05 µmol/L (with sensitivity of 65% and specificity of 72%) for disulfide.

Conclusion: The balance of thiol/disulfide may play a role in the pathogenesis of PE and could be used as a biological marker for PE.

Keywords: Preeclampsia, hypertension, oxidative stress, thiol/disulfide, ischemia-modified albumin

Öz

Amaç: Preeklampsi (PE) gebeliğin tehlikeli bir komplikasyonudur ve hala anne-fetal morbidite ve mortalitenin ana nedenidir. Etiyoloji büyük ölçüde bilinmemektedir, ancak oksidatif stres aracılı bir enflamasyon ileri sürülmektedir. Bu çalışmanın amacı oksidatif stres ve preeklampsi arasındaki ilişkiyi ve preeklampsi öngörüsünde serum iskemi modifiye albümin (İMA) düzeyi ve tiyol/disülfit dengesi gibi oksidatif stres göstergelerinin kullanılabilirliğini araştırmaktır.

Gereç ve Yöntemler: Çalışmaya 47 preeklamptik ve 57 sağlıklı gebe dahil edildi. Serum İMA, natif (doğal) tiyol, total tol ve disülfit düzeyleri ölçüldü. Optimal cut-off değerleri alıcı işletim karakteristiği eğrisi analizi ile belirlenmiştir.

Bulgular: Anne yaşı, vücut kitle indeksi, gravida ve parite arasında fark bulunmadı. Preeklamptik hastalarda disülfit ve İMA düzeyleri yüksek olduğunda natif ve total tiyol düzeyleri düşük bulundu ($p<0,05$). İMA seviyesi albümin seviyesi (İMAR) ile düzeltildiğinde, iki grup arasındaki anlamlı fark ortadan

PRECIS: The balance of thiol/disulfide may play a role in the pathogenesis of preeclampsia.

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Received/Geliş Tarihi: 06.03.2020 **Accepted/Kabul Tarihi:** 10.04.2020

kayboldu. Ayrıca natif ve total tiyol konsantrasyonlarının sistolik ve diyastolik kan basıncı ile ilişkili olduğu bulundu. Preeklampsi tahmini için optimal cut-off değerleri; natif tiyol için 178,45 µmol/L (%72 sensitivite ve %83 spesifite), total tiyol için 232,55 µmol/L (%75 sensitivite ve %85 spesifite) ve disülfit için 29,05 umol/L (%65 sensitivite ve %72 spesifite) olarak hesaplandı.
Sonuç: Tiyol/disülfit dengesi preeklampsinin patogenezinde rol oynayabilir ve preeklampsi için biyolojik bir belirteç olarak kullanılabilir.
Anahtar Kelimeler: Preeklampsi, hipertansiyon, oksidatif stres, tiyol/disülfit dengesi, iskemi modifiye albumin

Introduction

Preeclampsia (PE) is a leading cause of both maternal-fetal morbidity and mortality, and it affects about 5%-10% of pregnancies[1]. PE is characterized by gestational hypertension with one or more of the following conditions detected after ≥20 weeks' gestation: proteinuria, acute kidney injury, liver dysfunction, hematologic features, neurologic features, and placental dysfunction[2]. Unfortunately, the only treatment for PE is still delivery, and PE causes iatrogenic preterm birth in about 15% of pregnancies[3].

The etiology of PE is still unknown. It is believed that the defect starts from the implantation of the placenta. The oxidative damage that occurs in the placenta causes inflammation, apoptosis, and the release of anti-angiogenic agents and cytokines into maternal circulation. These placenta-originating substances that pass into the maternal circulation cause endothelial dysfunction, which is the main component of PE pathophysiology[4]. Additionally, it has been shown that physiological oxidative stress, which is present in the early stages of pregnancy, stimulates the normal cell differentiation and cytotrophoblast proliferation before the initiation of feto-maternal circulation; however, its role in the development of PE is still unknown[5].

Albumin is a vital part of the antioxidant systems. Its structure undergoes changes during oxidative stress, which lead to a reduction in the metal binding capacity. Subsequently, it is transformed into a new molecule called ischemia-modified albumin (IMA)[6]. The formation of reactive oxygen species (ROS) and free radicals temporarily changes the N-terminal region of albumin, which causes an increase in IMA concentration[7]. Furthermore, it has been shown to increase in the healthy pregnant women and other pregnancy-related situations[8-10].

Another antioxidant system is the thiol group consisting of sulfur and hydrogen attached to the carbon atoms[11]. The circulating thiol comprises albumin thiols, protein thiols, and thiols having a low molecular weight. Thiol groups are reversibly converted to the disulfide bonds in the presence of oxygen radicals. Thiol/disulfide homeostasis (TDH) is protected by the conversion between the thiol and disulfide groups[12]. TDH plays an important role in the mechanisms such as programmed cell death and antioxidant protection[13,14].

In the literature, there are studies evaluating the levels of TDH and IMA in pregnancy complications such as gestational diabetes, hyperemesis gravidarum, PE, and intrauterine growth retardation[9,15-17]. Because PE remains an important obstetric complication, there have been ongoing studies on the biochemical markers for the early detection of this disease. The investigation of serum markers related to oxidative stress involved in the etiology of PE can be useful in this matter. Based on this observation, the purpose of this study is to investigate two antioxidants, serum IMA and TDH, and compare these markers between the patients with PE and healthy pregnant women in the control group.

Materials and Methods

We conducted this study between May 2017 and September 2018 after receiving the approval of the local Ethics Committee at the Yozgat Bozok University Faculty of Medicine, Department of Obstetrics and Gynecology (April 18, 2017, 2017-11/01). Importantly, we obtained written informed consent from all the pregnant women who agreed to participate in the study.

The study group consisted of 47 patients who were diagnosed with PE according to the recommendations of the International Society for the Study of Hypertension in Pregnancy[2]. The control group consisted of 57 normotensive pregnant women (blood pressure less than 140/90 mmHg). The blood pressure of participants in the outpatient clinic was measured with an adult-type blood pressure monitor (Perfect Aneroid 48, ERKA, Germany), whereas the inpatient follow-up was performed by using a patient monitor (Vista 120, Dräger, Germany). A 5 mL of fasting venous blood sample was taken from all the participants for the analysis of biochemical parameters. In the study group, proteinuria was measured in a 24-hour urine protein test. We did not included pregnant women with a history of PE, chronic gestational hypertension, renal, hepatic and thyroid diseases, and type I and type II diabetes mellitus in this study.

TDH parameters were measured as described previously by Erel and Neselioglu[18]. The total and native thiol levels were measured by a fully automated spectrophotometric method by using an autoanalyzer-cobas® 6000 analyzer series (Roche Diagnostic Corp., Mannheim, Germany). The amount of dynamic disulfide was calculated as half of the difference between the total thiol and native thiol levels. After the determination of native and total thiol levels, the disulfide amounts, disulfide/total thiol percentage ratios, native thiol/total thiol percentage ratios, and disulfide/native thiol percentage ratios were calculated.

The serum IMA level was evaluated by using the method proposed by Bar-Or et al.[7]. A 200-mL patient sample was taken and 50 mL of cobalt chloride ($CoCl_2{\cdot}6H_2O$, 1 g/L) was added to it. This procedure was followed by vigorous mixing. The mixture was incubated for 10 minutes to ensure the binding of cobalt albumin. A 50-mL (1.5 mg/mL) amount of dithiothreitol was added as a coloring agent and later mixed. After a two-

minute incubation period, 1.0 mL of sodium chloride (0.9%) was added. The absorbance of assay mixtures was read at a wavelength of 470 nm by using a spectrophotometer (Thermo Scientific, Madison, WI). A blank was similarly prepared with the exclusion of the dithiothreitol. The results were reported as absorbance units (ABSU). The serum IMA and IMA/albumin ratio (IMAR) was also calculated. Serum IMAR was expressed as absolute units per gram (ABSU/g) of albumin.

Statistical Analysis

We performed statistical analysis by using the Statistics Package for Social Sciences software (ver. 20.0; SPSS Inc., Chicago, IL). Descriptive analyses were presented as mean ± standard deviation. We analyzed the fit of the variables to the normal distribution by visual (histogram) and analytical (Shapiro-Wilk test) methods. Importantly, we compared the data with normal distribution by using the Student's t-test, whereas we compared the data without normal distribution by using the Mann-Whitney U test. The correlation coefficient was calculated by the Pearson or Spearman tests according to the normal distribution of data. We used the receiver operating characteristic (ROC) curve analysis to determine the optimal cutoff value. A p-value of less than 0.05 was considered significant within a 95% confidence interval.

Results

We divided 104 pregnant women who agreed to participate in this study into two groups. Group 1, the study group, consisted of 47 pregnant women with PE, whereas group 2, the control group, consisted of 57 healthy pregnant women. Table 1 shows the descriptive data from the study and control groups. There was no difference with respect to maternal age, BMI, gravida, and parity between the groups (p>0.05). We compared systolic and diastolic blood pressures, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, creatinine levels and platelet counts, and determined a significant difference (p<0.05) between the groups as we expected (Table 1).

Table 1. The Characteristics of the preeclampsia and control groups

	Control (n=57)		Preeclampsia (n=47)		
	Mean	SD	Mean	SD	p
Age	28.95	5.38	30.15	4.72	0.375
BMI (kg/m^2)	26.27	2.50	27.47	2.16	0.607
Gravida	2.70	1.90	2.81	1.57	0.500
Parity	1.11	1.01	1.43	1.17	0.163
Gestational age (years)	29.21	4.98	30.45	5.90	0.409
Systolic blood pressure (mmHg)	104.04	10.67	149.55	12.25	**<0.001**
Diastolic blood pressure (mmHg)	64.91	8.89	92.66	9.66	**<0.001**
Urine protein (mg/24 hours)	-	-	637.53	1012.46	-
AST (iu/L)	16.69	5.68	35.43	35.40	**<0.001**
ALT (iu/L)	15.38	8.73	30.48	39.95	**0.034**
Creatinine (µmol/L)	0.55	0.05	0.61	0.10	**0.001**
LDH (iu/L)	178.36	31.19	256.34	101.86	**<0.001**
Platelet (×10^3/µL)	224.70	47.30	223.90	77.70	**0.001**
Albumin (gr/dL)	3.86	1.17	3.56	0.73	0.088
IMAR	0.22	0.08	0.24	0.06	0.065
IMA (ABSU/g)	0.76	0.07	0.80	0.07	**0.037**
Nthiol (µmol/L)	191.31	36.94	142.41	45.93	**<0.001**
Tthiol (µmol/L)	251.64	37.95	198.68	44.24	**<0.001**
Disulfide (µmol/L)	0.12	0.03	0.15	0.04	**0.001**
Disulfide/native thiol ratio	0.16	0.05	0.23	0.11	**<0.001**
Disulfide/total thiol ratio	0.12	0.03	0.15	0.04	**0.001**
Native thiol/total thiol ratio	0.76	0.05	0.70	0.09	**<0.001**

Mann-Whitney U test, IMAR: Ischemia-modified albumin/albumin, IMA: Ischemia-modified albumin, ABSU: Absorbance units, Nthiol: Native thiol, Tthiol: Total thiol, LDH: Lactate dehydrogenase, SD: Standard deviation, BMI: Body mass index, AST: Aspartat aminotransferaz, ALT: Alanin aminotransferaz

IMA, native thiol, total thiol, the disulfide and disulfide/native thiol ratio, the disulfide/total thiol ratio, and the native/total thiol ratio were found to be significantly different between the groups (p<0.05) (Table 1). The native and total thiol levels were found to be low when the disulfide and IMA levels were high in the patients with PE. When the IMA level was corrected by the albumin level (IMAR), the significant difference between the two groups disappeared. Further analysis was conducted within the PE group to determine whether the biochemical parameters showed any correlations with each other and with blood pressure (Table 2). Furthermore, a significant negative correlation between total thiol and systolic blood pressure [Spearman's Rho Coefficient (rs) –0.519, p<0.001) and diastolic blood pressure (r_s: -0.512, p<0.001)] was found. Additionally, there was a significant and moderate negative correlation between the native thiol and systolic blood pressure [r_s: -0.495, p<0.001] and diastolic blood pressure (r_s: -0.496, p<0.001).

We performed ROC analysis to evaluate the diagnostic performance of significant parameters in the prediction of PE (Figure 1). The optimal cutoff values were: native thiol, 178.45 µmol/L (with sensitivity of 72% and specificity of 83%); total thiol, 232.55 µmol/L (with 75% sensitivity and 85% specificity) and disulfide, 29.05 µmol/L (with sensitivity of 65% and specificity of 72%).

Discussion

This case-control study investigated the relationship between PE and serum oxidative stress markers. It also found that the levels of native thiol, total thiol, and disulfide were significantly different in the PE group. Additionally, the levels of serum IMA were higher in the PE group as compared to the control group; however, this difference was eliminated after the correction for total albumin (IMAR) concentrations.

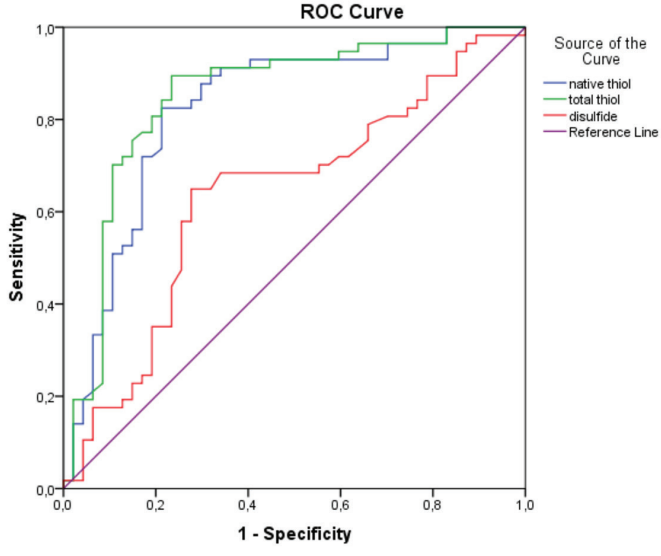
Table 2. Correlations of biochemical parameters

Parameters	r_s	p
Nthiol-IMAR	-0.337	<0.001
Nthiol-systolicBP	0.495	<0.001
Nthiol-diastolicBP	-0.496	<0.001
Nthiol-disulfide	-0.096	0.331
Tthiol-systolicBP	-0.519	<0.001
Tthiol-diastolicBP	-0.512	<0.001
Tthiol-IMAR	-0.357	<0.001
Tthiol-disulfide	0.089	0.389
Nthiol-tthiol	0.973	**<0.001**
IMAR-disulfide	-0.222	0.134

Spearman's rho test. AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, IMAR: Ischemia-modified albumin/albumin, IMA: Ischemia-modified albumin, Nthiol: Native thiol, Tthiol: Total thiol, SystolicBP: Systolic blood pressure, DiastolicBP: Diastolic blood pressure

Despite decades of research, the pathogenesis and pathophysiology of PE are yet to be fully understood. Moreover, insufficient placentation at the beginning of pregnancy is believed to be the trigger for PE. The early 1990s witnessed the proposal of "two-stage model of PE" hypothesis[19]. In this hypothesis, PE consists of Stage 1 (pre-clinical stage) with inadequate placentation and Stage 2 (clinical stage) with maternal syndrome. It was not fully understood how PE progressed from stage 1 to stage 2. It was believed that endothelial dysfunction, which leads to the emergence of clinical picture, may be the link between stage 1 and 2[20]. While the two-stage model of PE hypothesis describes PE as a homogeneous disease, subsequent studies have shown that PE is a heterogeneous disease and that this hypothesis cannot explain some of the PE cases[19,21]. In early pregnancy, spiral arteries lose the muscle layer and adapt to pregnancy. The problems in the remodeling process affect the flow rate rather than the flow volume of the blood[22]. It has been shown that ischemia-reperfusion injury and oxidative stress caused by this high-pressure abnormal flow lead to more damage in the placenta than chronic hypoxia[22]. It has been suggested that severe oxidative stress is associated with maternal clinical symptoms of PE[23].

Moreover, inadequate placentation causes the occurrence of ischemia-reperfusion injury and vasoactive agents such as soluble fms-like tyrosine kinase-1 and soluble endoglin[24].



Parameters	AUC[a]	Cut off (µmol/L)	Sensitivity (%)	Specificity (%)	95% Confidence Interval
Native thiol	0.825	178.45	72	83	0.740-0.910
Total thiol	0.850	232.55	75	85	0.769-0.931
Disulfide	0.635	29.05	65	72	0.526-0.745

[a]: Area under curve,

Figure 1. Receiver operating characteristic analysis (Specificity, Sensitivity, and the Cutoff Levels of Thiol/Disulfide Homeostasis in Preeclampsia)

These anti-angiogenic vasoactive agents show their effects through oxidative stress, induced systemic inflammation, and endothelial cell damage[25,26]. PE is characterized by a deterioration in the oxidant-antioxidant balance in the favor of oxidative stress[27]. ROS are the most important components of oxidative damage[28]. ROS shows their vasoconstrictive effects by inhibiting the endothelial-dependent vasodilation pathways (such as nitric oxide). This action suggests that oxidative stress play a pivotal role in the development of PE.

Thiol, also known as mercaptan, is an organic compound that contains the sulfhydryl groups[11]. The thiol/disulfide system, which is one of the most important antioxidant systems of the human body, can be oxidized in the presence of free oxygen radicals due to the thiol groups and can be reversibly converted to the sulfhydryl bonds[29]. TDH has been investigated for many physiological conditions such as apoptosis, antioxidant defense mechanisms as well as for pathological processes such as cancer, diabetes mellitus, intrauterine growth restriction, obstructive sleep apnea, and so on[13,14,30-33]. Hydrogen sulfide (H_2S), a functional group of native thiol, regulates the vascular tone through nitric oxide[34]. As indicated by Holwerda et al.[35], the production of H_2S is less in the placental samples from the patients with PE. The oxidative damage from ROS on the vascular structures increases with the weakening of TDH. In PE, Ozler et al.[15] first identified TDH and showed that TDH may play a role in the pathogenesis of PE. Native and total thiol levels were found to be low and the disulfide levels were high in patients with PE; these observations were similar to our results. Recent studies found a correlation between the severity of PE and the impairment of TDH[36]. As in line with the literature, our study showed that TDH significantly deteriorated in the favor of PE. Additionally, it also found that the native and total thiol concentrations were correlated with the systolic and diastolic blood pressures.

Although IMA levels were first studied in myocardial ischemia, they have been studied for many conditions, such as multiple sclerosis, PE, and acute appendicitis[9,37,38]. The IMA levels have showed contradictory results in previous studies conducted on PE. The study by Van Rijn et al.[39] examined the IMA levels in three groups: 12 pregnant women with PE, 12 normotensive pregnant women, and 12 healthy non-pregnant women showed no significant difference. The study by Üstün et al.[9] included 54 pregnant women and found that the IMA level was significantly higher in the PE group. Additionally, the severity of the disease and IMA levels were positively correlated in the same study. Studies investigating the level of IMA in healthy pregnant women and healthy non-pregnant women have shown that pregnancy is a factor that significantly increases the IMA level on its own[8,39]. In this study, the IMA level was significantly different in both the groups. However, this difference disappeared when the IMA level was corrected with albumin. The IMA levels during pregnancy are higher in pregnant women than in healthy non-pregnant women. A hypoxic environment is required to increase placentation. In our opinion, the hypoxic environment in the early period of pregnancy activates the cytotrophoblasts and increases the level of IMA.

Study Limitations

This study has several limitations. First, the obstetric and neonatal outcomes could not be included due to the insufficiencies of neonatal intensive care units' recording system. Second, most of these patients could not give birth in our center. Other limitations were the differences in the severity of PE among the study group and a small sample size. However, the evaluation of the parameters of two different antioxidant defense systems at the same time is a factor that adds weight to our research.

Conclusion

Oxidative stress is an important part of the pathophysiology of PE. This study evaluated two different oxidative stress markers, and found that TDH was significantly different in the PE group, but there was no significant difference for IMAR. According to our hypothesis, TDH may play a role in the pathogenesis of PE and serum levels or ratios can be used to predict PE. To confirm these results, there is a need for future prospective randomized controlled studies researching the serum levels also in the early gestational weeks with higher numbers of subjects and groups.

Ethics

Ethics Committee Approval: Yozgat Bozok University Faculty of Medicine, Department of Obstetrics and Gynecology (approval number: 2017-11/01, date: 18.04.2017).
Informed Consent: It was obtained.
Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Clinical Investigation / Araştırma

DOI: 10.4274/tjod.galenos.2020.82652

Turk J Obstet Gynecol 2020;17:108-14

Local uterine resection with Bakri balloon placement in placenta accreta spectrum disorders

Plasenta akreta spektrum bozukluklarında Bakri balon yerleştirilmesi ile lokal uterin rezeksiyon

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Abstract

Objective: Placenta accreta spectrum (PAS) is a potentially life-threatening condition characterized by the abnormal adherence of the placenta to the implantation site. We sought to evaluate the efficacy, surgical feasibility, risks, and advantages of local uterine resection in cases complicated with PAS.

Materials and Methods: This study included 97 patients with PAS, which was confirmed during surgery and by histopathological examination between January 2013 and December 2019. The patients were divided into two groups based on operative approach. The study population (local resection group) consisted of 30 cases in whom total resection of adherent placenta and myometrium was performed, whereas the control group (hysterectomy group) of 67 cesarean hysterectomy cases.

Results: Patients who underwent hysterectomy had significantly more bleeding than the local resection group (1180±160 mL vs 877±484 mL; p=0.002). The mean number of transfused packed red blood cells (pRBCs) was greater in the hysterectomy group (4.5±2.3) than in the local resection group (2.6±3.1; p=0.001). Transfusion rate of four and/or more pRBCs was 67.2% in the hysterectomy group and 33.3% in the local resection group, which indicated a statistically significant difference (p=0.002). Of patients, 29.6% required intensive care unit in the hysterectomy group and 6.7% in the local resection group (p=0.023).

Conclusion: Local resection can be performed safely in selected PAS cases. In these cases, using a standardized protocol in terms of patient selection and surgical procedure will reduce morbidity and mortality.

Keywords: Conservative technique, placenta accreta, placenta accreta spectrum, placenta percreta, local resection

Öz

Amaç: Plasenta akreta spektrumu (PAS) plasentanın implantasyon alanına anormal olarak yapışması ile karakterize hayatı tehdit edici bir durumdur. PAS ile komplike olgularda lokal uterin rezeksiyonun etkinliğini, cerrahi fizibilitesini, risklerini ve avantajlarını değerlendirmeye çalıştık.

Gereç ve Yöntemler: Ocak 2013-Aralık 2019 tarihleri arasında ameliyat sırasında ve histopatolojik inceleme ile doğrulanan PAS tanısı almış doksan yedi hasta çalışmaya dahil edildi. Hastalar operatif yaklaşıma göre iki gruba ayrıldı. Çalışma popülasyonu (lokal rezeksiyon grubu) plasenta ve miyometriumun total rezeksiyonu yapılan 30 olgudan oluşmaktaydı. Kontrol grubu (histerektomi grubu) 67 sezaryen histerektomi olgusundan oluştu.

Bulgular: Histerektomi yapılan hastaların lokal rezeksiyon grubuna göre anlamlı derecede daha fazla kanaması vardı (1180±160 mL vs 877±484 mL; p=0,002). Ortalama transfüze edilen paketlenmiş eritrosit sayısı histerektomi grubunda lokal rezeksiyon grubuna göre daha fazlaydı (histerektomi grubu için 4,5±2,3, lokal rezeksiyon grubu için 2,6±3,1; p=0,001). Dört ve/veya daha fazla pRBC'nin transfüzyon oranı histerektomi grubunda% 67.2 ve lokal rezeksiyon grubunda% 33.3 idi ve bu da istatistiksel olarak anlamlı bir farklılık gösterdi (p: 0.002). Histerektomi grubunda hastaların %29,6'sı yoğun bakım ünitesine ihtiyaç duyarken, bu oran lokal rezeksiyon grubu için %6,7 idi (p=0,023).

Sonuç: Lokal rezeksiyon seçilmiş PAS olgularında güvenle yapılabilir. Bu durumlarda, hasta seçimi ve cerrahi prosedür açısından standart bir protokol kullanılması morbidite ve mortaliteyi azaltacaktır.

Anahtar Kelimeler: Konservatif teknik, plasenta akreta, plasenta akreta spektrumu, plasenta perkreta, lokal rezeksiyon

PRECIS: Local uterine resection can be performed safely in selected cases with placenta accreta spectrum disorder.

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Received/Geliş Tarihi: 17.04.2020 **Accepted/Kabul Tarihi:** 18.05.2020

Introduction

Placenta accreta spectrum (PAS) is a potentially life-threatening condition characterized by the abnormal adherence of the placenta to the implantation site[1]. It has been more than 80 years since PAS was first defined[2]. In a review of 18 cases, the condition was accurately defined as the abnormal adherence of the placenta in whole or partially to the uterine wall[2]. It has been shown that iatrogenic damage to the endometrial lining and underlying myometrium can be linked to PAS in subsequent pregnancies[3-5]. Risk factors for PAS primarily include previous uterine surgery. Epidemiological data indicate that previous cesarean section delivery history and placenta previa diagnosis are major risk factors, and others include advanced maternal age, smoking, dilatation and curettage, and uterine artery embolization[5-7]. The prevalence of PAS in the general population varies according to local and regional cesarean delivery rates[8]. The overall prevalence of PAS has been reported to be 5.2 per 1000 pregnancies, although rates as high as 12.2 per 1000 pregnancies have been reported[8].

Planned cesarean hysterectomy leaving the placenta ***in situ*** is currently the recommended approach by the American College of Obstetricians and Gynecologists[9]. Similarly, the Royal College of Obstetricians and Gynecologists state that cesarean hysterectomy is the preferable approach in PAS[10]. However, conservative approach has been described in the literature to preserve future fertility and avoid hysterectomy-related complications such as massive transfusion, coagulopathy, and operative injury[11]. The conservative approach defines various surgical techniques that aim to avoid hysterectomy. Four types of conservative management have been described: Extirpative approach, leaving the placenta ***in situ***, one-step surgery, and the triple-P procedure[12]. The one-step surgery is defined as the resection of the entire adherent placenta with the underlying myometrium[13]. The main advantage of this procedure is the relatively lower blood loss compared with manual extirpation as the technique basically consists of controlled surgical en-block excision of the adherent placenta. In addition, as no placental tissue remains following the procedure, persistent risk of bleeding or infection is minimal. The technique has a high success rate, but only few studies with small sample sizes have been reported so far[13-15]. Therefore, in this study, we sought to evaluate the efficacy, surgical feasibility, risks, and advantages of local uterine resection in the case of PAS.

Materials and Methods

This study is a retrospective analysis of cases that were followed up or referred with a diagnosis of PAS at the University of Health Sciences Turkey, Bursa Yüksek İhtisas Training and Research Hospital, Clinic of Gynecology, which is a tertiary referral medical center with approximately 13,000 deliveries each year. The study was reviewed by the Ethics Committee of University of Health Sciences Turkey, Bursa Yüksek İhtisas Training and Research Hospital, (approval number: 2011-KAEK-25 2019/08-14) and was conducted in accordance with the ethical standards described in an appropriate version of the 1975 Declaration of Helsinki, as revised in 2000. After the approval of the ethics committee, medical records of 135 patients with PAS, which were confirmed during surgery and by histopathological examination between January 2013 and December 2019, were evaluated. Patients who were not diagnosed during the antenatal period and emergency operations and who underwent cesarean hysterectomy were excluded if they did not meet the inclusion criteria of conservative surgery (cases with invasion into the parametrium and/or cervix and invasion of more than 50% of the anterior surface of the uterus). Cases that were converted to hysterectomy during conservative surgery were also excluded from the study. Finally, 97 patients were included (Figure 1), and the patients were recruited into two groups based on operative approach. The study population (local resection group) consisted of cases in whom total resection of adherent placenta and myometrium was performed, whereas the control group (hysterectomy group) of cesarean hysterectomy cases.

The diagnosis of PAS was suspected when transvaginal sonography combined with Doppler studies revealed placenta

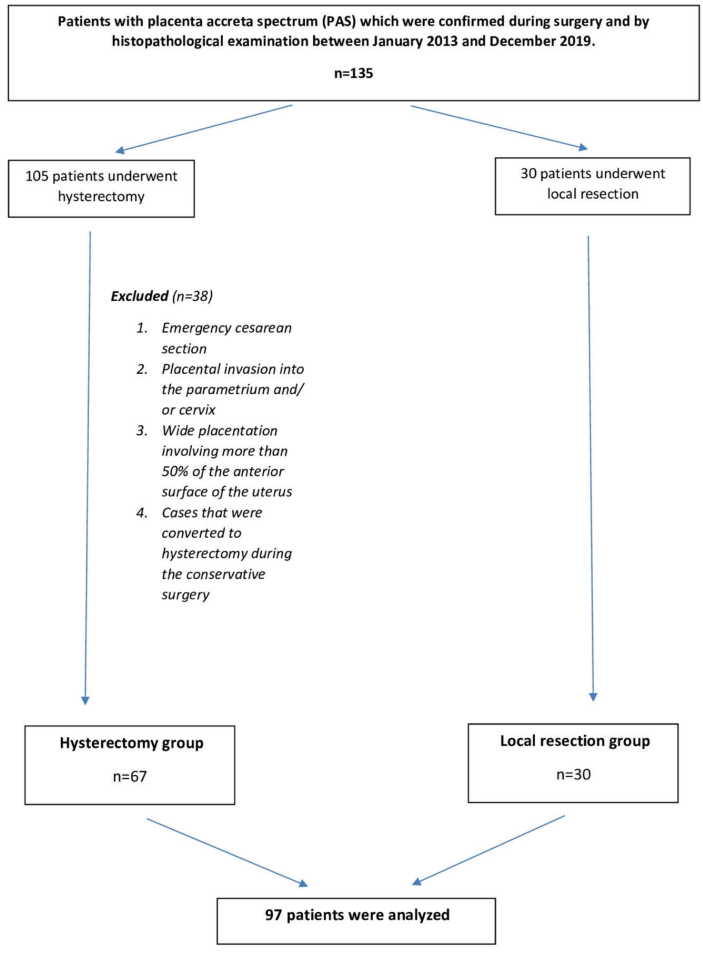

Figure 1. Flowchart of the study
PAS: Placenta accreta spectrum

previa with additional sonographic findings[16]. At our institution, hysterectomy is preferred primarily in PAS cases. However, if sonographic and intraoperative findings are appropriate in patients who prefer the preservation of the uterus, uterine sparing surgery is performed. Conservative surgery is not performed in cases with invasion into the parametrium and/or cervix and invasion of more than 50% of the anterior surface of the uterus.

All patients prenatally diagnosed with PAS were fully informed of benefits and risks of the surgical procedures. Signed informed consent was obtained from the patients before the surgery. All operations were performed by experienced surgeons using a standard technique.

All patients were placed in the dorsal lithotomy position during the surgeries. A vertical midline skin incision was made in both hysterectomy and conservative operations. The surgical technique for classical hysterectomy can be briefed as a fundal uterine incision devoid of placental attachment, delivery of the baby, rapid closure of the incision leaving the placenta in situ, and performance of hysterectomy.

As for local resection, the first step is the creation of a plane between the placenta and bladder. Advanced bipolar device (LigaSure, Covidien, Boulder, CO, USA) was used to dissect the vesicouterine space. Dissection was performed until the cervical internal ostium level. The second step was to make a transverse incision to the uterus close but not through the placental insertion site and delivery of the fetus. The next step was the resection of all invaded myometrial tissue and adherent placenta in one piece. Following surgical procedures for hemostasis, the myometrium was sutured in two planes. Intrauterine balloon tamponade (Bakri Postpartum Balloon, Cook Medical, Spencer, IN, USA) and pelvic drains were used in all cases for at least 24 hours.

The following data were obtained from the patients' records: age, parity, body mass index, uterine surgery history (including cesarean, myomectomy, or dilatation and curettage), gestational age at delivery, perioperative and postoperative bleeding, and histopathological specimen diagnosis. The following data were obtained from the operative note: operative time, estimated blood loss, number of packed red blood cell (pRBC) transfusions, and presence of intraoperative complications. Maternal postoperative complications, neonatal birthweight, and outcomes were also retrieved from the patients' charts.

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences version 18 (Chicago, IL, USA). Student's t-test was performed for parametric variables between groups that distribute normally. Mann-Whitney U test was performed for parametric variables without normal distribution, and the chi-square test for nonparametric variables between groups. Multivariate logistic regression analysis was used to investigate the factors affecting transfusion requirement and intensive care unit (ICU) admission. The data were adjusted for other confounders such as age, gravidity, parity, previous cesarean delivery, curettage, and myomectomy. A p-value less than 0.05 was considered significant.

Results

Clinical and demographic features of the study population are depicted in Table 1. Patients in the hysterectomy group were older those in the local resection group (33.2±4.7 vs 31.1±5.4, p=0.048). Parity >3 was more frequent in patients who had undergone hysterectomy (28.4% vs 13.3%; p=0.036). A previous cesarean delivery history was more frequent in patients in the hysterectomy group (100% vs 76.6%, p<0.001), whereas a previous myomectomy history was more frequent in the local resection group (36.7% vs 10.4%, p=0.002). The rate of previous dilatation and curettage was similar in both groups (p=0.575), and there were no significant differences in histopathologic diagnoses between the groups (p=0.485).

Perioperative data and maternal and neonatal outcomes are presented in Table 2. There were no statistically significant differences between the groups regarding gestational age at delivery and preoperative and postoperative hemoglobin and fibrinogen levels. Likewise, the duration of operation was

Table 1. Characteristics of the study population

	Local resection (n=30)	Hysterectomy (n=67)	p
Age (years)	31.1±5.4	33.2±4.7	**0.048**
Body mass index (kg/m^2)	24.6±2.5	24.9±2.0	0.480
Parity	-	-	**0.036**
0	2 (6.7%)	0	-
1-3	24 (80%)	48 (71.6%)	-
>3	4 (13.3%)	19 (28.4%)	-
Previous cesarean delivery	-	-	**<0.001**
0	7 (23.3%)	0	-
1-2	19 (63.3%)	57 (85.1%)	-
≥3	4 (13.3%)	10 (14.9%)	-
Previous myomectomy	11 (36.7%)	7 (10.4%)	**0.002**
Previous uterine curettage	4 (13.3%)	12 (17.9%)	0.575
Histopathologic diagnoses	-	-	0.485
Accreta	18 (60%)	45 (67.2%)	-
Increta	10 (33.3%)	15 (22.3%)	-
Percreta	2 (6.7%)	7 (10.4%)	-

All data are reported as mean ± standard deviation or n (%)

similar in both groups (102±12 min for the local resection group vs 99±15 min for the hysterectomy group; p=0.255). Patients in whom hysterectomy was performed had significantly more bleeding than the local resection group (1180±160 mL vs 877±484 mL; p=0.002). The mean number of transfused pRBCs was greater in the hysterectomy group (4.5±2.3) than in the local resection group (2.6±3.1; p=0.001).

Intraoperative and postoperative complications occurred at a higher rate in patients in the hysterectomy group than those in the local resection group. Four and more pRBCs transfusion rates were 67.2% in the hysterectomy group and 33.3% in the local resection group, which indicated a statistically significant difference (p=0.002). In the hysterectomy group, two patients developed disseminated intravascular coagulation, and one developed acute renal failure. The rate of bladder injury in the hysterectomy group was higher than the local resection group, but that did not reach statistical significance [15 (22.4%) vs 3 (10.0%); p=0.147, respectively). The rate of ICU admission was higher in the hysterectomy group than the local resection group. Of patients, 29.6% required ICU in the hysterectomy group and 6.7% in the local resection group (p=0.023). Neonatal outcomes in terms of birthweight, 5-min Apgar scores, and neonatal ICU admission were similar in both groups.

In the multivariate logistic regression analysis model, after adjusting for relevant confounding factors (age, gravidity, parity, previous cesarean delivery, curettage, and myomectomy), hysterectomy was an independent risk factor for four or more pRBC transfusion requirement (odds ratio (OR): 9.442, 95% confidence interval (CI): 2.072-43.026, p=0.004) and ICU admission (OR: 10.092, 95% CI: 2.363-42.376, p=0.007; Tables 3, 4).

Discussion

PAS frequency is increasing rapidly because of the increase in cesarean section rates today. Planned cesarean section hysterectomy has been considered the main treatment option

Table 2. Perioperative data and maternal and neonatal outcomes

	Local resection (n=30)	Hysterectomy (n=67)	p
Gestational age at delivery (weeks)	35.1±2.4	34.8±2.0	0.555
Duration of operation (minimum)	102±12	99±15	0.255
Preoperative hemoglobin levels (g/dL)	9.8±1.8	9.5±1.2	0.344
Postoperative hemoglobin levels (g/dL)	8.9±1.4	8.9±1.2	0.999
Nadir fibrinogen (mg/dL)	362±108	334±119	0.268
Fibrinogen <200 mg/dL	2 (6.7%)	10 (14.9%)	0.254
No of pRBCs transfusion	2.6±3.1	4.5±2.3	**0.001**
Intraoperative, mean (minimum-maximum)	1.1 (0-4)	1.1 (1-3)	0.850
Postoperative, mean (minimum-maximum)	1.5 (0-8)	3.4 (0-15)	**0.001**
Intraoperative bleeding (mL)	877±484	1180±160	**0.002**
Postoperative bleeding (mL) (Drain ± Bakri balloon tamponade)	111±38	178±87	**<0.001**
Pelvic vessel ligation	4 (13.3%)	17 (25.4%)	0.183
Complications			
Bladder injury	3 (10.0%)	15 (22.4%)	0.147
≥4 pRBC transfusion	10 (33.3%)	45 (67.2%)	**0.002**
Acute renal failure	0	1 (1.5%)	0.501
DIC	0	2 (3%)	0.339
Wound infection	4 (13.3%)	7 (10.4%)	0.679
ICU admission	2 (6.7%)	18 (29.6%)	**0.023**
Length of hospital stay (days)	5.3±2.8	6.4±1.8	**0.022**
Neonatal birthweight (g)	2627±655	2567±332	0.555
5 minimum Apgar score <7	3 (10%)	4 (6%)	0.478
NICU admission	4 (13.3%)	5 (7.5%)	0.357

All data are reported as mean ± standard deviation or n (%), DIC: Disseminated intravascular coagulation, ICU: Intensive care unit admission, NICU: Neontatal ICU, pRBC: Packed red blood cell

Table 3. Logistic regression analysis for factors affecting four or more packed red blood cell transfusion requirement

Variable	Unadjusted			Adjusted		
	Odds ratio	95% CI	p	Odds ratio	95% CI	p
Age	1.040	0.958-1.128	0.349	1.110	0.937-1.316	0.229
Body mass index	0.952	0.791-1.146	0.601	1.210	0.893-1.640	0.218
Parity	1.406	1.057-1.871	**0.019**	0.054	0.001-4.282	0.191
Previous uterine curettage	1.722	0.794-3.732	0.168	0.061	0.001-6.330	0.238
Previous cesarean delivery	2.117	1.100-4.072	**0.025**	1.740	0.807-3.750	0.158
Previous myomectomy	1.394	0.499-3.891	0.526	5.556	0.426-72.536	0.191
Surgery	-	-	-	-	2.072-43.026	**0.004**
Local resection (RC)	1.00	-	-	1.00	-	-
Hysterectomy	4.091	1.639-10.208	**0.003**	9.442	-	-

R^2 Nagelkerke: 0.260, RC: Reference category, CI: Confidence interval

Table 4. Logistic regression analysis for the factors affecting intensive care unit admission

Variable	Unadjusted			Adjusted		
	Odds ratio	95% CI	p	Odds ratio	95% CI	p
Age	1.046	0.947-1.155	0.375	1.092	0.927-1.285	0.291
Body mass index	1.033	0.825-1.294	0.776	1.011	0.709-1.444	0.950
Parity	0.904	0.669-1.220	0.508	6.449	0.100-41.539	0.381
Previous uterine curettage	1.008	0.461-2.204	0.984	0.039	0.000-4.305	0.177
Previous cesarean delivery	0.884	0.573-1.362	0.576	0.820	0.304-2.214	0.695
Previous myomectomy	2.361	0.495-11.247	0.281	6.608	0.719-23.997	0.085
Surgery	-	-	-	-	-	**0.007**
Local resection (RC)	1.00	-	-	1.00	-	-
Hysterectomy	5.143	1.110-23.819	**0.036**	10.092	2.363-42.376	-

R^2Nagelkerke: 0.274, RC: Reference category, CI: Confidence interval

for these cases, consistent with the American College of Obstetricians and Gynecologists recommendations[17]. However, many patients are young and with low parity, and uterine conservative approaches should be considered in these patients with a further fertility desire. Palacios-Jaraquemada et al.[18] reported that the uterus could be preserved in 80% of patients without causing additional morbidity in the study where they examined 248 PAS cases. In a prospective study involving 20 PAS cases, only 1 (5%) patient required hysterectomy when performing the triple-P procedure, which includes removal of the fetus through a separate incision over the placental site, ligation of bilateral uterine artery, and excision of the relevant myometrial region without separating the placenta[19].

Both definitive and conservative surgical approaches of patients with PAS are associated with increased risk of maternal morbidity and mortality. The important point here is that uterine-sparing interventions should not pose an extra risk in patients in terms of complications such as bleeding and adjacent organ injuries compared with cesarean section hysterectomy. According to published data, transfusion is required in up to 90% of these patients[20]. Estimated blood losses related to cesarean hysterectomy in PAS cases are 3000-5000 mL[21,22]. In a meta-analysis, which examined 29 studies including 7001 PAS cases, the frequency of transfusion-requiring hemorrhage was 46.9%[23]. In the publications related to conservative PAS surgery, the average amount of bleeding is 1630 cc, and the average pRBC transfusion is 3.9 units[24]. Bladder injury, reported as approximately 10% to 30%, is another common complication in PAS cases[25,26]. In a study involving 65 PAS cases, urinary tract injury was detected in 31.4% (16/51) and 14% (2/14) of those who underwent cesarean hysterectomy and conservative surgery, respectively[27]. Here, bladder injury occurred 2.5 times more than ureter injury[27].

In this study, we investigated whether conservative surgery is acceptable in selected PAS cases. The findings indicate that local resection causes less morbidity in selected PAS cases compared

with hysterectomy. Local resection was associated with reduced bleeding, transfusion requirement, and ICU admission rate compared with hysterectomy. After adjusting for relevant confounding factors, hysterectomy was an independent risk factor for four or more pRBC transfusion requirements and ICU admission. Additionally, the rate of bladder injury was higher in patients who underwent hysterectomy, although this did not reach statistically significant difference. Our findings are consistent with the results of publications related to conservative PAS surgery[18,24,28-30]. In many studies, it is reported that bleeding and bladder injuries occur during vesicouterine space dissection, which is a common step in both local resection and hysterectomy[24,27]. Despite these data, some explanations can be made about why these complications occur less frequently in conservative surgery. Many factors such as placental location and invasion depth, time of diagnosis, transfusion capabilities of the center where the operation is performed, and the surgeon's experiences affect the morbidity and mortality in PAS cases. Many clinics, including us, begin performing conservative procedures after gaining enough experience in PAS surgery[18]. Another point is that conservative surgery may have been preferred in relatively low-grade PAS cases. In addition, the fact that hysterectomy is an extensive surgical procedure than local resection may also contribute to the increase in morbidity in hysterectomy cases.

In our view, some important points should be considered to perform a conservative surgery in PAS cases without increasing morbidity and mortality. Conservative surgery should be preferred only in selected PAS cases. Thus, the cases should be evaluated in detail with ultrasonography and other imaging modalities before operation. Each surgeon should determine the conservative surgical acceptance criteria according to his or her own experience and skills. The most important step of surgery is the dissection of the vesicouterine space where major bleeding occurs due to neovascularization. We believe that performing this step initially before delivery of the fetus and using advanced bipolar device can significantly decrease the amount of bleeding. During the bladder dissection or at any operation stage, any bleeding that cannot be controlled is encountered, and definitive surgical procedure should not be delayed. It has been reported that balloon tamponade reduces blood loss and transfusion amounts, although it has a higher failure rate in the presence of PAS[31-33] (AJOG). We believe that the routine use of Bakri in these cases is beneficial in terms of reducing and following up bleeding in the postpartum period. In our institution, we do not perform prophylactic hypogastric artery ligation. We believe that this approach is time consuming and not effective. It is performed only if the previous steps such as balloon tamponade or hysterectomy have failed to control the bleeding.

Study Limitations

This was a retrospective study with susceptibility to selected bias. The subjective criteria of the surgeon may have influenced the selection of the surgical type of the patients. The severity of PAS cases was basically evaluated according to ultrasonography and surgery notes. Since it was not specified in detail in some surgical and sonography records, the hysterectomy group may have included more serious cases than the local resection group. One of the strengths of this study is that unlike other published studies, two comparable groups were provided by excluding hysterectomy cases that did not meet the criteria for conservative surgery. Additional strengths include relatively larger sample size and standard surgical technique application in operations.

Conclusion

Our findings suggest that local resection can be performed safely in selected PAS cases. In these cases, using a standardized protocol in terms of patient selection and surgical procedure will reduce morbidity and mortality.

Ethics

Ethics Committee Approval: The study was reviewed by the Ethics Committee of University of Health Sciences Turkey, Bursa Yüksek İhtisas Training and Research Hospital, (approval number: 2011-KAEK-25 2019/08-14) and was conducted in accordance with the ethical standards described in an appropriate version of the 1975 Declaration of Helsinki, as revised in 2000.

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

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

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Clinical Investigation / Araştırma

DOI: 10.4274/tjod.galenos.2020.12129

Turk J Obstet Gynecol 2020;17:115-22

Patients' perceptions toward and the driving factors of decision-making for opportunistic bilateral salpingectomy at the time of cesarean section

Sezaryen sırasında profilaktik bilateral salpenjektomiye hastaların bakış açısı ve kararlarını etkileyen faktörler

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Abstract

Objective: Enough data can be found in the literature regarding the protective effect of tubal ligation on gynecological cancers. In addition, a large body of evidence revealed that prophylactic bilateral salpingectomy had no significant negative effect on the ovarian function, quality of life, sexuality, surgery duration, and cost-effectivity. This study was aimed at exploring the underlying factors that motivate women for either opportunistic bilateral salpingectomy (OBS) or tubal ligation, particularly focusing on their preferences, knowledge, and beliefs toward female sterilization, satisfaction from counseling, and body image following the salpingectomy.

Materials and Methods: A total of 54 patients who had undergone surgical sterilization with either OBS or tubal ligation were included in this prospective cohort study. The acceptance rate of the OBS at the time of cesarean section among pregnant women seeking surgical sterilization was calculated. The underlying reasons for women's acceptance or refusal for salpingectomy were assessed by a non-validated data collection tool that had 14 open-ended questions focusing on the women's preferences, knowledge, beliefs toward female sterilization, satisfaction from counseling, and body image following the salpingectomy.

Results: The acceptance rate of OBS at the time of cesarean section among pregnant women and electively among non-pregnant women were 93.5% (n=43/46) and 75% (6/8), respectively. The main driving factors influencing the decision of preferring OBS over tubal ligation were the risk-reducing effect for ovarian cancer and superior pregnancy prevention.

Conclusion: The acceptance rate of OBS at the time of cesarean section was found to be very high, and it should therefore be offered at the time of cesarean section to women who desire permanent contraception.

Keywords: Opportunistic salpingectomy, permanent contraception, postpartum sterilization, prophylactic salpingectomy, risk-reducing salpingectomy

Öz

Amaç: Tubal ligasyonun jinekolojik kanserler üzerindeki koruyucu etkisi hakkında literatürde veriler vardır. Ayrıca, profilaktik bilateral salpinjektominin yumurtalık fonksiyonu, yaşam kalitesi, cinsellik, cerrahi süresi ve maliyet etkinliği üzerinde olumsuz bir etkisi olmadığı ortaya koyulmuştur. Bu çalışmada kadınların profilaktik bilateral salpinjektomi veya tubal ligasyon tercihlerini etkileyen faktörlerin araştırılması amaçlanmıştır.

Gereç ve Yöntemler: Bu prospektif kohort çalışmaya profilaktik bilateral salpinjektomi veya tubal ligasyon ile cerrahi sterilizasyon uygulanan toplam 54 hasta dahil edildi. Cerrahi sterilizasyon isteyen gebe kadınlarda sezaryen anında profilaktik bilateral salpinjektomiyi tercih edenlerin oranı belirlendi. Kadınların salpinjektomiyi seçmesinin veya reddetmesinin altında yatan nedenler, 14 açık uçlu soru içeren bir form ile değerlendirildi.

Bulgular: Gebelerin %93,5'i (n=43/46) gebe olmayan kadınların ise %75'i (6/8) sezaryen sırasında profilaktik bilateral salpinjektomiyi kabul etmişlerdir. Tubal ligasyon yerine profilaktik bilateral salpinjektomiyi tercih etmek için başlıca motivatörleri salfenjektominin over kanseri riskini azaltma ve kontrasepsiyondaki üstünlüğü olmuştur.

PRECIS: Obstetricians should be eager to offer opportunistic bilateral salpingectomy (OBS) at the time of cesarean section to women desiring permanent contraception following a detailed counseling of its potential benefits. The most common motivators of women for consenting to an OBS procedure were risk-reducing potential for ovarian cancer and superior pregnancy prevention.

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Received/Geliş Tarihi: 03.05.2020 **Accepted/Kabul Tarihi:** 10.05.2020

Sonuç: Sezaryen sırasında profilaktik bilateral salpinjektomiyi kabul eden hastaların oranı yüksek bulunmuştur. Obstetrisyenler kalıcı kontrasepsiyon isteyen hastalara sezaryen sırasında profilaktik bilateral salpinjektomiyi önermelidirler.
Anahtar Kelimeler: Profilaktik salpingektom, kalıcı kontrasepsiyon, postpartum sterilizasyon

Introduction

Tubal sterilization either with tubal occlusion or ligation and mid-isthmic partial salpingectomy is one of the most popular and effective methods of permanent contraception worldwide[1]. More than one-fifth women in the United States undergo a surgical female sterilization as a method of contraception[2]. Postpartum tubal ligation is performed after approximately 8-9% of all births. The cumulative 10-year probability of pregnancy is as low as 0.75%[3].

There are now solid data about the protective effect of tubal ligation on gynecological cancers. A pooled systematic review and meta-analysis of all types of tubal procedures showed that tubal sterilization reduced the endometrial cancer risk approximately by 42%[4]. Contrary to the endometrial cancer, epithelial ovarian cancer lacks an effective screening method and is the leading cause of mortality due to gynecological cancers in the developed countries, and the second highest globally[5]. It has been hypothesized previously that the fallopian tubes are very likely to be the origin of high-grade serous cancers[6], and thus, prophylactic or opportunistic salpingectomy at the time for hysterectomy and other benign procedures may be beneficial. The incidence of ovarian cancer among women who had undergone prophylactic salpingectomy along with hysterectomy for benign condition was found to be reduced to 30-64%[7]. In addition, a large body of evidence revealed that prophylactic bilateral salpingectomy had no significant negative effect on the ovarian function, quality of life, sexuality, surgery duration, and cost-effectivity[7].

Prophylactic salpingectomy is a cost-effective and feasible strategy recommended for reducing the risk of ovarian cancer at the time of gynecologic surgery in women past childbearing age[8]. A similar body of evidence for opportunistic approach at cesarean section is also growing. It has been calculated that opportunistic salpingectomy would lead to approximately 17 fewer ovarian cancer diagnoses, 13 fewer ovarian cancer deaths, and 25 fewer unwanted conceptions compared to tubal ligation for every 10,000 opportunistic salpingectomy at the time of cesarean section[9].

However, salpingectomy refers to the surgical removal of a female reproductive organ. Some women may have apprehensions with respect to salpingectomy due to religious concerns, reduced self-image, or tubal re-anastomosis, and the decision-making process might be influenced by sociodemographic features and lack of knowledge[10-12].

The investigators have experienced denials from women who were seeking tubal ligation as a sterilization procedure during cesarean section after a comprehensive counseling for prophylactic salpingectomy. It was aimed to explore the underlying factors that motivate women for either opport unistic bilateral solpingectomy (OBS) or tubal ligation, particularly focusing on their preferences, knowledge and beliefs toward female sterilization, satisfaction from counseling, and body image following the salpingectomy.

Materials and Methods

This descriptive cohort study was conducted at a secondary center between February and June 2019 and included women who agreed to surgical sterilization with either OBS or tubal ligation. The study was approved by the local administration board and registered with the National Clinical Trials Registry (NCT #03830502). The study were approved by the University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital Local Ethics Committee (approval number: 1182, date: 05/03/2019). Data were prospectively collected and retrospectively analyzed. The study included pregnant and non-pregnant women aged >18 years who either electively or at the time of cesarean section gave their consent for surgical sterilization. However, women with category-1 CS, clinical conditions that lead to planned cesarean hysterectomy such as placenta percreta, a history of ovarian cancer, previous chemotherapy or radiation, those who had previously undergone sterilization or withdrawn their consent prior to the surgery or whose surgical procedure could not be completed were excluded from the study. Once the patients' desire for sterilization was confirmed, surgical sterilization was discussed with the patients in the presence of indications. After the 32th gestational week, pregnant women were initially approached with OBS during cesarean section as a primary surgical sterilization procedure. While a standard bilateral salpingectomy was performed in those who gave consent for salpingectomy, a tubal ligation with Pomeroy technique was performed in those who did not. For nonpregnant women, a laparoscopic tubal ligation was proposed rather than a hysteroscopic procedure due to technical and financial reasons. Further, pregnant women who had vaginal birth were proposed immediate contraception with intrauterine device or oral contraceptives; however, they were irrelevant to the objective of this study. While the primary outcome of the study was the acceptance rate of OBS at the time of cesarean section among pregnant women who seek surgical sterilization, the secondary outcomes were the patients' multifaceted perceptions toward sterilization and OBS and the driving factors behind the decision-making for OBS at the time of cesarean section. The secondary outcomes were measured using a non-validated data collection tool with 14 open-ended questions assessing the factors behind the decision of salpingectomy or tubal ligation (Table 1). The data collection tool did not have a scoring or a range and questioned the underlying reasons for women's acceptance or refusal to salpingectomy in detail, focusing on

Table 1. Outline of the questionnaire

Preference of the women toward the female sterilization
Q1: Why did you prefer tubal operation among other methods?
Q4: Why did you not prefer oral contraceptives?
Q9: What is the leading reason of having tubal sterilization?
Q10: Whose wish was the tubal sterilization?
Q11: What is the leading reason of preferring the removal of tubes instead of tubal ligation?
Q12: If you prefer tubal ligation, what is the leading reason of not choosing the removal of tubes?
Knowledge of the women toward the female sterilization
Q2: Do you believe that you have enough knowledge about other contraception methods?
Q3: Is it possible to reopen your tubes following a tubal ligation and is the success rate high?
Q7: Do you think that you have enough information about what options do you have following the removal of tubes should you ever desire to having another child?
Q8: Do you have enough knowledge about the success rates of assisted reproductive techniques following the removal of tubes?
Religious beliefs of the women about salpingectomy and tubal ligation
Q5: Do you think it is a sin to have tubal ligation?
Q6: Do you think it is a sin to have the tubes removed?
Satisfaction of the women with the counseling
Q13: Are you satisfied with the counseling on the benefits of the removal of the tubes?
Body image following the salpingectomy
Q14: Do you think that you would feel incomplete following the removal of your tubes?

their preferences (Q1, 4, 9-12), knowledge (Q2, 3, 7, 8) and beliefs (Q5, 6) toward female sterilization, satisfaction (Q13) from counseling, and body image following the salpingectomy (Q14). Finally, the open-ended answers were combined under similar answers. The income of the women were scaled between 1 and 3 (1: low-, 2: middle-, 3: high-income), and their occupations were scaled between 1 and 4 (1: unemployed, 2: worker, 3: government employee, 4: tradesmen/craftsmen). Informed consent was obtained.

Statistical Analysis

The data collected through the questionnaires were analyzed using the IBM SPSS Statistics (version 22.0; IBM Corporation, Armonk, NY). The demographic variables and specific scale measures were then presented as mean, standard deviation, standard error of mean, median, interquartile range (IQR), and frequency for the relevant items.

Results

A total of 58 women agreed to undergo a sterilization surgery and gave their consent for it. However, four women were later excluded from the study as three of them withdrew their consent for sterilization prior to the procedure and one of them had extensive adhesions due to which the procedure was abandoned in order not to increase the morbidity in the patient. Finally, a total of 54 surgical sterilization were performed (Figure 1).

The mean age of the women was 37.9±1.8 years and ranged between 34 and 42 years. The mean body mass index was 28.9±3.8 and ranged between 21 and 40. While the median parity was 3 (IQR: 2, minimum: 1, maximum: 6), the median income of the families was medium-income and the median occupation of the partner was governmental employee.

The acceptance rate of OBS at the time of cesarean section among pregnant women and electively among non-pregnant women were 93.5% (n=43/46) and 75% (6/8), respectively.

The answers to the questions regarding the preferences (Q1, 4, 9-12), knowledge (Q2, 3, 7, 8) and beliefs (Q5, 6) toward female sterilization, satisfaction (Q13, 14) from counseling, and body image following the salpingectomy (Q15) were schematized (Figures 2-15).

Discussion

This study revealed that 91% of the participating women overwhelmingly preferred OBS over a standard tubal ligation. The women who preferred tubal ligation over OBS did so due a lack of knowledge about the procedure and further menstruation irregularities, possibility of re-opening of the tubes in the future, reduced body image, and influence of the partner. The main driving factor behind the decision preferring OBS over tubal ligation was the risk-reducing effect for ovarian cancer in 63% of the patients. The second most common motivation was superior pregnancy prevention in 19% of the women.

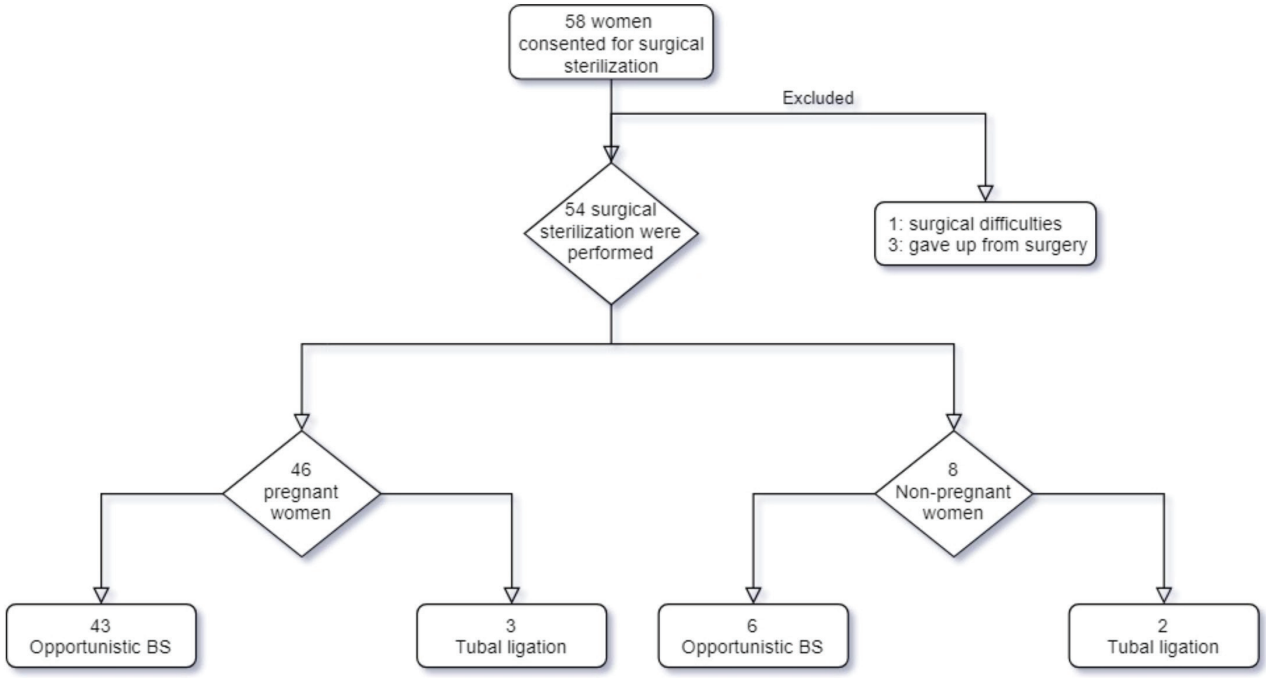

Figure 1. Flowchart of the women included in the study

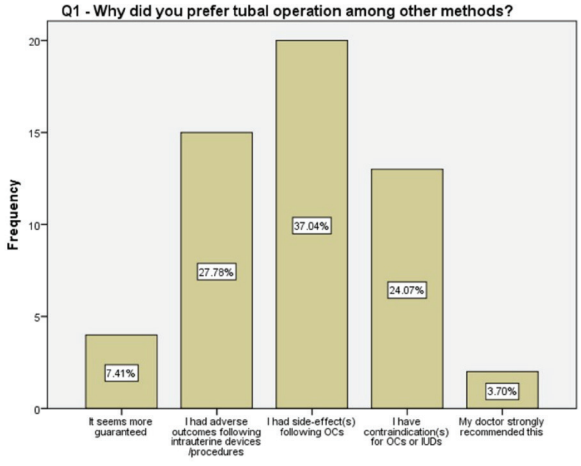

Figure 2. The reason for women's preference of tubal surgery

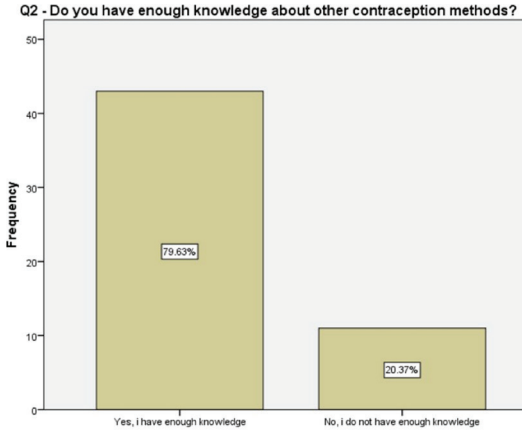

Figure 3. Women's knowledge of other contraception methods

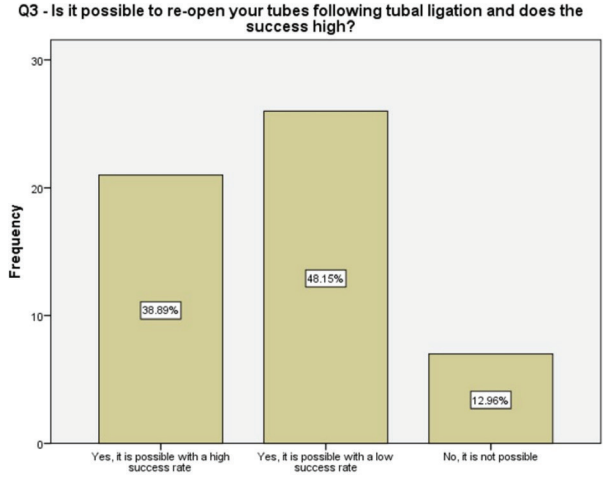

Figure 4. Women's knowledge toward the reversal of tubal ligation

A recent survey study of all women seeking permanent contraception revealed a high accepting OBS rate of 63% in pregnant and 85% in nonpregnant women[11]. Comparable to our results, the two main motivational factors for choosing salpingectomy were superior pregnancy prevention and risk reduction in ovarian cancer with 61% and 33%, respectively[11]. OBS at the time of hysterectomy or interval sterilization has become a routine practice for reducing the risk of ovarian cancer. In 2015, an American College of Obstetricians and Gynecologists Committee Opinion recommended that obstetricians should discuss the possible risk-reducing benefits of bilateral salpingectomy with patients who wish to have permanent contraception[13]. However, the embracement of this strategy at the time of cesarean delivery for pregnant

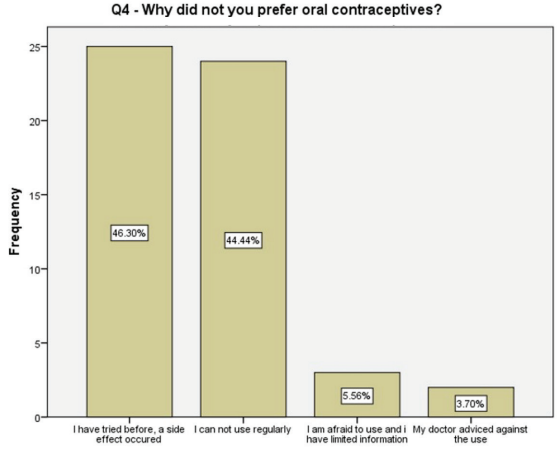

Figure 5. Underlying reasons for not choosing oral contraceptives

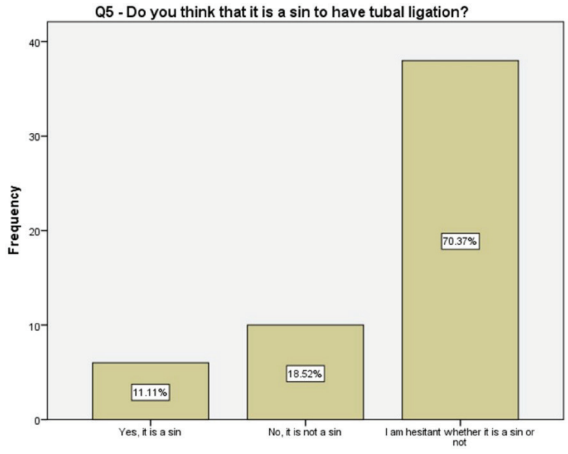

Figure 6. Women's religious beliefs toward the salpingectomy

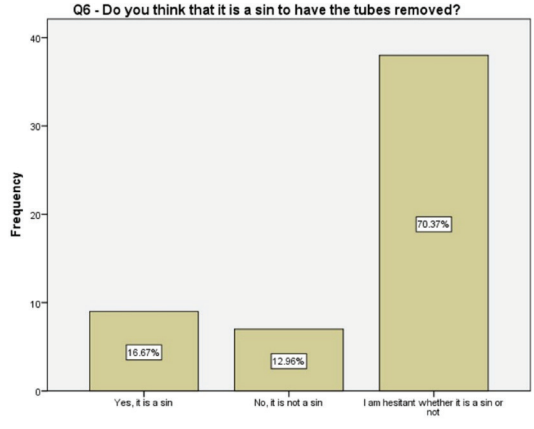

Figure 7. Women's religious beliefs toward the tubal ligation

women who desire permanent sterilization has not been widely adopted, probably due to a lack of available data including the surgical and psychological data in this setting[14]. By 2017, the overall proportion of salpingectomies in patients who underwent a permanent contraception procedure was reported to be as high as 61.5%, in a nationwide data analysis[15]. In a large retrospective cohort study of seven years, almost half of the women preferred OBS as the mode of contraception at either elective or unscheduled cesarean section, which implies that OBS has a high acceptable rate for its higher contraceptive efficacy and risk-reduction benefit for ovarian cancer[16].

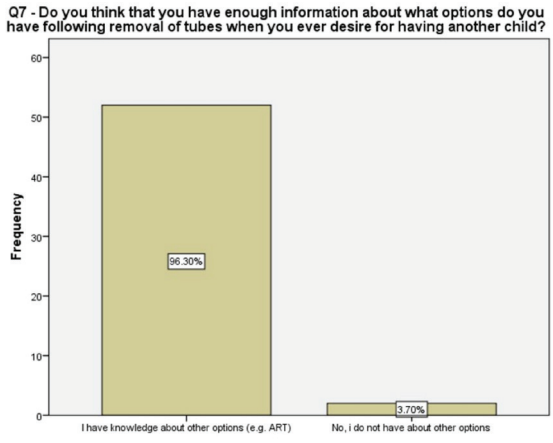

Figure 8. Women's knowledge of the future treatment options following the salpingectomy

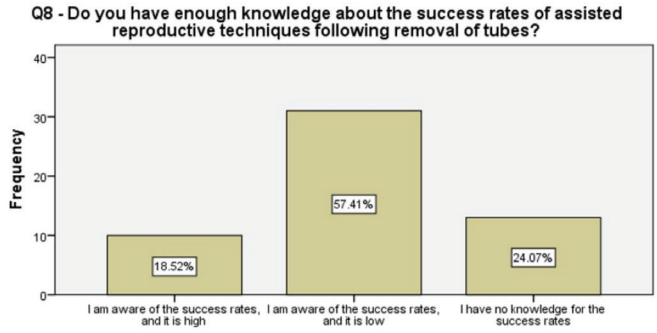

Figure 9. Women's knowledge of the success for future ART following the salpingectomy

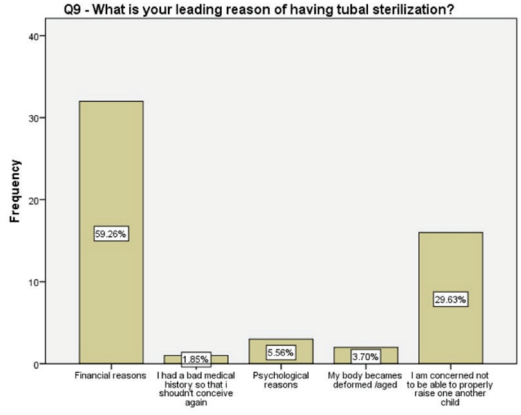

Figure 10. Women's main motivation for having tubal sterilization

About one-fifth of the women reported that they did not have enough information about other contraception methods prior to our detailed counseling, half of the women were not informed properly about the future recanalization of ligated fallopian tubes, 96% of the women were familiar with the options that were available following a salpingectomy should

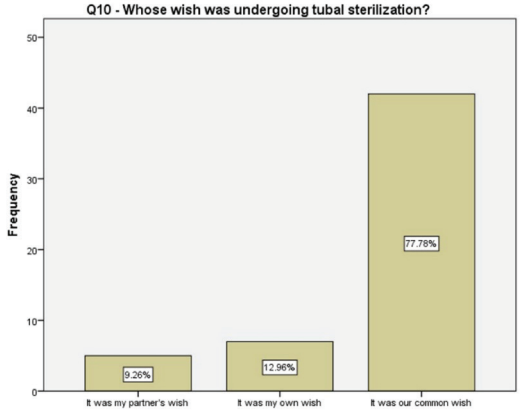

Figure 11. Decision-making on having tubal sterilization

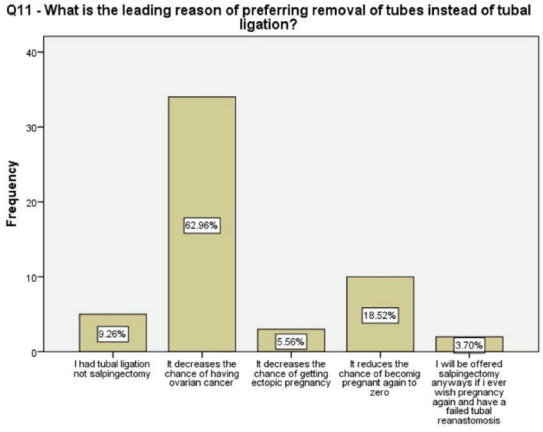

Figure 12. Women's main motivation for having salpingectomy instead of tubal ligation

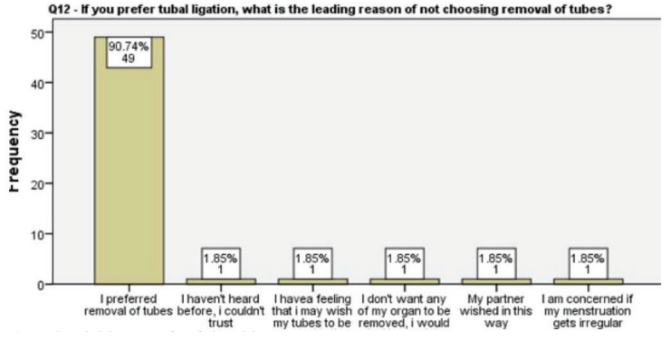

Figure 13. Underlying reasons for refusing salpingectomy

they desire fertility in future, and about 57% of them had accurate information about the success rates of future assisted reproductive techniques. These results enlightened the authors about the importance of the detailed counseling prior to suggesting the OBS option and, more importantly, encouraging the clinicians about non-inferiority of the procedure to comply with this risk-reducing strategy. A survey among physicians performing OBS reported that 46% of the surgeons had barriers such as suspicions about increased complications, decreased ovarian reserve, and increased counseling time while performing salpingectomy along with hysterectomy[17]. Therefore, a fully

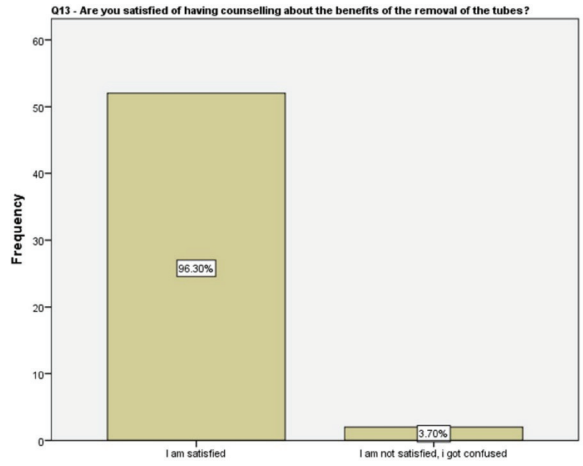

Figure 14. Women's satisfaction with the detailed counseling on salpingectomy

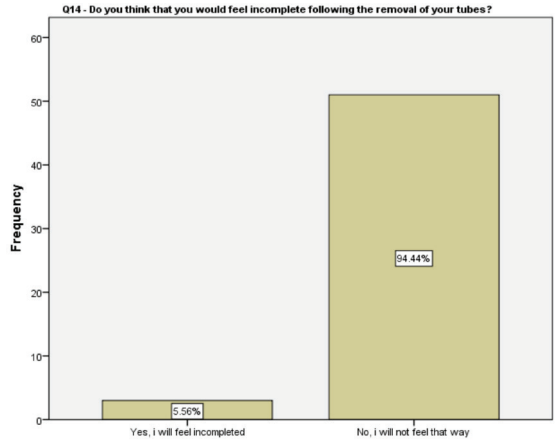

Figure 15. Women's body image upon salpingectomy

detailed counseling on the major advantages of OBS is crucial, following which, 96% of the women in our study reported being satisfied.

Of the women who preferred a tubal surgery in the current study, about 90% either had a contraindication for the use of other oral or intrauterine methods, or experienced side effects, or had difficulties on their regular use. Almost 60% of them sought permanent contraception due to financial difficulties and 30% expressed their concerns on raising more than one child. Although the women with two different answers surely had common thoughts, the latter may have underlying social and lifestyle difficulties that has to be investigated in future studies.

Interestingly, 70% of the women participating in this study were not sure if tubal ligation and removal of tubes are a sin or not. The authors could not find any related information in the literature while writing this article. However, despite that knowledge gap, majority of the women preferred salpingectomy. Although the authors have postulated that it might be related to their idea of body image, 95% of the women stated that they did not feel incomplete following the removal of fallopian tubes and

losing their fertility. Determining the reasons and developing a strategy to overcome this issue and to increase the OBS rates are certainly the matters of future research.

A recent systematic review and meta-analysis of OBS at the time of cesarean section in women who underwent permanent sterilization revealed that although the bilateral salpingectomy slightly increased the operative time, it was comparable to tubal ligation in terms of complications, completion rate, and short-term ovarian reserve with a greater cost-effectiveness[18]. Another larger and more recent systematic review and meta-analysis determined similar results in which OBS was not associated with more adverse outcomes than tubal ligation[19]. Providing those favorable data to the women who seek permanent contraception might have affected the high consent rates for OBS in the current study.

However, while tubal sterilization is a highly effective method of contraception, its effectiveness varies by the surgical method, and the prevalence of regret has been reported to be between 0.9 and 26% with a cumulative probability of 12.7%[20]. Therefore, the future regret rates should be carefully assessed to better inform patients about the local circumstances. Authors postulated that the mean age of 38 years in the current study will probably reduce the regret rates, although they currently do not have the data.

Prophylactic and OBS is an increasing trend among obstetricians and has also proven to be an effective risk-reducing method for ovarian cancer. Future studies should focus on the underlying reasons behind last-minute refusals, the rates and features of unmet contraception needs, and the rates and outcome of patients who desire fertility again in the future following the OBS at the time of cesarean section.

Study Limitations

One of the limitations of the study is the small number of cases. The other limitation is the lack of data related to other factors like education, underlying reasons of last-minute refusals, the rates and features of unmet contraception needs which may also affect the decision of patients.

Conclusion

The acceptance rate of OBS at the time of cesarean section was found to be very high. The main driving factor behind the decision of preferring OBS over tubal ligation was its risk-reducing effect for ovarian cancer and superior pregnancy prevention. Obstetricians are recommended to take every chance of offering OBS at the time of cesarean section to women who desire permanent contraception.

Ethics

Ethics Committee Approval: The study were approved by the University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital Local Ethics Committee (approval number: 1182, date: 05/03/2019).

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.Y., Ç.P., Design: M.Y., Ç.P., Data Collection or Processing: M.Y., Ç.P., Analysis or Interpretation: M.Y., Ç.P., Literature Search: M.Y., Ç.P., Writing: M.Y., Ç.P.

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

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

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Clinical Investigation / Araştırma

DOI: 10.4274/tjod.galenos.2020.90699

Turk J Obstet Gynecol 2020;17:123-7

Efficacy and safety of bevacizumab in Turkish patients with metastatic and recurrent cervical cancer

Metastatik ve rekürren serviks kanser tanılı Türk hastalarda bevasizumabın etkinlik ve güvenliği

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Abstract

Objective: To evaluate the efficacy of bevacizumab a monoclonal, antivascular endothelial growth factor antibody in combination with cytotoxic chemotherapy in Turkish patients with recurrent and metastatic cervical cancer.

Materials and Methods: Data of 64 patients with metastatic or recurrent cervical cancer, receiving bevacizumab with first-line cisplatin or carboplatin and paclitaxel chemotherapy between 2013 and 2017 were retrospectively evaluated.

Results: The mean age of the patients was 49 years (range, 28-68), the median follow-up time was 12 months (range, 2-53), the median progression-free survival (PFS) was eight months, and the median overall survival (OS) was 23 months. All 64 patients received a median of 6 (range, 1-12) bevacizumab and 6 (range, 2-12) chemotherapy cycles. The chemotherapy regimens used with bevacizumab were cisplatin and paclitaxel in 31 (48%) and carboplatin and paclitaxel in 33 (52%) patients. The survival in patients treated with bevacizumab and cisplatin plus paclitaxel was better-particularly in patients with no previous cisplatin-based radiosensitizer therapy-than those treated with carboplatin, paclitaxel, and bevacizumab (p=0.023). The bevacizumab dose was 7.5 mg/kg in 30 patients (47%) and 15 mg/kg in 34 patients (53%) every 21 days. No significant difference was reported in the OS and the PFS between the two groups. While the most common all-grades adverse events were nausea, neutropenia, anemia, and peripheral sensory neuropathy, the most common grade ≥3 adverse events were neutropenia, anemia, and peripheral sensory neuropathy.

Conclusion: Adding bevacizumab to platinum and paclitaxel chemotherapy in a case of metastatic or recurrent cervical cancer is an effective and tolerable treatment for Turkish patients.

Keywords: Cervical cancer, bevacizumab, metastatic

Öz

Amaç: Monoklonal, antivasküler endotelyal büyüme faktörü antikoru olan bevasizumabın sitotoksik kemoterepilerle birlikte kullanımının metastatik, tekrarlayan serviks kanserli Türk hasta popülasyonunda etkinliğini değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Metastatik, tekrarlayan serviks kanseri tanısıyla 2013 ve 2017 yılları arasında ilk seri tedavide sisplatin veya carboplatin ve paklitaksel kemoterapisi ile bevasizumab kullanan hastaların dosyalarını geriye dönük olarak inceledik.

Bulgular: Altmış dört hastanın verisini değerlendirdik. Ortalama yaş 49 (aralık, 28-68), ortanca takip süresi 12 aydı (aralık, 2-53), ortanca progresyonsuz sağkalım süresi 8 ay ve ortanca genel sağkalım süresi 23 aydı. Ortanca bevasizumab ve kemoterapi kür sayısı altı idi. Bevasizumab ile birlikte kullanılan kemoterapi rejimleri 31 hastada (4%8) sisplatin ve paklitaksel, 33 hastada (%52) karboplatin, ve paklitakseldi. Daha önce radyoterapi duyarlılaştırıcı olarak sisplatin almayan hastalarda sağkalım süresi sisplatinli tedavi alan hastalarda karboplatinli tedaviden daha iyiydi (p=0,023). Bevasizumab dozu 30 hastada (%47) 7,5 mg/kg ve 34 hastada (%53) 15 mg/kg 21 günde bir idi. İki grup arasında genel sağkalım ve progresyonsuz sağkalım farkı yoktu. Tüm gradlarda en sık görülen yan etkiler bulantı, nötropeni, anemi ve periferal duysal nöropati, en sık görülen grad ≥3 yan etkiler ise nötropeni, anemi ve periferal duysal nöropatiydi.

PRECIS: Adding bevacizumab to chemotherapy in advanced stage cervical cancer is an effective and tolerable treatment for Turkish patients.

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Received/Geliş Tarihi: 11.09.2019 **Accepted/Kabul Tarihi:** 12.05.2020

Sonuç: Metastatik ve tekrarlayan serviks kanserli Türk hasta popülasyonunda platin ve bevasizumab tedavisi etkin ve güvenli bir tedavidir.
Anahtar Kelimeler: Serviks kanseri, bevasizumab, metastatik

Introduction

Cervical cancer is the third most commonly diagnosed gynecologic malignancy and the third most common cause of death among all gynecologic cancers in the United States[1]. In 2012, cervical cancer accounted for an estimated 528,000 new cancer cases and for 266,000 deaths worldwide[2]. However, it can be prevented and usually cured if detected early[3]. The therapeutic paradigms in the primary management of cervical cancer are well-established, that is, early lesions are usually treated surgically and locally advanced lesions are managed with concurrent cisplatin chemotherapy and pelvic radiation[4,5]. When women with metastatic disease (stage IV B) are treated with systemic cisplatin combination regimens, the median survival is only 9-10 months[4,6,7].

Vascular endothelial growth factor (VEGF) signaling is an important target for cancer therapy because of its role in tumor angiogenesis and its potential role in tumor cell survival. Bevacizumab acts as a monoclonal antibody against VEGF[8,9] and this has been supported by a Phase 3 trial in which the survival of the women with metastatic cervical cancer increased when first-line chemotherapy was added[10]. The current retrospective study was conducted to assess the tolerability, safety, and activity of bevacizumab-containing therapy in Turkish patients with advanced cervical cancer.

Materials and Methods

Data of 64 patients with radiologically confirmed stage IVB, persistent or recurrent cervical cancer diagnosis, and undergoing platinum (cisplatin or carboplatin) plus paclitaxel and bevacizumab treatment between 2013 and 2017 were retrospectively evaluated.

The patients were divided into two categories: those who had previously received chemoradiotherapy (including cisplatin) and those who had not. The patients were classified according to the bevacizumab dose and chemotherapy regimen in which bevacizumab was added to cisplatin or carboplatin, and the metastatic region of the patients was lymphatic or visceral.

Ethical approval was received from the Kartal Dr. Lütfi Kırdar Training and Research Hospital, Non-interventional Clinical Research Ethics Committee (approval number: 2016/514/88/18, date: 29.07.2016). No patient consent was required.

Statistical Analysis

The overall survival (OS) and the progression-free survival (PFS) were calculated using the Kaplan-Meier method starting from the first day of the chemotherapy. Data were expressed as mean, standard deviation, median lowest value, median highest value, frequency, and rates. All p-values were 2-sided, and p=0.05 was considered as statistically significant. Data were analyzed using the SPSS software version 22.

Results

The mean age of the 64 patients whose data were included in this study was 49 years (range, 28-68) (Table 1), and the median follow-up time was 12 months (range, 2-53). While the median PFS was 8 months, the median OS was 23 months (Table 2).

Table 1. Clinicopathologic and treatment characteristics

Characteristics		No	%
Age	20-29	1	1.6
	30-39	14	21.9
	40-49	14	26.6
	50-59	19	29.7
	60-69	13	20.3
Grade	1	5	7.8
	2	16	25.0
	3	10	15.6
	Unknown	29	45.3
Performance status	0	38	59.4
	1	24	37.5
	2	2	3.1
Prior chemoradiotherapy (cisplatin)	No	39	60.9
	Yes	25	39.1
Prior hysterectomy	No	53	82.8
	Yes	11	17.2
Chemotherapy regimen	Cisplatin/paclitaxel	31	48.0
	Carboplatin/paclitaxel	33	52.0
Initial stage	1B	14	21.5
	2A	1	1.5
	2B	12	18.5
	3	9	13.8
	4A	11	16.9
	4B	18	27.7
Histological type	Squamous cell	57	89.1
	Adenocarcinoma	5	7.8
	Adenosquamous	2	3.1
Bevacizumab dose	7.5 mg/kg every 21 days	30	47.0
	15 mg/kg every 21 days	34	53.0
Metastasis region	Systemic	25	39.0
	Lymphatic	39	61.0

The 64 treated patients received a median of six (range, 1-12) bevacizumab cycles and six (range, 2-12) chemotherapy cycles. Of those, 25 patients (39%) had previously received chemoradiotherapy with cisplatin. The survival with cisplatin, paclitaxel, and bevacizumab treatment was better in patients without a previous cisplatin-based radiosensitizer therapy than those treated with carboplatin, paclitaxel, and bevacizumab (p=0.02). There was no difference in the survival between the two regimens in patients who had previously received cisplatin (p=0.55) (Figures 1, 2).

The recommended bevacizumab dose was 7.5 mg/kg in 30 patients (47%) and 15 mg/kg in 34 patients (53%) every 21 days. No significant difference was observed in the OS and the PFS between the two groups. While 17 patients (26%) had metastases at the time of diagnosis and the median survival for them was 10 months, 47 patients (74%) had recurrent disease with the median survival of 24 months (p=0.14). The metastatic regions were visceral organs in 25 (39%) and lymphatic region in 39 patients (61%). The median survival was 10 months in patients with visceral and 51 months in those with lymphatic metastases (p=0.10).

Table 2. Follow-up and survival characteristics

		Min	Max	Median	n	%
Follow-up duration (months)		2	53	12	-	-
Response	Complete response	-	-	-	9	14.0
	Partial response	-	-	-	37	58.0
	Stable	-	-	-	4	6.0
	Progression	-	-	-	14	22.0
Overall response	Present	-	-	-	86	78.0
	Absent	-	-	-	14	22.0
Status	Died	-	-	-	29	45.0
	Alive	-	-	-	35	55.0
Overall survival (OS) (months)		-	-	23	-	-
OS rate	1 Year OS	-	-	-	-	66.0
	2 Year OS	-	-	-	-	44.0
Progression	Present	-	-	-	47	73.0
	Absent	-	-	-	17	27.0
Progression-free survival (PFS) (months)		-	-	8	-	-
PFS Rate	1 Year PFS	-	-	-	-	35
	2 Year PFS	-	-	-	-	24

Min: Minimum, Max: Maximum

While the most common all-grade adverse events were nausea, neutropenia, anemia, and peripheral sensory neuropathy, the most common grade ≥3 adverse events were neutropenia, anemia, and peripheral sensory neuropathy. Fistula and toxic death were not observed (Table 3).

Discussion

This retrospective study was conducted with an aim to assess the tolerability, safety, and activity of bevacizumab-containing therapy in Turkish patients with advanced cervical cancer. Although, chemotherapy remains the standard treatment for

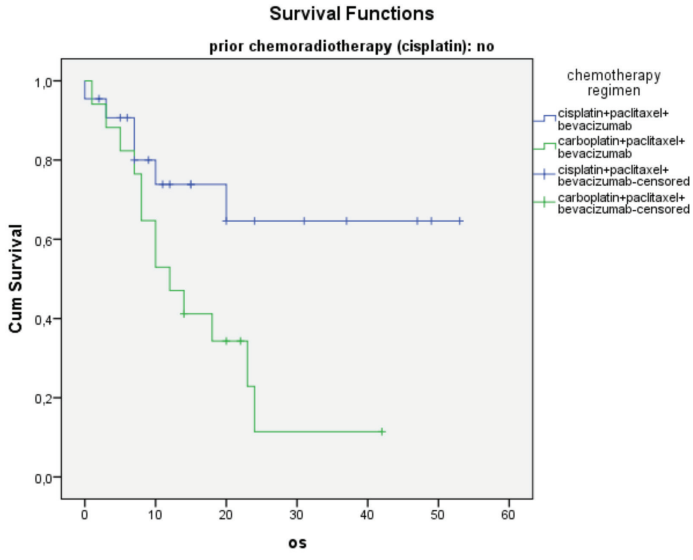

Figure 1. Overall survival according to chemotherapy regimen (prior chemoradiotherapy absent subgroup)

OS: Overall survivol

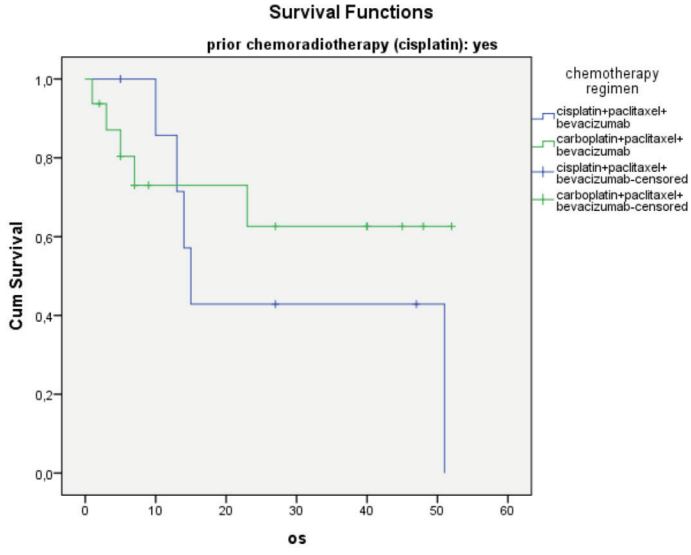

Figure 2. Overall survival according to chemotherapy regimen (prior chemoradiotherapy present subgroup)

OS: Overall survival

Table 3. Adverse events

Adverse effect	Grade (no)				
	0	1	2	3	4
Leucopenia	40	20	3	4	0
Thrombocytopenia	55	4	3	2	0
Neutropenia	40	19	2	3	0
Anemia	26	17	13	6	2
Hypertension	62	4	3	0	0
Thrombosis	63	0	0	1	0
Constitutional	42	18	2	2	0
Neuropathy	51	9	3	4	0
Hepatotoxicity	61	2	1	0	0
Nausea	38	18	6	2	0
Gastrointestinal bleeding	57	2	5	0	0
Bowel obstruction	63	0	1	0	0
Pain	27	5	3	2	0

patients with stage IVB, persistent or recurrent cervical cancer, no long-term disease control is achieved through this treatment[11]. Based on the results of the GOG204 and JCOG0505 studies, paclitaxel/cisplatin and paclitaxel/carboplatin are considered to be the recommended treatments for patients with recurrent cervical cancer[12,13]. VEGF plays a key role in the angiogenesis of the tumor, and although it is directly related to the extent of the disease, it is inversely related to the survival[14]. Bevacizumab is an antibody that recognizes and neutralizes all major isoforms of VEGF, inhibits endothelial cell proliferation, and inhibits receptor binding and vascular formation[15].

In this study, the median PFS was reported as 8 months and the median OS as 23 months, and the overall response rate was 78%. About 39% of the patients had previously received a platinum-based radiosensitizer therapy. The survival with cisplatin, paclitaxel, and bevacizumab treatment was better in patients without a previous cisplatin-based radiosensitizer therapy than those who were treated with carboplatin plus paclitaxel and bevacizumab (p=0.023). No difference was observed in the survival between the two regimens in patients who had previously received cisplatin (p=0.556). Also, there was no significant difference in the OS and the PFS between patients with bevacizumab doses of 7.5 mg/kg (n=30) and patients with 15 mg/kg (n=34). The survival was 10 months in patients with systemic and 51 months in patients with lymphatic metastases. Although there was a numeric difference between the two groups, there was no statistical significance. This may be due to the insufficient number of patients (p=0.10). There was no toxic death due to treatment, no patient developed fistula, and grade ≥3 and higher side effects were in-line with the literature. The efficacy of bevacizumab has been seen in a wide range of solid tumor types, including in case of advanced cervical cancer. Wright et al.[16] in 2006 retrospectively evaluated 6 patients who had previously received median 3 systemic treatments. The authors reported that patients receiving bevacizumab with chemotherapy had a response rate of 67% and a median time of 4.3 months to tumor progression. Therefore, in this small cohort study, bevacizumab was well-tolerated.

In the first Phase 2 study conducted by Monk et al.[17] in 2009, the efficacy of bevacizumab alone in patients receiving first- or second lines of systemic therapy for recurrent disease was investigated. The PFS in the study was reported as 3.4 months and the OS as 7.29 months. It was therefore shown to be an effective and well-tolerated treatment in the second- and third lines of therapy.

Later, in 2011, Schefter et al.[18] conducted Phase 2 and 3 studies. In this study, 49 local advanced (stage IB-IIIB) patients were treated with chemoradiotherapy and bevacizumab 10 mg/kg every 2 weeks. Researchers concluded that the addition of bevacizumab in chemoradiotherapy is a feasible and safe treatment.

In Phase 3 trial, the investigators randomly assigned 452 patients to chemotherapy with or without bevacizumab at a dose of 15 mg/kg. Chemotherapy consisted of cisplatin plus paclitaxel or topotecan, and paclitaxel. Topotecan/paclitaxel was not superior to cisplatin/paclitaxel. Bevacizumab, as compared with chemotherapy alone, was associated with an increased incidence of grade 2 or higher hypertension, grade 3 or higher thromboembolic event, and grade 3 or higher gastrointestinal fistulas. The addition of bevacizumab to a combination chemotherapy in patients with recurrent, persistent, or metastatic cervical cancer was associated with an improvement of 3.7 months in median OS[10].

Further, in 2016, Sugiyama et al.[19] showed that cisplatin plus paclitaxel and bevacizumab treatment are effective, tolerable, and safe in Japanese patients with a small single-arm study (seven patients).

Although, owing to cytological screening and DNA testing for high-risk human papilloma virus types, the rate of cervical cancer has significantly reduced in developed countries, it, however, remains a major problem in undeveloped countries. If diagnosed at an early stage, patients can be cured by surgery, radiotherapy, and chemoradiotherapy treatments. However, in patients with recurrent metastatic disease or after platinum therapy, survival is poor with systemic treatments, and most cases cannot be cured. The newly targeted therapies and immunotherapy trials in advanced-stage patients continue to produce better survival outcomes and cure. Preventive vaccination and early detection of the disease are very important factors in survival. There is no study in the literature that compares carboplatin-paclitaxel and bevacizumab treatment with cisplatin-paclitaxel and bevacizumab treatment in patients with cervical cancer, and there is no study comparing the dose of bevacizumab 7.5 mg/kg with a dose of 15 mg/kg. In this retrospective study, we aimed to report our experience with

such subjects and the efficacy and safety data of bevacizumab in our patient population.

Study Limitations

Being a retrospective study, covering small number of patients and short follow-up time are the limitations of the study.

Conclusion

The introduction of bevacizumab has been one of the most important recent advances for patients with advanced-stage cervical cancer. It is an effective and tolerable treatment for Turkish population with metastatic or recurrent cervical cancer.

Ethwics

Ethics Committee Approval: Ethical approval was received from the Kartal Dr. Lütfi Kırdar Training and Research Hospital, Non-interventional Clinical Research Ethics Committee (approval number: 2016/514/88/18, date: 29.07.2016).
Informed Consent: No patient consent was required.
Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: M.A., Design: M.G., Data Collection or Processing: D.T., H.S., M.D., M.İ., Literature Search: M.Ö., Ö.E.
Conflict of Interest: No conflict of interest was declared by the authors.
Financial Disclosure: The authors declared that this study received no financial support.

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Clinical Investigation / Araştırma

DOI: 10.4274/tjod.galenos.2020.70104

Turk J Obstet Gynecol 2020;17:128-32

The effects of menopausal uterine fibroids on the prognosis of endometrium cancer

Menapoz sonrasına bırakılan uterin miyomların gelişen endometrium kanseri üzerine etkilerinin incelenmesi

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Abstract

Objective: This study aimed to evaluate any potential associations between uterine leiomyomas and endometrial cancer.

Materials and Methods: This is a retrospective study of 153 female patients who have been operated because of endometrial carcinoma in our hospital between 2012 and 2017. Data were collected from hospital records. Study participants were divided into two groups according to the presence and absence of leiomyomas. These two groups were compared in terms of histopathological adenocarcinoma type, nuclear and histological grades, disease stage, para-aortic lymph node involvement, and myometrial invasion. For data analysis, Statistical Package for Social Sciences 15.0 software package was used. Comparison between the two groups was made using the chi-square test, and each variable was tested with the Student's t-test for statistical significance.

Results: No statistically significant differences were found between the groups with respect to age, tumor type, myometrial invasion, nuclear grade, or histological grade (p>0.05 for all). A significant difference was found between leiomyomas presence and lymph node metastases. The lymph node metastases were more common in patients without uterine leiomyomas (20.55%) than in those with them (5%; p=0.004). Analysis using the Federation of Obstetrics and Gynecology stages for the presence of leiomyomas indicated that the mean stages were 1A and 1B in patients with and without uterine leiomyomas, respectively (p=0.002).

Conclusion: Uterine leiomyomas did not adversely affect the prognosis of patients with endometrial carcinoma. Moreover, lymph node involvement was less common, and stages were lower in patients with leiomyomas.

Keywords: Endometrial carcinoma, uterine leiomyomas, myoma uteri, risk factors, post-menopause

Öz

Amaç: Uterus leiomyomları ve endometriyal kanser arasındaki olası ilişkileri araştırmayı amaçladık.

Gereç ve Yöntemler: Bu çalışmaya hastanemizdeki 2012-2017 yılları arasında endometriyal karsinom nedeniyle cerrahi girişim uygulanan 153 hasta dahil edildi. Hasta dosyaları retrospektif olarak incelendi. Leiomyom varlığı ve yokluğuna göre iki gruba ayrılan hastalar her iki grup karsinomun histopatolojik tipi, nükleer ve histolojik derece, hastalık evresi, paraaortik lenf nodu tutulumu ve miyometriyal invazyon açısından karşılaştırıldı. Çalışma verilerinin analizinde SPSS 15.0 yazılım paketi, Student's t-testi ve ki-kare testi kullanıldı.

Bulgular: Leiomyoma varlığı ile yaş, tümör tipi, miyometriyal invazyon, nükleer derece veya histolojik derece arasında istatistiksel olarak anlamlı bir ilişki bulunmadı (hepsi için, p>0,05). Leiomyom ve lenf nodu metastazlarının varlığı arasında anlamlı ilişki saptandı. Lenf nodu metastazları uterus leiomyomları olmayan hastalarda (%20,55) iken uterin leiomyomalı hastalardan %5 ile daha sıktır (p=0,004). Hastalık evrelerinin leiomyom varlığı ile analizi, uterus leiomyomları olan hastalarda ortalama evre 1A iken, uterus leiomyomları olmayan hastalarda ortalama evre 1B olduğunu gösterdi (p=0,002). Diğer bir deyişle, uterin leiomyomu olan hastalarda lenf nodu tutulumu daha az yaygındı ve endometriyal karsinomda hastalık evreleri daha düşüktür.

Sonuç: Uterin leiomyomlar, endometriyal karsinomun prognostik değişkenleri üzerinde olumsuz bir etkiye sahip değildir.

Anahtar Kelimeler: Endometrial karsinom, uterin leiomyom, myom uteri, risk faktörleri, menopoz sonrası

PRECIS: Uterine fibroids in post-menopausal women do not have a negative impact on developing endometrium cancer.

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Received/Geliş Tarihi: 18.07.2019 **Accepted/Kabul Tarihi:** 09.03.2020

Introduction

The prevalence of endometrial carcinoma has a significant tendency to increase in developed countries and has become the most common cancer of the female genital tract in these countries[1,2]. Endometrial carcinoma is the most prevalent gynecological malignancy in the United States (USA), and 60,050 new cases of endometrial carcinoma with 10,470 endometrial cancer-related deaths have been reported in 2016[3].

Based on the 2012 data, the estimated numbers of new cancer cases and cancer deaths worldwide were 14.1 million and 8.2 million, respectively[4]. Endometrial carcinomas accounted for 3.6% of new cancer cases and 1.8% of cancer deaths[5]. Of patients, 90% were over the age of 50 years, and the mean age was 63 years. However, 4% of patients diagnosed with endometrial carcinoma were under the age of 40 years[6].

The prevalence of uterine leiomyomas is also high among women, and one out of every four women develops uterine leiomyoma. In a study conducted in the USA, leiomyomas were responsible for 46% of a total of 1.7 million hysterectomy procedures performed because of benign tumors[7].

Every leiomyoma is derived from a single progenitor myocyte; therefore, each leiomyoma in the same uterus may have an independent cytogenetic origin[8]. The essential mutation underlying tumorigenesis remains unknown; however, karyotype abnormalities have been found only in 40% of leiomyomas. Several specific aberrations have been detected in chromosomes 6, 7, 12, and 14, which are associated with the direction and rate of tumor growth[9].

A reduction is usually seen in the leiomyoma size during the postmenopausal period, and a new tumor development is usually rare during this period. Nearly all leiomyomas regress after menopause, which also result in the resolution of complaints associated with leiomyomas, such as bleeding and pain[10]. As physicians, we always favor conservative approaches in leiomyomas in premenopausal women for the abovementioned reasons and consider surgery as the last treatment option. During transition to menopause, we try to avoid surgery and follow up women with leiomyomas under medical treatment, if possible.

However, we do not know whether these leiomyomas, which are left uncontrolled, have any unfavorable effect on endometrial carcinoma, in the event that the patients develop this condition. Is it possible that leiomyomas left in place are associated with unfavorable prognostic factors if endometrial carcinoma occurs? Are there any associations between leiomyomas and factors that may impact survival? In this study, we aimed to investigate the potential relationships between endometrial cancer and fibroids.

Materials and Methods

Patients with endometrial carcinoma who were operated in the obstetrics and gynecology clinics between 2012 and 2017 were included in this study. Histopathological studies conducted in the department of pathology of our hospital were retrospectively collected. A total of 153 patients were enrolled, and Ethics approval was obtained from the University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar Training and Research Hospital, Institutional Review Board (approval number: 2018/514/122/18, date: 30/01/2018).

In our study, we investigated whether the presence or absence of leiomyoma impacts the prognosis of endometrial carcinoma. Accordingly, patients with and without uterine leiomyomas were compared according to demographics, such as age, histopathological endometrial carcinoma type, nuclear and histological grades, disease stage, pelvic para-aortic lymph node (LN) involvement, and myometrial invasion depth. Potential associations between these parameters and the uterine leiomyoma size were also compared in subjects with uterine leiomyomas.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation, and categorical variables as percentages. The Student's t-test was used to compare normally distributed variables, and the results were interpreted within 95% confidence interval with a significance level of $p<0.05$. Statistical Package for Social Sciences software for Windows 15.0 was used for statistical analyses. The chi-square test was used for categorical variables.

Results

A total of 153 patients were included in this study, and of whom, 135 had endometrioid endometrial carcinoma and 18 other types of endometrial carcinoma. Furthermore, 80 had concomitant leiomyomas, with 64 having tumors less than 3 cm and 16 larger than 3 cm. Myometrial invasion was less than one-half in 97 patients and more than one-half in 56. LN metastasis assessment revealed that 134 patients were LN positive and 19 negative. Of all patients, 52.99% were under the age of 60 years, and 88.24% had endometrioid tumors. Leiomyomas were present in 80 patients (52.29%), and tumors were less than 3 cm in size in 64 (80%) of these patients. Demographic characteristics of these patients are shown in Table 1.

Comparisons of age, tumor type, invasion, and LN metastases by the presence of leiomyomas revealed a significant association between leiomyoma presence and LN metastases. LN metastases were significantly more common in patients without leiomyomas (20.55%) than in patients with leiomyomas (5%; $p=0.004$). No significant associations were found between leiomyoma presence and age, tumor types, or invasion ($p>0.05$ for all; Table 2).

The stage comparisons by leiomyoma presence revealed that the mean stages were 1A and 1B in patients with and without uterine leiomyomas, respectively ($p=0.002$). The comparisons of nuclear and histological grades by leiomyoma presence did not reveal any significant associations ($p>0.05$).

The comparisons of age, tumor type, invasion, and LN metastases by leiomyoma size indicated that the prevalence of LN metastases was significantly higher in patients with leiomyomas larger than 3 cm (18.75%) than in those with less than 3 cm (1.56%; p=0.005). No significant associations were found between leiomyoma size and age, tumor type, and invasion (p>0.005 for all; Table 3).

The comparisons of stages by leiomyoma presence did not reveal any significant associations between the leiomyoma size and disease stages (p>0.05), and the assessment of nuclear and histological grades by the leiomyoma size did not reveal any significant associations either (p>0.05).

The assessments of nuclear and histological grades by age in overall patients revealed a weak correlation. Nuclear (r=0.184, p=0.023) and histological grades (r=0.193, p=0.017) increased as the age increased (Table 4).

When fibroid presence was examined by regression analysis, it was not associated with age, tumor type, and invasion, and fibroid presence was found to decrease the risk of LN metastasis by 3.89 times (Table 5).

Table 1. Demographics of patients

		n	%
Age (years)	<60	80	52.29
	≥60	73	47.71
Tumor type	Endometroid	135	88.24
	Other	18	11.76
Myometrial invasion	<1/2 invasion	97	63.40
	>1/2 invasion	56	36.60
Pelvic para-aortic lymph node metastasis	Positive	134	87.58
	Negative	19	12.42
Stage	1A	85	55.56
	1B	29	18.95
	2	14	9.15
	3A	4	2.61
	3B	1	0.65
	3C	12	7.84
	4A	7	4.58
	4B	1	0.65
Nuclear grade	1	30	19.61
	2	100	65.36
	3	23	15.03
Histologic grade	1	56	36.60
	2	71	46.41
	3	26	16.99
Myoma	Negative	73	47.71
	Positive	80	52.29
Size of myoma (cm)	<3	64	80.00
	≥3	16	20.00

Table 2. Comparison of age, tumor type, invasion, and lymph node metastasis according to the presence of myoma

		Myoma				p
		Negative		Positive		
		n	%	n	%	
Age (years)	<60	38	52.05	42	52.50	0.956
	≥60	35	47.95	38	47.50	
Tumor type	Endometroid	63	86.30	72	90.00	0.478
	Other	10	13.70	8	10.00	
Myometrial invasion	<1/2 invasion	41	56.16	56	70.00	0.076
	>1/2 invasion	32	43.84	24	30.00	
Lymph node metastasis	Negative	58	79.45	76	95.00	0.004
	Positive	15	20.55	4	5.00	

Table 3. Comparison of age, tumor type, invasion, and lymph node metastasis according to the size of myoma

		Myoma size (cm)				p
		Under 3		Three and over		
		n	%	n	%	
Age (years)	<60	35	54.69	7	43.75	0.433
	≥60	29	45.31	9	56.25	
Tumor type	Endometroid	59	92.19	13	81.25	0.192
	Other	5	7.81	3	18.75	
Myometrial invasion	<1/2 invasion	47	73.44	9	56.25	0.180
	>1/2 invasion	17	26.56	7	43.75	
Lymph node metastasis	Negative	63	98.44	13	81.25	0.005
	Positive	1	1.56	3	18.75)	

Table 4. Correlation between age and nuclear and histological grades in all patients

		Age	Nuclear grade	Histologic grade
Age (years)	r	-	0.184	0.193
	p		0.023	0.017
Nuclear grade	r	0.184	-	0.742
	p	0.023		0.000
Histologic grade	r	0.193	0.742	-
	p	0.017	0.000	

Table 5. Presence of fibroids is examined by regression analysis

Variables in the equation									
		B	S.E.	Wald	df	Sig.	Exp (B) Lower	95% CI for EXP (B) Upper	
Step 1[a]	Age	0.034	0.033	1.101	1	0.294	1.035	0.971	1.103
	Type (1)	-3.346	0.888	14.194	1	0.000	0.035	0.006	0.201
	Inv (1)	-3.009	0.934	10.383	1	0.001	0.049	0.008	0.308
	Myoma (1)	1.360	0.742	3.362	1	0.067	3.897	0.910	16.680
	Constant	-1.211	2.254	0.289	1	0.591	0.298	-	-

[a]Variable(s) entered on step, 1: Age, type, invasion, and myoma, CI: Confidence interval

Discussion

Important factors for recurrence and survival in endometrial cancer are age, tumor type, grade, myometrial invasion, and LN metastasis. Similarly, the type of operation may vary after surgical staging, although sometimes, it is sufficient to perform a type 1 hysterectomy, and in some cases, radical surgery such as pelvic para-aortic LN dissection and omentectomy may be required[11]. In this study, we compared the prognostic factors such as age, tumor type, grade, amount of myometrial invasion, and LN metastasis by dividing endometrium cancer patients into two groups. According to the presence or absence of fibroids or adenomyosis, this study aimed to investigate whether fibroids have a negative effect on endometrial cancer.

The relationship between fibroid presence and endometrial cancer was first suspected by Giammalvo in 1958. He reported an increase in the frequency of adenomyosis in women who were operated for endometrial cancer[12]. In a study by Greenwood in 1976, adenomyosis was seen in 19.4% of 175 patients operated for endometrial cancer, 20.5% in 254 endometrial hyperplasia, and 16.7% in 203 prolapse cases and found to be statistically similar[13]. On the other hand, 136 patients with endometrial cancer and 222 with hysterectomy for uterine prolapse were examined in another study. The incidence of adenomyosis was found to be higher in cases of endometrial cancer, especially in women with postmenopausal endometrial cancer, reporting 1.5-2 times more adenomyosis and uterine fibroids[14]. A study in Turkey examined hysterectomy specimens from those operated because of benign conditions and found that the incidence of fibroids and adenomyosis was 21.6%[15]. When 130 endometrial cancers were examined in a study by Menczer et al.[16], the frequency of fibroids was 56.9%. In our study, the presence of fibroids or adenomyosis was 52.29% in patients with endometrial cancer and 2-2.5 times higher than the general population, and this was found to be consistent with previous studies.

The degree of myometrial invasion is one of the most important parameters in surgical staging. According to the research of Taneichi et al.[17] with 362 endometrial cancers in 2014, myometrial invasion is deeper in the case of adenomyosis and fibroids and two times deeper in myometrial invasion. They claimed that even with the presence of adenomyosis, recurrence and mortality did not increase, and it may lead to deep myometrial invasion. This claim was not supported in other studies[16,18-20].

In a study by Studzinski et al.[18], 136 cases were examined, and fibroids did not affect the stage and surveillance of endometrial cancer patients. Similarly, 130 patients with endometrial cancer were examined in another study; myometrial invasion, LN invasion, and metastasis presence and pathology did not change the stage[16]. Gizzo et al.[19] examined 289 endometrial cancers in their study and reported that in the presence of adenomyosis and fibroids, the stage is lower; myometrial invasion and LN metastasis were also less common. In our study, even if not statistically significant, the presence of deep endometrial invasion in the presence of fibroids was less common. Similarly, patients who have myoma were diagnosed at an earlier stage.

Metastasis in endometrial cancer usually occurs by lymphatic route. LN metastasis is crucial for disease recurrence and surveillance[20]. According to a study, with the presence of adenomyosis and fibroids, LN metastasis has been seen less commonly[21]. A study by Koshiyama et al.[22] in 2004 divided 179 endometrial cancer patients into four groups, namely, adenomyosis, endometriosis, fibroids, and endometrial cancer alone. Patients were reported to be diagnosed at an earlier age in the presence of adenomyosis and fibroids. They reported that this may be due to the patients' earlier admission to hospital because of additional symptoms. In our study, in the presence of fibroids, LN metastasis was detected less frequently and was found to be consistent with the literature.

In our study, we also divided the patients into two groups: 3 cm below and above. We classified the patients according to the fibroid size and compared the variables, including age, tumor type, myometrial invasion, and LN metastasis. When we examined the literature, we could not find any study examining the relationship between fibroid size and endometrial cancer. In our study, no significant relationship was found between fibroid size and age, tumor type, and myometrial invasion. Thus, statistically similar results were observed. LN metastasis was found to be higher in patients with fibroid size over 3 cm,

and this was statistically significant. Since the total number of patients with fibroids and LN metastasis is very small, we believe that larger randomized studies are needed.

Study Limitations

This study has limitations that should be acknowledged. Firstly, the number of patients is low, especially in some subgroups. Secondly, there is a lack of data on long-term results of patients. Finally, we had difficulty comparing our study with other studies in the literature because there were not enough studies.

Conclusion

Uterine leiomyomas did not adversely affect the prognosis of patients with endometrial carcinoma. In addition, LN involvement was seen less, and stages were lower in patients with leiomyomas.

Ethics

Ethics Committee Approval: Ethics approval was obtained from the University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar Training and Research Hospital, Institutional Review Board (approval number: 2018/514/122/18, date: 30/01/2018).
Informed Consent: Retrospective study.
Peer-review: Internally peer-reviewed.

Author Contributions

Concept: Ö.S., R.D., G.G., Z.M.P., A.D.A., M.S.Ç., Design: Ö.S., R.D., G.G., Z.M.P., A.D.A., M.S.Ç., Data Collection and Processing: Ö.S., R.D., G.G., Z.M.P., A.D.A., M.S.Ç, Analysis and Interpretation: Ö.S., R.D., G.G., Z.M.P., Literature Search: Ö.S., R.D., G.G., Z.M.P, Writing: Ö.S., R.D., A.D.A.
Conflict of Interest: The authors declare no conflicts of interest.
Financial Disclosure: This study did not receive any financial support.

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Clinical Investigation / Araştırma

DOI: 10.4274/tjod.galenos.2020.25675

Turk J Obstet Gynecol 2020;17:133-8

The impact of Loop Electrosurgical Excision Procedure and cold-knife conization training model on the surgical skills and confidence level

Döngü Elektrocerrahi Eksizyon Prosedürü'nü ve soğuk konizasyon eğitim modelinin cerrahi beceri ve güven üzerine etkisi

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Abstract

Objective: The purpose of this study is to evaluate the impact of loop electrosurgical excision procedure (LEEP) and cold-knife conization (CKC) active training model on the surgical education and confidence levels of gynecologists.

Materials and Methods: The LEEP and CKC hands-on training model consists of sausage, which is 2.5 cm in diameter, as cervix; plastic cup as vagina; foam rubber as posterior and anterior fornices; and cotton plate as the leukoplakia area. In total, 34 participants performed LEEP and CKC procedures on the training model under the guidance of mentors after theoretical lessons about the transformation zone, indications, and surgical techniques of LEEP and CKC. Afterward, a web-based survey was conducted to measure the effectiveness of this surgical model, and participants graded their learning and confidence levels on the same.

Results: We evaluated the educational levels of the course, which were based on the basic surgical steps of LEEP and CKC procedures, and the confidence levels of the participants with regard to the previous practice or expertise of LEEP and CKC. Importantly, participants in each group had similar learning gains irrespective of previous practice or expertise. Despite a significantly higher pre-course confidence level of participants who had previously performed LEEP ($p<0.001$) and CKC ($p<0.001$) against their non-practitioner counterparts, the post-course confidence levels were similar in each group ($p=0.127$ and $p=0.845$, respectively). In both groups, the participants had increased mean confidence scores, which were statistically significant for participants who had not previously performed the procedures ($p=0.003$, LEEP and $p=0.002$, CKC, respectively).

Conclusion: This surgical training model on LEEP and CKC can impart a better level of education in participants, irrespective of their previous expertise/practice.

Keywords: LEEP, conization, surgery, cervix, education

Öz

Amaç: Döngü Elektrocerrahi Eksizyon Prosedürü (LEEP) ve soğuk konizasyon (SK) eğitim modelinin jinekologların cerrahi eğitimi ve güven duygusu üzerine etkisini değerlendirmektir.

Gereç ve Yöntemler: LEEP ve SK uygulamalı eğitim modeli; 2,5 cm çapta bir serviksi oluşturan sosis, vajinayı oluşturan plastik bardak, posterior ve anterior forniksi oluşturan köpük madde ve lökoplaki alanını sembolize eden pamuktan oluşmuştur. Transformasyon zonu, LEEP ve SK endikasyonları ve cerrahi tekniği üzerine verilen teorik derslerden sonra, toplamda 34 katılımcı LEEP ve SK eğitim modelini eğitmenler eşliğinde uygulamıştır. Uygulama

PRECIS: The surgical training model on LEEP and cold knife conisation will be used to improve the surgical skills and confidence level of gynecologists.

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Received/Geliş Tarihi: 22.10.2019 **Accepted/Kabul Tarihi:** 19.03.2020

sonrası, bu cerrahi modelin etkinliğini değerlendirmek üzere web tabanlı bir anket çalışması yapılmış olup, katılımcılar öğrenme düzeylerini ve güven duygusunu değerlendirmiştir.
Bulgular: Kursun LEEP ve SK'ye ait temel cerrahi basamaklar ve güven duygusu üzerine etkisi daha önce LEEP ve SK yapmış olma durumuna göre değerlendirilmiştir. Her gruptaki katılımcılar daha önceki uygulamalarından bağımsız olarak benzer öğrenme değerleri elde etmiştir. Daha önce LEEP ve SK yapmış katılımcılarda yapmamış olanlara göre anlamlı daha yüksek kurs öncesi güven duygusu olmasına rağmen (p<0,001), kurs sonrası güven duygusu her iki grup için de benzerdir. Her iki grup için, ortalama güven duygusundaki artış daha önceden işlemi uygulamayan grup için istatistiksel olarak anlamlıdır (p=0,003, LEEP ve p=0,002, SK).
Sonuç: LEEP ve SK cerrahi eğitim modeli daha önceden işlemi uygulamadan bağımsız olarak katılımcılar için iyi bir eğitim seviyesi oluşturmuştur.
Anahtar Kelimeler: LEEP, konizasyon, cerrahi, serviks, eğitim

Introduction

Loop electrosurgical excision procedure (LEEP) and cold-knife conization (CKC) are well-known surgical operations that are applied in the treatment of cervical intraepithelial neoplasia (CIN) with similar success rates[1]. CIN is a precancerous lesion that is classified in three grades. The second- and third-grade (high grade) lesions can persist and progress further into invasive cervical cancer in the span of 10-20 years[2]. Additionally, after a colposcopic examination, LEEP or CKC will provide a complete histologic evaluation of the transformation zone both for the treatment of high grade CIN and diagnosis of a cervical malignity[3].

LEEP is frequently performed in the gynecology practice, especially in office settings. Despite being a relatively easy procedure, the surgeon should be careful during the excision of cervical tissue in achieving minimal thermal artifact[4]. Nevertheless, the most common complications such as bleeding and infection are not as dangerous as the risk of future obstetric complications. CKC is also an excisional procedure, which is performed at the operation theater/room under general anesthesia mostly with an excessive tissue volume as compared to LEEP[5]. The risks of bleeding and other unfavorable obstetric outcomes, especially preterm labor, are slightly higher after CKC[6].

As compared with CKC, LEEP is a simple procedure, which is performed at the office setting. Additionally, the need of experience and practice to complete the learning curve of LEEP is lesser than CKC[7]. During obstetrics and gynecology residency, many residents attend to LEEP and CKC operations. However, to gain the adequate experience, residents should perform these procedures independently; otherwise, there will be a lack of education. The lack of standardized surgical education will lead to many undesirable outcomes[8]. Many training models have been proposed so far to improve the surgical knowledge, skills, and confidence levels of a surgeon before he/she performs a live surgery[9,10]. This research focuses on the efficacy of a training model of LEEP and CKC, which mimics the surgical procedure and conditions.

Materials and Methods

The purpose of this study is to measure the role of LEEP and CKC active training model in imparting education in gynecologists after they attended "LEEP and Cold-Knife Conization Hands-On Practice Workshop, 2018", which was held at the University of Health Sciences Turkey, Zekai Tahir Burak Woman's Health Training and Research Hospital, Ankara, Turkey. This one-day program was based on both theoretical and practice sessions. After the sessions, the responses of the participants were recorded on a web-based questionnaire. Importantly, after attending detailed didactic lectures about the transformation zone, the indications of excisional procedures for cervical pathologies, and the surgical techniques of LEEP and CKC, the participants watched the videos of LEEP and CKC procedures. The LEEP and CKC hands-on training model comprised sausage, 2.5 cm in diameter as cervix; plastic cup as vagina; foam rubber as posterior and anterior fornices; and cotton plate as leukoplakia area (Figure 1).

During the practice session, the senior surgeons in gynecology and gynecologic oncology practice first performed LEEP and CKC on the model and showed the procedure to 34 participants. The neutral electrode was positioned on the posterior part of the training model and then attached to the sausage to maintain the current of electrocautery. Different sizes of LEEP loops were used to excise the transformation zone entirely in one movement, neither slowly nor quickly. During CKC, the hemostatic sutures were first placed on the lateral side of cervix at 3 and 9 o'clock positions. Afterward, the anterior part of sausage was held by forceps and laterally to the leukoplakia area from the outer part of planned transformation zone. By using number 11 scalpel blade, a circumferential incision was made toward the endocervical canal to excise the cervical tissue as a cone. Finally, hemostasis was maintained by a ball electrode, set at 40 watts on the spray mode.

The cost of one model was less than one euro, and vaginal speculum was not used for maintaining the low cost. One

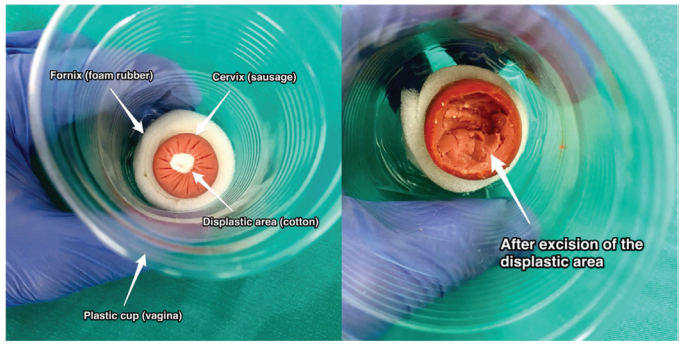

Figure 1. Loop Electrosurgical Excision Procedure and cold-knife conization hands-on training model

electrosurgical generator and grounding pad were used during the practice session. Additionally, a smoke evacuator produced a comfortable working area. Turkey sausages were preferred to be used as cervix due to the cost effectiveness of the turkey sausages, the low rate of fatty tissue generated a less smoky working climate[10].

After the workshop, a web-based survey was conducted to measure the effectiveness and clinical relevance of this surgical training model. Participants rated their learning levels for theoretical lessons and surgical techniques. In the end, they assessed their confidence levels for pre-training and post-training conditions. The satisfaction and success scores were rated between 1 (very bad) and 5 (very good). Participants were categorized into two groups and statistical analyses were performed with regard to the previous practice of LEEP and CKC. Age of participants, number of obstetrics and gynecology residents and specialists, theoretical lectures, similarity to the real anatomy, hemostasis, better handling of LEEP loop or scalpel, proper excision of dysplastic area, excision in one piece, unharming the vaginal wall during excision, general educational level of training, as well as pre- and post-course confidence levels were evaluated. Since the article is based on a questionnaire method and besides no patient data is used, there is no need for an ethical approval.

Statistical Analysis

We performed statistical analyses by using IBM SPSS Statistics 25. Additionally, we presented descriptive statistics as either mean ± standard deviation or median, continuous variables as interquartile range, and categorical variables as the frequency with proportions. We used the Two-Way repeated measure analysis of variance for the statistical analysis of pre-/post-test confidence levels and Mann-Whitney U test for the comparison between the two groups.

Results

All the 34 participants submitted their responses in the web questionnaire. Most of the participants were residents (29/34, 85.3%) and between 25-30 years of age (21/34, 61.8%) (Table 1). Participants were generally satisfied from the theoretical lectures (median score: 4.0). The training model was found to be highly similar to the real anatomy (median score: 4.0), and learning how to control bleeding for hemostasis was not a complex process (median score: 5) (Table 2).

The educative level of the course on the basic surgical steps of LEEP and CKC procedures was evaluated with regard to the previous practice/expertise of LEEP and CKC. Ten participants (10/34, 29.4%) had previously performed LEEP, whereas 12 participants (12/34, 35.3%) had previously performed CKC. On the contrary, participants in each group had similar learning gains, irrespective of previous expertise (p>0.05) (Table 3).

Moreover, pre-course and post-course mean confidence levels during the conduct of procedures were also analyzed in terms of previous practice of LEEP and CKC. Despite a significantly higher pre-course confidence level for participants who had previously performed LEEP (p<0.001) and CKC (p<0.001) (against the participants who have never performed LEEP or CKC) (Table 4, time variable), the post-course confidence levels were similar in each group among the participants who had either previously performed LEEP or CKC or had not performed LEEP or CKC (p=0.127 and p=0.845, respectively). Additionally, in both groups, participants had increased mean confidence scores, which were statistically significant for participants who have not previously performed the procedure [p=0.003 (Figure 2) p=0.002 (Figure 3) (Table 4, group variable), respectively].

Table 1. General characteristics of the participants of Loop Electrosurgical Excision Procedure and cold-knife conization hands-on practice course

Parameters		Number (%)
Age of participants	25-30	21 (61.8)
	30-35	11 (32.4)
	35-40	1 (2.9)
	>40	1 (2.9)
Resident		29 (85.3)
Specialist		5 (14.7)

Discussion

There is a need of post-graduate education and hands-on workshops, especially if the resident is still on the learning stage of a specific type of procedure during the obstetrics and gynecology residency. The key point we found in this research is that a simple and cheap training model on LEEP and CKC procedures will provide satisfactory and successful results in terms of gaining the adequate technical knowledge and skills.

HPV infection is a public health problem, the prevalence of cervical premalignant lesions has increased with time. Many of these patients need a colposcopic evaluation, and LEEP provides an excellent diagnostic and therapeutic option in the management of CIN. Despite similar efficacy and clinical success

Table 2. Mean and median scores for theoretical lessons and the model

Parameters		Mean ± SD	Median
Theoretical lectures	Transformation zone	4.18±0.83	4.0
	Indications of LEEP and CKC	4.18±0.83	4.0
	LEEP surgical technique	4.32±0.77	4.0
	CKC surgical technique	4.15±0.99	4.0
Similarity to the real anatomy		3.94±1.15	4.0

LEEP: Loop Electrosurgical Excision Procedure, CKC: Cold-knife conization, SD: Standard deviation

Table 3. Educative level of the course on the basic surgical steps of Loop Electrosurgical Excision Procedure and cold-knife conization procedures

Variables	Previous LEEP practice			Previous CKC practice		
	Yes (n=10) median (IQR)	No (n=24) median (IQR)	p	Yes (n=12) median (IQR)	No (n=22) median (IQR)	p
Better handling of LEEP loop electrodes	5.0 (1)	4.0 (1)	0.118	5.0 (2)	5.0 (1)	0.606
Proper excision of dysplastic area	5.0 (0)	5.0 (2)	0.159	5.0 (2)	5.0 (1)	0.736
Excision in one piece	5.0 (0)	5.0 (2)	0.238	5.0 (1)	5.0 (1)	0.929
Unharming the vaginal wall during loop excision	5.0 (0)	4.5 (1)	0.137	4.5	4.5	0.643
Educational level of LEEP training	5.0 (0)	4.0 (1)	0.101	4.5 (2)	5.0 (1)	0.403
Learning how to control bleeding	5.0	5.0	0.653	5.0 (0)	5.0 (1)	0.328

LEEP: Loop Electrosurgical Excision Procedure, CKC: Cold-knife conization, IQR: Interquartile range

Table 4. Pre-course and post-course confidence levels regarding the previous practice of Loop Electrosurgical Excision Procedure and cold-knife conization

Variables	Pre-course		Post-course		Time		Group x time	
	Previous practice		Previous practice					
	Yes	No	Yes	No	p	η^2	p	η^2
LEEP	4.40±0.70	2.38±1.50	4.80±0.42	4.29±0.81	<0.001	0.363	0.003	0.156
CKC	4.00±1.04	2.55±1.50	4.25±0.87	4.32±0.84	<0.001	0.312	0.002	0.177

LEEP: Loop Electrosurgical Excision Procedure, CKC: Cold-knife conization

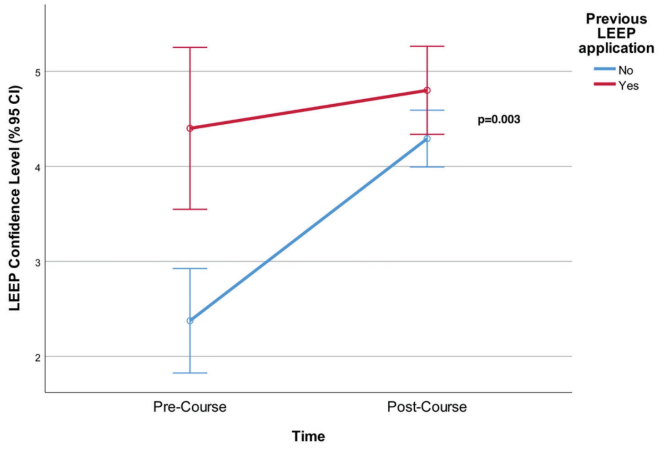

Figure 2. The increase in the mean confidence levels of participants who previously had expertise/practice of Loop Electrosurgical Excision Procedure (LEEP) and participants who did not any expertise/practice of LEEP. The increase was statistically significant for non-practitioners (p=0.003)

LEEP: Loop Electrosurgical Excision Procedure, CI: Confidence interval

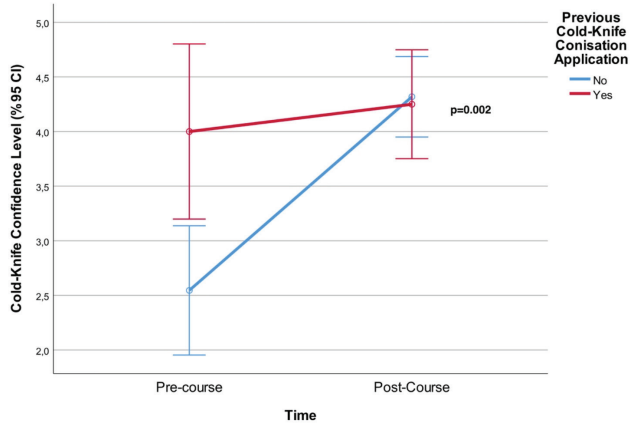

Figure 3. The increase in the mean confidence level of participants who had previous practice/expertise of cold-knife conization (CKC) and participants who did not any expertise of CKC. The increase was statistically significant for non-practitioners (p=0.002)

CI: Confidence interval

rates, the CKC procedure is performed in the selected cases because of the relatively higher risk of positive margin status or thermal artifact during LEEP[1,4]. Over the last two decades, the creativity-directed post-graduate surgical education toward the simulation projects outside the operating theater/room both for the safety of patient and completion of learning curve. There are few studies targeting the training models that aim to improve the surgical skills during LEEP; however, this study is the first one to assess the CKC technique within a training model[10-13]. A well-equipped and practical educational system during residency under the supervision of senior surgeons will improve

the knowledge and confidence levels during the independent practice of surgical procedures. The more you practice, the more you will gain experience. Additionally, the lack of practice decreases the preparedness of obstetrics and gynecology residents in the post-graduate or fellowship period[14]. Overcoming this deficiency and reducing the concerns on the risk of probable complications or an unsuccessful operation will be achieved by attending the hands-on practical courses on training models or cadavers[11,15].

One of the major problems during the simulation of a surgical procedure is the cost of the model. Although the cadaveric workshops are held with a limited number of participants to manage self-practice or dissection under the guidance of a mentor, the course fees are not economical for the residents[16,17]. Moreover, the 3D-printed or virtual reality models also provide a good surgical experience with quite more reproducibility; nevertheless, these are neither simple techniques nor cheap models[18]. Hefler et al.[11] suggested the use of sausages to mimic the uterine cervix as they resemble the real tissue both in resistance and thickness. Connor et al.[10] recommended the use of sausages with lower fatty content to produce less smoke. Beef or pork meat may also be used, even though it is much better not to prefer the previously frozen or thawed ones[12]. During this study the cost of one model was less than one euro, and this LEEP and CKC hands-on training model provided a high yield of reproducibility in a cost effective manner, especially for low-income regions.

Performing a procedure first on a live patient will increase the strain both on the patient and surgeon. The patient will be nervous and stressful as she will be aware of the fact that the resident will be practicing his/her first surgical procedure on her; simultaneously, the resident surgeon will also be anxious. Additionally, one major difficulty of LEEP procedure is the narrow space of vagina, which may cause injuries on the vaginal wall. Operating on a narrow field without adequate experience while the patient is awake will be stressful as well as increase the incidence of complications and decrease the levels of learning. Additionally, before operating on the live surgeries, completing the training steps on the models will improve the learning curve and provide better practice[13,19].

The coordination of hand and eye movements is very important to achieve the best surgical outcomes without harming the nearby tissue, vagina, rectum, or bladder. The excision of the ectocervical tissue in one piece with a correct speed by using the hot wire loop requires adequate practice; otherwise, the excised tissue may be unsuitable for histopathologic evaluation, may not consist the total dysplastic area, or may have a wide thermal artifact[12]. This hands-on model aimed to increase the technical ability to coordinate the hand movements; however, performing the procedure without moving the model was the disadvantage detected by us. To overcome this problem, the mentor kept the model stable. If the model is stabilized on the table with a tape or fixed to a specific board, then this will decrease the unintentional movements during the surgical practice. A colposcopic evaluation before LEEP provides an adequate view of the transformation zone, and if there is a doubt of residual lesion after one piece of excision with LEEP loop, then a smaller or rectangular loop will maintain an additional resection. For the first time, a LEEP course was conducted via this study in Turkey, and we mainly focused on the practice of LEEP to improve the skills of gynecologists during the hand movements. From this point, performing an additional resection or endocervical curettage was the limitation of this course.

The widespread use of colposcopy-directed cervical biopsy or LEEP decreased the rates of CKC procedure; nevertheless, it is still a remarkable diagnostic and therapeutic tool in the selected cases. When there is a need of high-volume tissue resection or when the histo-pathologic evaluation has shown critical outcomes such as glandular or microinvasive lesions, CKC is mostly preferred treatment. CKC requires general anesthesia, and bleeding is an important complication[20]. Despite many variations in the surgical technique[21], we used the lateral hemostatic sutures at 3 and 9 o'clock positions, and the mentor described the proper borders with regard to the bladder and rectum to totally excise the dysplastic area.

Despite carrying a higher risk for complications due to the relative difficulty of procedure, CKC could successfully be performed by the residents after a well-equipped practical training period; however, the recent literature analyses did not reveal a course targeting to improve the skills for the CKC procedure[22]. During the course, the participants also performed the surgical steps of CKC on the sausage, hemostatic sutures, circumferential incision, cone-shaped excision, and cauterization of the cervix.

This study showed a higher degree of pre-course confidence level for a previous expertise of LEEP or CKC; however, the confidence levels were similar for participants who had a previous expertise or those did not at the end of the course. This result showed that participants who did not have any previous expertise had a higher rate of increased confidence levels. On the contrary, the learning gains were similar irrespective of the previous expertise/practice among the LEEP and CKC groups. Ultimately, the course produced a better source of understanding and learning with the purpose of improving technical skills related to LEEP and CKC.

Although the results were successful and promising for improving the surgical technique and skills, drawing a conclusion based on these results can invite misinterpretation.

Study Limitations

Small number of sample size in the study cohort and subjective grading are the limitations of this research.

Conclusion

The LEEP and CKC hands-on training model is simple, cheap, and promising to improve the surgical skills and confidence levels before performing the procedure on a real operation setting.

Ethics

Ethics Committee Approval: Since the article is based on a questionnaire method and besides no patient data is used, there is no need for an ethical approval.
Informed Consent: Patient consent was not required.
Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Y.Ü., Y.E.Ü., I.S., H.Y., Design: Y.Ü., Y.E.Ü., Data Collection or Processing: B.E., Analysis or Interpretation: M.U., Literature Search: Ş.Ö., Y.E.Ü., Writing: İ.S.
Conflict of Interest: The authors declare no potential conflicts of interest for the publication of this study.
Financial Disclosure: The authors declare that this study received no financial support.

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Clinical Investigation / Araştırma

DOI: 10.4274/tjod.galenos.2020.64280

Turk J Obstet Gynecol 2020;17:139-42

Single-step hysteroscopic myomectomy for submucous leiomyoma

Submüköz leiomyoma için tek seanslı histeroskopik miyomektomi

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Abstract

Objective: Leiomyomas are most commonly observed benign tumors in the female genital tract. Depending on the size, number, and location, the complete resection of Type 0, 1, and 2 leiomyomas by hysteroscopy can be completed in a single-step or multi-step procedure. The purpose of this study is to document the cases of hysteroscopic myomectomy performed via the resectoscopic technique in the gynecology department of a university hospital. Moreover, we assessed the applicability of single- or multi-step hysteroscopic myomectomy with respect to the diameter of the leiomyoma.

Materials and Methods: We retrospectively reviewed the records of hysteroscopic myomectomy performed between 2012 and 2018. According to the diameter of the submucous leiomyomas, we divided 46 patients into 2 groups. Group 1 (n=25) consisted of patients with submucous leiomyomas <3 cm, whereas patients in group 2 (n=21) had submucous leiomyomas ≥3 cm in diameter. We recorded the number of removed leiomyomas and completed hysteroscopy sessions.

Results: Myomectomy was completed by single-step hysteroscopy in all the patients of group 1, whereas eight patients in group 2 needed multiple sessions of hysteroscopy. None of the patients in group 1 had fluid overload; however, two patients in group 2 had mild asymptomatic hyponatremia.

Conclusion: The success of hysteroscopic myomectomy depends on the diameter, localization, and number of the leiomyomas. This study revealed that Type 0, 1, and 2 leiomyomas of less than 3 cm can be resected by single-step hysteroscopy. For larger leiomyomas, the possibility of need for further sessions should be shared with the patients.

Keywords: Hysteroscopy, myomectomy, leiomyoma

Öz

Amaç: Leiomyomalar, kadın genital sisteminde en sık görülen benign tümördür. Boyut, sayı ve lokasyona göre tip 0, 1 ve 2 miyomların histeroskopik olarak tek veya multiple-step rezekziyonu gerçekleştirilebilir. Bu çalışmada bir üniversite hastanesinde rezektoskopi tekniğiyle histeroskopik miyomektomi yapılan olgular değerlendirilmiştir. İlaveten leiomyomanın çapına gore tek veya multiple step histeroskopik miyomektomi uygulanabilirlği incelenmiştir.

Gereç ve Yöntemler: 2012-2018 yılları arasında histeroskopik miyomektomi yapılan hastaların kayıtları retrospektif olarak incelenmiştir. Kırk altı hasta submüköz leiomyomanın çapına göre 2 gruba ayrılmıştır. Grup 1 (n=25) submüköz leiomyoma çapı <3 cm olan ve grup 2 (n=21) submüköz leiomyoma çapı ≥3 cm olan hastalardan oluşmaktadır. Çıkarılan leiomyomaların sayısı ve yapılan histeroskopi seanslarının sayısı kaydedilmiştir.

Bulgular: Grup 1'de tüm hastalarda miyomektomi tek basamak histeroskopi ile tamamlanırken, grup 2'deki hastalardan 8'inde multiple step histeroskopi ihtiyacı olmuştur. Grup 1'deki hastaların hiçbirisinde sıvı yüklenmesi izlenmezken, grup 2'deki hastalardan 2'sinde hafif asemptomatik hiponatremi görülmüştür.

Sonuç: Histeroskopik miyomektominin başarısı miyomların çapına, lokasyonuna ve sayısına bağlıdır. Bu çalışmada çapı <3 olan tip 0, 1 ve 2 leiomyomların tek basamak histeroskopi ile rezekte edilebileceği gösterilmiştir. Daha büyük çaplı leiomyomalarda birden fazla histeroskopi seansının gerekebileceği olasılığı hastalara anlatılmalıdır.

Anahtar Kelimeler: Histeroskopi, miyomektomi, leiomyoma

PRECIS: We have retrospectively evaluated the applicability of single- or multi-step hysteroscopic myomectomy regarding the diameter of the leiomyoma.

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Received/Geliş Tarihi: 18.06.2019 **Accepted/Kabul Tarihi:** 24.04.2020

Introduction

Leiomyomas are most commonly observed benign tumors in the female genital tract[1], and they are observed in 70%-80% of women in reproductive age[2]. A total of eight types of leiomyomas are listed in the International Federation of Gynecology and Obstetrics (FIGO) classification system. According to the FIGO classification system, submucous leiomyomas are described in three groups. Type 0 refers to the completely intracavitary leiomyomas, Type 1 refers to the leiomyomas with the largest diameter in the uterine cavity, and Type 2 refers to the leiomyomas with the largest diameter in the myometrium[3,4]. Type 0, 1, and 2 leiomyomas make up about 5.5%-16.6% of all the uterine leiomyomas[5] and are often associated with abnormal uterine bleeding, heavy menstrual bleeding, pelvic pain, dysmenorrhea, and infertility[6]. Hysteroscopic resection is the first-line treatment for intracavitary leiomyomas[7].

Neuwirth and Amin[8] first performed hysteroscopic myomectomy through the transcervical approach, and this procedure has become the gold standard treatment of choice[8,9] for Type 0, 1, and 2 leiomyomas. Nevertheless, factors such as desire for future fertility; size, number, and location of the submucous leiomyomas; relationship of the deepest aspect of the myoma to the uterine serosa (in Type 2 leiomyomas); training, experience, surgical expertise of the surgeon, and availability of appropriate equipment affect the route of surgical intervention[10]. Experienced surgeons can remove leiomyomas of up to 4-5 cm in diameter under hysteroscopic direction. Depending on the above factors, the complete resection of Type 0, 1, and 2 leiomyomas by hysteroscopy can be completed in a single-step or multi-step procedure.

The hysteroscopic removal of the submucous leiomyomas might be carried out by different techniques such as resectoscopic excision by slicing, cutting of the base of the myoma and its extraction, ablation by Neodymium-doped Yttrium Aluminum Garnet (Nd: YAG) laser, and vaporization or morcellation by intrauterine morcellator[11]. The purpose of this study is to document the cases of hysteroscopic myomectomy performed via resectoscopic technique in the gynecology department of a university hospital. Moreover, we also assessed the applicability of single- or multi-step hysteroscopic myomectomy with respect to the diameter of the leiomyoma.

Materials and Methods

Since the study consisted of retrospective analysis of the data, we did not have ethics committee approval.

We retrospectively reviewed the records regarding hysteroscopic myomectomy performed between 2012 and 2018 in a university gynecology department. According to the records, two expert surgeons having the same skill level and educational background performed the surgical procedures. We also analyzed the demographic variables and details regarding the hysteroscopic treatment for 46 patients. According to the diameter of the submucous leiomyomas, we divided the patients into two groups. Group 1 (n=25) consisted of patients who had submucous leiomyomas <3 cm in diameter, whereas patients in group 2 (n=21) had submucous leiomyomas ≥3 cm in diameter. Importantly, we recorded the data regarding the number of removed leiomyomas, number of completed hysteroscopic sessions, menopausal status, infertility status, and histopathological examination results of the specimens.

The patients were evaluated preoperatively by ultrasonography for the number, diameter, and the localization of the leiomyomas. Hysteroscopic myomectomy was performed under general anesthesia while using the monopolar loop resectoscope. Glycine 1.5% was used as the distension medium, and fluid deficit was observed throughout the operation in all the cases.

Statistical Analysis

We performed the statistical analysis by using IBM® SPSS® Statistics for Windows version 22.0. We also performed Shapiro-Wilk tests for all the measurements to test for normality. Additionally, we compared the different groups by using the Mann-Whitney U test wherever it was appropriate. A p-value of less than 0.05 was considered statistically significant for this study.

Results

In total, 46 patients underwent hysteroscopic myomectomy for Type 0, 1, and 2 leiomyomas. In total, 25 patients had submucous leiomyomas <3 in diameter (group 1), whereas 21 patients had submucous leiomyomas ≥3 cm in diameter (group 2). Table presents the demographic variables as well as operative and histopathological findings of the participants. Myomectomy was completed as single-step hysteroscopy in

Table 1. Characteristics and hysteroscopic findings of the patients

Variable	Group 1 (n=25)	Group 2 (n=21)	p
Age (years) (mean ± SD)	42.64±8.0	43.19±8.19	0.820
Nulliparity (n, %)	10 (40%)	6 (28.5%)	0.538
GnRHa* (n, %)	1 (4%)	3 (14.2%)	0.306
Infertility (n, %)	4 (16%)	0	0.114
Menopause (n, %)	3 (12%)	2 (9.5%)	0.788
Leiomyoma diameter (cm) median (min-max)	2 (0.5-2.5)	4 (3-6)	p<0.003**
No of patients with >1 leiomyoma (n, %)	4 (16%)	2 (9.5%)	NA
Single-step H/S (n, %)	25 (100%)	13 (61.9%)	NA
Multiple-step Hs (n, %)	-	8 (38.09%)	NA
Adenomyoma (n, %)	3 (12%)	2 (9.5%)	NA
Fluid overload (n, %)	-	2 (9.5%)	NA

*Patients with GnRH use up to three months preoperatively, **p<0.05, NA: Not applicable, SD: Standard deviation, GnRHa: Gonadotropin-releasing hormone agonist, min: Minimum, max: Maximum

all patients of group 1, whereas 8 patients in group 2 needed multiple sessions of hysteroscopy (ranged between one and four) for complete excision. None of the patients in group 1 had fluid overload, whereas two patients in group 2 had mild asymptomatic hyponatremia.

Discussion

Hysteroscopy is accepted as the gold standard treatment of choice for Type 0, 1, and 2 leiomyomas[7]. The success of the treatment mainly depends on the diameter, localization, and number of the leiomyomas but also on the experience of the surgeon and the available equipment. This study revealed that Type 0, 1, and 2 leiomyomas of less than 3 cm can be resected by single-step hysteroscopy by using monopolar energy modalities. For larger myomas and multiple myoma cases, more than one session might be needed for the complete resection to avoid fluid overload and other related complications when monopolar modalities are used. Single-step intervention was fully curative for only 61.9% of the cases with Type 0, 1, and 2 leiomyomas with size ≥3 cm.

In the latest French guidelines, the complete hysteroscopic resection of intracavitary leiomyomas was recommended as a first-line treatment for symptomatic Type 0, 1 (grade B), and 2 (grade C) leiomyomas up to 4 cm (grade C). But it was also stated that complete hysteroscopic resection was possible for fibroids of 4-6 cm. A two-stage resection was recommended in the incomplete first resection[7]. The diameter of the lesion appears to be the most important factor correlated with the need for multiple interventions due to the association between the diameter and the volume increments. For example, a myoma of 3x3x3 cm would have a volume of 13.5 cm^3, whereas a myoma of 4x4x4 cm would have a volume of 32 cm^3, which is almost twice as large than the previous one. Therefore, it was also previously stated that myoma diameters exceeding 3-5 cm were associated with the incomplete resection of leiomyomas and a further requirement for more than one hysteroscopy sessions[12]. A retrospective study including 1,244 patients who underwent hysteroscopic myomectomy using either cold loop technique or resectoscopic excision by slicing with a monopolar electric loop also revealed that the type and size of the myoma were significant for the discrimination between single-step and multi-step procedure. The authors also pointed out that leiomyomas with a diameter more than 3 cm were more often associated with multiple-step hysteroscopy[13]. It has already been revealed that submucous leiomyomas with a diameter more than 3-5 cm are better removed in the multiple sessions of hysteroscopy[7]. Our findings complies with the previous studies. Nevertheless, larger studies may clarify the exact cut-off values.

The limitation of hysteroscopic myomectomy is the risk of fluid overload. Fluid overload is more common in the cases of monopolar instrument employment because of non-conductive distending media usage[10]. In our study, all the cases were operated by monopolar energy, which necessitates the use of hypo-osmolar distention media. The utilization of bipolar instrument is associated with less fluid overload because electrolyte-containing solutions are less likely to cause undesired changes in the serum sodium levels and osmolality. Although the use of bipolar energy modalities decreases the risk of fluid overload, it is not available at our clinic. There were only two cases and both of them had asymptomatic hyponatremia. They were in group 2 and simply treated with loop diuretics. But it should be kept in mind that fluid overload might end up with even life-threatening serious complications.

Study Limitations

The limitations of this study are a small sample size and a retrospective analysis. However, the results comply with the further studies, which support multiple-step intervention risk for Type 0, 1, and 2 leiomyomas bigger than 3 cm in diameter.

Conclusion

The hysteroscopic resection of uterine leiomyoma is a well-tolerated, safe, and effective procedure. The sufficient preoperative evaluation and diagnosis is important for the selection of patient. Adequate instrumentation, careful fluid evaluation, and meticulous orientation of the anatomy will reduce complications. Each patient should be evaluated on an individual basis for the feasibility of the hysteroscopic approach, and the possibility of need for further sessions for the cases with submucous leiomyomas ≥3 cm in diameter should be shared with the patients before the procedure.

Ethics

Ethics Committee Approval: Since the study consisted of retrospective analysis of the data, we did not have ethics committee approval.

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: M.K., A.Y.G., A.A., G.S.Ç., Design: M.K., A.Y.G., A.A., G.S.Ç., Data Collection or Processing: D.D., Analysis or Interpretation: M.K., A.Y.G., A.A., G.S.Ç., Literature Search: G.S.Ç., D.Ç., R.Ç., Writing: M.K., A.Y.G.

Conflict of Interest: The authors report no conflict of interest

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

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Case Report / Olgu Sunumu

DOI: 10.4274/tjod.galenos.2020.01709

Turk J Obstet Gynecol 2020;17:143-5

Laparoscopic hemi-hysterectomy in a non-communicating uterine horn: The critical steps to be considered

Non-komünikan uterin horn olgusunda laparoskopik hemi-histerektomi: Dikkat edilecek kritik basamaklar

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Abstract

Various congenital anomalies of the female tract such as agenesis, vertical or lateral fusion failure, and canalization failure occur when the normal development of the Müllerian duct disrupts in any stage of developmental milestones. A cavitated non-communicating rudimentary horn is reported in about 20%-25% of women with unicornuate uterus. A 36-year-old patient, gravida 2 para 2, was admitted to the hospital with a complaint of worsening lower abdominal pain occurring on each menses for 8 months. A 6-cm accessory cavitated left uterine mass suggestive of hematometra was shown on ultrasound examination. It was decided to perform hemi-hysterectomy to remove the left uterine horn by the laparoscopic route. Here we aimed to demonstrate the laparoscopic management of a rudimentary horn case and emphasize the crucial steps that surgeons should safely perform during the operation.
Keywords: Uterine horn, laparoscopy, hemi-hysterectomy

Öz

Gelişim basamaklarının herhangi bir evresinde Mülleryan kanal gelişimi sekteye uğradığında, agenezis, vertikal veya lateral füzyon bozukluğu ve kanal oluşumu başarısızlıkları gibi çeşitli konjenital anomaliler meydana gelir. Kaviteli non-komünikan rudimenter horn unikornuat uterusu olan kadınların yaklaşık %20-25'de bildirilmiştir. Otuz altı yaşında, G2P2 hasta, 8 aydır devam eden, her menstrüasyon döngüsüyle artış gösteren alt karın ağrısı şikayeti ile hastaneye başvurdu. Ultrasonografide hematometrayı düşündüren, 6 cm, aksesuar, kaviteli sol uterin kitle tespit edildi. Laparoskopik yolla sol uterin hornun hemi-histerektomi yapılarak çıkarılması planlandı. Burada, rudimenter horn olgusunun laparoskopik yolla yönetimi ve cerrahinin güvenle yapılması için izlenecek kritik adımların tanımlanması planlandı.
Anahtar Kelimeler: Uterin horn, laparoskopi, hemi-histerektomi

Introduction

Various congenital anomalies of the female tract such as agenesis, vertical or lateral fusion failure, and canalization failure occur when the normal development of the Müllerian duct disrupts any stage of the developmental milestones. The unicornuate uterus is caused by the normal maturation of only one Müllerian duct. In some cases, the contralateral Müllerian duct is absent or partially develops, called a rudimentary horn, which may or may not communicate with the normally developed one Müllerian duct, called a unicornuate uterus.

A cavitated non-communicating rudimentary horn is reported in about 20%-25% of women with a unicornuate uterus[1,2]. The symptoms differ with the functionality of the endometrial cavity, and the patients' symptoms depend on the presence of an obstructive anomaly causing pain regarding hematometra, hematosalpinx, or endometriosis due to retrograde menstruation[3]. There have been studies reporting reproductive outcome improvement by removing the rudimentary horn, but information on such approach is still lacking.

In the present case, we aimed to discuss the laparoscopic management of a multiparous patient with a rudimentary horn presenting with dysmenorrhea and dyspareunia symptoms in her late 30s.

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Received/Geliş Tarihi: 16.08.2019 **Accepted/Kabul Tarihi:** 04.02.2020

Case Report

A 36-year-old patient, gravida 2 para 2, was admitted to the hospital with a complaint of worsening lower abdominal pain occurring on each menses for 8 months. Her external and internal genitalia, including the cervix, were normal except for the 6 cm accessory cavitated left uterine mass suggestive of hematometra that is compressing the urinary bladder without any other genitourinary system pathologies shown on ultrasound examination (Figure 1). Diagnostic hysteroscopy revealed a single cervix without any vaginal malformations and a relatively small uterine cavity with right tubal ostium and without left tubal ostium. It was decided to remove the left uterine horn (Class U4a/Hemi Uterus)[4] by the laparoscopic route. Evaluation of the abdominal cavity revealed a left non-communicating rudimentary horn tightly residing on the lateral abdominal wall and two grossly normal ovaries and tubes (Figure 2). A probable occult occlusion of the tube might be present, and this tubal occlusion might cause this late occurrence. However, neither endometriosis nor any prior tubal or abdominal operation history was noted.

First, to remove the fallopian tubes from the left uterine horn, they were coagulated and divided by careful tissue transection. Second, the vesicouterine peritoneum was divided to create the bladder flap from the cervix and the left uterine horn. Third, dissection of the retroperitoneal space beneath the round ligament to identify the ureter and the left hypogastric artery branches was performed. The broad ligament was fenestrated to lateralize the left ureter and facilitate transection of the utero-ovarian pedicle. The retroperitoneum was dissected, and the ureter tract was followed. Posterior peritoneum was also opened to create distance from the ureter and provide a place for the division of the horn by a monopolar hook. After the dissection and coagulation of the left uterine artery at the origin of the left hypogastric artery to minimize the bleeding during excision of the uterine horn by an advanced bipolar energy device (Figure 3), the resection of the rudimentary horn was achieved using a monopolar hook[5]. After controlling the bleeding and irrigating and suctioning the abdominal cavity, no other hemostasis sutures were required, and the operation was completed successfully. The patient was discharged on the first postoperative day, and normal regular menstrual cycles without any pain and complaints during the 6 and 12 months after the surgery were noted.

The patient signed an informed consent that allowed us to use her data.

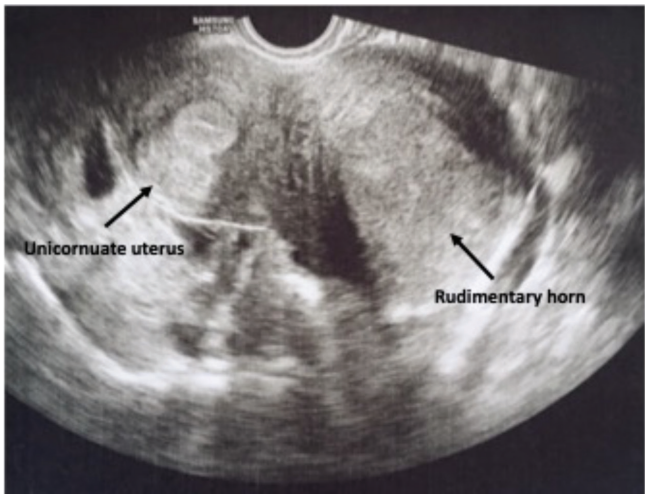

Figure 1. Cavitated left uterine mass suggestive of hematometra

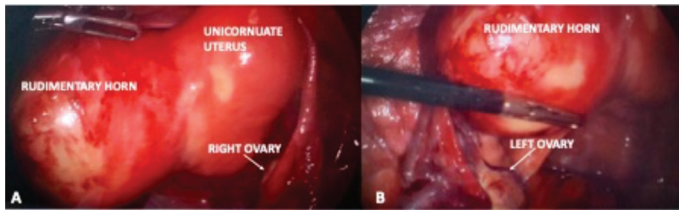

Figure 2. A) The abdominal cavity revealing a left noncommunicating rudimentary horn tightly resided on the lateral abdominal wall and **B)** two normal-looking ovaries and tubes

Discussion

Since the first documentation of laparoscopic removal of the rudimentary horn in 1990 by Canis et al.[6], laparoscopy has become the standard treatment with proven advantages, including short operative time and hospital admission duration and less blood loss and postoperative pain. Although laparoscopic excision of the rudimentary uterine horn seems to be an effective and feasible surgical approach in experienced hands, it should always be remembered that anatomical landmarks and retroperitoneal space must be defined as the cleavage planes of the uterine horn and that the unicornuate uterus is not well defined all the time.

Two anatomical variations in the attachment of the rudimentary horn to the unicornuate uterus were reported, and one can be attached by either a band of tissue or firmly to the latter. When no fusion occurs with the contralateral duct, a fibrous or fibromuscular band connects the two horns[7]. Here, the rudimentary horn was attached firmly to the right unicornuate

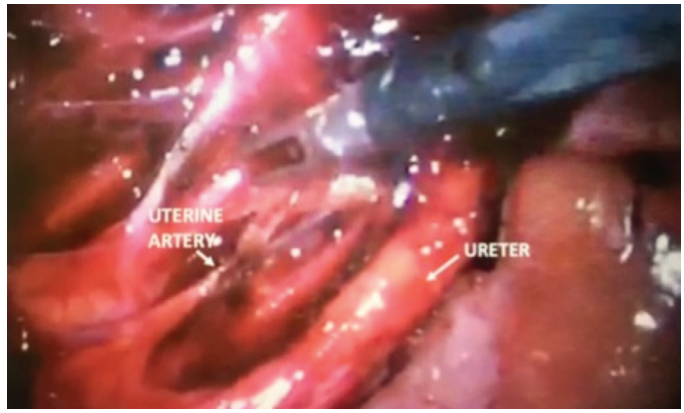

Figure 3. Dissection of the retroperitoneal space showing the ligated left uterine artery and the left ureter

uterus and the left sidewall. When the borders are firm and not easy to distinguish, it can be difficult to remove the horn. To minimize the risk of penetration into the cavity of the hemiuterus while laparoscopic dissection, a hysteroscopic transillumination technique was performed in three cases by Nezhat et al.[8]. In a recent study by Jan et al.[9] , this technique was detailed in a technical video demonstrating the hysteroscopic transillumination of the plane of the dissection between the rudimentary horn and the uterus. At the beginning of the operation, we first performed a hysteroscopic evaluation of the uterine cavity to visualize the relation.

Besides, the most important point about these anomalies is the preoperative evaluation of the patients because other probable concomitant female reproductive tract anomalies and renal and skeletal system abnormalities may co-occur with Müllerian anomalies[10]. Anomaly observation of these coexisting defects should be performed, and the right treatment should be planned after defining the anatomy of pathology as possible with proper imaging techniques such as an ultrasound scan and magnetic resonance imaging. Regarding the definition of the anatomy of the pathology, type of attachment, and communication between the rudimentary horn and the hemiuterus considering other probable pathology exclusions like myomas or an obstructed hemivagina, the right treatment option should be discussed and performed.

After defining the anatomy of pathology, type of attachment, and communication between the rudimentary horn and the hemiuterus, the right treatment option should be discussed and performed. Here, preoperative examinations including transvaginal ultrasonography and an intravenous pyelogram showing the normal kidneys and ureters were performed.

Another step of the operation depends on the blood supply of the rudimentary horn as it may not always be from the ipsilateral uterine artery but also from the contralateral uterine artery[2]. Therefore, the ligation of the major blood supply from the uterine artery at the isthmus level may be impossible to achieve, so the dissection of the retroperitoneal space to develop a plane for the ipsilateral ureter lying adjacent to the vascular supply of the uterine horn is of great importance to prevent injury of the uterine artery during coagulation and ligation at the level of the hypogastric origin. A monopolar hook may not be sufficient while resecting the rudimentary horn; thus, advanced bipolar energy devices are needed to control the bleeding as the rudimentary horn may receive blood from the myometrial arcuate arteries of the contralateral uterine artery[2]. In cases where a firmly attached horn is present, the laparoscopic surgeon should handle large myometrial defect with sutures for reconstruction after removal of the horn[9]. Moreover, if the patient has a desire for a future pregnancy, the myometrial defect should also be sutured to avoid probable uterine rupture. The removal of the ipsilateral fallopian tube should always be performed to prevent a tubal pregnancy and cancer development.

In conclusion, a careful preoperative examination should be performed to detect the anatomical subtype, attachment type, and other coexisting genital malformations. Although the laparoscopic approach in these abnormalities seems to be effective and feasible, it should always be remembered that the anatomical landmarks and retroperitoneal space must be defined, and careful hemostasis must be performed in every step of the operation.

Ethics

Informed Consent: The patient signed an informed consent that allowed us to use her data.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: Ş.K.A., Design: Ş.K.A., Data Collection or Processing: Ş.K.A, Ö.L.T., Analysis or Interpretation: Ş.K.A., Ö.L.T., M.Ü., Ö.M.T., Literature Search: Ş.K.A., M.Ü., Writing: Ş.K.A., Ö.L.T.

Conflict of Interest: The authors declare no conflict of interest.

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

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Case Report / Olgu Sunumu

DOI: 10.4274/tjod.galenos.2020.64624

Turk J Obstet Gynecol 2020;17:146-8

Spontaneous unilateral quadruplet tubal ectopic pregnancy

Spontan unilateral tubal ektopik dördüz gebelik

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Abstract

Ectopic pregnancy (EP) is defined as the implantation of the fertilized ovum outside the uterine cavity. Importantly, the implantation site is tubal in 95% of the cases. Multiple EPs are extremely rare. We present a case of a 25-year-old patient, gravida 2 para 1, with amenorrhea accompanied by the complaints of vaginal bleeding and abdominal pain. She was admitted to the emergency department. Trans-vaginal ultrasound revealed a left ovarian anechoic cyst of 30 mm and four embryos in the right tube with positive cardiac activities. An emergency laparotomy found the rupture of tubal pregnancy on the right side, which ultimately led to hemo-peritoneum. Therefore, we performed right salpingectomy. This is the first well-documented case of a patient with spontaneous unilateral quadruplet tubal EP.

Keywords: Ectopic pregnancy, multiple gestations, quadruplet

Öz

Ektopik gebelik (EG), fertilize ovumun uterin kavite dışına implantasyonu olarak tanımlanır ve olguların %95'inde implantasyon bölgesi tuba uterinadır. Multipl EG'ler çok nadir görülür. Gravida 2 para 1 yirmi beş yaşında hasta, acil servise amenore, vajinal kanama ve karın ağrısı şikayeti ile başvurdu. Trans-vajinal ultrasonda sol overde 30 mm'lik anekoik kist ve sağ tubada kalp atımları izlenen dört embriyo saptandı. Acil laparotomi yapıldı ve sağ tarafta rüptüre tubal EG ve hemo-peritonyum tespit edildi. Sağ salpenjektomi yapıldı. Bu olgu bugüne kadar iyi dökümante edilmiş ilk spontan unilateral tubal ektopik dördüz gebelik olgusudur.

Anahtar Kelimeler: Ektopik gebelik, multipl gestasyon, dördüz

Introduction

Ectopic pregnancy (EP) occurs when developing blastocysts are implanted outside the endometrium in the uterine cavity[1]. The primary site of implantation is the fallopian tube, generally in the ampullary region, in more than 98% cases of EPs. The other cases of EPs occur in the abdominal cavity, on the ovary, or in the cervix[2,3]. EP occurs in 1%-2% of all the pregnancies[4]. Interestingly, 6%-16% of the women admitted to the emergency department with first-trimester bleeding, pain, or both are diagnosed with EP[2,5,6]. A history of EP, tubal surgery, tubal ligation, tubal pathology, in utero Diethylstilbestrol exposure, or the current use of intrauterine device (at the time of admission) are the prominent risk factors of EP[6]. The main complication of EP is tubal rupture, which can eventually cause massive intra-abdominal bleeding and possibly death[1,2].

Multiple EPs are rare and might result from simultaneous bilateral ovulation or superfetation, with or without trans-peritoneal migration[7]. Unilateral and bilateral twin ectopic gestations have been reported in the literature. Additionally, up-to-date cases and several spontaneous unilateral triplet tubal pregnancies have also been documented[7,8].

To our knowledge, this is the first well-documented case of a patient with spontaneous unilateral quadruplet tubal EP.

Case Report

A 25-year-old patient, gravida 2 para 1, was admitted to the emergency department at seven weeks plus two days of amenorrhea accompanied with the complaints of vaginal bleeding and abdominal pain. She did not carry any of the risks for EP and was not using any method for contraception. Physical examination revealed that her blood pressure was 80/50 mmHg

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Received/Geliş Tarihi: 11.12.2019 **Accepted/Kabul Tarihi:** 17.02.2020

with a pulse rate of 110 beats per minute. It also reported postural hypotension. There was also the presence of abdominal guarding and rebound tenderness. Vaginal examination revealed slight-moderate bleeding; however, she felt pain mainly on the right side during the bimanual examination. Trans-vaginal ultrasound revealed left ovarian anechoic cyst of 30 mm and four embryos in the right tube (Figure 1). All the embryos had cardiac activities and crown rump length measurements were consistent with average seven weeks of pregnancy. There was free fluid and coagulum in the pouch of Douglas and the right para-ovarian space. Hemoglobin and hematocrit levels were 9.8 gr/dL and 29%, respectively. Clinical and laboratory findings were consistent with the tubal rupture. More importantly, the presence of hemodynamic instability led us to perform an emergency laparotomy. Informed consent was obtained from the patient. Under general anesthesia, the abdominal cavity was accessed via Pfannenstiel incision. Further exploration revealed that tubal pregnancy on the right side had ruptured, which ultimately led to hemo-peritoneum with approximately 800 mL of blood and coagulum. The left tube and the cornual portions of the uterus were intact. Right salpingectomy was performed, and all the materials were sent to pathology. The final pathology report revealed tubal quadruplet pregnancy and chronic salpingitis. A detailed gross examination of the right tube revealed that its diameter was 40 mm in its widest part and four embryos were identified between the pieces of coagulum (Figure 2).

Discussion

Since the publishing of Dr. Wilmer Krusen's report of a patient with spontaneous unilateral triplet tubal pregnancy in 1902, several reports of similar triplet ectopic pregnancies have also been published[9]. Multiple ectopic pregnancies can also present as a component of a heterotopic pregnancy, which can be more difficult to diagnose. The prevalence of HP has increased from 1 in 30,000 normal gestations to 152 in 100,000, which is believed to be related to the advent and growing use of technologies such as ovulation induction and assisted reproductive technology[10]. Other important risk factors for EP include a history of EP, damage to the fallopian tubes, pelvic infection, pelvic or fallopian tube surgery, and infertility. Other less significant risk factors include cigarette smoking and patients older than 35 years[11]. But one half of all the women who were diagnosed with EP do not present any known risk factors like the presented case[12].

The management of an EP depends on the hemodynamic status of the patient, the location, gestational age, the activity of the trophoblast human chorionic gonadotropin-beta, as well as the presence of a concomitant pregnancy (heterotopic pregnancy) and obstetric history of the patient. Methotrexate treatment can be considered for women with a confirmed diagnosis of EP who are hemodynamically stable, who have an unruptured mass, and who do not have absolute contraindications for methotrexate[11]. The decision for the surgical management or medical management of EP should be guided by the initial clinical, laboratory, and radiologic data as well as patient-informed choice based on a discussion of the benefits and risks of each approach. Also, women who are treated with methotrexate therapy should be counseled about the importance of follow-up. In our case, we chose to perform salpingectomy through laparotomy based on the volume of the hemo-peritoneum, the patient's hemodynamic instability, ultrasound-documented viable four ectopic pregnancies, and signs of tubal rupture.

Our case is the first well-documented report of a patient with spontaneous live quadruplet tubal EP, and this case report highlights that multiple ectopic pregnancies can occur in relation to assisted reproductive technology, but they can also occur spontaneously.

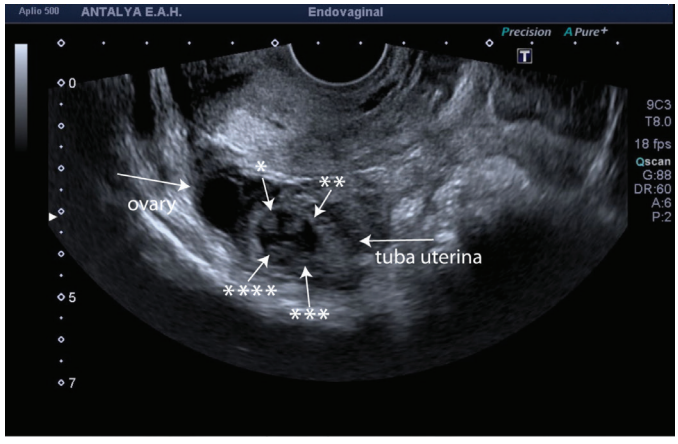

Figure 1. Sonographic appearance of right tubal quadruplet ectopic pregnancy. *indicates the order number of embryos in the tubal gestational sac

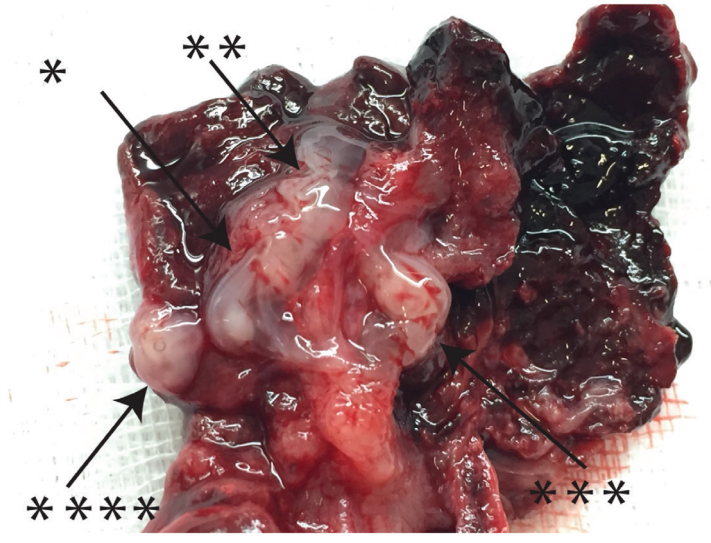

Figure 2. Postoperative gross examination of the tubal mass. *indicates the order number of embryos in the postoperative specimen

Ethics

Informed Consent: Informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Consept: C.G., S.K., B.K., B.A.Y., Desing: C.G., S.K., B.K., B.A.Y. Literature Search: C.G., S.K., Writing: B.K., B.A.Y.

Conflict of Interest: We declare that we have no conflict of interest.

Financial Disclosure: We do not have a financial relationship with the organization that sponsored the research.

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