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

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Procedure and Instruments	200 words	2,000 words (~8 pages)	4	10
Letters	NA	350 words	4	5

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TURKISH JOURNAL OF OBSTETRICS AND GYNECOLOGY

LETTER FROM THE PRESIDENT

Dear Colleagues,

During these trying times of Coronavirus Pandemic, it was not possible to conduct our yearly National Congress of Obstetrics and Gynecology. Instead we met through webinars, online lectures and meetings. We hope that we can return to normal and restart doing our conventions together as soon as possible.

However, even though we can't meet, it should not mean that we should stop searching, learning and discovering. As medical doctors and scientists, we should be giving our all especially in these times. Your additions and contributions matter more than ever as this is a crucial time for the future of medicine.

We want to take a significant, strong and a reliable part of the scientific World as the Turkish Journal of Obstetrics and Gynecology Journal with your support. We are looking forward to your precious submissions to publish in our journal.

Sincerely,

Ateş Karateke, Prof. MD
President of TJOD

Clinical Investigation / Araştırma

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Pregnancy worsens the morbidity of COVID-19 and this effect becomes more prominent as pregnancy advances

Gebelik COVID-19 morbiditesini kötüleştirmekte ve bu etki gebelik ilerledikçe daha belirgin hal almaktadır

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Abstract

Objective: To investigate pregnancy outcomes and compare the clinical characteristics of coronavirus 2019 (COVID-19) disease in pregnant and age-matched non-pregnant women.

Materials and Methods: Hospital records of four tertiary care centers were reviewed retrospectively. The subjects comprised 188 pregnant patients and 799 non-pregnant women who were admitted to these hospitals.

Results: Pregnancy significantly affected the clinical severity of COVID-19 and this effect was more prominent in pregnant women at >20 weeks gestation (p<0.001). Rates of oxygen support (10.1% vs 4.8%; p≤0.001), intensive care unit admission (3.2% vs 0.6%; p=0.009), presence of fever (12.8% vs 4.4%; p<0.001), tachypnea (7.0% vs 2.4%; p=0.003) and tachycardia (16.0% vs 1.9%; p<0.001) were significantly more frequent in pregnant women compared with non-pregnant women. Pregnancy was strongly associated with the need for oxygen support [relative risk (RR), 2.125; 95% confidence interval (CI): 1.25-3.60] and admission to the intensive care unit (RR, 5.1; 95% CI: 1.57-16.53) compared with non-pregnant women. Some 14.4% of the pregnant women had co-morbidities. Sixty of the 188 pregnant women (31.9%) delivered during the Severe Acute Respiratory syndrome coronavirus-2 infection, 11 (18.3%) had vaginal deliveries and 49 (81.7%) were by cesarean section. Of these 60 deliveries, 40 (66.7%) were <37 weeks gestation.

Conclusion: Pregnancy worsens the morbidity of COVID-19 and this effect seems to increase as the pregnancy advances, but not the mortality rate.

Keywords: SARS-CoV-2, COVID-19, pregnancy, morbidity, intensive care unit admission, preterm birth

Öz

Amaç: Gebe ve aynı yaş grubundaki gebe olmayan kadınlarda koronavirüs 2019 (COVID-19) kliniğinin karşılaştırılmasıdır.

Gereç ve Yöntemler: Dört tersiyer merkezin tıbbi kayıtları geriye dönük incelendi. Çalışma kapsamına 188 gebe ve 799 gebe olmayan COVID-19 tanısı konfirme edilmiş kadın dahil edildi.

Bulgular: Gebelik COVID-19 kliniğini istatistiksel olarak önemli ölçüde etkilemiştir. Bu etki 20. gebelik haftasından sonra artmaktadır (p<0,001). Oksijen desteği (%10,1 vs. %4,8; p≤0,001), yoğun bakımda yatış (%3,2 vs. %0,6; p=0,009), ateş (%12,8 vs. %4,4; p<0,001), taşipne (%7,0 vs. %2,4; p=0,003) ve taşikardi (%16 vs. %1,9; p<0,001) oranları gebe grupta daha yüksekti. Gebelik durumu oksijen ihtiyacı [rölatif risk (RR), 2,125; %95 güven aralığı (GA), 1,25-3,60] ve yoğun bakım yatışı (RR: 5,1; %95 GA: 1,57-16,53) ile ilişkili bulundu. Gebelerin %14,4'ü komorbid hastalardı. Yüz seksen sekiz gebenin hastalık seyri esnasında 60'ı (%31,9) doğum yaptı. Bu doğumların 11'i (%18,3) vajinal, 49'u (%81,7) sezaryen ile gerçekleşti. Doğumların 40'ında (%66,7) 37. gebelik haftası tamamlanmamıştı.

Sonuç: Gebelik COVID-19 morbiditesini kötüleştirmekte ve bu etki gebelik ilerledikçe daha belirgin hal almaktadır fakat mortalite oranlarında değişiklik saptanmamıştır.

Anahtar Kelimeler: SARS-CoV-2, COVID-19, gebelik, morbidite, yoğun bakım ünitesi, erken doğum

PRECIS: The clinical severity of COVID-19 pneumonia is worse in pregnant women than in non-pregnant women.

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Introduction

The clinical presentation of Severe Acute Respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, which has been responsible for the current pandemic in 2020, varies from asymptomatic to severe disease and age, sex, presence of co-morbidities, and viral load have been suggested to a play role in the severity of this disease[1-3]. However, less is known about the clinical picture of pregnant women.

There are a limited number of studies in the literature, some suggesting a similar clinical picture of SARS-CoV-2 infection in pregnancy to that of non-pregnant women, and some showing different results. Regarding altered immunity and response to viral infections in pregnancy, one may suppose a different course of the disease in pregnant women[1-3]. The outcome of pregnancies infected with SARS-CoV-2 is also still unclear[4]. In the current study, it was aimed to investigate pregnancy outcomes and compare the clinical characteristics of coronavirus 2019 (COVID-19) disease in pregnant and age-matched non-pregnant women.

Materials and Methods

In this study, the subjects were pregnant COVID-19 women who admitted to four tertiary care hospitals with symptoms related to pregnancy or COVID-19 and those of non-pregnant women in the same age group (18-45 years) admitted with reasons related to COVID-19 to the same hospitals between March 11th and June 30th, 2020. All patients were managed according to the national treatment protocols.

A total of 987 patients who were diagnosed as having COVID-19 were enrolled in the study. Of these, 188 patients were pregnant (19%) and 799 were non-pregnant (81%). Four tertiary centers (Şehit Prof. Dr. İlhan Varank Training and Research Hospital, İstanbul; Kartal Dr. Lütfi Kırdar Training and Research Hospital, İstanbul; Darıca Farabi Training and Research Hospital, Kocaeli; Medeniyet University Hospital, İstanbul) provided data of 557 (105 pregnant), 280 (30 pregnant), 147 (50 pregnant) and three (three pregnant) women diagnosed as having SARS-CoV-2 infection, respectively. There were no excluded patients. Data were retrospectively collected from health records using a standardized data collection form. Pregnant women diagnosed as having COVID-19 infection up until June 30th, 2020, were included as the study group. Data for the clinical, obstetric and laboratory outcomes were regularly updated until July 7th, 2020. Primary outcome measures were the comparison of the clinical severity of the COVID-19 infection, mortality, rates of need for intensive care unit (ICU), oxygen support, and clinical and laboratory findings. The secondary outcome measure was the obstetric outcomes. Each institution obtained approval from the local administration board, regional ethical committee, and national scientific research platform (approval no: 20/207, date: 05.06.2020).

The diagnosis of COVID-19 infection was made by either with reverse transcription real time polymerase chain reaction (RT-PCR) testing for SARS-CoV-2 or imaging studies including chest computed tomography, lung ultrasound or chest X-ray. The clinical severity of COVID-19 disease was classified according to the World Health Organization (WHO)[1]. Patients with mild-to-moderate disease and severe-to-critical disease were classified as symptomatic patients who did not require oxygen support and those who received oxygen support, respectively. The decision for oxygen support, tracheal intubation and admission to the ICU were made with the consultation with anesthesiology team on clinical grounds. First trimester of pregnancy was defined as <14 weeks, second trimester between 14 weeks and 27 weeks and 6 days, and third trimester as ≥28 weeks until birth. Extremely preterm (<28 weeks), very preterm (28-32 completed weeks of gestation), moderate-to-late preterm (>32 - <37), early term (37 - <39), and term (≥39 weeks of gestation) birth was defined according to the WHO classification[5].

Statistical Analysis

The collected data were analyzed using the SPSS software version 22.0 (IBM Corp., Armonk, NY, USA). The normality of the demographic data was assessed using the Shapiro-Wilk test. Demographic data are summarized as the median ± inter-quartile range for non-normally distributed data and as the mean ± standard deviation for normally distributed data. Pearson's chi-square test was used to assess whether pregnancy and the clinical severity of the COVID-19 infection were related. Student's t-test and the chi-square test were used to compare the means and rates of independent groups as indicated. A p-value of <0.05 was considered to indicate a significant difference.

Results

Demographic Data

The median age of all patients was 31±12 (range, 18-45) years. In all women, the diagnosis of infection was performed using RT-PCR testing for SARS-CoV-2 in 89.7% (n=885) and the remainder (n=102, 10.3%) was diagnosed only through imaging studies. RT-PCR testing confirmed the infection in 95.7% of pregnant women (n=180) and the diagnosis was confirmed only with imaging studies in 4.3% of pregnant women (n=8).

Disease Severity

Pregnancy significantly affected disease severity (p≤0.001). Pregnancy was strongly associated with the need for oxygen support [relative risk (RR), 2.125; 95% confidence interval (CI): 1.25-3.60] and admission to the ICU (RR: 5.1; 95% CI: 1.57-16.53) compared with non-pregnant women. Pregnant and non-pregnant patients with mild-to-moderate symptoms and those who needed are O_2 illustrated in Table 1. A triple comparison is given in Table 2, where the pregnant women were further divided into two according to gestational age (≤ or >20 weeks gestation), and first, second and third-trimester groups are given in Table 3. These data show that besides pregnancy state, gestational age also affects the disease severity.

Among 799 non-pregnant patients, 353 (44.2%) had a positive contact history with a confirmed person with COVID-19 and 446 (55.8%) did not, whereas these values were 57 (30.3%) and 131 (69.7%) in pregnant women, respectively (chi-square test, p=0.001).

Clinical and Laboratory Features

As given in Table 4, the presence of fever, tachypnea, tachycardia, and admission to ICU rates differed significantly between pregnant women and non-pregnant women. Three non-pregnant women and none of the pregnant women died of COVID-19 (p>0.05). The difference did not reach to the level of significance in the intubation/mechanical ventilation rates in the non-pregnant women and the pregnant women (0.6% and 2.1%, respectively; Fisher's Exact test, p=0.073). Rates of having normal leucocyte and lymphocyte counts were also worse in pregnant women compared with non-pregnant women (p<0.001, Table 4). None of the patients received extracorporeal membrane oxygenation. Hospitalization period, and serum values of lactate dehydrogenase and D-dimer were found as similar between pregnant and non-pregnant women (Table 5).

Pregnancy Outcomes

The median gestational week of the pregnant women was 26±20 (range, 5-41) weeks at the time of admission. The median parity of the pregnant women was 1±2 (range, 0-7) pregnancies.

Sixty pregnant women (31.9%) delivered at a median gestation week of 38 (±2 weeks). Of these 60 deliveries, one was extremely preterm (1.7%; 27th week), two were very preterm (3.3%; 31st and 31st weeks), 11 were moderate/late preterm (18.3%), 26 were early term (43.3%), and 20 (33.3%) were term. Eleven (18.3%) of the deliveries were vaginal and 49 (81.7%) were by cesarean section. None of the cesarean operations was performed under general anesthesia. Indications for cesarean delivery were maternal compromise in eight (16.3%), fetal compromise in 21 (42.9%), obstetric reasons (e.g. previous cesarean, failed progress labour) in 18 (36.7%), and maternal request in two (4.1%). Three of the pregnant women had abortion (1.6%) at their 7th gestational week.

No maternal-fetal transmission of SARS-CoV-2 was observed. None of the RT-PCR tests received from all neonates delivered from mothers with COVID-19 (first immediately after birth and second 48 hours later) were positive. None of these neonates manifested any signs related to COVID-19.

Of all 188 pregnant women, 27 (14.4%) had maternal co-morbidities including obesity (n=8), asthma (n=8), chronic bronchitis (n=1), advanced maternal age (n=2), type 1 diabetes mellitus (n=2), chronic hypertension (n=2), hypothyroidism (n=3), hyperthyroidism (n=1), and arrhythmia (n=1). The

Table 1. Clinical severity of pregnant and non-pregnant women infected with COVID-19

n (%)	Asymptomatic	Symptomatic	
		O_2 not required	Received O_2
Non-pregnants	418 (52.3%)	343 (42.9%)	38 (4.8%)
Pregnant	62 (33.0%)	107 (56.9%)	19 (10.1%)
Total	480 (48.6%)	450 (45.6%)	57 (5.8%)

Pearson chi-square χ^2 25.775, p≤0.001, COVID-19: Coronavirus 2019

Table 2. The clinical severity of COVID-19 in non-pregnants and pregnants ≤ or >20 weeks gestation (chi-square test, χ^2=32.913, p<0.001)

n (%) Trimester	Asymptomatic	Symptomatic		Total
		O_2 not required	Received O_2	
Non-pregnants	418 (52.3%)	343 (42.9%)	38 (4.7%)	799 (100%)
≤20 weeks	31 (41.9%)	39 (52.7%)	4 (5.4%)	74 (100%)
>20 weeks	31 (27.2%)	68 (59.7%)	15 (13.2%)	114 (100%)

COVID-19: Coronavirus 2019

Table 3. The clinical severity of COVID-19 in the 1st, 2nd and 3rd trimesters of pregnancy (Pearson chi-square χ^2=12.167, p=0.016)

n (%) Trimesters	Asymptomatic	Symptomatic	
		O_2 not required	Received O_2
First	17 (46.0%)	17 (46.0%)	3 (8.1%)
Second	27 (39.7%)	38 (55.9%)	3 (4.4%)
Third	18 (21.7%)	52 (62.7)	13 (15.7%)

COVID-19: Coronavirus 2019

Table 4. Clinical features and leukocyte and lymphocyte states of the pregnant and non-pregnant women with COVID-19

n (%)		Non-pregnant	Pregnant	p
Fever	Absent	764 (95.6%)	164 (87.2%)	0.000[a]*
	Present	35 (4.4%)	24 (12.8%)	
Tachypnea	Absent	780 (97.6%)	174 (93.0%)	0.003[a]*
	Present	19 (2.4%)	13 (7.0%)	
Tachycardia	Absent	784 (98.1%)	158 (84.0%)	0.000[a]*
	Present	15 (1.9%)	30 (16.0%)	
Admission to ICU	Absent	794 (99.4%)	182 (96.8%)	0.009[b]*
	Present	5 (0.6%)	6 (3.2%)	
Intubation/Mechanical ventilation	Absent	794 (99.4%)	184 (97.9%)	0.073[b]*
	Present	5 (0.6%)	4 (2.1%)	
Exitus	Absent	796 (99.6%)	188 100.0%	0.530[b]
	Present	3 (0.4%)	0 (0.0%)	
Leucocyte count	Normal	639 (80.0%)	108 (57.4%)	0.000[a]*
	Leukopenia	109 (13.6%)	13 (6.9%)	
	Leukocytosis	51 (6.4%)	67 (35.6%)	
Lymphocyte count	Normal	669 (83.7%)	119 (63.3%)	0.000[a]*
	Lymphopenia	92 (11.5%)	69 (36.7%)	
	Lymphocytosis	38 (4.8%)	0 (0.0%)	

[a]Pearson chi-square test, [b]Fisher's exact test, *: Statistically significant, COVID-19: Coronavirus 2019, ICU: Intensive care unit

Table 5. Comparison of symptomatic pregnant and symptomatic non-pregnant women with COVID-19

		n	Mean	SD	p
Hospitalization Period (days)	Pregnant	379	7.57	3.93	0.401
	Non-pregnant	125	7.94	5.03	
[LDH] (U/L)	Pregnant	249	264.75	177.10	0.865
	Non-pregnant	94	268.35	168.74	
[D-dimer] (µg/mL)	Pregnant	176	201.92	2095.52	0.121
	Non-pregnant	111	766.79	4028.42	

SD: Standard deviation, t-test with independent samples, COVID-19: Coronavirus 2019, LDH: Lactate dehydrogenase

clinical severity of COVID-19 was not found to differ by means of having any of these maternal co-morbidities in pregnancy (chi-square test =0.809, p=0.667).

Pregnancy was complicated with preeclampsia in six (3.2%) patients, all of whom delivered by cesarean section. For women with COVID-19, two were asymptomatic, one had mild symptoms, one had moderate symptoms but did not receive O_2, and two were admitted to the ICU. Another two patients (1.1%) had twin pregnancies and received O_2 support and recovered thereafter. They had ongoing healthy pregnancies at their 14th and 32nd gestational weeks. Guillain-Barré syndrome developed in one patient with moderate disease severity who did not require O_2 support. One asymptomatic patient had an ectopic pregnancy and was managed surgically because of unstable hemodynamics. Gestational diabetes was diagnosed in one asymptomatic patient who currently had an otherwise normal pregnancy at her 25th gestational week. Placenta previa was diagnosed in two patients (one asymptomatic and one with mild symptoms) who underwent cesarean section.

Discussion

Debate still exists as to whether pregnancy is adversely affected by the clinical features of COVID-19. Previous studies suggested increased morbidity of the disease in pregnancy, but opposing findings have also been reported[1-4]; in our opinion, all of which had limitations, which makes the results impossible to generalize.

An early study conducted by Barbero et al.[6] on 91 women with SARS-CoV-2 infection during pregnancy and puerperium. Their analysis showed that 40 patients developed pneumonia, bilateral in most cases, with a 46.2% rate of hospitalization and four patients requiring ICU admission. In the UKOSS study, data were made available for 427 pregnant women admitted to hospitals in the United Kingdom with confirmed SARS-CoV-2 infection between March 1st and April 14th, 2020. Indications of hospitalization of the subjects were both

symptoms of COVID-19 and other obstetric indications with co-existent SARS CoV-2 infection; 38 of 427 women (9%) required level-3 critical care, four women (<1%) received extracorporeal membrane oxygenation, and five women died (1.2%). Forty-two percent were treated successively and discharged whilst still pregnant. On the other hand, 59% of the deliveries consisted of cesarean births (20% received general anaesthesia), nearly half were due to maternal or fetal compromise. They did not make a comparison with non-pregnant women[7]. Kasraeian et al.[4] conducted a meta-analysis including 87 pregnant women who were SARS-CoV-2 positive. Mild or moderate symptoms for SARS-CoV-2 were reported as 78%. No vertical transmission was seen and the pregnancy complications did not differ from those of non-infected pregnant women. In their report, no direct comparison was included, but they still put forward a similar pattern of the clinical characteristics of COVID-19 pneumonia in pregnant women to that of other adult populations. They did not stratify the pregnant patients according to gestational age. Breslin et al.[8] reported the results of 43 test-confirmed COVID-19 cases at a pair of affiliated New York city hospitals. The patients were collected either by hospital admission due to the COVID-19 disease symptoms or by universal testing for all obstetrical admissions. Of these, 29 were symptomatic at presentation and three developed severe disease. The authors compared their findings with a previously published study by Wu and McGoogan[9] and concluded that these rates were similar to the rates of the non-pregnant women. Blitz et al.[10] shared data from seven hospitals in New York State between March 2nd and April 9th, 2020. After excluding patients with incomplete data, the incidence of ICU admission was compared between pregnant and non-pregnant women with COVID-19 aged between 15-49 years. Of these, 332 were non-pregnant females, and 82 were pregnant females. In all, 50 non-pregnant females (15.1%) and eight pregnant females (9.8%) were admitted to the ICU for worsening respiratory status, with no statistically significant difference.

On the other hand, the Public Health Agency of Sweden analyzed SARS-CoV-2 infection treated in ICUs in Sweden between March 19th and April 20th, 2020, and compared pregnant and non-pregnant women of similar age. Fifty-three women aged 20-45 years with SARS-CoV-2 were reported and 13 of these women were either pregnant or postpartum (<1 week). The results indicated that the risk of being admitted to the ICU was greater in pregnant and postpartum women with laboratory-confirmed SARS-CoV-2 compared with non-pregnant women of similar age[11]. A similar result was seen in a study conducted by Ellington et al.[12] that analyzed national data of the United States of America. Data on pregnancy states were available for 91,412 women with laboratory-confirmed SARS-CoV-2 infections; among these, 8207 were pregnant. Some 31.5% of pregnant women and 5.8% of non-pregnant women of reproductive age were hospitalized. The risk for ICU admission and intubation were also greater in pregnant women, but the risk for death was similar.

The results of the present study also show pregnancy as a risk factor for COVID-19. A comparison of the confirmed SARS-CoV-2 infected women revealed that pregnant women had significantly higher rates of COVID-19 related symptoms, fever, tachypnea, tachycardia, ICU admission, and abnormalities in leucocyte and lymphocyte counts. Five (0.6%) non-pregnant women and four (2.1%) pregnant women required mechanical ventilation (p>0.05). Three (4%) non-pregnant women and none of the pregnant women died of COVID-19 (p>0.05, Tables 1, 4).

On the other hand, when the pregnancies were further dichotomized according to gestational age, those with >20 weeks gestation represented even worse rates (being asymptomatic, need for O_2 support, and ICU admission) than those with ≤20 weeks gestation (Tables 2, 3, 6). A significant difference was also found between symptomatic and asymptomatic pregnant women in each trimester of pregnancy (Table 3).

The discrepancy of many studies, including ours with the above-mentioned studies that show no difference in the morbidity of COVID-19 in pregnant women compared with non-pregnant patients in the reproductive age group, could be secondary to the different gestational ages of the included pregnant patients. During pregnancy, besides the alteration in immunity, some anatomic and physiologic changes might make women more vulnerable to SARS-CoV-2 infection. Hyperemia, edema, and friability of mucosa and hypersecretion in the upper respiratory system[13,14] may provide a better route of entry for viruses. Also, the enlarged uterus displaces the diaphragm upwards leaving less room for the lungs to expand, hence leading to decreased functional capacity and residual capacity. Moreover, increased metabolic demands and oxygen[13,14] may decrease the threshold of pregnant women to compensate for the signs and symptoms of SARS-CoV-2 infection.

In a meta-analysis conducted by Khalil et al.[15], 20 studies on pregnant women with RT-PCR-confirmed SARS-CoV-2 involving 2567 women were analyzed. Among all the pregnant women in these studies, 73.9% were in their third trimester; 52.4% had delivered, 48.3% by cesarean section. The rate of preterm birth (<37 weeks) was found as 21.8%, which were mostly (18.4%) iatrogenic. The ICU admission rate was 7.0%

Table 6. Intensive care unit admission in pregnants ≤ and >20 weeks and non-pregnants (chi-square test, X^2=9.355, p=0.009)

n (%)	Admission to ICU		Total
	No	Yes	
Non-pregnants	794 (99.4%)	5 (0.6%)	799 (100%)
Pregnants ≤20 weeks	72 (97.3%)	2 (2.7%)	74 (100%)
Pregnants >20 weeks	110 (96.5%)	4 (3.5%)	114 (100%)

ICU: Intensive care unit

and the intubation rate was 3.4%. Maternal mortality was about 1%. Maternal age over 35 years was a risk factor for all co-morbidities and ICU admission. Neonatal nasopharyngeal RT-PCR swabs were positive in 1.4%.

In the present study, 60 of the 188 pregnant women (31.9%) delivered at a median of 38 (±2 weeks) of gestation. Of these 60 deliveries, 40 (67%) were preterm (<37 weeks). Eleven (18.3%) of the deliveries were vaginal and 49 (81.7%) were by cesarean section. None of the cesarean operations was performed under general anesthesia. The indications of the cesareans were maternal compromise in 8 (16.3%), fetal compromise in 21 (42.9%), obstetric reasons (e.g. previous cesarean, failed progress labour) in 18 (36.7%), and maternal request in two (4.1%). Three of the pregnant women had abortion (1.6%) at their ~7th gestational week. No maternal-fetal transmission of SARS-CoV-2 was observed.

In our opinion, the relatively higher rate of preterm delivery seen in our results might be related to the severity of the SARS-CoV-2 infection. Different modes of medications and morbidities in the cohorts of the patients might be the underlying reason for the discrepancies observed in studies involving pregnant women infected with SARS-CoV-2 in the literature. Larger studies are needed to define whether a better controlled maternal disease could decrease the risk of preterm birth in COVID-19.

Currently, all studies in the literature, including ours, have been performed on a hospital basis. In our view, studies in which subjects collected by screening the general population could give the exact rates of the COVID-19 morbidity and mortality.

Conclusion

Pregnancy worsens the morbidity of COVID-19 and this effect seems to increase as the pregnancy advances, but not the mortality rate.

Ethics

Ethics Committee Approval: Each institution obtained approval from the local administration board, regional ethical committee, and national scientific research platform (approval no: 20/207, date: 05.06.2020).

Informed Consent: Data were retrospectively collected from health records using a standardized data collection form.

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

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Anxiety levels and obsessive compulsion symptoms of pregnant women during the COVID-19 pandemic

COVID-19 pandemisi süresince gebelerin anksiyete düzeyleri ve obsesif kompülsiyon semptomları

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Abstract

Objective: Reliable data regarding maternal mental well-being during the Severe Acute Respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic are scarce. This study aimed to assess the state/trait anxiety and obsessive-compulsive symptoms of pregnant women and compare those with the non-pregnant population using patient-reported validated outcome measures.

Materials and Methods: This prospective case-control study was conducted at a tertiary 'Coronavirus Pandemic Hospital' in İstanbul, Turkey in April, 2020. Pregnant and non-pregnant women were consecutively allocated to two groups regardless of gestational age. The primary outcome was to identify the anxiety levels and obsessive-compulsive symptoms of pregnant women during the SARS-CoV-2 pandemic using the State-Trait Anxiety inventory (STAI) and Maudsley Obsessive-Compulsive inventory (MOCI), respectively.

Results: Two hundred three pregnant women and 101 non-pregnant women were included. The mean STAI-S questionnaire score of pregnant and non-pregnant women was 41.96±9.15 and 46.62±12, respectively (p=0.001). The overall incidence of STAI >40 in pregnant and non-pregnant women was 62.6% and 73.3%, respectively. The mean total score of MOCI was 17.9±6.7 and 15±6.6 in pregnant and non-pregnant women, respectively. The overall incidence of 30-item-MOCI ≥13.1 in pregnant and non-pregnant women was 61.6% (125/203) and 30.7% (31/103), respectively (p<0.001).

Conclusion: State anxiety and obsessive-compulsive symptoms in pregnant women were found increased during the current SARS-CoV-2 pandemic. Pregnant women showed more favourable anxiety levels compared with non-pregnant women. These findings can be used to improve the coping skills of pregnant women during the pandemic, to prepare for the post-pandemic period, and to deal with the long-term mental health impact of COVID-19.

Keywords: Anxiety, COVID-19, obsessive-compulsion, pregnancy, SARS-CoV-2

Öz

Amaç: Şiddetli Akut Solunum Yolu sendromu koronavirüsü-2 (SARS-CoV-2) pandemisi esnasında maternal mental iyilik hali hakkında güvenilir data literatürde azdır. Bu çalışmada gebelerin mevcut ve durum anksiyeteleri ve obsesif-kompülsif semptomlarının değerlendirilmesi ve gebe olmayan kadın popülasyonu ile valide ölçekler kullanılarak karşılaştırılması amaçlandı.

Gereç ve Yöntemler: Bu olgu-kontrol çalışması İstanbul, Türkiye'de, 2020 Nisan ayında tersiyer bir Koronavirüs Pandemi Hastanesi'nde yürütülmüştür. Gestasyonel yaştan bağımsız olarak gebe ve gebe olmayan kadınlar sırasıyla iki gruba atanmıştır. Primer Hedef Durumluluk-Süreklilik Anksiyete ölçeği (STAI) ve Maudsley Obsesif-Kompülsif ölçeği (MOCI) kullanılarak anksiyete ve obsesif-kompülsiyon semptomlarının değerlendirilmesidir.

Bulgular: İki yüz üç gebe ve 101 gebe olmayan kadın çalışmaya dahil edilmiştir. STAI-S ortalama skorları gebe ve kontrol grubu için sırasıyla 41,96±9,15 ve 46,62±12 olarak bulunmuştur (p=0,001). Gebe ve kontrol grubunda STAI >40 skor insidansı sırasıyla %62,6 ve %73,3 olarak bulunmuştur. MOCI ortalama total skoru gebe ve kontrol grubunda sırasıyla 17,9±6,7 ve 15±6,6'dır. Otuz soruluk MOCI anketinin skorunun 13,1'den büyük olması durumunun insidansı gebe ve kontrol grubu için sırasıyla %61,6 (125/203) ve %30,7 (31/103) olarak görülmüştür (p<0,001).

Sonuç: Gebelerde durum anksiyetesi ve obsesif-kompülsiyon skorları SARS-CoV-2 pandemisinde yüksek seyretmiştir. Gebeler, gebe olmayan kadınlara göre daha iyi anksiyete seviyelerine sahip olarak görülmüştür. Bu bulgular gebelerin pandemi süresince başa çıkma becerilerini artırmada, pandemi sonrası periyoda hazırlanmada ve COVID-19'un uzun dönem mental etkilerinin yönetiminde kullanılabilir.

Anahtar Kelimeler: Anksiyete, COVID-19, obsesif-kompülsiyon, gebelik, SARS-CoV-2

PRECIS: Anxiety and obsessive-compulsive symptoms were increased in pregnant women during the SARS-CoV-2 pandemic but anxiety was worse in non-pregnant.

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Introduction

The coronavirus 2019 (COVID-19) pandemic is a global major health crisis that brought with it a profound psychological and psychosocial morbidity[1]. The mental health impact of the pandemic may take a long time to be noticed and become completely apparent[2]. The future secondary effects of COVID-19 on the general population including the deterioration of financial conditions, quarantine conditions, and psychological reactions during emergencies can cause several negative psychiatric outcomes[3]. Those adverse psychological consequences may include depression, stress, anxiety, emotional dysregulation, and may include the exacerbation of pre-existing conditions or symptom[1,3,4].

It is evident that the special populations that are vulnerable to mental health problems will be affected by the secondary psychological impacts of the pandemic to a greater extent[1]. Pregnant women, along with children, adolescents, the geriatric population, and patients with pre-existing mental problems deserve special attention.

An important call for action was announced for investigating the psychological effects of the COVID-19 pandemic across the general and vulnerable population, which will be likely required in the event of a second wave of infection[5]. Apart from many letters, correspondence, and commentaries, there are only a few large-scale observational studies available investigating the mental consequences of the pandemic to date[2]. Observational studies that focused on pregnant women are even more limited[6,7]. The knowledge about the short- and long-term maternal mental wellbeing during this pandemic is scant in the literature and thus, potential negative psychological outcomes should be taken as a critical public health problem in order to improve optimal maternity care[8].

A recent review concluded that depressive and anxiety symptoms had been reported in up to 28% of subjects screened for common psychological reactions as a response to the COVID-19 pandemic[2]. Concern was also raised about obsessive-compulsive symptoms, which are more common among pregnant women than the general population, are currently being neglected and the possibility of an increase in their frequency and intensity during and after the pandemic[9,10]. The number of individuals at risk for obsessive-compulsive disorder (OCD) that would not develop otherwise is thought to have increased along with the fear of pandemic[11].

Given the increased risk for the occurrence of OCD in both the pregnancy and the postpartum period[12], and the increased adverse fetal outcomes related with obsessive-compulsive symptoms during pregnancy such as fetal loss[13], the changes in obsessive-compulsive traits of pregnant women during the current pandemic need to be determined.

An individuals' response to the pandemic and coping skills are inevitably influenced by multiple psychological and social factors[1]. At this point, more objective data are urgently needed to provide reliable detailed information and psychological support to pregnant women[1,5,14,15]. In this study, it was aimed to assess the psychological response of pregnant women to the COVID-19 pandemic with a multi-perspective approach. Their state and trait anxiety and obsessive-compulsive traits were evaluated.

Materials and Methods

This case-control study presents an analysis of prospectively collected data yielded at a single tertiary 'Coronavirus Pandemic Hospital' centre in April, 2020. The cohort consisted of a study and a control group from consecutively included women who presented to the outpatient clinic. Women with a confirmed singleton healthy pregnancy were included in the study group regardless of gestational age. The control group comprised non-pregnant women aged between 20 and 50 years. Participants were assigned in a 2:1 fashion. Women either with signs and symptoms of COVID-19 or were suspected of having COVID-19 or diagnosed labour or women with any obstetric indication that required admission to the hospital and women with any current/prior known psychiatric disorder and gynaecological malignancy were excluded from the study prior to enrollment.

Women were asked to complete a form consisting of a demographic enquiry and three validated patient-reported questionnaires to assess the anxiety, obsessive-compulsive symptoms and metacognition, with anonymity preservation. The questionnaires were the State-Trait Anxiety inventory (STAI) and the Maudsley Obsessive-Compulsive inventory (MOCI)[16,17]. Demographic data included age, body mass index (BMI), gestational week, parity, economic status, household size, and if the family was responsible for looking after an elder family member. The official minimum wage was used to distinguish low, middle, and high income. The participants completed the questionnaires anonymously, taking an average of 20 minutes to finish. The primary outcome was to identify the anxiety levels and obsessive-compulsive symptoms of pregnant women in the era of current Severe Acute Respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic. All patients gave written informed consent and approved for publication before data collection. All procedures were in accordance with the 1964 Helsinki Declaration and its later amendments. The Ethics Committee of the University (registry no: 20/203), Scientific Board of the Health Ministry and the local institutional administration board approved the study.

Measures

The Spielberger State-Trait Anxiety Inventory

The Spielberger STAI measures the presence and severity of current symptoms of anxiety and a generalized propensity to be anxious[17]. The STAI enables to differentiate the temporary condition of state anxiety and the continuity of anxiety, which shows the tendency throughout life by using two separate

20-item self-report questionnaires[18]. Scoring is reversed for anxiety-absent items. Both subscales have a total score ranging from 20 to 80 points. High scores indicate high levels of anxiety. A cut-off point of 39-40 has been suggested to detect clinically significant symptoms for the S-Anxiety scale[17].

MOCI

The MOCI is a 30-item self-report questionnaire using a true/false format, which measures the severity of obsessive-compulsive symptoms and assesses the types of obsessive-compulsive symptoms on four subscales: checking-control, cleaning-hygiene, slowness, and doubting[19]. In the 37-item version, seven items were added to the original form to additionally evaluate ruminations[20]. Higher scores reflect more severe obsessive-compulsive symptoms. Both scores for 30- and 37-item versions are provided in this study. A reliability generalization meta-analysis found the average mean scores of 11.40 and 13.11 for sub-clinical and clinical samples, respectively[16].

Statistical Analysis

The SPSS-22 software was used for data analysis. The independent samples t-test was used to compare the means of the scales. Variables are reported by their mean ± standard deviation and mean difference. Internal consistency was assessed using Cronbach's alpha, and an α value of between 0.70 and 0.95 was considered to reflect good internal consistency. Pearson's correlation test was used to assess the association between the scales using r-values. A p-value of less than 0.05 was considered significant.

Results

Two hundred three pregnant women and 101 non-pregnant women were included. The mean age and BMI of the pregnant women were 27.4±5.3 years and 27.83±4.33 kg/m^2, respectively. The mean age and BMI of the control group were 27.6±4.1 years and 23.48±5.08 kg/m^2, respectively. The ages of both groups were similar (p=0.698), the BMI was significantly higher in pregnant women with a mean difference of 4.35 kg/m^2 (p<0.001). Median gestational week of the pregnant women was 35 weeks (interquartile range: 11) and ranged between 4 and 42 weeks. Among all the pregnant women, 8.4% were in the first, 21.7% in the second, and 70% in the third trimester of pregnancies.

Reliability coefficients, mean scores of the primary outcomes, and their comparisons within both groups of anxiety and obsessive-compulsive are presented in Table 1.

The mean STAI-S questionnaire score of pregnant and non-pregnant women was 41.96±9.15 and 46.62±12, respectively. The overall incidence of STAI >40 in pregnant and non-pregnant women was 62.6% (76/203) and 73.3% (74/103), respectively (Figure 1). State anxiety levels did not differ among first, second, and third trimesters [p=0.793, f=0.232, One-Way analysis of variance (ANOVA)].

The mean total score of MOCI was 17.9±6.7 and 15±6.6 in pregnant and non-pregnant women, respectively (Table 1). Note, these results belong to the 37-item version of the MOCI. Following re-analysis for the 30-item version to enable future comparisons, the mean total score of the MOCI was found as 15.4±5.1 and 12.4±5.6 in pregnant and non-pregnant women, respectively. The overall incidence of 30-item-MOCI ≥13.1 in pregnant and non-pregnant women was 61.6% (125/203) and 30.7% (31/103), respectively (re-calculated for the first 30 items, Figure 1).

The internal consistency for the total scores of the STAI-S, STAI-T, and MOCI scales was found sufficient at moderate-to-good levels (Table 1). The results of the correlation analyses are presented in Table 2. In the correlation analysis, current anxiety status (STAI-S) was found to be positively associated

Table 1. The total and subscale scores of state and trait anxiety and obsessive-compulsive symptoms for pregnant and non-pregnant women

Mean		Pregnant women		Control group				
		SD	Mean	SD	Mean Difference	p	Cronbach's α (study group)	
STAI	State anxiety	41.96	9.15	46.62	12	-4.66	0.001**	0.860
	Trait anxiety	43.16	8.19	44.64	8.48	-1.48	0.143	0.842
MOCI	Total score (37-item)	17.91	6.65	14.98	6.60	2.93	0.000**	0.870
	Total score (30-item)	15.40	5.14	12.40	5.58	3.00	0.000**	0.838
	Checking - control	3.47	2.49	2.83	2.20	0.64	0.029*	0.779
	Cleaning - hygiene	6.99	1.63	5.36	2.51	1.63	0.000**	0.422
	Slowness	2.17	1.89	2.12	1.70	0.05	0.83	0.737
	Doubting	3.73	1.41	3.18	1.40	0.56	0.001**	0.443
	Rumination	3.11	2.46	3.21	2.30	-0.10	0.734	0.779

Independent samples t-test, **: Correlation is significant at the 0.01 level, *: Correlation is significant at the 0.05 level, STAI: State-trait anxiety inventory, STAI-T: Trait anxiety, MOCI: Maudsley obsessive-compulsive inventory, SD: Standard deviation

with all obsessive-compulsion symptoms except the cleaning and hygiene subscale (p<0.01). The associations of state anxiety with other measures were found to be weak to moderate (r<0.60).

The monthly income of the pregnant women was low in 45.8%, medium in 52.2%, and high in 2%. The monthly income of the control group was low in 5.9%, medium in 79.2%, and high in 14.9%. One-Way ANOVA of the measures comparing three different economic status showed a significant difference only in cleaning-hygiene subscale of the metacognition test (p=0.002) and doubting subscale of the MOCI test (p=0.04). An increased cleaning-hygiene score with a mean difference of 1.7 was observed in women with low income compared with those with high income (p=0.004). An increased doubting score with a mean difference of 0.9 was observed in women with low income compared with women with high income (p=0.033).

Table 2. The correlation of objective scales and their subscales

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
(1) STAI-S	1	0.49*	0.30*	0.38*	-0.01	0.35*	0.23*	0.36*	0.28*
(2) STAI-T		1	0.50*	0.53*	0.26*	0.40*	0.28*	0.58*	0.45*
(3) MOCI-37 Total score			1	0.89*	0.63*	0.80*	0.80*	0.89*	0.98*
(4) CC				1	0.40*	0.75*	0.63*	0.79*	0.89*
(5) CH					1	0.29*	0.32*	0.41*	0.65*
(6) Sl						1	0.67*	0.75*	0.81*
(7) Do							1	0.65*	0.81*
(8) Ru								1	0.80*
(9) MOCI-30 Total score									1

STAI-S: State anxiety subscale of state-trait anxiety inventory, STAI-T: Trait anxiety, MOCI-37 Total score: Total score of maudsley obsessive-compulsive inventory-37 item version, CC: MOCI Checking - control, CH: MOCI Cleaning hygiene, Sl: MOCI Slowness, Do: MOCI Doubting, Ru: MOCU Rumination, MOCI-30 Total score: Total score of Maudsley Obsessive-Compulsive Inventory-30 item version, *: Correlation is significant at the 0.01 level (2-tailed)

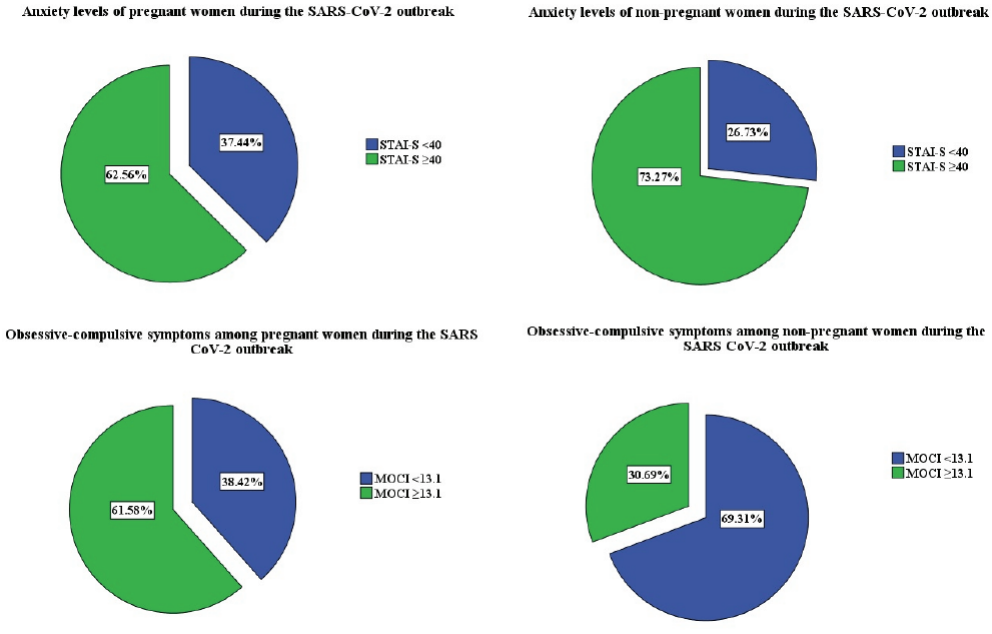

Figure 1. Anxiety levels and obsessive-compulsive symptoms of pregnant and non-pregnant women during the SARS-CoV-2 outbreak

The pie chart depicts the proportion of women with unfavourable measure results. Charts at the upper-line show pregnant and non-pregnant women with increased state-anxiety level scores when the cut-off was considered as 40. Charts at the lower line show pregnant and non-pregnant women with increased obsessive-compulsive symptom scores when the cut-off was considered as 13.1.

SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2, STAI: State anxiety sub scale of State Trait Anxiety inventory, MOCI: Maudsley Obsessive-compulsive inventory

Discussion

This survey study showed increased anxiety and obsessive-compulsive symptoms in pregnant women during the current SARS-CoV-2 pandemic. More than 60% of the pregnant women and more than 30% of non-pregnant women reported increased obsessive-compulsive symptoms with regard to the proposed cut-off values[16]. Pregnant women showed more favourable anxiety levels compared with non-pregnant women. To the best of our knowledge, this is the first study in the literature to assess the obsessive-compulsive symptoms of pregnant women during the SARS-CoV-2 pandemic and compare those and their anxiety levels in a case-control fashion.

A recent Italian study investigating the psychological impact of COVID-19 in pregnant women found a similar anxiety rate at 68%[6]. Another study that validated the STAI in pregnant women addressed an overall score of 35.3 for use in the general pregnant population[21]. The mean state anxiety scores of this study were also found considerably higher than those specified levels.

Although both groups expressed higher state anxiety during the pandemic than the normal population in the literature, state anxiety scores were significantly higher in the control group ($p=0.001$), but similar for trait anxiety ($p=0.14$). The authors believe that this difference in state anxiety levels between pregnant and non-pregnant women may be related to paid lay-off restrictions specifically for pregnant women and the high self-isolation rates in Turkey. Comparable trait anxiety implies that pregnant women were not significantly more prone to being anxious compared with the control group.

Pregnancy is associated with the onset of obsessive-compulsive symptoms. Forray et al.[22] found that 15% of women who had ever given birth had their obsessive-compulsive disease onset during pregnancy. Brockington et al.[23] observed that one-tenth of pregnant women who were referred to specialist psychiatric services had an obsessive activity or symptoms during pregnancy usually obsessive cleaning or housework, including a new-onset rate of 6%. In this study, pregnant women showed more obsessive traits than non-pregnant women in the MOCI total score ($p<0.001$) and in the checking, cleaning, and doubting subscales ($p<0.005$). The mean total scores of MOCI (30-item version, for comparison reasons) were found as 15.4 and 12.4 in pregnant and non-pregnant women, respectively. A reliability generalization meta-analysis found average mean scores of 11.40 for sub-clinical and 13.11 for clinical samples[16]. In our cohort, more than half of the pregnant women (61.6%) and almost one-third of the non-pregnant women (30.7%) were found to have higher obsessive symptom scores than the proposed mean values in the literature. More specifically, a mean total score of 7.6 was found in a large cohort of pregnant women who were admitted to the clinic for delivery, which is far below our current findings[24]. Although it is known that obsessive-compulsive symptoms generally worsen during pregnancy and puerperium[25], the authors believe that those higher scores than the mean values of the above-mentioned literature should be conveniently linked to the current SARS-CoV-2 pandemic. In this study, current state anxiety status was found to be positively associated with all obsessive-compulsion symptoms except the cleaning and hygiene subscale ($p<0.01$). The high obsessive-compulsion symptoms among pregnant women of the current study may be biased due to the lower economic status than that of the non-pregnant women. In this study, 45% of the pregnant women reported having low-income, whereas only 6% of the non-pregnant women had low income. One-quarter of all pregnant women with low socio-economic status seen in primary care settings in Brazil have been shown to have obsessive symptoms[26]. However, the significant impact of the COVID-19 pandemic is evident considering the increased rates of obsessive-compulsion symptoms in non-pregnant women when compared with the literature. It has previously been suggested that integrating cognitive behavioural therapy-based prevention programs into antenatal education classes for women at risk of developing OCD was associated with significantly lower levels of obsessive-compulsive traits following childbirth[27]. This important finding should be kept in mind during the outbreak, and strategies should be developed to prevent antenatal and postnatal obsessive-compulsive treats. Screening the psychological status of pregnant women may be integrated into universal screening programs[28] to achieve long-term success and reductions in symptoms of anxiety and depression simultaneously in a short time frame.

Study Limitations

The major limitation of this study is that its design did not include the comparison of psychiatric levels of pregnant women in pre-pandemic versus pandemic period, which would make a clear sense for the effect of the pandemic on pregnant women. However, a strong relationship was found between the target population and the mean scores of MOCI[16]; therefore, our results can be used as control scores for further comparisons in future studies. Another strength of this study is the relatively larger and controlled sample size. In addition, this study contributes to the literature by being one of the rare studies that assessed obsessive-compulsive symptoms of pregnant women during the pandemic. The internal consistency of the STAI and MOCI at sufficient levels was also provided in the current study to be used in further studies.

Conclusion

State anxiety and obsessive-compulsive symptoms in pregnant women were found increased during the current SARS-CoV-2 pandemic. Pregnant women showed increased obsessive-compulsive symptoms and more favourable anxiety compared with non-pregnant women. These findings can be used to improve the coping skills of pregnant women during the pandemic and to deal with the long-term mental health impact of COVID-19.

Ethics

Ethics Committee Approval: The Ethics Committee of the University (Registry no: 20/203), Scientific Board of the Health Ministry and the local institutional administration board approved the study.
Informed Consent: All patients gave written informed consent and approved for publication before data collection.
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Obstetric outcomes in pregnant women with seizure disorder: A hospital-based, longitudinal study

Nöbet bozukluğu olan gebe kadınlarda obstetrik sonuç: Hastane temelli, uzunlamasına bir çalışma

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Abstract

Objective: To study the association of seizure disorder with adverse obstetric outcome in terms of maternal and perinatal complications.

Materials and Methods: This longitudinal study was conducted at Maulana Azad Medical College, New Delhi over 15 months among women attending the antenatal clinic (ANC) outpatient department. Fifty pregnant women with seizure disorder with their first ANC visit before 28 weeks were recruited as the case group, excluding patients with eclampsia. The control group included 120 matched healthy pregnant women. After obtaining informed consent, subjects were recruited and followed till one week postpartum and obstetric outcomes were analyzed.

Results: Women with seizure disorder had significantly increased incidence of severe preeclampsia (cases =8%, controls =0%, p<0.001), antepartum hemorrhage (cases =4%, controls =0%, p<0.001), babies with early neonatal complications such as asphyxia (cases =4.1%, controls =0.5%, p=0.04), respiratory distress (cases =14.5%, controls =5.1%, p=0.02), necrotizing enterocolitis (cases =2.0%, controls =0%, p=0.04), early neonatal death (cases =2.0%, controls =0%, p=0.04) and Neonatal Intensive Care Unit admission (cases =20.8%, controls =8.6%, p<0.001) when compared with women without seizure disorder. No significant difference was observed in rates of induction of labor, cesarean section, abortion, congenital anomalies in babies, still births.

Conclusion: Women with seizure disorder are at higher risk of hypertensive disorders, antepartum hemorrhage, and early neonatal complications. Appropriate obstetric, pediatric and neurology care is required during preconception, pregnancy, labor, delivery, and postpartum.

Keywords: Seizure disorder, anti-epileptic drugs, maternal and perinatal complications

Öz

Amaç: Nöbet bozukluğunun olumsuz obstetrik sonuçla ilişkisini maternal ve perinatal komplikasyonlar açısından incelemektir.

Gereç ve Yöntemler: Bu uzunlamasına çalışma doğum öncesi kliniğine (ANC) katılan kadınlar arasında 15 ay boyunca Yeni Delhi Maulana Azad Tıp Koleji'nde gerçekleştirildi. Yirmi sekiz haftadan önce ilk ANC ziyareti ile nöbet bozukluğu olan 50 gebe kadın, eklampsi hastaları hariç olgu grubu olarak alındı. Kontrol grubuna 200 sağlıklı hamile kadın dahil edildi. Bilgilendirilmiş onam alındıktan sonra denekler işe alındı ve doğum sonrası 1 haftaya kadar takip edildi ve obstetrik sonuçlar analiz edildi.

Bulgular: Nöbet bozukluğu olan kadınlarda şiddetli preeklampsi insidansı (olgular =%8, kontroller =%0, p<0,001), doğum öncesi kanama (olgular =%4, kontroller =%0, p<0,0001), erken neonatal komplikasyonları olan bebekler asfiksi ile ilişkili (olgular =%4,1, kontroller =%0,5, p=0,04), solunum sıkıntısı (olgular =%14,5, kontroller =%5,1, p=0,02), nekrotizan enterokolit (olgular =%2,0, kontroller =%0, p=0,04), erken neonatal ölüm (olgular =%2,0, kontroller =%0, p=0,04) ve yenidoğan yoğun bakım ünitesi kabulü (olgular =%20,8, kontroller =%8,6, p<0,001) nöbet bozukluğu olmayan kadınlarla karşılaştırıldığında doğum indüksiyon oranları, sezaryen, kürtaj, bebeklerde doğuştan anomaliler, hala doğum oranları arasında anlamlı bir fark gözlenmemiştir.

Sonuç: Nöbet bozukluğu olan kadınlar hipertansif bozukluklar, antepartum hemoraji ve erken neonatal komplikasyon riski altındadır. Gebelik öncesi, gebelik, doğum ve doğum sonrası dönemde uygun obstetrik, pediatrik ve nöroloji bakımı gereklidir.

Anahtar Kelimeler: Nöbet bozukluğu, anti-epileptik ilaçlar, anne ve perinatal komplikasyonlar

PRECIS: Women with seizure disorder are at higher risk of hypertensive disorders, antepartum haemorrhage and early neonatal complications.

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Introduction

Seizure disorder is characterized by an episode of abnormal, uncontrolled neuronal activity in the brain resulting in various manifestations ranging from dramatic convulsive activity, altered consciousness, abnormal sensations to experiential phenomena not readily discernible by an observer[1]. Epilepsy as described by International League Against Epilepsy (ILAE) 2014 includes at least 2 unprovoked (or reflex) seizures occurring more than 24 hours apart[2]. It is the second most common neurologic problem encountered in pregnancy after headaches with a prevalence of 0.3-0.7%[3].

Women with Epilepsy (WWE) are considered at high risk in pregnancy with maternal mortality 10 times higher than women without seizure disorder[4]. Although 90% of WWE have uneventful pregnancies, many studies have shown its association with increased complications[5]. Individual studies provide inconclusive estimates of the association between seizure disorder and pregnancy complications such as antenatal [miscarriage, gestational hypertension, preeclampsia, gestational diabetes mellitus (GDM), antepartum hemorrhage (APH), preterm delivery, fetal growth restriction (FGR)], intranatal (need for induction of labor, cesarean section), postnatal [postpartum hemorrhage (PPH)], fetal [low-birth-weight (LBW) babies, need for Neonatal Intensive Care Unit (NICU) admission, congenital fetal anomalies, still births][6-9].

Newborns exposed to anti-epileptic drugs (AEDs) in utero have been shown to have 2-3-fold increased (3.3-9%) prevalence of major congenital abnormalities compared with unexposed newborns[10].

Commonly seen congenital malformations include cleft lip and palate, cardiac defects, neural tube defects, skeletal abnormalities, and hypospadias. These malformations are observed more frequently with increased doses of AEDs, higher serum levels of AEDs, and polytherapeutic approaches[6]. Folic acid deficiency may also be responsible for the occurrence of major complications to some degree as folic acid supplementation in women under anticonvulsant medications has been shown to decrease malformation rates[11].

Approximately two-thirds of patients experience no change or decrease in the frequency of seizure episodes, whereas the remaining one-third have an increase in frequency. Some of the changes can be attributed to pregnancy-associated physiologic changes and psychological stress. Deliberate patient noncompliance secondary to the fear of the effect of AEDs on the fetus is more likely to be blamed for the increased seizure frequency. It has been seen that lower the number of seizures occurring in the 9 months before conception, the lower the risk of experiencing seizure episodes during pregnancy[12].

Therefore, as the outcomes of pregnant women with seizure disorder is conflicting, we aimed to study the obstetric outcomes of women with seizure disorder and establish whether pregnant such women had an increased risk of complications compared with a control group of matched healthy pregnant women.

Aims and Objectives

1. To study the profile of pregnant women with seizure disorder.
2. To study the obstetric outcome in women with seizure disorder in terms of maternal and perinatal outcomes.
3. Compare the outcomes with a control group comprising healthy pregnant women.

Materials and Methods

This was a longitudinal study conducted after obtaining clearance from the Institutional Ethics Committee among women attending the antenatal outpatient department (OPD)/ high-risk OPD/gyne casualty in the department of Obstetrics and Gynecology, Maulana Azad Medical College and associated Lok Nayak Hospital, Govind Ballabh Pant Institute of Postgraduate Medical Education and Research (GIPMER) hospital, New Delhi, from November 2016 to January 2017 (15 months) (approval number: 113, date: 04/11/2016). It included 250 pregnant women, out of which 50 women were cases and 200 controls as per the following criteria:

Selection of Cases

Inclusion criteria: Pregnant women with known case of seizure disorder with first antenatal clinic (ANC) visit between 18 to 28 weeks of gestation.

Exclusion criteria: Pregnant women with eclampsia at the time of enrolment.

- Selection of controls: Age, body mass index (BMI), and gestational age-matched healthy pregnant women. Pregnant women with known medical problems (e.g. chronic hypertension, pre-existing diabetes, asthma, pre-existing hypothyroidism) were excluded.
- Primary outcome: To study obstetric outcomes in women with seizure disorder when compared with women without seizure disorder in terms of maternal complications such as antenatal (abortion, gestational hypertension, preeclampsia, GDM, hypothyroidism, intrahepatic cholestasis of pregnancy, APH, preterm delivery), intranatal (need for induction of labor, caesarean section), postnatal (PPH), fetal (FGR, LBW babies, NICU admissions, congenital fetal anomalies, still births, early neonatal complications such as respiratory distress related, asphyxia related, intraventricular hemorrhage, necrotizing enterocolitis, neonatal hypoglycemia, and 1 and 5-minute Apgar scores).

After obtaining written informed consent from the subjects, data were collected and recorded on a questionnaire. It included baseline demographic details such as age, education status, weight at first visit, height, BMI, significant obstetric history, menstrual history, significant past and family history, pre-pregnancy and trimester-wise intake of folic acid, and preconception counselling.

Detailed history of seizure was recorded in known cases such as time since diagnosis of seizure disorder, seizure type as per the ILAE 2017 classification by a neurologist, underlying cause, date of last seizure prior to pregnancy, seizure episodes

during pregnancy and postpartum period, AED intake prior to pregnancy, AEDs consumed during pregnancy, any change in the antiepileptic medication.

For quantifying change in seizure episodes, the frequency in the pre-pregnancy year was taken as the baseline. Increased seizure frequency was defined as a ≥50% increase in the number of seizure episodes from baseline during pregnancy and postpartum period. Decreased seizure frequency was defined as a ≥50% decrease in the number of seizure episodes from baseline during pregnancy and the postpartum period. Any change in seizure frequency between these was defined as unchanged. Abortion is defined as a clinically recognized pregnancy loss before the 20th week of gestation. The World Health Organization defines abortion as expulsion or extraction of an embryo or fetus weighing 500 g or less. Different countries have their own laws for defining criteria for abortion[13]. In India, this has been fixed administratively at 28 weeks, when the fetus weighs approximately 1000 g[14]. So, any delivery before 28 weeks was categorized as abortion.

Subjects were diagnosed as having gestational hypertension when either systolic blood pressure (BP) was 140 mm Hg or greater or diastolic BP was 90 mm Hg or greater or both, in at least two recordings, at least 4 hours apart[15]. Preeclampsia was also defined using criteria by the Task Force on Hypertension in Pregnancy under the American College of Obstetrician and Gynecologists.

To screen and diagnose GDM, the 75 g oral glucose tolerance test as was performed recommended by American Diabetic Association and International Association of Diabetes and Pregnancy Study Groups at first ANC visit for high-risk women or at 24-28 weeks. The cut-offs were taken as follows: fasting blood glucose ≥92 mg/dL, postprandial 1 hour ≥180 mg/dL, postprandial 2 hours ≥153 mg/dL. One or more abnormal values lead to the diagnosis of GDM[16].

Hypothyroidism was defined as per the gestational age specific cut-off for thyroid stimulating hormone, as recommended by American Thyroid Association[17].

FGR was defined as a baby with estimated fetal weight (EFW) or abdominal circumference (AC) less than 10th centile, and severe FGR as EFW AC less than 3rd centile. Fetuses with growth restriction were identified using INTERGROWTH-21st charts[18].

Fetal birth weight was recorded and was further classified as normal (2.5-4.2 kg), LBW (less than 2.5 kg) or large baby (more than 4.2 kg)[19]. Apgar scores at 1 and 5 minutes were recorded by a pediatrician.

As per the protocol, all newborns received a 1 mg injection of vitamin K at delivery[20].

Fetal malformations and early neonatal problems were recorded by a pediatrician. They were classified as major or minor malformations. Major congenital anomalies were defined as structural changes that had significant medical, social or cosmetic consequences for the affected individual, and typically require medical intervention. Examples include cleft lip, spina bifida, gastroschisis, meningocele. Minor congenital anomalies were defined as structural changes that posed no significant health problems in the neonatal period and tended to have limited social or cosmetic consequences for the affected individual. Examples include single palmar crease and clinodactyly[21].

Follow-up: Patients were followed up from their first ANC visit till 1 week after delivery to look for early neonatal complications and postpartum seizure episodes.

Statistical Analysis

Data were analyzed and statistically evaluated using the Statistical Package for the Social Sciences version- Personal Computer (SPSS-PC-17) software.

Quantitative data are expressed in mean, standard deviation, and differences between two comparable groups were tested using Student's t-test (unpaired) or the Mann-Whitney U test. Qualitative data are expressed as percentages. Statistical differences between the proportions were tested using the chi-square test or Fisher's Exact test. P-values less than 0.05 were considered statistically significant. Further, odds ratio (OR) and 95% confidence intervals (CI) were used to quantify the risk factors. Univariate analysis was performed, and factors that were found to be significant with p-values ≤0.1 were entered in multivariate analysis.

Results

The baseline demographic data of the study population are shown in Table 1. Preconception counselling was attended by a significantly ($p<0.01$) greater number of women with seizure disorder (24%) as compared with the controls (2%). Periconception folic acid intake was also observed to be significantly higher ($p<0.01$) among cases as compared with controls as depicted in the Table 1.

It was also seen that the women with seizure disorder (63%) had a significant ($p<0.01$) history of abortions in the past when compared with healthy pregnant women (28.5%).

As depicted in Table 2, generalized onset seizure disorder (n=44, 88%) was the most common type seen. Most of the WWE (n=48, 96%) had motor type of seizures and tonic-clonic was the commonest (n=42, 84%) subtype.

Around 46% (n=23) had a seizure disorder of duration between 1-5 years. Among the 30 (60%) women who experienced seizure episodes during pregnancy, the highest number (n=8, 26.6%) had it during the third trimester. Out of these, one woman was not on any AEDs, seven (24.1%) were not compliant with AED intake, and 22 (75.9%) were regularly taking their medication. History of seizure in previous pregnancy had no significant impact on the occurrence of seizure in the current pregnancy (p=0.26).

The cause of seizure disorder was unknown in 66% (n=33) of the cases. The various causes found are shown in Figure 1.

Out of the 50 women enrolled with seizure disorder, 49 (98%) were taking AEDs. Out of these, six (12%) were started on AEDs during the pregnancy. Most of the women (n=24, 48.9%) were taking second-generation AEDs. Monotherapy was given to 33 (67.2%) women with levetiracetam being the most commonly prescribed AED (n=19, 38.7%).

The most commonly observed change in therapy was the addition of a drug to the pre-existing treatment as seen in 8 (16.3%) women (Table 3).

Women with seizure disorder had a higher incidence of preeclampsia (case n=6, control n=4, p<0.01) and APH (case n=2, control n=0, p<0.01) with no significant difference in the rate of other antenatal complications, as detailed in Table 4. A higher number of women with seizure disorder underwent instrumental vaginal delivery [adjusted odds ratio (aOR)=3.68, CI=1.07-9.64] when compared with the controls. Among the 14 women with seizure disorder who were delivered by cesarean section, two (14.3%) had APH, one (7.1%) had cephalopelvic disproportion, three (21.4%) had failed induction, six (42.8%) had fetal distress, and two (14.3%) had malpresentation.

None of the women with seizure disorder who crossed the period of viability (n=48) had still birth.

Overall, congenital anomalies were observed in three (6.2%) cases and five (2.5%) controls, the difference was not statistically significant. However, minor congenital malformations were significantly (p<0.01) more frequent among the cases (n=2%) than in the controls (0%), as depicted in Table 5. The major congenital malformations among the cases included posterior urethral valve with bilateral hydronephrosis, cleft palate, and polydactyly. Babies with posterior urethral valves had early neonatal demise. Babies born to mothers with seizure disorder had a significantly increased incidence of early neonatal complications (Table 5).

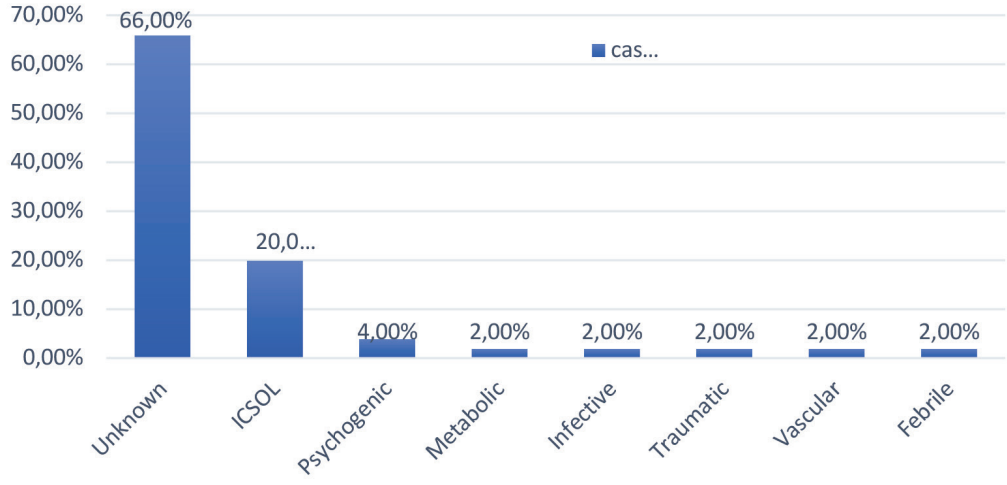

Figure 1. Causes of seizure disorder in cases

Table 1. Demographic parameters of subjects

Parameter	Case (n=50)	Control (n=200)	p
Age (years) (mean ± SD)	25.38±4.32	25.02±3.07	0.36
Illiterate, % (n)	16 (8)	7.5 (15)	0.06
Weight (kg) mean ± SD	54.48±8.85	55.23±10.37	0.63
Height (cm)	152.49±5.61	154.95±12.04	0.16
Gestational age at recruitment (weeks) (mean ± SD)	22 weeks 6 days ±3 weeks 2 days	22 weeks ±3 weeks	0.11
Nulliparous, % (n)	56 (28)	44 (88)	0.12
Previous cesarean section, % (n)	10 (3)	21.8 (29)	0.20
History of abortion, % (n)	63 (19)	28.5 (38)	<0.01
Preconception counselling %, (n)	24 (12)	2 (4)	<0.01
Preconception folic acid intake, % (n)	30 (15)	1 (2)	<0.01
First-trimester folic acid intake, % (n)	76 (38)	64 (128)	0.03

SD: Standard deviation

Discussion

Preconceptional counselling holds an important place in the planning of pregnancy in women with seizure disorder because a careful balance is required between the type, number, and doses of AEDs for the best possible maternal and fetal outcome, thus challenging both the obstetrician and the neurologist.

A significantly higher number of women with seizure disorder went for preconception counselling (case =24%, control =1%, p<0.01) and consumed periconception folic acid (case =30%, control =1%, p<0.01). This reflected increased the awareness created among women with seizure disorder by the referring neurologists at the associated GIPMER hospital regarding preconception counselling and the advantage of intake of folic acid in the prenatal period. Folic acid intake was also documented by Borthen et al.[3] to be significantly greater in WWE than in women without epilepsy (case =43.6%, control =28.5%, p<0.001).

The majority of the cases were on monotherapy (67.3%) with levetiracetam being the most commonly prescribed newer AED (38.7%). Carbamazepine was the second most commonly used AED (14.2%), and the most commonly used old antiepileptic drug. Despite the established risk of teratogenicity with valproate[10]. it was consumed by 16.3% of the subjects, either as monotherapy or a part of polytherapy. This could be because our hospital serves as a referral center and most of the time we receive late referrals when women have already taken valproate in periconceptionally and in the early weeks of pregnancy. Here, lies the importance of awareness of preconception counselling and the need for neurologists to avoid valproate in women of reproductive age group wherever possible. In the study by Mawer et al.[22], monotherapy was prescribed to 66.8% of the women, and carbamazepine was the most commonly prescribed drug (26.7%), followed by valproate in 20.6% of subjects. Also, in the study by Ozdemir et al.[23], carbamazepine was the most commonly prescribed AED (27.5%)[23].

The occurrence of seizure episodes was found higher in women with unknown etiology (63.6%) than in women with known etiology (52.9%), but the results did not reach the level of significance (p=0.54) as observed by Chawla and Subbaiah [24].

It was observed that out of the 30 (60%) women who experienced seizure episodes during pregnancy, 16 (53.3%) had a history of seizure episodes within the 9-month period prior to pregnancy. No significant association (p=0.9) was found between a 9-month seizure-free interval and the prediction of

Table 2. Seizure disorder profile of cases

Parameter		n=50	%
Type of seizure disorders			
Focal -Aware -Impaired awareness		5 4 1	10.0 8 2
Generalized		44	88.0
Focal to generalized		1	2.0
Duration of seizure disorders	Up to 1 year	7	14.0
	1-5 year	23	46.0
	6-10 year	9	18.0
	>10 year	11	22.0
Date of last seizure prior to pregnancy	≤9 months	27	54.0
	>9 months	23	46.0
History of seizure in previous pregnancies		11	36.3
Seizure episodes in current pregnancy		30	60
Seizure episodes in postpartum period		3	6

Table 3. Antiepileptic drug profile of cases

Parameters		n	%
Patients not on AED in current pregnancy		1	2.0
Antiepileptic drugs started in current pregnancy		6	12.0
Patient not compliant to AED therapy		13	26.5
AEDs taken during pregnancy			
First generation		18	36.7
Second generation		24	48.9
First and second generation		7	14.3
Others			
-Clonazepam		2	4.0
-Clobazam		6	12.0
Monotherapy		33	67.3
-Levetiracetam		19	38.7
-Carbamazepine		7	14.2
-Valproate		3	6.1
-Phenytoin		2	4.1
-Oxcarbamazepine		1	2.0
-Phenobarbital		1	2.0
-Lamotrigine		0	0
Polytherapy (2 drugs)		16	32.6
-Valproate containing		5	10.2
Change in treatment	Drug added	8	16.3
	Drug deducted	4	8.2
	Dose increased	4	8.2
	Dose decreased	1	2.0
	Drug changed	2	4.1

AED: Anti-epileptic drugs

Table 4. Antenatal complications and delivery outcomes among subjects

Antenatal complications	Cases (n=50) No (%)	Controls (n=200) No (%)	p-value	Adjusted OR (95% CI)#
GDM	3 (6)	11 (5.5)	0.92	1.06 (0.31-1.89)
Hypertensive disorders	9 (18)	15 (7.5)	0.02	-
Gestational hypertension	3 (6)	11 (5.5)	0.92	1.11 (0.69-2.11)
Mild PE	2 (4)	4 (2)	0.4	2.24 (0.39-8.65)
Severe PE	4 (8)	0 (0)	<0.001	3.16 (1.67-6.43)*
FGR	11 (22)	38 (19)	0.63	1.24 (0.57-2.69)
Threatened abortion	2 (4)	6 (3)	0.66	1.37 (0.26-7.02)
Hypothyroidism	1 (2)	9 (4.5)	0.69	0.39 (0.04-3.23)
IHCP	2 (4)	7 (3.5)	0.86	1.17 (0.23-5.86)
Abortion	2 (4)	4 (2)	0.34	-
Antepartum haemorrhage	2 (4)	0 (0)	<0.001	
Delivery outcomes	**Cases (n=48)**	**Controls (n=196)**		
Preterm delivery	13 (26)	30 (15)	0.066	
Operative vaginal delivery	5 (10.4)	6 (3.1)	0.13	3.68* (1.07-9.64)
Caesarean section	14 (29.10)	39 (19.8)	0.06	1.66 (0.81-3.40)
Induction of labor	19 (39.5)	52 (26.5)	0.1	1.73 (0.92-3.34)

#Adjusted for age, education, previous LSCS (lower segment caesarean section), past history of TB and history of abortion, *Significant at <0.01 level, OR: Odds ratio, CI: Confidence intervals, GDM: Gestational diabetes mellitus

Table 5. Neonatal outcomes

Neonatal outcomes	Cases (n=48) n (%)	Control (n=197) n (%)	p-value	Adjusted OR# (95% CI)
Still birth	0 (0)	2 (1)	0.49	-
Low birth weight (<2.5 kg)	13 (27.1)	42 (21.5)	0.41	1.39 (0.66-2.92)
APGAR at 1 minutes ≤7	3 (6.2)	6 (3.1)	0.38	2.13 (0.51-8.89)*
APGAR at 5 minutes ≤7	0 (0)	4 (2)	0.97	
Congenital anomalies	**(n=50)**	**(n=200)**		
Major (M)	2 (4)	5 (2.5)	0.57	1.44 (0.53-3.06)
Minor (m)	1 (2)	0 (0)	<0.01	
Early neonatal complications	**n=48**	**n=196**		
Respiratory distress	7 (14.5)	10 (5.1)	0.02	2.96 (1.14-6.97)
NEC	1 (2)	0 (0)	0.04	-
Asphyxia related	2 (4.1)	1 (0.5)	0.04	1.23 (0.86-1.96)
MAS	0 (0)	3 (1.5)	0.39	-
Meningitis	0 (0)	1 (0.5)	0.11	-
Diarrhea	1 (2)	1 (0.5)	0.29	-
Early neonatal death	1 (2)	0 (0)	0.04	-
NICU admission	10 (20.8)	11 (5.6)	<0.001	3.47 (1.76-9.35)**

#Adjusted for age, education, previous LSCS, past history of TB and history of abortion,*Significant at 0.05 level, **Significant at 0.01 level, NEC: Necrotizing enterocolitis, NICU: Neonatal Intensive Care Unit, MAS: Meconium aspiration syndrome

seizure during pregnancy, which was observed in a study by Thomas[25].

The difference in findings could be attributed to their larger sample size.

In this study, seizure frequency was increased in 48% of the subjects, unchanged in 34%, and decreased in 18%. The non-compliance or discontinuation of anticonvulsants might be explained by the women's concerns about teratogenic effects of these drugs. However, no significant difference was observed in noncompliant patients who did (24.1%) and did not (30%) have seizures during pregnancy (p=0.2). Thus, it could mainly be due to subtherapeutic AED levels occurring due to physiologic alterations in pregnancy leading to increased clearance of the drug[13].

It was also observed that women with seizure disorder had a significantly higher incidence of abortions in previous pregnancies (p<0.001). Both spontaneous and induced abortions were included. It could be the effect of seizure disorder or voluntarily induction out of concern for teratogenicity in the babies or ultrasound findings suggestive of a congenital anomaly.

In this study, 28 (56%) women with seizure disorder developed antenatal complications against 90 (45%) women in the control group, but the difference was not statistically significant (p=0.068). Overall, there was a significantly higher incidence of hypertensive disorders in women with seizure disorder in this study (case =18%, control =7.5%, p=0.02). The rates of gestational hypertension were not significant between the two groups (case =6%, control =5.5%, p=0.92). Preeclampsia with severe features was highly significant in women with seizure disorder in this study (p<0.001) and it was found to be nearly three times more common in women with seizure disorder [adjusted relative risk (aRR)=3.16, CI: 1.67-6.43]. This is similar to the outcome observed by a register-based study on AED-using women where an increased risk of preeclampsia was observed[26]. However, the American Academy of Neurology in their report concluded that the evidence was insufficient to support or refute an increased risk of gestational hypertension or preeclampsia in WWE-taking AEDs[27].

APH was significantly higher in women with seizure disorder (p<0.001). Harden et al.[27] also concluded that there was a moderately increased risk of late pregnancy- related bleeding complications. On the other hand, Richmond et al.[7] and Katz et al.[8] reported no increased association of placental abruption in WWE.

No increased association was established in the rates of GDM (p=0.98, aRR=1.06, CI: 0.31-1.89), hypothyroidism (aRR=0.39, CI: 0.04-3.23), intrahepatic cholestasis of pregnancy (aRR=1.17, CI: 0.23-5.86) in women with seizure disorder in this study. Chawla and Subbaiah [24] also found similar outcomes in their study.

Most of the women with seizure disorder in the present study had a normal vaginal delivery (60.4%). However, this number was significantly less than among healthy pregnant women (73.7%, p=0.01). Risk of instrumental delivery was found to be around 3.7 times higher in women with seizure disorder than in healthy pregnant women. The number of women with seizure disorder who underwent cesarean section were 1.6 times higher than in the controls, but the difference did not reach the level of significance (p=0.06). Harden et al.[27] also concluded a moderately increased risk of cesarean delivery in women with seizure disorder.

LBW babies were born to around 27% mothers with seizure disorder. This rate was slightly higher than among the healthy mothers and was not statistically different (aRR=1.39, CI: 0.66-2.92). Katz et al.[8] also reported no significant association between seizure disorder and LBW babies (p=0.62).

Overall, the incidence of congenital anomalies in this study population was 3.2%. Women with seizure disorder had an incidence of 6% and healthy pregnant women had an incidence of 2.5%. Major congenital anomalies were found in 4% (n=2) of babies born to mothers with seizure disorder and 2.5% (n=5) of the healthy mothers. Out of the three babies of case group with a congenital malformation, two (66.6%) babies were on polytherapy and the mother of one (33.3%) baby was receiving monotherapy with phenytoin. In the polytherapy group, one mother with valproate-based polytherapy gave birth to a baby with polydactyly and the other mother who was on a carbamazepine-based polytherapy had a baby with posterior urethral anomaly.

In the present study, the rates of congenital malformations were 1.4 times higher than in the controls, but it was not statistically significant (aRR=1.4, CI: 0.53-3.06). Borthen et al.[6] found a significantly higher rate of congenital malformations in WWE on anticonvulsive drugs, compared with the control group (p=0.007).

Babies of mothers with seizure disorder in this study were found to have a significantly higher incidence of respiratory distress (p=0.02), necrotizing enterocolitis (p=0.04), asphyxia-related complications (p=0.04), and early neonatal death (p=0.04). The baby who died in the early neonatal period was born preterm, had LBW and also had bilateral posterior urethral valve and went into multiorgan failure. Razaz et al.[28] found an increased risk of neonatal complications in WWE when compared with controls such as hypoglycemia (OR=1.53, CI: 1.34-1.75), infections (OR=1.42, CI: 1.17-1.73), asphyxia-related complications (OR=1.75, CI: 1.26-2.42), and respiratory distress (OR=1.48, CI: 1.30-1.68).

In this present study, admission to the NICU was reported to be 3.4 times more frequent in babies born to women with seizure disorder than in the controls (aRR=3.4, CI: 1.76 -9.35) and was found significant (p=0.01). In a recent meta-analysis by Viale et al.[29], rates of NICU admission were significantly higher in WWE when compared with heathy controls.

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In the present study, the rates of congenital malformations were 1.4 times higher than in the controls, but it was not statistically significant (aRR=1.4, CI: 0.53-3.06). Borthen et al.[6] found a significantly higher rate of congenital malformations in WWE on anticonvulsive drugs, compared with the control group (p=0.007).

The risk of congenital anomalies was not increased in women with seizure disorder. This could be attributed to significantly higher intake of periconceptional folic acid in women with seizure disorder and higher consumption of least teratogenic drugs in this study such as levetiracetam and carbamazepine as was shown by Peterson et al.[30].

Study Limitations

Large sample size studies are needed to be performed in a prospective manner in order to assess the impact of seizure disorder on maternal and neonatal outcomes. Also, studies need to focus on seizure control in pregnancy, individual AEDs and their dose, and their effect on pregnancy complications.

Conclusion

Women with seizure disorder and AED use had an increased risk of preeclampsia and APH. The risk of induction of labor and cesarean section was not increased but there was increased risk of instrumental vaginal delivery. Babies of mothers with seizure disorder had an increased risk of early neonatal complications, early neonatal death, and NICU admissions. The risk of congenital anomalies and LBW babies was not increased in women with seizure disorder.

Interpretation

On the basis of findings of this study, women with seizure disorder should be informed that there is small but significant risk of obstetric complications. Women with seizure disorder should be monitored regularly for BP for the early detection of hypertensive disorders. Attention should be given to women in labor for the early detection and management of APH. Periconception folic acid intake should be encouraged and these women should be managed with the least teratogenic AEDs at the lowest possible dose to diminish the risk of complications, and also maintain good seizure control. Babies born to women with seizure disorder need expert pediatrician follow-up for the management of neonatal complications.

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Ethics

Ethics Committee Approval: This was a longitudinal study conducted after obtaining clearance from the Institutional Ethics Committee among women attending the antenatal outpatient department (OPD)/high-risk OPD/gyne casualty in the department of Obstetrics and Gynecology, Maulana Azad Medical College and associated Lok Nayak Hospital, Govind Ballabh Pant Institute of Postgraduate Medical Education and Research (GIPMER) hospital, New Delhi, from November 2016 to January 2017 (15 months) (approval number: 113, date: 04/11/2016).

Informed Consent: Informed consent was obtained from the participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: T.P.K., L.S., Design: A.M.R., S.B., Data Collection or Processing: T.P.K., L.S., Analysis or Interpretation: T.P.K., L.S., Literature Search: A.M.R., Writing: T.P.K., L.S.

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Evaluation of prenatally diagnosed fetal sacrococcygeal teratomas: A case series of seventeen pregnancies from South-central Turkey

Prenatal dönemde tanı konulan sakrokoksigeal teratomlu fetüslerin değerlendirilmesi: Doğu Akdeniz Bölgesinden on yedi gebelik olgu serisi

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Abstract

Objective: To evaluate sacrococcygeal teratoma (SCT) cases according to associated cardiac, extracardiac, and chromosomal anomalies in the prenatal period, and to review their outcomes.
Materials and Methods: Data of pregnancies with a prenatal diagnosis of SCT between 2009 and 2019 were retrospectively reviewed.
Results: One ongoing pregnancy was excluded. There were five medically terminated cases, three due to severe heart failure and the remaining two due to additional congenital defects. Two infants who had heart failure due to hyperdynamic flow died in the neonatal period. Nine infants are well and alive at the time of writing.
Conclusion: When a lesion is detected in the sacrococcygeal region during fetal sonography, the differential diagnosis should be made with an appropriate evaluation with emphasis on a possible diagnosis of fetal SCT. Tumor growth and heart failure should be monitored with serial scans when SCT has been diagnosed prenatally.
Keywords: Prenatal diagnosis, teratoma, sacrococcygeal region

Öz

Amaç: Prenatal dönemde tanısı konmuş sakrokoksigeal tümörlü (SKT) fetüslerin kalp, kalp dışı ve kromozom anomaleri ışığında prognozlarının saptanması amaçlanmıştır.
Gereç ve Yöntemler: 2009 ila 2019 tarih aralığında tanısı konmuş SKT'li olguların verileri retrospektif olarak değerlendirildi.
Bulgular: Bir devam eden gebelik çalışmaya dahil edilmedi. Üçü ciddi kalp yetmezliği ve ikisi ek konjenital defektlere bağlı olmak üzere toplam beş olguya tıbbi sonlandırma uygulanmıştı. Hiperdinamik kalp yetmezliği gelişen iki olgunun yenidoğan döneminde öldüğü saptandı. Dokuz olgu, makale yazımında sağ ve sağlıklıdır.
Sonuç: Fetal sonografi ile sakrokoksigeal bölgede saptanan lezyonların ayırıcı tanısı, fetal SKT tanısı da göz önünde bulundurularak, uygun şekilde ele alınmalıdır. Antenatal SKT tanısı konulduğunda seri muayeneler ile tümörün seyri ve kalp yetmezliği gelişimi takip edilmelidir.
Anahtar Kelimeler: Prenatal tanı, teratom, sakrokoksigeal bölge

PRECIS: In present study, we evaluated prenatally diagnosed cases with sacrococcygeal teratoma and associated anomalies

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Introduction

Sacrococcygeal teratomas (SCT) are one of the most common congenital tumors with an incidence of 1/35,000 to 40,000 of live births[1,2]. The teratomas detected in the perinatal period mostly derive from pluripotent primitive stem cells in Hensen's node in the sacrococcygeal region[3,4]. Teratomas are classified histologically as mature and immature, and immature elements are composed of primitive neuroglial tissues[5].

Altman et al.[6] described four types of SCTs according to anatomic location. Type 1 tumors are the most common with the majority of the tumor growing outward. In type 2 and type 3 tumors, the tumor has grown into the pelvis and out of the pelvis, respectively, with type 3 tumors growing more extensively into the pelvis. Type 4 tumors are entirely located in the pelvis. According to this classification, the best prognosis is in type 1 tumors[6]. Type 1, 2, and 3 tumors can be seen externally because they grow as an exophytic mass (Figure 1). Type 1, 2, and 3 tumors are easier to diagnose in both the prenatal and neonatal periods and have low malignant potential[7]. Type 4 tumors are usually diagnosed in the postnatal period and have higher potential for malignancy[8].

SCTs appear as irregular thick-walled masses with cystic and solid components on ultrasound imaging[3,9,10] and should be distinguished from spina bifida. Spina bifida has a significant bone defect and intracranial findings, which tends to be a higher level of the spine. Differential diagnosis includes myelocystocele, lipoma, hamartoma, hemangioma, lymphangioma, and ependymoma in fetal sacrococcygeal region masses[11].

The prenatal course of SCTs is generally unpredictable. However, fetal heart failure due to fetal anemia and high blood flow into the mass can cause fetal hydrops, polyhydramnios, and preterm delivery[12,13]. SCTs have become much more detectable in the prenatal period with the increased use of ultrasound scan. Close monitoring and serial ultrasound imaging are supposed to identify some fetuses requiring fetal intervention and preterm birth.

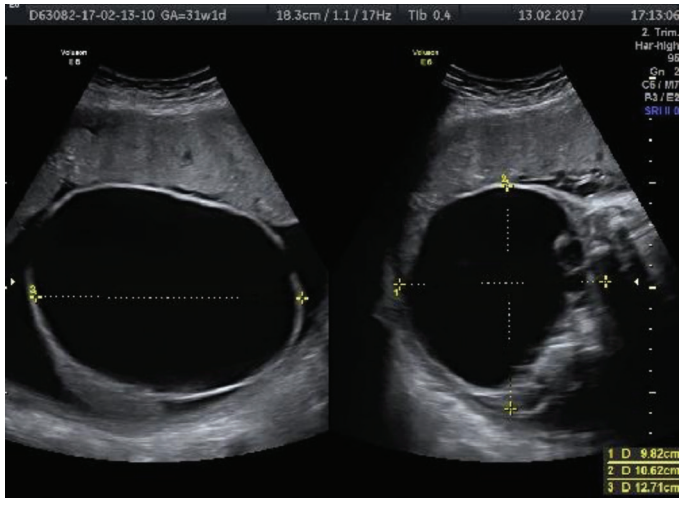


Figure 1. A case of sacrococcygeal teratoma with a cystic component originating from the sacrococcygeal region. The absence of intracranial findings excludes the diagnosis of spina bifida

The present case series from a single institution throughout a 10-year-period aimed to assess the characteristics and short- to medium-term follow-up of prenatally diagnosed cases of SCT.

Materials and Methods

This retrospective study was conducted at Çukurova University Hospital (academic tertiary referral center) Prenatal Ultrasound Unit. All women diagnosed as having fetal SCT from January 2009 to September 2019 were analyzed. Data were collected from the digital patient archiving system. All pregnant women were informed, and written content was obtained. The study was subject to local ethics committee approval (approval no: 14, date: 5.10.2018).

All of the sonography evaluations were performed by one of the seven authors, using a convex volumetric probe (RAB 6-D 2-7 MHz and RAB2 5L). In general, fetal anatomy scans are performed between 18-22 gestational weeks in the present clinic. The authors also evaluate potential fetal anomalies referred from other centers.

When a heterogeneous mass was seen in the sacrococcygeal region, a differential diagnosis was made. The diagnosis of spina bifida was excluded by demonstrating the continuity of the spinal canal. Color and power Doppler were used to determine blood flow into the mass. Serial ultrasonographic examinations were performed to detect hyperdynamic heart failure, development of fetal hydrops, and tumor growth. Routine fetal karyotyping was not recommended.

Neonatal outcomes were obtained from electronic medical reports, or the family was contacted by phone call. The antenatal findings of all cases with neonatal loss and termination of pregnancy were confirmed with autopsy examinations, except for first trimester terminations.

Statistical Analysis

The study is the case series. Statistical analysis methods are not used.

Results

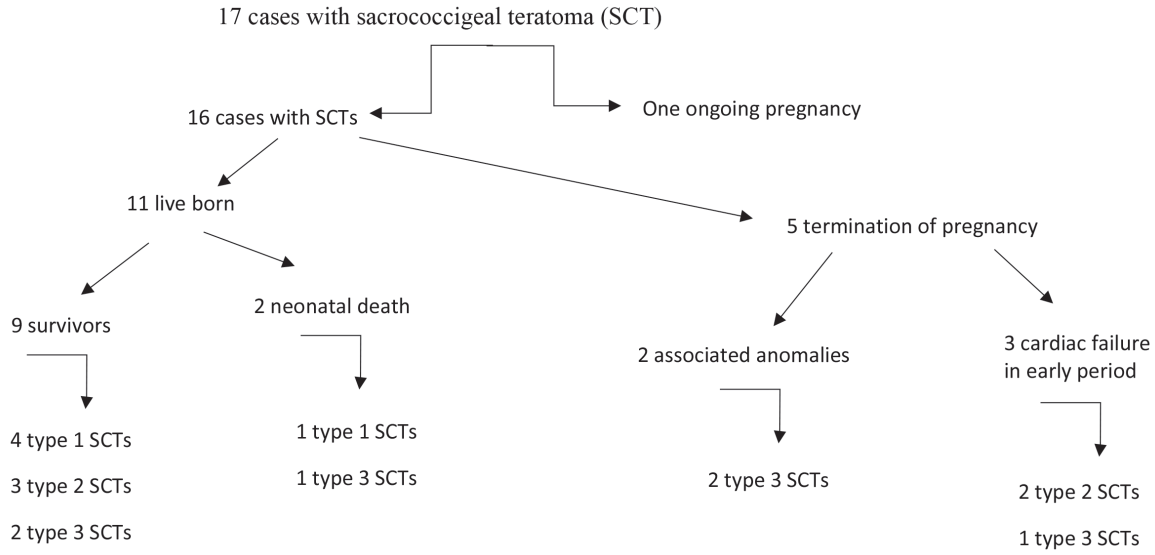
Out of a total of 18,500 fetal anatomy scans throughout the 10-year study period, SCT was detected in 17 pregnancies, revealing a 0.92/1000 incidence rate among high-risk cases in our tertiary setting. The gestational age at diagnosis ranged from 16 to 34 weeks (Table 1). Of the only two fetal karyotypes performed, both were normal. Five of the SCT pregnancies underwent termination of pregnancy. The indication for medical termination was early-onset cardiac failure (n=3) and additional fetal central nervous defects (n=2). Three fetuses had hydronephrosis due to the urinary obstruction (all with type 3 SCT). Two fetuses

Table 1. Associated anomalies, clinical features, and outcomes in 16 cases with sacrococcigeal teratoma

No	GA at diagnosis	Tumor type	Tumor size at diagnosis (cm)	Tumor size at birth (cm)	Additional findings	Delivery and outcome	Histopathology
1	18	2	4x3	11x10		CS at 37 weeks, 3470 g, operated, 29 months, alive and well	Mature cystic teratoma
2	18	1	7x5	13x9		CS at 39 weeks, 4380 g, operated, 24 months, alive and well	Mature cystic teratoma
3	29	2	12x13	15x15		CS at 32 weeks, 2500 g, operated, 21 months, alive and well	Mature cystic teratoma
4	26	3	8x9	8x9	DWM, CCA, MCDK	Termination at 26 weeks, karyotype analysis was normal	
5	16	2	5x4	7x5		Termination at 16 weeks, karyotype analysis was normal	Immature teratoma
6	26	1	5x4	8x5		CS at 37 weeks, 2700 g, operated, 10 months, alive and well	
7	16	3	3x3	3x3	Polyhydramnios	Termination	
8	21	2	3x3			CS at 29 weeks, 1525 g, operated, 10 months, alive and well	
9	23	3	6x3	11x8	Polyhydramnios	CS at 38 weeks, 4550 g, 8 months, alive and well	Immature teratoma
10	22	1	4x3			CS at 38 weeks, 3500 gr, 10 months, alive and well	
11	31	1	10x12	20x14		CS (classic incision) at 37 weeks, 5850 g, 6 months, alive and well	Mature cystic teratoma
12	26	1	10x9		Polyhydramnios PPROM	CS at 28 weeks, 1650 g, exitus in neonatal period	
13	34	3	8x9	10x8	Polyhydramnios	CS at 36 weeks, 3150 g, 3 months, alive and well	Immature teratoma
14	26	3	16x13		Polyhydramnios PPROM	CS at 29 weeks, 1750 g, exitus in neonatal period	
15	17	2	8x8			Termination	
16	24	3	10x9		DWM, polyhydramnios, fetal anemia	Termination	

CCA: Agenesis of corpus callosum, cm: Centimeter, CS: Cesarean section, DWM: Dandy-Walker Malformation, GA: Gestational age, g: Gram, MCDK: Multicystic dysplastic kidney, PPROM: Preterm premature rupture of membranes

had fetal cardiomegaly and fetal cardiac failure due to the hyperdynamic flow, and these two fetuses died in the neonatal period. During cesarean section, a classic incision was required in one case, and lower segment transverse incision was used in the others. Almost half of the survivors had type 1 tumors. Nine out of 11 live born infants were alive at the time of writing. The cases are summarized in Scheme 1.



Scheme 1. Seventeen cases with sacrococcygeal teratoma (SCT)

Discussion

The incidence rate of SCTs in the present design was significantly higher than that reported previously, probably due to referrals to our tertiary setting. Population-based studies are required to delineate the true incidence of SCT in Turkey.

The prognosis of SCTs detected in the prenatal period is worse than those detected in the neonatal period[14,15], explained by the fact that larger-sized tumors are more prone to be detected in fetal life. Tumors detected early in gestation may have a greater growth potential. The prognosis seems to deteriorate when the ratio of tumor volume to estimated fetal weight increases[16,17]. In the present study, cases diagnosed at earlier weeks of gestation were associated with adverse prenatal outcomes such as heart failure and termination of pregnancy. Hence, all fetuses with SCT can be monitored for the possible development of heart failure. However, there is no precise information about the most appropriate monitoring protocol because previous data are generally dependent on case series.

SCTs are not usually associated with chromosomal abnormalities. However, cases related to chromosomal abnormalities have also been described[18-21], although this coexistence may be incidental. A previous report described tethered spinal cord associated with SCT[22]. In addition, there was no correlation between the ultrasonographic appearance (cystic or solid components) and the pathology of the tumor. The follow-up of our patients with immature teratoma is ongoing, and no complication has been observed to date.

Fetal magnetic resonance imaging (MRI) may be particularly useful in the differential diagnosis of SCT. Tumor type, solid component content, and tumor volume can also be detected successfully using MRI. However, the authors propose that fetal MRI may be unnecessary except for clinical studies. In the author's opinion, tumor type, blood flow into the tumor, placenta size, and amount of amniotic fluid can be successfully demonstrated with ultrasound.

Tumor morphology is also important in prognosis. In some small case studies, solid tumors have been reported to have a worse prognosis than cystic tumors[15,23,24]. There is an increased risk of fetal cardiac insufficiency in solid tumors. These solid tumors may tend to be more vascular and cause more shunting of blood away from the placenta because they grow larger. Solid tumor volumes and derived indices are predictive of mortality and high-output cardiac failure[12,25]. We did not measure the tumor solid component volume in our cases, but we confirmed that the prognosis was worse in tumors with solid components. Although there is no consensus on the mode of delivery, the authors recommend cesarean delivery except for early pregnancy termination or very early preterm deliveries. Tumor rupture during delivery can cause bleeding in varying proportions depending on the amount of vascularization of the tumor. It should be kept in mind that larger tumors may require classic uterine incisions. In the presence of a large tumor, an improper incision may cause detrimental tears in the uterus, leading to postpartum hemorrhage.

Study Limitations

There are some limitations of the present study. First, the study was designed retrospectively. However due to the rarity of the tumor, information on this subject is usually based on retrospective case series. Recommendations such as approach and follow-up frequency in these cases are not based on randomized studies but as an expert opinion. Second, autopsy was declined in most of the cases. When an autopsy is not performed, a definitive pathologic diagnosis of a tumor considered as teratoma with ultrasound cannot be confirmed. Therefore, a false-positive rate cannot be given. Another

significant limitation is the short follow-up period, especially in immature teratoma cases. Despite these, the most important advantage of our study is the high number of cases of a sporadic rare tumor.

Conclusion

When a tumor is detected in the sacrococcygeal region, the differential diagnosis including SCT should include an appropriate evaluation. With serial examinations, it is necessary to determine the course of the disease and whether it will lead to heart failure.

Ethics

Ethics Committee Approval: The study was subject to local ethics committee approval (approval no: 14, date: 5.10.2018).
Informed Consent: All pregnant women were informed, and written content was obtained.
Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.Ö., S.B., M.S., E.A., S.M., Ç.A., M.K., S.C.D., İ.C.E., Concept: M.Ö., S.B., S.C.D., Design: M.Ö., M.S., E.A., İ.C.E., Data Collection or Processing: Ç.A., M.K., S.M., Analysis or Interpretation: S.C.D., İ.C.E., S.B., Literature Search: S.M., Ç.A., M.S., Writing: M.Ö., M.K., E.A.
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Do external female genital measurements affect genital perception and sexual function and orgasm?

Kadın dış genital ölçümleri, genital algıyı, cinsel fonksiyonları ve orgazmı etkiler mi?

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Abstract

Objective: To provide baseline data for the anatomy of the external female genitalia and to investigate the correlation between those measurements and sexual function and genital perception.

Materials and Methods: This prospective cohort study consisted of 208 healthy premenopausal women. The Female Sexual Function index (FSFI) and the Female Genital Self-image scale (FGSIS) questionnaires were administered. Participants were divided into two groups according to their female sexual dysfunction (FSD) status. External genital measurements and anterior and posterior vaginal length were measured.

Results: The external female genital measurements were (cm, mean ± standard deviation): clitoral prepuce length 2.05±0.48; clitoral glans length 0.87±0.21; clitoral glans width 0.60±0.15; clitoris to urethra 2.24±0.55; anterior fornix depth 7.75±0.92; posterior fornix depth 9.25±0.75; labia minora width, right 2.12±0.86, left 2.20±0.96. A weak negative correlation was found between total FGSIS scores and clitoral prepuce length (p=0.01, r=-0.17), whereas a weak positive correlation was seen between total FGSIS scores and anterior-posterior vaginal lengths (p=0.04, r=0.13; p=0.02, r=0.15, respectively). No statistically significant difference was found between the genital measurements of participants with FSD (n=82, 39.4%) and those without FSD (n=126, 60.6%), and the total FSFI scores and orgasm subdomain scores.

Conclusion: The female genital measurements were found to be distributed over a wide range. Although the relationship between genital measurements and genital perception varied, no significant relationship was found between genital measurements and sexual functions or orgasm. These findings suggest that a more cautious approach should be taken towards genital surgeries for cosmetic purposes.

Keywords: Female external genitalia, genital measurements, sexual function, genital perception

Öz

Amaç: Kadın genital organının anatomisine dair temel veri edinmek ve bu ölçümler ile cinsel işlev ve genital algı arasındaki korelasyonu araştırmak.

Gereç ve Yöntemler: Bu prospektif kohort çalışma, 208 sağlıklı premenopozal kadın ile yapıldı. Kadın Cinsel İşlev indeksi (FSFI) ve Kadın Genital Benlik İmajı ölçeği (FGSIS) anketleri uygulandı. Katılımcılar kadın cinsel işlev bozukluğu (FSD) durumuna göre iki gruba ayrıldı. Dış genital ölçümler ile ön ve arka vajinal uzunluk ölçüldü.

Bulgular: Dış kadın genital ölçümleri (cm, ortalama ± standart sapma): klitoral prepus uzunluğu 2,05±0,48; glans klitoris uzunluğu 0,87±0,21; glans klitoris genişliği 0,60±0,15; üretra-klitoris mesafesi 2,24±0,55; ön forniks derinliği 7,75±0,92; arka forniks derinliği 9,25±0,75; labia minora genişliği, sağ 2,12±0,86, sol 2,20±0,96. Toplam FGSIS skorları ile klitoral prepus uzunluğu arasında zayıf negatif korelasyon bulundu (p=0,01, r=-0,17), toplam FGSIS skorları ile anterior-posterior vajinal uzunluklar arasında zayıf pozitif korelasyon saptandı (p=0,04, r=0,13; p=0,02, r=0,15). FSD'li katılımcıların (n=82, %39,4) ve FSD'si olmayanların (n=126, %60,6) genital ölçümleri ile toplam FSFI skorları ve orgazm skorları arasında istatistiksel olarak anlamlı bir fark bulunmadı.

Sonuç: Kadın genital ölçümlerini geniş bir aralıkta bulundu. Genital ölçümler ile genital algı arasındaki ilişki değişkenlik gösterse de, genital ölçümler ile cinsel işlevler veya orgazm arasında anlamlı bir ilişki bulunmamıştır. Bu bulgular, kozmetik amaçlı genital cerrahilere daha temkinli bir yaklaşım gerektiğini göstermektedir.

Anahtar Kelimeler: Kadın dış genital ölçümleri, genital ölçümler, cinsel işlev, genital algı

PRECIS: The female genital measurements were found to be distributed over a wide range and no significant relationship was found between genital measurements and sexual functions or orgasm.

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Introduction

External female genital measurements vary widely[1-5]. There are few reports in the literature regarding overall 'normal' female genital appearance or 'normal' dimensions, and exact positioning of the vagina, clitoris, and labia minora and majora[1,5]. There has been a significant increase in female genital cosmetic surgery rates over the years[1-4,6]. For the degree of increased female genital cosmetic surgery, the main motivator was found as improvement in genital appearance integrated with their aesthetic and sexual demands[7].

It is known that body image and genital perception are related to sexual satisfaction[8,9]. Negative body image has been found to reduce sexual desire and arousability and was associated with fewer orgasms and less sexual satisfaction[10]. Among sexually active women, discomfort with the appearance of their genitals leads to anxiety and inhibitions during sexual activity[11,12]. A positive correlation has been determined between genital perception and sexual function[13]. However, it is not possible to evaluate sexual satisfaction and genital perception only with anatomic features due to the complexity and multifactorial structure of female sexuality[14]. It is important for the physician to recognize whether this discomfort is due to an anatomic reason or the perception of a defect. The media can negatively influence the genital perception of whom external genitalia are even in normal ranges[6]. In patients demanding an esthetic procedure in order to increase sexual satisfaction, an attempt should be made to correct genital perception before performing the surgery[11].

Due to limited data on the distribution of genital measurements, this study aimed to provide baseline data for healthy, reproductive-age female external genital anatomic measurements and to determine the relationship between these measurements and genital perception and sexual function.

Materials and Methods

Our prospective cohort study consisted of 208 healthy female participants. Our study included premenopausal patients aged over 18 years who were sexually active, and were seen in a medical faculty hospital polyclinic for routine gynecologic examinations between October 2017 and February 2018. The measurements and questionnaires were administered to healthy female participants who reported no known illnesses.

Exclusion criteria included postmenopausal and pregnant patients; those with previous vaginal and/or perineal, gynecological, or aesthetic surgical interventions; patients with stage >2 pelvic organ prolapse; urinary incontinence; menstrual irregularities; gynecological cancer; Polycystic Ovary syndrome (PCOS); patients using oral contraceptives or antidepressants; and those with intrauterine devices. Participants were taken to a quiet room, demographic data was recorded, and validated Turkish versions of the Female Sexual Function index (FSFI) [15] and the Female Genital Self-image scale (FGSIS)[16] were administered under the supervision of a physician.

The FSFI is a brief instrument consisting of 19 questions for the assessment of sexual function. Questions are scored for the domains of libido, arousal, lubrication, orgasm, satisfaction, and pain[17]. Female sexual dysfunction (FSD) was defined as a total score of 26 or less from a maximum possible score of 36[18]. The participants were divided into two groups according to their FSD status. The FGSIS is a seven-question survey that reveals female genital perception[19]. Genital perception is considered to be higher as the total score increases, with a maximum possible score of 28. The Beck Depression inventory was administered to patients who met the inclusion criteria and patients with a score of 17 and above were excluded from the study.

Subsequently, the participants were taken to the examination room and genital measurements were taken while in the lithotomy position. External genital measurements were made using a digital stainless-steel Vernier caliper, which can measure to 1/10 mm, and vaginal measurements were made using a hysterometer. The calipers were sterilized using ethylene oxide or were used by passing them through disposable bag gloves. The clitoral glans was measured by pulling back the prepuce. Labia minora and majora length and width were measured bilaterally. All measurements were made by two gynecologists who each had at least 10 years' experience.

The template in Figure 1 was used for the genital measurements, which were taken according to the following definitions.

The primary outcome was the determination of the measurements of the external female genitalia. The FSFI and FGSIS were administered to the participants in order to understand the degree to which the results were clinically relevant. The secondary outcome was the determination of the relationship of the measurements to sexual function and genital perception and the relationship between genital measurements and age, body mass index (BMI), and parity.

Ethical Approval

The institutional Ethics Committee approved the study (approval number: 2017/122), and written informed consent was obtained from all individual participants included in this study, which was conducted in accordance with the Helsinki Declaration.

Statistical Analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows 22.0 software (SPSS, Chicago, IL., USA). Descriptive statistics were calculated for subject demographics and dependent variables and were given as the mean, standard deviation, frequency and percentiles of 5%, 50% and 95%. Student's t-test was used for the comparison of quantitative variables between groups. Correlations between continuous data were analyzed using the bivariate Pearson correlation coefficient. Relations between categorical data and genital parameters were evaluated using Pearson's chi-square (χ^2) test, depending on the type of variables. Statistical significance was defined as $p<0.05$.

Results

The mean age of the participants in the study was 35.2±9.1 [mean ± standard deviation (SD); minimum =18, maximum =52] years, and the mean BMI was 25.1±4.6 (mean ± SD; minimum =16.3, maximum =41.5) kg/m^2. Of the patients, 17.3% (n=36) were nulliparous and 82.7% (n=172) were multiparous. It was determined that 58.4% (n=101) of the multiparas had normal deliveries, 32% (n=55) delivered via caesarean section, and 9.3% (n=16) delivered both via caesarean and normally. Episiotomy was performed in 65.6% (n=66) of the 101 patients who delivered normally. Of the patients, 41.3% were smokers. When the genital measurements of the nulliparous and multiparous patients were compared, the anterior vaginal length was longer in multiparous patients (p=0.009) and the clitoris-urethra distance was shorter in multiparous patients (p=0.03). When comparing the types of delivery, the anterior and posterior vaginal lengths of the patients who had delivered normally were longer compared with those of patients who had undergone cesarean section (p=0.001, p=0.02, respectively). In patients who had undergone episiotomy, the anterior vaginal length was longer (p=0.008); there was no difference in posterior vaginal length (p=0.12).

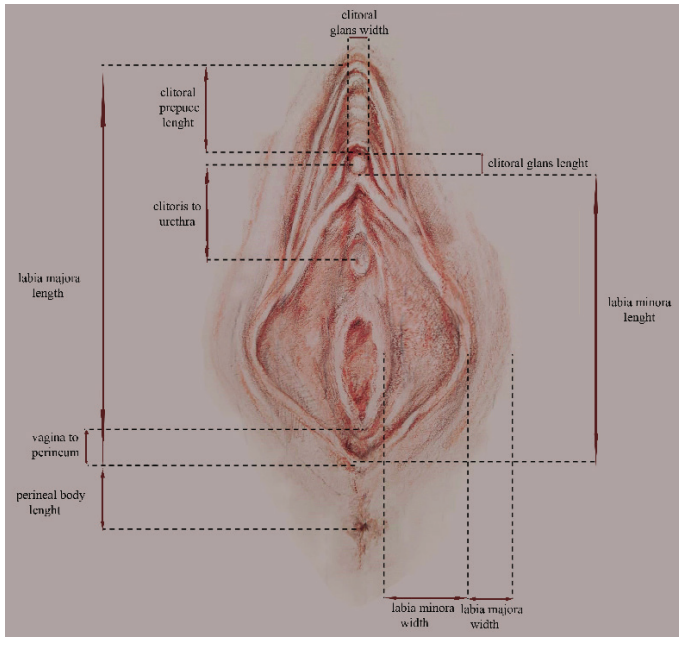

Figure 1. A schematic drawing of a part of the female external genitalia measurements.

Labia minora width: The length from the base of the labium minora to the widest lateral prominence.

Labia minora length: Longest craniocaudal length of the labium minora

Clitoral glans width: Transverse diameter of the clitoral glans

Clitoral glans length: Longest craniocaudal length of the clitoral glans

Clitoral prepuce length: Length of the skin fold on the clitoris

Clitoris to urethra: From mid-clitoral glans to mid-urethra

Perineal body length: The length from the posterior fourchette to mid-anal orifice

Vagina to perineum: From the point at the perineum where the labia minora begin to the hymen at 6 o'clock

Labia majora length: Longest craniocaudal length of labium majus

Labia majora width: Transvers length of labium majus

The external female genital measurements were distributed over a wide range. The external female genital measurements detected were as follows: clitoral prepuce length 2.05±0.48; clitoral glans length 0.87±0.21; clitoral glans width 0.60±0.15; clitoris to urethra 2.24±0.55; anterior fornix depth 7.75±0.92; posterior fornix depth 9.25±0.75; labia minora width, right 2.12±0.86, left 2.20±0.96; labia minora length, right 3.60±1.17, left 3.79±1.26; labia majora width, right 3.02±0.59, left 2.98±0.63; labia majora length right 7.43±0.95, left 7.40±0.79 (cm, mean ± SD). The distribution of the genital measurements and the mean ± SD, range, and the 5, 50, and 95 percentile values are shown in Table 1.

According to the FSFI scores, a comparison of the patient group with FSD (n=82, 39.4%) and the group without FSD (n=126, 60.6%) is shown in Table 2. No statistically significant difference was found between the measurements of the two groups, and no statistically significant relationship was detected between genital measurements and total FSFI scores or the orgasm subdomain scores (Table 3).

Correlation analysis was performed between the genital measurements and the variable parameters of age, parity, and BMI (Table 3). There was a negative correlation between age and clitoris glans size and width and left labia minora width (p=0.02, r=-0.21; p=0.01, r=-0.01; p=0.02, r=-0.15, respectively). There was a weak positive correlation between parity and clitoral prepuce measurements (p=0.04, r=0.13). Moreover, a weak positive correlation between BMI and clitoris glans length was detected (p=0.01, r=0.17). No statistically significant relationship was found between BMI and total FSFI scores, FSFI orgasm sub-domain scores, or FGSIS scores (p=0.98, p=0.93, p=0.10, respectively).

A statistically significant weak negative correlation was detected between the total FGSIS scores and clitoral prepuce length, and there was a statistically significant weak positive correlation between the total FGSIS scores and anterior-posterior vaginal lengths (p=0.01, r=-0.17; p=0.04, r=0.13; p=0.02, r=0.15, respectively). As parity increased, the total FGSIS score decreased (p=0.001). There was a positive correlation between the total FSFI score and the total FGSIS score (p≤0.001, r=0.32).

Discussion

A few studies have been conducted and they have shown that the range of female genital measurements can be quite extensive[1,2,4,5]. The current findings were consistent with the literature.

Vulvar morphology changes markedly with age[5]. Vagina size and labia minora width decrease with increasing age[4,5]. For this reason, postmenopausal patients were excluded from the study.

Table 1. Distribution of genital measurements

n=208	Mean ± SD	Range	min	max	5% percentiles	50% percentiles	95% percentiles
Clitoral prepuce length	2.05±0.48	3.0	0.5	3.5	1.1	2.1	2.8
Clitoral glans length	0.87±0.21	1.7	0.4	2.1	0.5	0.9	1.2
Clitoral glans width	0.60±0.15	0.8	0.3	1.1	0.4	0.6	0.9
Clitoris to urethra	2.24±0.55	3.5	0.7	4.2	1.4	2.1	3.2
Urethra to vagina	2.57±0.84	5.2	0.9	5.6	1.0	2.8	3.5
Perineal body length	2.56±0.73	6.7	1.1	7.8	1.3	2.5	3.7
Vagina to perine	1.26±0.50	2.2	0.3	2.5	0.5	1.1	2.3
Anterior fornix depth	7.75±0.92	6	4	10	5.8	7.7	9
Posterior fornix depth	9.25±0.75	7	5	12	8.0	9.5	9.9
Labia minora length							
Right	3.60±1.17	6.3	1.5	7.8	2.4	3.4	6.2
Left	3.79±1.26	5.6	1.9	7.5	2.4	3.5	6.5
Labia minora width							
Right	2.12±0.86	7.3	0.6	7.9	1.0	2.1	3.2
Left	2.20±0.96	6.9	0.7	7.6	1.0	2.1	3.7
Labia majora length							
Rigth	7.43±0.95	7.5	4	11.5	6.2	7.4	9.3
Left	7.40±0.79	6.4	4.6	11	6.0	7.3	8.6
Labia majora width							
Rigth	3.02±0.59	4.3	0.7	5	2.0	3.2	3.8
Left	2.98±0.63	4.3	0.7	5	1.8	3.1	3.8

min: Minimum, max: Maximum, Data was expressed by mean ± SD, range, minimum, maximum and 5, 50, 95 percentiles, measurements were given in centimeters, SD: Standard deviation

Table 2. Comparison of genital measurements of patients with and without sexual dysfunction

n=208	FSD (-) (n=126, 60.6%)	FSD (+) (n=82, 39.4%)	p-value
Clitoral prepuce length	2.06±0.50	2.05±0.45	0.926
Clitoral glans length	0.88±0.23	0.87±0.18	0.849
Clitoral glans width	0.60±0.16	0.60±0.13	0.956
Clitoris to urethra	2.24±0.59	2.25±0.50	0.899
Urethra to vagina	2.54±0.90	2.61±0.72	0.549
Perineal body length	2.58±0.82	2.53±0.57	0.616
Labia minora width			
Right	2.04±0.92	2.23±0.76	0.129
Left	2.14±1.01	2.29±0.87	0.271
Anterior fornix depth	7.71±0.82	7.80±1.06	0.491
Posterior fornix depth	9.23±0.80	9.28±0.68	0.673

FSD: Female sexual dysfunction, data was expressed by mean ± SD, Measurements were given in centimeters, Statistical significance was defined as $p<0.05$, SD: Standard deviation

Table 3. Correlation analysis of genital measurements and age, BMI, total FSFI scores, FSFI orgasm subdomain score and total FGSIS scores

	Age	Parity	BMI	FSFI total score	FSFI orgasm - subdomain score	FGSIS
	p r	p r	p r	p r	p r	p r
Clitoral prepuce length	0.67 -0.02	**0.04** 0.13	0.25 -0.07	0.15 -0.10	0.10 -0.11	**0.01** -0.17
Clitoral glans length	**0.02** -0.21	0.43 0.05	**0.01** 0.17	0.71 -0.02	0.96 0.03	0.47 0.05
Clitoral glans width	**0.01** -0.01	0.23 0.08	0.15 0.09	0.58 0.03	0.90 0.08	0.60 0.03
Clitoris to urethra	0.43 -0.05	0.47 -0.05	0.85 0.01	0.32 -0.06	0.14 -0.10	0.10 -0.11
Uretro to vagina	0.97 0.01	0.19 0.09	0.17 -0.09	0.25 0.08	0.12 0.10	0.12 0.10
Labia minora width						
Right **Left**	0.37 -0.06 0.02 -0.15	0.26 -0.07 0.10 -0.11	0.26 0.07 0.50 0.04	0.42 0.05 0.85 -0.01	0.55 0.04 0.65 -0.03	0.55 0.04 0.65 -0.03
Anterior fornix depth	0.66 -0.03	0.28 0.07	0.22 -0.08	0.20 0.08	0.12 0.07	**0.04** 0.13
Posterior fornix depth	0.43 0.05	0.49 0.04	0.07 -0.02	0.18 0.09	0.25 0.07	**0.02** 0.15

BMI: Body mass index, FSFI: Female Sexual Function index, FGSIS: Female Genital Self-image scale, Correlation significance was defined as $p<0.05$

Patients with PCOS were excluded because of the relationship between clitoral length and PCOS[20].

The parameters of parity and BMI were also thought to influence genital measurements[5]. There are studies showing an increase in sexual dysfunction as BMI increases[21,22]. Although the desire and pain subdomains were unchanged with weight, a negative correlation was found between BMI and the orgasm, arousal, lubrication, and satisfaction subdomains[22]. As weight and abdominal circumference increased, the incidence of vaginal orgasm decreased and the masturbation rate increased[21]. This finding seems to support the psychological effect of the vaginal orgasm. In our study, changes in sexual function were not observed with increased BMI.

No difference was seen in vaginal size with an increase in parity[1]. In the current study, when we compared multiparous and nulliparous patients, it was determined that anterior vaginal length was longer in multiparous women. The vaginal depth of those who had delivered normally and of those who had undergone episiotomy was greater than in those who had undergone cesarean section. These results, due to the mechanism of birth, were not surprising.

The prevalence of FSD varies across the world, with a prevalence of 38.4% in the United States[23]. In our study, 39.4% of the patients were identified as having FSD, as defined in the literature.

Clitoral measurements were taken via magnetic resonance, and the clitoral measurements of anorgasmic subjects were found to be significantly smaller in a study by Oakley et al.[24] Clitoral glans length measurements were between 1 and 2 cm and glans width was between 0.5 and 1 cm and no differences between clitoral dimensions according to age or weight were detected, whereas parity was found to increase the size of the clitoris in another study by Verkauf et al.[25]. In our study, clitoral measurements were consistent with the literature; however, although parity did not change the glans size, it was associated with an increase in the size of the prepuce.

In a study designed to directly examine sexual function with genital measurements using 32 samplings, no relation was found between genital measurements and sexual functions[3]. Our study, which used a wider sample, also found no significant difference between genital measurements and sexual function or orgasm.

Wallen and Lloyd[26], in their study, analyzed row data of two separate older studies (Bonaparte 1933 and Landis 1940) and found different orgasm ratios below and above the clitoris-urethral meatus distance (CUMD) of 2.5 cm. A difference of 0.7 mm was found between the means of the CUMD (2.2 vs 2.9) in

these two older studies. This difference was explained by the fact that in one study the measurement started from the middle of the glans, whereas the other started with the prepuce. We took our measurement from the middle of the glans, and our results were consistent with the literature. In our study, unlike in that study, no significant difference was found between the FSFI groups and the CUMD. Upon examination of the relationship between the FSFI orgasm subdomain and the genital perception scores, no significant difference was detected.

The FSFI orgasm subdomain was analyzed separately from the total score because it was thought that there could be a clinical relationship between the measurements and orgasm. However, no significant relationship was found between genital measurements, especially clitoral prepuce and labium minora length, and orgasm or sexual function. The very weak inverse relationship between genital perception scores and prepuce length can be explained by the influence of parity. With the increase in parity, an increase in the clitoral prepuce size and a decrease in genital perception were detected. This suggests that after clitoral hood reduction surgeries performed for the purpose of increasing sexual satisfaction, sexual outcomes should be compared with the status before the surgery.

Female genital esthetic operations were evaluated and sexual functions and their relationship with body image were investigated over a two-year period, in a prospective study[11]. The study found that, in the long term, these surgeries improved genital perception and sexual function. However, it was observed that the body-image perceptions, genital perceptions, and sexual functions of those who wanted surgery were lower than those of the control group[11].

Many factors may affect genital perception[27]. It is also known that genital and body perceptions can be changed by exposure to visuals such as video and photographic images[28]. There was a positive correlation between FSFI and FGSIS, associating high genital perception with high sexual function[11,13]. Our study results are consistent with other studies that found a positive correlation between FSFI and FGSIS. For this reason, it is necessary to evaluate the pre-operation genital and body perceptions of women who desire esthetic surgery for reasons other than function.

Study Limitations

The examination of female genital measurements and sexual functions along with genital perception created a powerful avenue of the study. The limitation of the study is that the study group reflected a part of society thought to be healthy. Multiparous patients were in the vast majority, and the lack of a categorical evaluation according to age and weight were other limitations. Another limitation was that the Body Dysmorphic Disorder scale was not administered to the patients. Future investigations dealing with the effects of surgical outcomes on sexual function and genital perception are recommended.

Considering the breadth of the distribution of the measurements, the fact that 'normal' female genital measurements can vary should be discussed with patients. For patients without functional impairment who want genital aesthetic surgery because of a desire to increase sexual satisfaction, an attempt should be made to first correct their genital perception. More research is needed on the subject of esthetic surgical procedures that change genital measurements and the contributions of this surgery to sexual function and genital perception.

Conclusion

The wide range of genital measurements observed makes it difficult to draw the boundaries of 'normal' regarding female external genitalia. Genital cosmetic surgeries should be considered more cautiously because negative genital perceptions are open to verbal and visual influence and because there is no significant relationship between genital measurements and sexual functions.

Ethics

Ethics Committee Approval: The institutional Ethics Committee approved the study (approval number: 2017/122).
Informed Consent: Written informed consent was obtained from all individual participants included in this study.
Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: A.E.K., A.B., Design: A.E.K., M.Y., Data Collection or Processing: O.D., C.Ö., Analysis or Interpretation: M.Y., E.Ç., Literature Search: A.B., C.Ö., Writing: A.E.K.
Conflict of Interest: The authors report no conflict of interest.
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Laparoscopic vaginal bead pull-through vaginoplasty technique using dental prosthesis material

Diş protez malzemesi kullanılarak laparoskopik vajinal boncuk çekme vajinoplasti tekniği

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Abstract

Objective: Many reconstructive surgical procedures have been described for vaginal agenesis. Almost all are surgically challenging, multistage, time-consuming or leave permanent scars on the abdomen or skin removal areas. The aim of this study was to introduce a simple and cheaper approach for laparoscopic vaginal bead-pull through.

Materials and Methods: In this retrospective study, we report a total of six patients with congenital absence of vagina [Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome] who were treated with a laparoscopic vaginal bead pull-through technique between 2018 till 2019 with a dental prosthesis material.

Results: Six patients with MRKH syndrome were treated with a laparoscopic vaginal bead pull-through technique. None of the women had any previous treatment. The mean age at the time of surgery was 18.7±3.1 years and mean body mass index was 25 (range, 19-38) kg/m^2. None of the patients had any additional malformations. In all patients, normal external genitalia and complete vaginal agenesis were observed during examination. The mean duration of surgery was 72 (range, 55-95) minutes. All patients were discharged on the 3rd postoperative day. No intraoperative complications were encountered. All patients had their urinary catheters removed within 12 hours after surgery. The mean vaginal length at discharge was 10 (range, 8-13) cm and all patients had adequate vaginal diameter, allowing introduction of three fingers easily. At the 12th postoperative month, the mean vaginal length was 9.2±1.6 cm. All patients had complete epithelization. All the women were sexually active one year after surgery.

Conclusion: The laparoscopic vaginal bead pull-through technique using dental prosthesis material can provide satisfactory results with shorter surgical time and lower cost.

Keywords: Absent vagina, Mayer-Rokitansky-Küster-Hauser, primary amenorrhea, vaginoplasty

Öz

Amaç: Vajinal ageneziye yönelik birçok rekonstrüktif cerrahi prosedür tanımlanmıştır. Hemen hemen hepsi cerrahi olarak zorlayıcı, çok aşamalı, zaman alıcıdır veya karın veya deri çıkarma bölgelerinde kalıcı izler bırakır. Bu çalışmanın amacı, basit ve daha ucuz bir yöntem olan laparoskopik vajinal boncuk çekme yaklaşımını sunmaktır.

Gereç ve Yöntemler: Bu retrospektif çalışmada, 2018-2019 yılları arasında diş protez malzemesi kullanılarak yapılan laparoskopik vajinal boncuk çekme tekniği ile tedavi edilen, doğuştan vajina yokluğu [Mayer-Rokitansky-Küster-Hauser (MRKH) sendromu] olan toplam altı hasta bildiriyoruz.

Bulgular: MRKH sendromlu altı hasta laparoskopik vajinal boncuk çekme tekniği ile tedavi edildi. Kadınların hiçbiri daha önce herhangi bir tedavi görmedi. Ortalama ameliyat yaşı 18,7±3,1 yıl ve ortalama vücut kitle indeksi 25 (aralık, 19-38) kg/m^2 idi. Hiçbir hastada ek malformasyon görülmedi. Tüm hastalarda muayene sırasında normal dış genital bölge ve tam vajinal agenez gözlendi. Ortalama ameliyat süresi 72 (dağılım, 55-95) dakika idi. Tüm hastalar postoperatif 3. günde taburcu edildi. İntraoperatif komplikasyonla karşılaşılmadı. Tüm hastaların idrar sondaları ameliyattan 12 saat sonra çıkarıldı. Taburculukta ortalama vajina uzunluğu 10 (8-13 cm) cm idi ve tüm hastaların yeterli vajinal çapı vardı ve üç parmağın kolayca girmesine izin verildi. Postoperatif 12. ayda ortalama vajina uzunluğu 9,2±1,6 cm idi. Tüm hastalarda tam epitelizasyon vardı. Tüm kadınlar ameliyattan bir yıl sonra cinsel olarak aktifti.

Sonuç: Diş protez materyali kullanılarak yapılan laparoskopik vajinal boncuk çekme tekniği, daha kısa cerrahi süre ve daha düşük maliyet ile tatmin edici sonuçlar sağlayabilir.

Anahtar Kelimeler: Vajinal agenezi, Mayer-Rokitansky-Küster-Hauser, primer amenore, vajinoplasti

PRECIS: The laparoscopic vaginal bead pull through technique using dental prosthetic material can provide satisfactory results with shorter surgical time and lower cost.

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Introduction

Development of the mullerian canal is one of the most incomprehensible issues in gynecology. Each section of the mullerian canal has different reproductive functions. Complete absence of mullerian development leads to aplasia; the common form of partial development leads to tubal and partial uterine development, and complete absence of the upper three-quarters of the vagina. In most cases of upper vaginal absence, the uterus is usually hypoplastic or primitive. The ovaries are normal, but are placed on the lateral pelvic wall along with the uterus. Classically, this is defined as Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome. The estimated prevalence is about 1:4000 to 5000 women[1]. There are many surgical options to create a neo-vagina. Free skin graft[2], intestinal or sigmoid vaginoplasty[3], amniotic graft[4], and pelvic peritoneum graft[5] have been used for these procedures. The disadvantages of previously defined procedures were stenosis, poor lubrication, scarring, contracture leading to dyspareunia, and the need for laparotomy. Transformation from free skin graft to squamous cell carcinoma and sigmoid to adenocarcinoma has been reported[6]. Recently, there have been reports of neovagina formation with endoscopic help based on the Vecchietti technique[7]. The use of peritoneum in vaginoplasty was first described in the Russian literature. This method was made popular by Davydov[8]. The formation of a neovagina using a laparoscope was first described by Semm[9]. More recently reported techniques describe laparoscopic application to replace the original Davydov procedure.

The aim of this report was to introduce a technique using a laparoscopic vaginal bead pull-through technique using dental prosthesis material.

Materials and Methods

After obtaining institutional ethics committee approval (University of Health Sciences Turkey, Zeynep Kamil Women and Children's Diseases Training and Research Hospital 2020/36), in this retrospective study, six patients with MRKH syndrome were treated with a laparoscopic vaginal bead pull-through technique with dental prosthesis material from 2018 till 2019. The patients were followed from postoperative day 7 to a maximum of 12 months. The patients' ages ranged between 15 and 24 years. Apart from the routine preoperative study, a diagnostic laparoscopy was performed to see the size and position of the uterus in the lateral pelvic walls to determine the feasibility of creating a pelvic anatomy to create a route to pull through the bead and to determine the possibility of neovagina formation.

Procedure

A modified vaginal bead set was prepared from an acrylic material that has been used as a prosthesis in dentistry (Figure 1). A vaginal bead was created to draw the blind vagina, which is 2 cm long, 1 cm wide, 1 cm high, with two holes in it. In order to apply internal traction to the bead, two polydioxanone (PDS) sutures were passed through the holes and their proximal ends were connected to each other under the vaginal bead. Following the modified set preparation, the abdomen was entered with a 10-mm trocar. Pneumoperitoneum was provided and suprapubic 5 mm trocars were placed on both sides. The bladder was removed cranioventrally from the anterior face of both round ligaments. The vaginal apex was sifted through the blind vagina using a thin Hegar cervical dilator, and the locations where the sutures were transported to the abdomen during laparoscopy were determined (Figure 2). The forceps of the 5 mm trocar were moved from under the peritoneum on both sides and the distal ends of the PDS sutures on the blind vaginal cuff were held with forceps and removed out of the abdomen under the peritoneum (Figure 3). Following abdominal washing, the procedure was terminated. The 10 mm trocar site was closed. The distal ends of both PDS sutures were pulled and traction was achieved with the vaginal bead in the blind vagina and the distal of the sutures were tied on a pad placed on the umbilicus. This pad on the umbilicus was used to stretch sutures to obtain the required vaginal length. The duration for hospital stay is 3 days in each case. After the traction technique is taught to the patient, she is

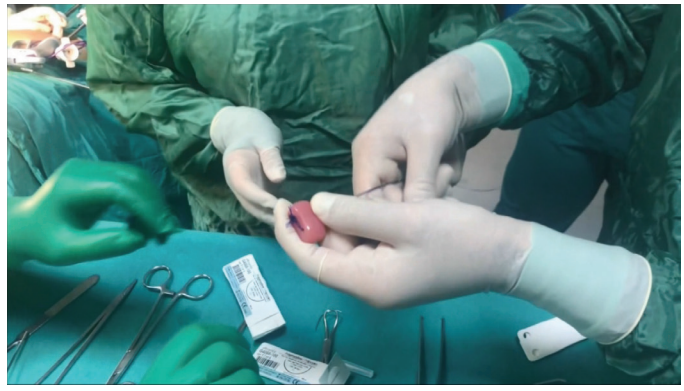

Figure 1. Cylindrical mass with two holes made of acrylic material used as a prosthesis in dentistry

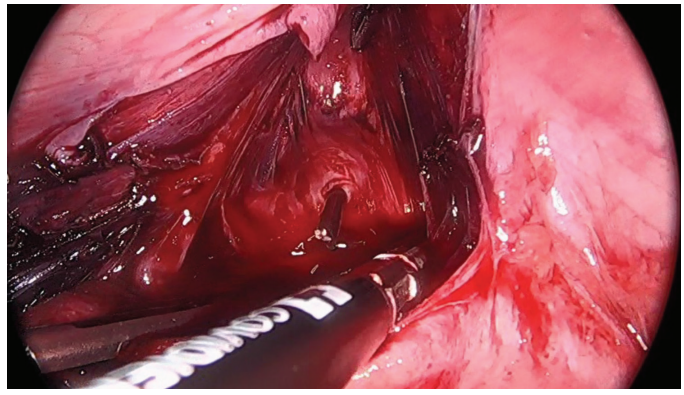

Figure 2. Pelvic peritoneal access using a Hegar cervical dilator through the neovagina

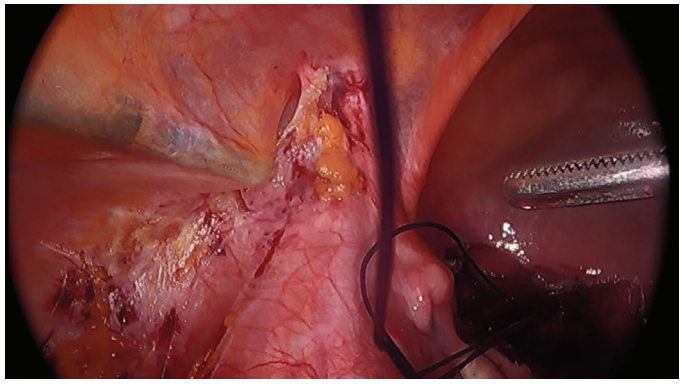

Figure 3. Extraperitoneally directed forceps to pull sutures from the neovagina to the lateral port sites

discharged. Patients perform traction on their own at home, using oral analgesics. The prosthesis is removed after a total of one week. Following removal of the prosthesis, dilatation was continued with a suitable mold accompanied by local estriol cream for 2 weeks. If the patient has a partner, coitus is recommended two days a week. A lubricant with ginseng or hyaluronic acid is recommended during intercourse. All participants were reevaluated at 12th months postoperatively to determine the vaginal length and sexual activity.

Statistical Analysis

The statistical parameters were computed using the Statistical Package for the Social Sciences version 21.0 (SPSS Inc., Chicago, IL, USA). The continuous variables were expressed as the mean ± standard deviation. The European categorical variables were expressed as the number and percentage.

Results

Six patients with congenital absence of vagina (MRKH syndrome) were treated using a laparoscopic vaginal bead pull-through technique.

None of the women had any previous treatment. The mean age at the time of surgery was 18.7±3.1 years and mean body mass index was 25 (range, 19-38) kg/m^2. None of the patients had any additional malformations. In all patients, normal external genitalia and complete vaginal agenesis were observed during examination. The mean duration of surgery was 72 (range, 55-95) minutes. All patients were discharged on the 3rd postoperative day. No intraoperative complications were encountered. All patients had their urinary catheters removed within 12 hours after surgery. The mean vaginal length at discharge was 10 (range, 8-13) cm and all patients had adequate vaginal diameter, allowing the introduction of three fingers easily. At the 12th postoperative month, the mean vaginal length was 9.2±1.6 cm. All patients had complete epithelization. All women were sexually active one year after surgery.

Discussion

In this report, we tried to present our case series of six women with congenital vaginal agenesis who underwent vaginoplasty with a bead pull-through technique using a dental prosthesis; our data analysis showed satisfactory results with lower cost.

MRKHS is caused by the hypoplastic embryologic development of the mullerian canal with the absence of the vagina, uterus or both[10]. Most patients have complete mullerian agenesis, and 47-84% of cases have uterine remnants with or without cavity[11]. As a result of anatomic insufficiency, patients are compromised in terms of sexuality and reproductive health. The main basis of MRKHS management is to create a new anatomically sufficient and satisfactory vagina[12] to provide comfortable intercourse with minimal intervention. To allow this function, the new vaginal canal must meet the following conditions; secretory function for sufficient width, length, axis, and also lubrication. None of the many techniques[13] proposed to date meet all these criteria. Following some conventional approaches for neovagina surgical techniques, newer modified forms of more satisfactory minimal invasive techniques have been introduced[14]; however, each procedure has been suggested to have specific disadvantages and complications based on the characteristics of the procedure and materials or tissues used to create a neovagina. A previously published review addressed all these specifically observed complications related to intestine, skin, buccal mucosa, and peritoneum[15]. Disadvantages specific for the procedures using peritoneum were defined as these procedures typically reserved for patients who have not had prior pelvic surgery and therefore its applications are limited. The risks of this procedure include injury to the bowel and bladder, as well as prolapse. Up to 23% of patients with a Davydov procedure will experience granulation tissue and 12% will have obliteration of the vaginal canal; furthermore, postoperative dilation is essential[16]. Self-lubricating neovagina has been provided by vaginal reconstruction using isolated bowel segments with low rates of failure and revision, additionally routine dilatation is not required for this procedure. It was reported that vaginoplasty using bowel was a safe and effective procedure[17]. Vecchietti and Davydov's methods have been introduced as two commonly preferred laparoscopic options. The Vecchietti operation relies on passive upwards traction with an externally replaced spherical device rather than dilatation[18], pain due to continuous traction and the need for prolonged hospitalization for continuous strong analgesia have been reported as the main disadvantages[19]. Finally, the device used for the technique has not yet been approved by the Unites States Food and Drug Administration, and it significantly increases the cost of the operation[14]. For this reason, some other alternative materials have been proposed to be used for this purpose[20]. In our proposal, we used a cheaper material that has been used as a prosthesis in dentistry, which indicates its safety for this procedure. The laparoscopic Davydov procedure is based on pulling down parietal peritoneum

and suturing it to the vaginal introitus. A comparison of the procedures reveals that both Vecchietti and Davydov's laparoscopic techniques are simple, safe, and effective surgical methods for vaginal reconstruction; Vecchietti's procedure is more time-efficient and minimally invasive, on the other hand, Davydov's procedure is associated with less pain, a longer vagina, and greater sexual satisfaction[11]. Evidence shows that laparoscopy-assisted peritoneal vaginoplasty by pushing down the peritoneum offers the advantages of reduced costs, complications, hospitalization, surgical time, and pain over the traditional technique[21]; however, further modifications may provide additional advantages for these approaches.

Conclusion

The laparoscopic bead pull-through technique using dental prosthesis material can provide satisfactory results with shorter surgical time and lower cost. As the dental prosthesis has been shown to be safe to use on oral mucosa, this property of material may prevent unexpected tissue reactions.

Ethics

Ethics Committee Approval: Ethics committee approval (University of Health Sciences Turkey, Zeynep Kamil Women and Children's Diseases Training and Research Hospital 2020/36).
Informed Consent: Retrospective study.
Peer-review: Externally peer-reviewed.

Author Contributions

Concept: Ç.K., Design: Ç.K., Data Collection or Processing: E.Ö., E.D., İ.Ş., Analysis or Interpretation: E.Ö., Literature Search: E.Ö., Writing: E.Ö., E.D.
Conflict of Interest: The authors declare no conflicts of interest.
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Spinal versus general anesthesia in gynecologic laparoscopy: A prospective, randomized study

Jinekolojik laparoskopide spinal ve genel anestezi: Prospektif randomize bir çalışma

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Abstract

Objective: To compare spinal anesthesia (SA) with general anesthesia (GA) in gynecologic laparoscopic surgery regarding anesthetic parameters and patient satisfaction together with an assessment of total oxidant, antioxidant levels, and Oxidative Stress index (OSI).

Materials and Methods: Sixty patients who were planned to undergo gynecologic laparoscopy were randomized into group G (GA) and group S (SA). Demographics, adverse events and anesthetic parameters were recorded before induction, after induction, and at the 5th, 10th, 15th, 30th, 60th, 90th, and 120th minutes. Patients and surgeons completed questionnaires. Total antioxidant capacity (TAC), total oxidant level (TOL), and OSI were measured.

Results: There was no difference between the groups in terms of hemodynamic parameters except heart rate at 30th minute and mean arteral pressure at 10th, 15th, 30th, and 60th minute ($p<0.05$). The postoperative arterial blood pH value was lower in group S ($p=0.021$). Intraoperative hypotension was lower in group S ($p=0.038$). There was more intraoperative hypotension in group S when compared with group G ($p=0.038$). Postoperative analgesic consumption was higher and onset of postoperative pain was shorter in group G ($p=0.001$ for both). There was no difference between the groups in terms of patient and surgeon satisfaction. There was no difference in terms of TAC, TOL, and OSI between the groups ($p=0.862$, $p=0.940$, and $p=0.728$, respectively).

Conclusion: SA may become a reliable alternative to GA in gynecologic laparoscopy when hemodynamic and respiratory parameters, patient and surgeon satisfaction, as well as total oxidant, antioxidant levels, and OSI are considered.

Keywords: Gynecologic laparoscopy, general anesthesia, spinal anesthesia, oxidative stress, patient satisfaction

Öz

Amaç: Jinekolojik laparoskopik cerrahide spinal anestezi (SA) ve genel anesteziyi (GA) anestezi parametreleri, hasta/cerrah memnuniyeti ve toplam oksidan, antioksidan düzeyleri ile Oksidatif Stres indeksi (OSI) yönünden karşılaştırmak.

Gereç ve Yöntemler: Jinekolojik laparoskopi yapılması planlanan 60 hasta grup G (GA) ve grup S (SA) şeklinde randomize edildi. Demografik veriler, istenmeyen olaylar ve anestezik parametreler indüksiyondan önce, sonra, 5., 10., 15., 30., 60., 90. ve 120. dakikalarda kaydedildi. Hastalar ve cerrahlar anketleri doldurdular. Toplam antioksidan kapasite (TAC), toplam oksidan seviyesi (TOL) ve (OSI) ölçüldü.

Bulgular: Gruplar arasında hemodinamik parametreler açısından 30. dakikada kalp hızı ve 10., 15., 30. ve 60. dakikalarda ortalama arteriyel basıncı dışında fark yoktu ($p<0,05$). Ameliyat sonrası arteriyel kan pH değeri S grubunda daha düşüktü ($p=0,021$). İntraoperatif hipotansiyon grup S'de daha düşüktü ($p=0,038$). Grup II'de Grup I ile karşılaştırıldığında intraoperatif hipotansiyon daha fazlaydı ($p=0,038$). G grubunda postoperatif analjezik tüketimi daha yüksek ve postoperatif ağrı başlangıcı daha kısa idi (her ikisi için $p=0,001$). Gruplar arasında hasta ve cerrah memnuniyeti açısından fark yoktu. Gruplar arasında TAC, TOL ve OSI açısından fark yoktu (sırasıyla $p=0,862$, $p=0,940$ ve $p=0.728$).

Sonuç: Seçilen hasta popülasyonunda hemodinamik ve solunum parametreleri, hasta ve cerrah memnuniyeti ile toplam oksidan, antioksidan düzeyleri ve OSI göz önüne alındığında SA jinekolojik laparoskopide GA'ya güvenli ve daha az invazif bir alternatif olabilir.

Anahtar Kelimeler: Jinekolojik laparoskopi, genel anestezi, spinal anestezi, oksidatif stress, hasta memnuniyeti

PRECIS: Spinal anesthesia may be a reliable alternative in gynecologic laparoscopy when anesthetic parameters, patient and surgeon satisfaction as well as total oxidant, antioxidant levels, and oxidative stress index are considered.

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Introduction

Laparoscopic procedures are commonly described as 'minimally invasive' and the word minimal is attributed to surgical trauma, pain, hospitalization interval, as well as surgery-induced stress[1]. Traditionally, general anesthesia (GA) with controlled ventilation is accepted as the safest technique for laparoscopic procedures, and various myths and dogmas discouraged the use of regional anesthesia, whereas the no anesthetic technique has been proved to be clinically superior to another[1]. Possible adverse effects due to pneumoperitoneum or the Trendelenburg position are among the main concerns regarding neuroaxial anesthetic techniques[2].

The stress response is formed due to both anesthetic and surgical interventions via several endocrine and metabolic changes[3]. Assessment of oxidative stress is one of the major indicators of the stress response[4]. Regional anesthesia is also 'minimally invasive' from the anesthetists' perspective and is currently preferred in many surgical procedures. Many papers have been published regarding the performance of laparoscopic procedures under spinal anesthesia (SA)[5,6].

Theoretically, combining a minimally invasive surgical procedure with a minimally invasive anesthetic technique might appear to lessen oxidative surgical stress that can be measured by oxidative stress markers. We aimed to compare SA with GA in gynecologic laparoscopic surgery regarding safety, patient tolerance, and anesthetic parameters, together with assessment of total oxidant, antioxidant levels and Oxidative Stress index (OSI).

Materials and Methods

The randomized prospective study was performed at the Department of Anesthesiology and Reanimation of a tertiary health care provider university hospital after approval of the Faculty Ethics Committee (no: 02-2009/46). The study was performed in accordance with the ethical standards described in an appropriate version of the 1975 Declaration of Helsinki, as revised in 2000.

Sixty patients aged between 18 and 45 years who were planned to undergo diagnostic laparoscopy combined with hysteroscopy for unexplained infertility with American Society of Anesthesiologists (ASA) I-II physical status, were enrolled in the study. Randomization was performed with a sealed envelope method and patients were randomized into two groups. None of the patients had premedication. Patients who had more than ASA II physical status, coagulation disturbance, were aged younger than 18 years or older than 45 years, who refused SA, who were cigarette smokers, patients with body mass index (BMI) >30 kg/m^2, and patients with conversion to laparotomy were excluded from the study. Written consent was obtained from all patients prior to their inclusion in the study.

Group G: General anesthesia group. Pre-oxygenation with 100% O_2 via face mask for 3 minutes, induction with propofol 2 mg/kg, atracurium 0.5 mg/kg, 0.5-1 µg/kg fentanyl and for the maintenance sevoflurane 2-3% and O_2-air mixture 50%. Additional doses of fentanyl (25 µg) were administered intravenously if patients had tachycardia, sweating, and hypertension due to inadequate surgical analgesia. Sevoflurane (Sevoflurane®, AbbVie, United Kingdom) 2-3% + O_2-air mixture 50% was stopped at last dermal suture. Patients were decurarized with neostigmine 0.06 mg/kg (Neostigmin® Biosel, Istanbul) at the end of the procedure. Patients were extubated when standard extubation criteria were maintained.

Group S: Spinal anesthesia group. All patients were informed about the details of the SA procedure - hydroxyethyl starch 6% (5 mL/kg) (Voluven® Fresenius Kabi) for avoiding hypotension due to spinal blockage and 3 L/kg 100% O_2 with nasal cannula. After stabilization of hemodynamic parameters, patients had SA performed in L_{2-3} with a 25-G Quincke spinal needle (Spinocan® Braun, Germany). Heavy bupivacaine 0.5% 10 mg (2 mL) with fentanyl 25 µg (0.5 mL) was injected to the subarachnoid space. The level of sensorial blockage was tested using a pinprick test. After achieving sensorial blockage at the level of T_4, patients had 1 mg midazolam intravenously. Saline (5-10 mL/kg/h) was infused during the procedure. Patients who had shoulder pain or surgical pain had 25-75 µg additional fentanyl doses intravenously and sedation was deepened with additional doses of midazolam intravenously. Despite medical treatment, patients who had persistent pain and agitation, conversion to GA as the same way performed in group I and excluded from the study.

Adverse events such as tachycardia, bradycardia, hypotension, hypertension, and conversion to laparotomy were recorded and treated accordingly, if present, in both groups. Also, intraoperative nausea/vomiting (N/V), shoulder pain, agitation, arise of blockage level, and conversion to GA was recorded in group S.

The same anesthetic and surgical teams (the authors of the study) performed spinal or GA, and laparoscopic surgery, respectively.

Patients had standard monitoring, after venous cannulation with 18 G at the dorsum of the hand, including electrocardiogram (5 channel), SpO_2, non-invasive blood pressure, heart rate, systolic arterial pressure, diastolic arterial pressure, mean arteral pressure, and only for the patients in group S, end-tidal CO_2 pressure ($PETCO_2$) were recorded before induction, after induction, at the incision, at the 5th, 10th, 15th, 30th minutes, and then every 30 minutes. Arterial blood sampling was performed preoperatively from all patients at room air, and also from the patients in group S in room air after the procedure was completed.

All surgeries were scheduled for the early follicular phase of the infertile patients after menses. The procedure was performed in a standard low lithotomy position. Patients were cleaned with 10% povidone-iodine solution and a sterile Foley catheter was inserted after anesthesia. Access into the abdomen was accomplished with closed Veress-needle entry technique after

a transumbilical vertical incision and insufflation of carbon dioxide gas up to a pressure of 18 mm Hg was preferred for adequate pneumoperitoneum. We inserted a primary 12-mm trocar at the umbilical incision, as well as other two ipsilateral 5-mm trocars for surgery. A 10-mm 0° laparoscope and operating instruments were inserted through the trocars. The working pneumoperitoneum pressure was lowered to 12 mm Hg after the introduction of all trocars. A Trendelenburg position of no more than 20° was used in both groups. Hysteroscopy was performed in the supine position with 5-mm 30° office hysteroscope using the "no-touch technique" with saline solution as the distention medium.

All patients were connected to a patient-controlled anesthesia (PCA) device (CADD-Legacy® PCA, Smiths Medical MD, Inc. St. Paul, MN, USA) at the end of the procedure. Infusion solution containing 300 mg of tramadol hydrochloride (tramadol HCl) (Contramal® Abdi İbrahim, İstanbul) and 3 mg of metamizole sodium (Novalgin® Aventis, İstanbul) was completed to 100 mL with sterile saline. PCA was set to deliver a bolus of 5 mL with a lockout interval of 15 minutes and 4-hour maximal dose of 20 mL (tramadol HCl 3 mg/mL + 0.03 mg/mL metamizole sodium).

All postoperative adverse events including N/V, sore throat, hoarseness, backache, hypotension, tachycardia, bradycardia, headache, hypertension, itching, itching, desaturation, and transient neurologic symptoms were recorded and treated appropriately.

Time of first mobilization (hour), time of passage of gas or stool (hour), onset time of postoperative pain (min) and postoperative analgesic consumption were recorded. Both the patients (24 hours after procedure) and surgeons (at the end of the procedure) completed simple questionnaires regarding satisfaction including three questions to provide comments about the operation (appendix I and II) adapted from Yuksek et al.[7].

Antecubital venous blood samples for assessment of total oxidant, antioxidant levels and OSI of 6 mL were obtained from all patients in both study groups at the end of the procedure. All blood samples were centrifuged at 1500^{-1} *g* for 10 min and were finally put into Eppendorf tubes within an hour and sera were stored at -80 °C.

A fully automated method developed by Erel[8] was used for the measurement of total oxidant level (TOL) and total antioxidant capacity (TAC)[9]. The novel automated method is based on the bleaching of characteristic color of a more stable ABTS [2.2-Azino-bis(3-ethyl-benzothiazoline-6-sulfonic acid)] radical cation by anti-oxidants. The assay has excellent precision values, which are lower than 3%. The results are expressed as mmol Trolox equivalent/L. Oxidants present in the sample oxidized the ferrous ion-o-dianisidine complex to ferric ion. The oxidation reaction was enhanced using glycerol molecules abundantly present in the reaction medium. The ferric ion produced a colored complex with xylenol orange in an acidic medium. The color intensity, which could be measured spectrophotometrically, was related to the total amount of oxidant molecules present in the sample. The assay was calibrated with hydrogen peroxide and the results are expressed in terms of micromolar hydrogen peroxide equivalent per liter (mmol H_2O_2 equivalent/L). The ratio of TOL to TAC was accepted as the OSI. For calculation, the resulting unit of TAC was changed to mmol/L, and the OSI value was calculated according to the following formula: OSI (arbitrary unit) =TOL (mmol H_2O_2 equivalent/L)/TAC (mmol L Trolox equivalent/L) [10].

Statistical Analysis

The normality of distribution of continuous variables was tested using the Shapiro-Wilk test. Student's t-test (for normal data) and the Mann-Whitney U test (for non-normal data) were used for the comparison of two independent groups, and Wilcoxon tests were used to compare numerical variables measured at two different time points. Pearson's chi-square test was used for testing relationships between categorical variables.

Mean ± standard deviations or median (minimum-maximum) are given as descriptive statistics for numerical variables. This is a pilot study and therefore power analysis was not performed. Statistical analysis was performed using the SPSS for Windows version 22.0 software and a p-value <0.05 was accepted as statistically significant.

Results

A total of 60 patients were enrolled in the study and there were 30 patients in both groups (G and S). There was no significant difference between the two groups in terms of age, BMI, ASA risk status, indications for laparoscopy, and surgical and anesthesia duration (Table 1).

The hemodynamic parameters of the patients at baseline, 0, 5th, 10th, 15th, 30th, 60th, 90th, and 120th minutes are shown in Table 2.

There was no significant difference between the groups in heart rate except at the 30th minute, at which heart rate was significantly lower in group S (p=0.01). Mean arterial pressure (MAP) at 10th, 15th, 30th, and 60th minutes was significantly lower in group S. There was no significant difference between the two groups in SpO_2 values.

$PETCO_2$ values of patients in group G at baseline, and the 0, 5th, 10th, 15th, 30th, 60th, 90th and 120th minutes were 32.73±4.58, 32.77±4.55, 33.37±4.00, 33.90±3.64, 34.80±3.68, 35.30±3.51, 35.58±3.69, 33.71±3.35, and 35.25±2.75 mm Hg, respectively.

Arterial blood gas (ABG) analyses of the patients are shown in Table 3.

There was no rise in sympathetic blockage above T_4, intraoperative surgical pain, and conversion to GA in any patient belonging to group S. There was no conversion to laparotomy and intraoperative desaturation in patients of either group.

Among the other intraoperative adverse events, intraoperative

Table 1. Demographic and operation characteristics of the patients

Variables	Group G (n=30)	Group S (n=30)	p*
Age (years)	31.47±5.01	29.83±6.02	0.258
BMI (kg/m2)	25.04±4.24	23.85±4.18	0.277
ASA status (I/II)	18/12	22/8	0.273
Laparoscopy indication			
Diagnostic	20	23	0.394
Operative	10	7	
Paratubal cystectomy	4	3	
Ablation of endometriotic foci	3	2	0.993
Adhesiolysis	3	2	
Operation time (min)	53.77±24.56	48.90±11.12	0.750
Anesthesia time (min)	61.30±25.81	52.00±10.30	0.557

*Student t-test for age and BMI, Mann-Whitney U test for surgical and anesthesia time, chi-square test for ASA and laparoscopy indication. Significant at p<0.05, BMI: Body mass index, ASA: American society of anesthesiologists

bradycardia was recorded in two patients in group G (6.66%), and three patients in group S (10%) (p=0.640). No patients had tachycardia. Intraoperative hypotension was recorded in two (6.66%) and eight patients (26.66%) in group G and group S, respectively (p=0.038). Hypotension was managed with intravenous saline infusion in all patients except one patient in group S, who also received a single dose of ephedrine intravenous. Intraoperative hypertension was recorded in only one patient (3.33%) in group G and was treated through the deepening of GA.

Among patients of group S, intraoperative N/V was present in two patients (6.66%), agitation in three patients (10%), and shoulder pain in 17 patients (56.6%). An additional dose of fentanyl and deepening of sedation was required in 12 patients who had shoulder pain, but the procedure was completed uneventfully. The remaining five patients (16.66%) reported discomfort and shoulder pain but did not request additional medication.

Postoperative analgesic consumption was significantly higher in group G when compared with group S, 128.00±25.11 mL (512±100 mg tramadol HCl, 3.84±0.75 metamizole sodium) vs. 63.17 ± mL (252.68 ± mg tramadol HCl, 1.89±0.48 metamizole sodium), respectively (p=0.001). Onset of postoperative pain was 8.56±8.13 min in group G and 138.67±41.50 min in group S (p=0.001). There was no statistically significant difference between the group G and S in terms of post-operative passage of gas 10.60±3.59 vs 9.73±2.15 hours (p=0.261) and also postoperative mobilization time 7.87±31.89 vs 8.20±0.66 hours (p=0.261), respectively.

The most common postoperative adverse event was N/V, which was observed significantly more in group G (14 patients, 46.6%) than in group S (four patients, 13.3%) (p=0.005). Thirteen patients (43.3%) had a sore throat and five patients (16.6%) had hoarseness in group G vs none in group S (p=0.001 and 0.02, respectively). Backache was present in four patients (13.3%) in group G and two patients (6.66%) in group S (p=0.389). Postoperative hypotension was detected in two patients (6.66%) in group S vs none in group G (p=0.15). There was only one patient (3.33%) with tachycardia and one patient with headache (3.33%) in group G vs none in group S (p=0.313). There were no postoperative bradycardia, hypertension, itching, desaturation, and transient neurologic symptoms in any patients.

The answers to the first question of the patient questionnaire revealed no significant difference in terms of comfort during surgery between the groups. Six and four (20%/13.33%) of the patients in group G and S, respectively, evaluated their comfort as “very good”, 15 and 17 (50%/56.66%) as “good”, and nine and six (30%/20%) evaluated the comfort of the operation as “moderate” and 0/3 (0/10%) as “poor” (p=0.248). Twenty-eight (93.3%) of patients in group G and 27 (90%) in group S were pleased after the operation (p=0.640). Twenty-nine (96.6%) patients in group G and 27 (90%) in group S would recommend this operation to others (p=0.301).

In the results of the questionnaire conducted for surgeons, abdominal relaxation of patients undergoing SA was evaluated as “good” for 20 (66.66%) patients and “moderate” for 10 (33.33%) patients. The surgeons stated about whether they had any technical problems arising from SA, “a lot” for none, “a little” for 4 (13.33%), and “none” for 26 (86.66%) patients. In the question of regarding whether there was a surgical difference in the operation of patients who underwent GA and those who underwent SA, surgeons stated that there was no difference in 29 (96.66%) patients.

The results of TAC (Figure 1), TOL (Figure 2), and OSI (Figure 3) are shown in Table 4. There was no significant difference in terms of TAC, TOL, and OSI between the groups (p=0.862, p=0.940, and p=0.728, respectively).

Discussion

Laparoscopy is a minimally invasive procedure that offers some multiple postoperative benefits including less surgical trauma, pain, pulmonary dysfunction, quicker recovery, and shorter hospital stay[11]. There is an increasing trend of preference in favor of laparoscopic procedures compared with laparotomy[12]. Traditionally, laparoscopic procedures are performed under GA. Regional anesthesia had not gained popularity in this new era of minimally invasive surgery and not preferred as a first-line choice in gynecologic laparoscopic procedures. According to the literature, regional anesthesia is considered more acceptable as an anesthetic alternative approach in diagnostic laparoscopic procedures of general surgery and laparoscopic cholecystectomies[1]. Most studies about SA in laparoscopic surgery involve laparoscopic cholecystectomy, with few cases of appendectomy and hysterectomy[5,6]. The main reasons for this withdrawal may be attributed to the fear of adverse effects caused by pneumoperitoneum, which is considered to be not well

Table 2. Hemodynamic variables of the patients

Variables	Group G (n=30)	Group S (n=30)	p*
Heart rate (bpm)			
Baseline	85.47±11.87	86.27±10.05	0.779
0 minutes	84.17±14.72	84.63±11.52	0.892
5th minute	85.53±16.04	82.73±9.46	0.414
10th minute	81.13±14.79	78.07±8.75	0.332
15th minute	79.13±19.05	75.33±6.79	0.308
30th minute	80.50±11.52	73.52±7.51	0.010*
60th minute	77.96±12.24	75.00±8.04	0.360
90th minute	74.83±10.05	68.00±9.90	0.436
120th minute	75.75±6.34	-	-
Mean arterial pressure (mmHg)			
Baseline	88.43±14.12	91.93±12.92	0.258
0 minutes	87.33±19.44	90.10±10.32	0.468
5th minute	93.83±19.37	82.10±7.62	0.014
10th minute	91.23±17.12	80.87±5.58	0.005*
15th minute	92.30±13.99	78.90±7.42	0.001*
30th minute	87.64±12.71	78.79±6.86	0.003*
60th minute	85.38±11.85	77.52±8.50	0.024*
90th minute	78.33±5.92	88.00±2.83	0.094
120th minute	82.50±4.43	-	-
SpO_2 (%)			
Baseline	99.20±0.96	99.03±1.22	0.797
0 minutes	99.83±0.46	99.50±0.86	0.065
5th minute	99.80±0.41	99.53±0.86	0.290
10th minute	99.63±0.56	99.70±0.65	0.418
15th minute	99.70±0.53	99.70±0.65	0.784
30th minute	99.63±0.67	99.87±0.35	0.161
60th minute	131.71±169.97	99.84±0.37	0.349
90th minute	99.86±0.38	100±0	0.593
120th minute	100±0	-	-

*Student's t-test for normal data and Mann-Whitney U test for non-normal data. Significant at p<0.05

tolerated by patients who are awake during the procedure, or the Trendelenburg's position. Data on laparoscopic cholecystectomy do not apply to hysterectomy because the former requires a reverse Trendelenburg position, resulting in more favorable pulmonary dynamics. Conversely, the Trendelenburg position carries concerns regarding pulmonary compliance, making it more challenging to manage the resultant hypercarbia[13-15].

An ideal anesthetic method should provide optimal surgical conditions without any physiologic and metabolic harm to the organism, preserve hemodynamic balance, and should also provide prompt and safe recovery in the postoperative period[16]. Therefore, a method that provides equable hemodynamic parameters is supposed to be favorable. There was no significant difference between the groups in terms of hemodynamic parameters except heart rate at the 30th minute and MAP at 10th, 15th, 30th, and the 60th minute was significantly lower in group S, which is an expected result due to the sympathetic blockage in SA[17,18].

Table 3. Arterial blood gas parameters of the patients

Variables	Group G (n=30)	Group S (n=30)	p*
pH			
Preoperative	7.41±0.04	7.42±0.03	0.075
Postoperative	7.35±0.07	7.37±0.04	0.021*
p	0.001	0.001	
pO_2			
Preoperative	89.85±17.31	93.08±19.09	0.367
Postoperative	94.23±26.4	90.6±16.15	0.994
p	0.992	0.032	
pCO_2			
Preoperative	32.61±4.84	31.24±4.04	0.176
Postoperative	36.49±8.01	35.25±5.89	0.790
p	0.026	0.001*	
HCO_3-			
Preoperative	22.07±2.21	23.11±3.23	0.162
Postoperative	21.11±1.93	21.38±2.1	0.865
p	0.004	0.001	
Base excess			
Preoperative	3.34±2.26	2.57±1.40	0.267
Postoperative	4.51±2.86	3.44±1.70	0.126
p	0.004	0.001	

*Mann-Whitney U test, significant at p<0.05

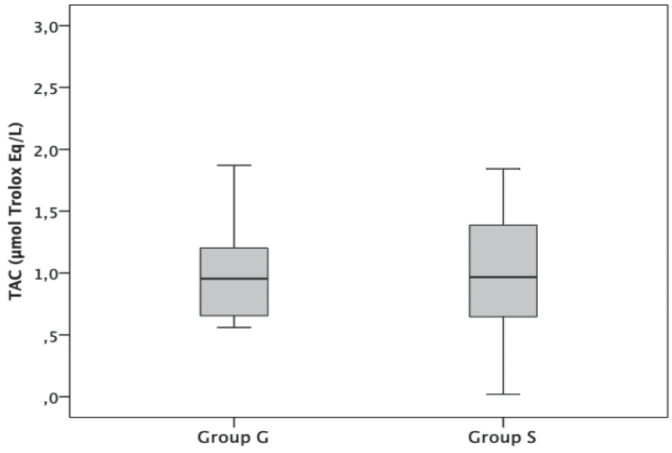

Figure 1. Total antioxidant capacity (TAC) of patients

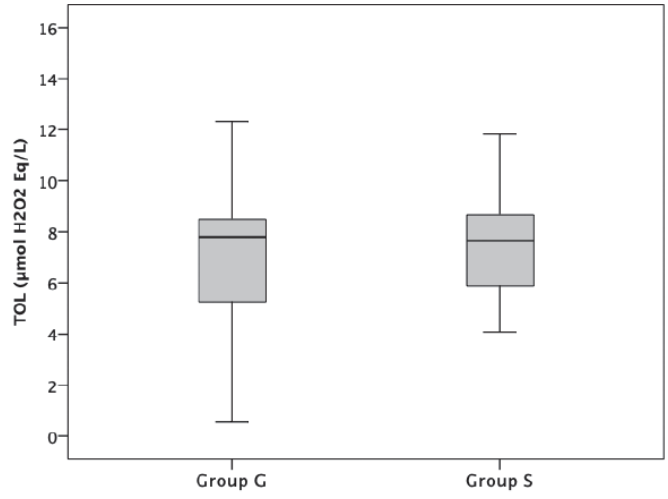

Figure 2. Total oxidant levels (TOL) of the patients

Table 4. Total antioxidant capacity, total oxidant levels and oxidative stress index of the patients

	Group G		Group S		
	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	p
TAC	1±0.4	0.95 (0.66-1.2)	0.99±0.47	0.97 (0.65-1.39)	0.862
TOL	6.76±3.43	7.8 (5.26-8.5)	7.12±2.75	7.65 (5.9-8.66)	0.940
OSI	0.83±0.48	0.9 (0.58-1.21)	1.94±4.78	0.79 (0.66-1.05)	0.728

Mann-Whitney U test for TAC, TOL and OSI, significant at p<0.05.
TAC: Total antioxidant capacity, TOL: Total oxidant levels, OSI: Oxidative Stress index, Min: Minimum, Max: Maximum, SD: Standard deviation

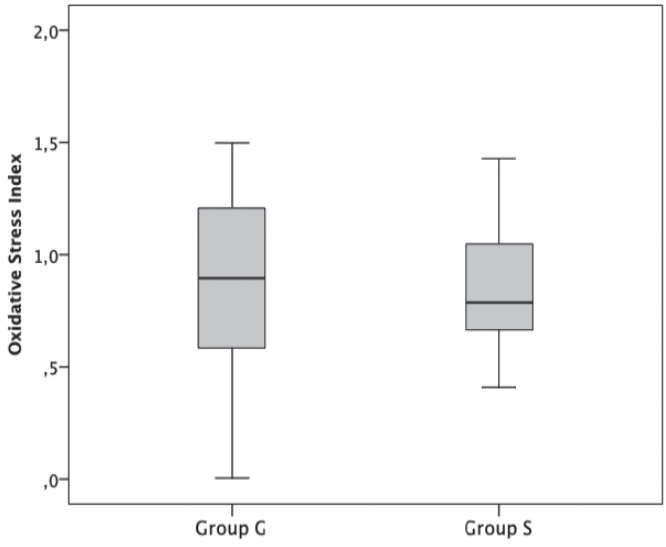

Figure 3. Oxidative Stress index (OSI) of the patients

Respiratory parameters regarding SA and GA during laparoscopic surgery are controversial. Spontaneous physiologic respiration during SA has been shown to have a better performance than assisted respiration in GA[18]. There were either small or no changes in respiratory function due to mid-thoracic levels of spinal anaesthesia in many studies and alterations in respiratory function that were clinically significant were minimal[19]. Also, there were no or little changes in respiratory rate and tidal volume - even with a high level of blockage with SA - and vital capacity decreased slightly[18]. Additionally, pulmonary functions return to normal in about 24 hours after laparoscopic procedures performed with GA[20]. In our study, respiratory functions were evaluated using ABG analysis. Only the postoperative mean pH value of group S was statistically higher than group G, but still in the physiologic range. This was probably due to hyperventilation of awake patients in group S. Patients in group S could increase the respiratory frequency to lessen the higher pCO_2 values due to CO_2 insufflation because they were awake. The mean pCO_2 values of group S were lower than in group G, which may explain the hyperventilation in this group of patients; however, this was not statistically significant. A greater increase in $PaCO_2$ after CO_2 pneumoperitoneum when the patient was under GA compared with patients breathing spontaneously was reported, which is similar to our results[21]. Sinha et al.[20] reported that there was no significant variation in PaO_2 or $PaCO_2$ during the procedure with SA. Similarly, all ABG parameters were within physiologic limits at the end of the surgery

Although hypotension in SA seems to be an adverse effect, it is rather a physiologic effect of sympathetic blockage. In addition to SA-related hypotension, the pneumoperitoneum induced rise in intra-abdominal pressure could be another cause for the persistence of hypotension. SA-related hypotension is supposed to be more significant in procedures such as laparoscopic cholecystectomy, which is performed in the Fowler position. Intraoperative hypotension was observed significantly less in patients of group G (6.66%) than in group S (26.6%) (p=0.038), which is also an expected result of SA. In the series of 4.645 patients of Sinha et al.[20], 2.992 underwent laparoscopic cholecystectomy, SA was performed to all patients, and hypotension was observed in 846 (18.21%) patients. This lower frequency of hypotension may be due to lower intraperitoneal insufflation pressure, which was limited to 8-10 mm Hg. In our study, the high-pressure entry technique together with a higher intraperitoneal working pressure during surgery (12 mm Hg) may have contributed to the higher frequency of hypotension in the SA group, but this technique is also safer[22]. Intraoperative hypotension frequency is reported between 5.4% and 40%[22-24]. None of the intraoperative hypotension situations required inotrope support. In our opinion, this may be due to the preoperative colloid administration.

In our study, no adaptation was performed in insufflation or working pressure, which remained constant as 12 mm Hg for the management of intraoperative bradycardia because it was transient without any need for an intervention. Higher intraperitoneal pressures may cause bradycardia due to activation of vagal reflexes and decreasing the insufflation or working pressure in selected cases with persistent bradycardia might improve the situation.

Awake and cooperative patients during laparoscopic procedures might be a preferable situation intraoperatively for communication and quick recovery. Paradoxically, there is a common desire to avoid the performance of SA for laparoscopic procedures. The main reason for this withdrawal is the fear of adverse effects caused by pneumoperitoneum, which is presumably not well tolerated by a patient who is awake during the procedure. Gynecologic laparoscopy in the Trendelenburg position increases infra-diaphragmatic pressure, which may lead to a sensation of pain. We observed neck and shoulder pain in 17 patients (56.66%), of whom 12 (40%) required an additional dose of analgesic. Surprisingly, five (16.6%) of them required no additional dose of analgesia due to the tolerable nature of the pain and all patients completed the procedure uneventfully without conversion to GA. Similarly, in the pilot study of Tzovoras et al.[25], two out of 15 patients had neck or shoulder pain and they were managed with ease. In another randomized controlled study of Tzovoras et al.,[26] pneumoperitoneum pressure was decreased to 10 mm Hg instead of 14 mm Hg and 43% of patients had shoulder pain that received no further treatment or conversion to GA. However, in a study with pneumoperitoneum pressure of 15 mm Hg, 16 patients (55.17%) had shoulder pain[7]. Eight patients were managed with intravenous analgesics and three patients needed GA. The remaining five patients had local irrigations of right diaphragmatic crus with local anesthetics[7]. In our study, we used 12 mm Hg as the pneumoperitoneum pressure and we did

not decrease this pressure in cases of neck and/or shoulder pain without any need for conversion to GA.

In our study, postoperative N/V was troublesome in 14 (46.6%) patients in group G and four (13.33%) patients in group S. This was an expected result due to adverse effects of medications in GA and is consistent with studies reported in the literature[6,7,20,25].

Another major concern that limits the preference of SA in laparoscopic surgery is the comfort and satisfaction of patients. Previous studies based on patient satisfaction reported similar results to ours. Most studies in the literature evaluated only SA and patients were mostly reported as being satisfied[6,7,20].

Questionnaires evaluating patient satisfaction showed that SA was a comfortable alternative anesthetic method. The patients in our study expressed similar comfort during and after the operation with both SA and GA, and they also recommend both anesthetic techniques in a similar fashion. However, the subjective character of this evaluation is a limitation. Theoretically, no patient can compare both anesthetic techniques because no one ever steps in the same river twice.

Inadequate abdominal muscle relaxation is one of the major problems experienced in laparoscopic surgery under SA. This is one of the leading problems reported by surgeons in every abdominal surgical procedure. Surgeons that performed laparoscopic cholecystectomy with SA were asked about their opinion regarding this issue in a study and all surgeons agreed that this anesthetic technique was satisfactory, abdominal relaxation was adequate for surgery, and they had no problems related to the anesthetic technique[7]. However, right shoulder pain was also reported as a disadvantage of SA, which resulted in increased intraabdominal pressure limiting laparoscopic exploration[7]. Nevertheless, laparoscopic surgery was performed uneventfully after intraoperative relief of the shoulder pain. We observed similar responses according to the answers of surgeons' questionnaire in our study. Abdominal relaxation was expressed as "good", there were generally no technical problems arising from SA, and there was no surgical difference between patients under SA and GA.

Reactive oxygen species (ROS) are produced in metabolic and physiologic pathways. Harmful oxidative reactions may occur in organisms, which cannot extinguish ROS via enzymatic and non-enzymatic mechanisms. In specific conditions, an increase in oxidants and decrease in antioxidants cannot be prevented and the balance between oxidative and antioxidative equilibrium changes in favor of an oxidative state[8]. Trauma, sepsis, and surgical injury (especially ischemia-reperfusion injury) are related to increased ROS production[4,27]. Many oxidant molecules exist in blood, which prevent and/or inhibit the harmful effects of ROS. The effects of antioxidant effects of plasma are additive and the measurement of total antioxidant status specifies the antioxidative status of plasma. Cooperation of various antioxidants in human plasma ensures protection against oxidative stress.

On the contrary, the increase of intraabdominal pressure, which depends on pneumoperitoneum, may cause splanchnic ischemia[28,29]. After deflation of the abdomen, intraabdominal pressure and splanchnic blood pressure normalization and reperfusion occur. Less surgical trauma and minimal tissue injury associated with laparoscopic procedures may be suggested to cause less oxidative stress. However, clinical outcomes of oxidative stress due to ischemia-reperfusion during laparoscopic procedures are still unclear[27].

Intraabdominal pressure increases to 10-15 mm Hg during the induction of pneumoperitoneum, and this pressure level is significantly higher than in the portal system (7-10 mm Hg). Previous human studies showed that pneumoperitoneum created a prominent decrease in gut perfusion and hepatic microcirculation[30].

Deflation of pneumoperitoneum results with a decrease in intraabdominal pressure and an increase splanchnic perfusion. Thus, laparoscopic surgery may present an ischemia-reperfusion model[31]. The term 'ischemia-reperfusion' includes the consumption of energy sources of cells and the accumulation of free radicals in the circulation due to high levels of O_2 following reperfusion. Oxygen-originated cytotoxic products may cause the current circumstance and free oxygen radicals play a critical role in injury brought about by ischemia-reperfusion. The main cause of toxicity in different tissues is this production of ROS, which lead to an inflammatory response and tissue injury by activating various mediators[4]. High levels of hydrogen peroxide and other peroxides diffuse to plasma in physiologic or pathologic conditions[9]. The ratio of total peroxide to total antioxidant potential is called OSI, which is an indicator of the level of oxidative stress[10]. In our study, OSI was higher in the GA group than in the SA group, even though sevoflurane was used instead of halothane, which disrupts lipid peroxidation and antioxidant defense. However, this difference was not statistically significant. Free radicals are probably produced in laparoscopic procedures and they attack lipid molecules, and they interact with low-molecular-weight antioxidants in plasma. However, the results of our study reveal that similar TAC levels are reached in gynecologic laparoscopic surgery under SA and GA.

Our study is, as far as we know, the first to evaluate the effects of SA and GA on oxidative-antioxidative status in gynecologic laparoscopic surgery. Monitoring of TAC, TOL, and OSI may become important biochemical indicators in future clinical settings in terms of evaluating and preventing oxidative cell and tissue injury during laparoscopic surgery. In light of our findings, we can speculate that SA causes no more oxidative stress in gynecologic laparoscopy cases than GA. Evaluation of TAC, TOL and OSI with other clinical parameters may ensure better management of surgical treatment, especially in patients with unexplained infertility.

Study Limitations

Among the limitations of our study are the relatively small sample size (although this is a pilot study) and subjective nature of the questionnaire.

Conclusion

In the era of minimally invasive surgical approaches, anesthetic techniques should decrease the impact of surgical stress to organisms and the postoperative complications arising from anesthesia and surgery, and help patients and surgeons feel more comfortable. Also, one can comment on the protective benefits of SA compared with GA for all operating room staff including surgeons, anesthetists, and others in the "new-normal era" after the coronavirus 2019 outbreak.

SA may become a reliable and less invasive alternative to GA in gynecologic laparoscopy when equivalent and even advantageous features in terms of hemodynamic and respiratory parameters, patient and surgeon satisfaction, as well as total oxidant, antioxidant levels, and OSIs are considered. The need for further large-scale randomized prospective studies is evident to provide convincing evidence for the routine use of this safe and patient-friendly technique.

Ethics

Ethics Committee Approval: The randomized prospective study was performed at the Department of Anesthesiology and Reanimation of a tertiary health care provider university hospital after approval of the Faculty Ethics Committee (no: 02-2009/46).

Informed Consent: Written consent was obtained from all patients prior to their inclusion in the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.K.U., E.Ö., M.G.U., Concept: B.K.U., Ö.B., M.G.U., Design: B.K.U., Data Collection or Processing: B.K.U., Analysis or Interpretation: B.K.U., M.G.U., Literature Search: B.K.U., Writing: B.K.U., L.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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The impact of dysmenorrhea and premenstrual syndrome on academic performance of college students, and their willingness to seek help

Üniversite öğrencilerinde dismenore ve premenstrüel sendromun akademik performans üzerine etkisi ve yardım isteme eğilimleri

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Abstract

Objective: To reveal the characteristics and prevalence of dysmenorrhea and Premenstrual syndrome (PMS) among college students and to investigate their impact on their academic performance.

Materials and Methods: This cross-sectional study was conducted between December 2017 and January 2018 at Koç University, Turkey. An online survey that included multiple-choice and short paragraph questions was prepared. Female students aged between 18 and 27 years were invited with an email to provide online informed consent to proceed to the survey.

Results: The final analysis included 352 students. The prevalence of dysmenorrhea was found as 90.1%. Fifty-six percent of the participants reported lower academic performance during menstruation. However, only 32.8% of the students with dysmenorrhea presented to the gynecology clinic. The prevalence of PMS alone and with dysmenorrhea was 71.3% and 65.9%, respectively. The most common symptom among those who reported affected academic performance was depression (prevalence of 27.5%). However, only 19.9% of students with PMS consulted a healthcare professional.

Conclusion: Symptoms of dysmenorrhea and PMS are generally neglected by students. Quality of life can be affected more than estimated. Considering the reluctance to disclose menstrual disorders, health care providers should be aware of them and ask women about their symptoms during routine visits.

Keywords: Dysmenorrhea, premenstrual syndrome, pelvic pain, survey, academic performance

Öz

Amaç: Dismenore ve Premenstrüel sendromun (PMS) üniversite öğrencilerindeki karakteristiklerini ve prevalansını ortaya çıkarmak ve akademik performansları üzerindeki etkilerini incelemek.

Gereç ve Yöntemler: Bu kesitsel çalışma Aralık 2017-Ocak 2018 tarihleri arasında Koç Üniversitesi'nde gerçekleştirilmiştir. Çoktan seçmeli ve kısa paragraf soruları içeren çevrimiçi bir anket hazırlanmıştır. On sekiz ve 27 yaş aralığındak kadın öğrenciler e-posta ile ankete davet edilmiş ve ankete başlayabilmeleri için çevrimiçi aydınlatılmış onam formu doldurmaları istenmiştir.

Bulgular: Üç yüz elli iki öğrencinin katıldığı çalışmada dismenore prevalansı %90,1 idi. Katılımcıların %56'sı menstruasyon sırasında daha düşük akademik performans belirtti. Ancak, dismenoresi olan öğrencilerin sadece %32,8'i jinekoloji kliniğine başvurduğunu belirtti. Tek başına ve dismenore ile birlikte olan PMS prevalansı sırasıyla %71,3 ve %65,9, olarak bulundu. Akademik performansını etkilediğini bildirilenler arasında en sık görülen semptom depresyon (%27,5 prevalans) idi. Bununla birlikte, PMS'si olanların sadece %19,9'u bir sağlık merkezine başvurduğunu belirtti.

Sonuç: Dismenore ve PMS semptomları genellikle öğrenciler tarafından ihmal edilmektedir. Yaşam kalitesi tahmin edilenden daha fazla bozulabilir. Menstrüel bozuklukları paylaşmadaki isteksizlik göz önüne alındığında, sağlık personeli bunların farkında olmalı ve rutin ziyaretleri sırasında kadınlarda bu semptomların varlığını sorgulamalıdır.

Anahtar Kelimeler: Dismenore, premenstrüel sendrom, pelvik ağrı, anket çalışması, akademik performans

PRECIS: PMS and dysmenorrhea are ignored by college students. Early education can be an efficient method to increase awareness and prevent delays in diagnosis and management.

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Introduction

Primary dysmenorrhea, defined as recurrent lower abdominal and/or pelvic pain during menstruation affects 45 to 95% of women of reproductive age[1]. Primary dysmenorrhea refers to dysmenorrhea in the absence of an organic pathology, and secondary dysmenorrhea can occur due to gynecologic disorders such as endometriosis, adenomyosis or uterine fibroid, as well as others.

Premenstrual syndrome (PMS) presents with at least one affective symptom (irritability, anxiety, confusion, depression, anger outburst, or social withdrawal) and at least one somatic symptom (abdominal bloating, breast tenderness, headache, or swelling of extremities) during the five days prior to menses and presenting in at least three consecutive menstrual cycles[2]. Also, within four days of the onset of menses, symptoms should be alleviated. The most severe form of PMS is premenstrual dysphoric disorder, which is defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria as one or more of the following symptoms; mood swings/sudden sadness/increased sensitivity to rejection, anger/irritability, sense of hopelessness/depressed mood/self-critical thoughts, or tension/anxiety/feeling on edge[3]. The prevalence of PMS was reported as 47.8% in a meta-analysis, which called for further studies from different countries (95% confidence interval: 32.6-62.9)[4].

The impact of dysmenorrhea and PMS on the academic performance of female students has not been studied fully. A survey conducted among female high school adolescents revealed that dysmenorrhea alone or together with PMS was associated with school absenteeism[5]. Another survey conducted among female university students focused only on dysmenorrhea and reported a negative effect on the quality of life[6].

The primary aim of this study was to reveal the characteristics and prevalence of dysmenorrhea and PMS in a college population. The secondary aim was to investigate their impact on the academic performance of college students.

Materials and Methods

This cross-sectional study was conducted at Koç University in Istanbul, Turkey, between December 13th, 2017, and January 15th, 2018. We prepared an online survey that included multiple-choice and short paragraph questions. To standardize the survey, we conducted a literature review from PubMed; afterwards, we prepared the final form of the survey questions regarding our above-mentioned research purposes. This study was approved by Koç University Institutional Review Board (IRB) (2017. 216.IRB3.119). Female students aged between 18 and 27 years were invited by email for participation. Students whose first language was not Turkish were excluded from the study.

The sample size was calculated as 347 via the Australian National Statistical Service Sample Size Calculator Tool. The total number of female students was 3511, and 347 respondents were needed for 95% confidence and 0.05 as the confidence interval, with a standard error and relative standard error of 0.025 and 5.10, respectively.

Participants/Materials, Setting, Methods

Participants were required to provide online informed consent in order to proceed to the questionnaire. Identification information was not collected.

Regular menstruation was defined as one occurring with 21 to 35 days intervals. Visual analogue scale (VAS) scores from 0 to 10, where 10 represented the most severe form of pain, were used to quantify pain. The diagnosis of PMS was made according to previously defined criteria[2].

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) Version 24.0 (Chicago, IL, USA) was used to analyze the data. The statistical analysis was performed with a mean, median, and percentage.

Questionnaire

The questionnaire comprised three sections. The first section consisted of descriptive questions including age, school, age at menarche, and menstruation characteristics such as regularity and duration. The second section questioned the presence of dysmenorrhea and its characteristics including severity, persistency, duration, accompanying symptoms (nausea, vomiting, headache, migraine, back pain, breast tenderness, decrease in appetite, dizziness, constipation, painful defecation, painful urination, and others), and the respondent's perception of whether the pain affected their academic performance, annual school absenteeism in days due to dysmenorrhea, whether they disclosed the fact that absence was due to painful menstruation to their instructor, the magnitude of the impact on daily life and social life, if they ever presented to a gynecologist and/or emergency department regarding dysmenorrhea, whether a pelvic ultrasound revealed pathology that would cause dysmenorrhea, their diagnosis for dysmenorrhea, coping mechanisms for the pain (herbs, exercise, rest, hot shower, hot pack, oral/intramuscular/intravenous analgesics, oral contraceptive pills, and intrauterine device), whether they changed their coping mechanisms in the course of time, family history (Fhx) of dysmenorrhea including their mothers, sisters, aunts, and grandmothers, and the diagnosis if Fhx was positive. The third section included questions regarding PMS. The ten PMS symptoms (irritability, anxiety, confusion, depression, angry outburst, social withdrawal, abdominal bloating, breast tenderness, headache, and swelling of extremities) were listed, and the participants were asked to choose the ones they encountered five days prior to their menstrual bleeding. Secondly, they selected the most disturbing symptom among the reported symptoms. Because PMS was described previously as the presence of at least one of the ten symptoms in at least

three consecutive menstrual cycles[2], they were asked to choose whether they had the symptoms during more or less than three consecutive menstrual cycles. Whether they consulted a physician about PMS, if yes, their speciality, treatment, and whether they benefited from the treatment were questioned. They were asked to identify the symptom that most affected their academic performance. Annual school absenteeism in days due to PMS and whether or not they disclosed that absence was due to PMS to their instructor were asked. Finally, they were asked to report and quantify the medical conditions they experienced before their period.

Results

A total of 457 students completed the survey with a participation rate of 13.0%. Only 353 students completed the entire survey. One participant was excluded due to conflicting responses. Hence, the final analysis included 352 students. Demographic features and menstrual cycle characteristics, including menarche, cycle length, duration of bleeding, and regularity of the participants are presented in Table 1.

The prevalence of dysmenorrhea was found as 90.1%, where the proportion of never, occasionally, usually, and always responses were 9.9%, 38.6%, 31.3%, 20.2%, respectively (Figure 1). The median (25th - 75th percentile) VAS was 8 (7-9). The persistence of dysmenorrhea was 46.3%. The median duration of dysmenorrhea per cycle was 2 (range, 1-6) days. Accompanying symptoms and the coping mechanisms of dysmenorrhea are shown in Table 2. Thirty-one percent of women changed their coping mechanisms over time.

Fifty-six percent of the participants reported lower academic performance during menstruation. The median school absenteeism due to dysmenorrhea was three days annually for 201 people (range, 1-24). Only 12.8% of the students stated that they could disclose that their absence was due to painful menstruation with their instructors without hesitation. Only seven of the nursing and 12 of the medical students shared their menstrual disorders (25.9% and 26%, respectively). Ninety-five percent of the participants reported that dysmenorrhea did not affect their daily life; however, 92% of reported a negative effect on social life. Admission to an outpatient gynecology clinic and the emergency department was 32.8% and 25.8%, respectively. Almost sixty-six percent of the students with dysmenorrhea indicated a positive Fhx for dysmenorrhea. On the other hand, 40% of the students without dysmenorrhea indicated positive Fhx for dysmenorrhea.

According to the aforementioned PMS criteria, we found the prevalence of PMS alone and with dysmenorrhea was 71.3%, and 65.9%, respectively. The distribution of symptoms from most to least common among the students diagnosed with PMS was abdominal bloating 215 (85.7%) and irritability 202 (80.5%), breast tenderness 187 (74.5%), angry outburst 182 (72.5%), anxiety 158 (62.9%), confusion 158 (62.9%), depression 141 (56.2%), social withdrawal 92 (36.7%), headache 74 (29.5%), and swelling of extremities 54 (21.5%) where the participants were allowed to choose more than one option. The most disturbing symptom reported by the students was anger outburst with a prevalence of 25.1% (63 students). Only 19.9% of the students with PMS had consulted a gynecologist, psychiatrist, neurologist, psychologist or endocrinologist (15.5%, 1.6%, 1.2%, 1.2%, and 0.4%, respectively). As treatment among the students with PMS, 7.6% of the participants reported using oral contraceptives. The most common symptom among those who reported affected academic performance was depression with a prevalence of 27.5%. One hundred twenty-two students reported school

Table 1. Demographic features of the participants together with menstrual cycle characteristics

Variable	Number
Age (years)	
Median (25th - 75th percentiles)	21 (20-22)
Range	18-27
Departments (%)	
The Social Sciences and Humanities	106 (30.0)
College of Administrative Sciences and Economics	68 (19.3)
School of Medicine	50 (14.4)
College of Engineering	43 (12.2)
School of Nursing	31 (8.8)
Law School	30 (8.5)
College of Sciences	24 (6.8)
Total	352 (100)
Menarche (years)	13 (12-13)*
Cycle length (days)	28 (28-30)*
Duration of bleeding (days)	5 (4-6)*
Menstrual Cycle Regularity (%)	
Regular	265 (75.3)*
Irregular	87 (24.7)*

*Median (25th -75th percentiles)

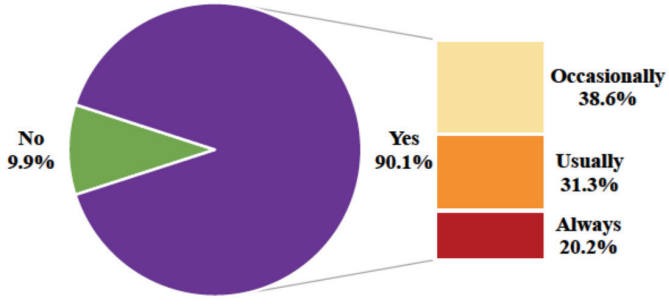

Figure 1. Dysmenorrhea prevalence

absenteeism (range, 1-38 days, annually) due to PMS. However, only 11 (4.4%) students stated that they could share that the absence was due to PMS with their instructors without hesitation. Among the nursing and medical students who reported that school absenteeism was due to PMS, 22.2% and 18.2%, respectively, could share with their instructors without hesitation. Finally, the severity of the PMS symptoms is listed in Table 3.

Discussion

Our survey indicates that dysmenorrhea is a common problem among university students. More than half of the participants reported that dysmenorrhea affected their academic performance mainly due to absenteeism. Our results also showed that depression was the most common symptom affecting their academic performance, which could perhaps be prevented by consulting a health professional and sharing their problems. Also, more than 70% of students reported experiencing PMS symptoms, and the most common symptom was anger outburst, which affects social life negatively.

Table 2. Accompanying symptoms† and coping mechanisms† of dysmenorrhea

	Number (%)
Accompanying symptoms*	
Back pain	210 (59.7)
Breast tenderness	206 (58.5)
Nausea	117 (33.2)
Diarrhea	123 (34.9)
Headache	101 (28.7)
Decrease in appetite	74 (21)
Dizziness	56 (15.9)
Constipation	52 (14.8)
Migraine	41 (11.6)
Painful defecation	38 (10.8)
Vomiting	38 (10.8)
Painful urination	25 (7.1)
None	12 (3.4)
Coping mechanisms	
Analgesics	294 (92.6)
Oral Intramuscular Intravenous	251 (79.1) 26 (8.2) 17 (5.3)
Hot pack	201 (63.4)
Hot shower	179 (56.6)
Rest	110 (34.8)
Herbs	47 (14.8)
Oral contraceptive pills	32 (10.0)
Exercise	31 (9.7)
Hobbies	26 (8.2)
Intrauterine device	0 (0)

*Ranked from the most frequent to the least, †Participants were allowed to choose more than one option

Surveys are prone to bias when the response rate is too low. The participation rate in our study was 13%, likely because we inactivated the survey when we reached the calculated sample size. It is possible that students with dysmenorrhea and/or PMS were more likely to complete the questionnaire. This might have caused an overestimation of dysmenorrhea and PMS prevalence. Our study group homogenously consisted of educated women, and the study was anonymous, which gave the confidentiality of identity.

Menstrual disorders such as dysmenorrhea and PMS can affect academic performance, mental well-being, and quality of life. Menstrual disorders are estimated to affect almost 2.5 million women every year[7]. The symptoms can be physical, emotional, or behavioral, which is thought to be derived from hormonal fluctuations[8]. Even PMS is thought to result from ovulation and hormonal fluctuations and primary dysmenorrhea from increased production of prostaglandins resulting in painful uterine contractions and decreased blood flow; however, the etiology of menstrual disorders is yet to be identified[8,9].

A strong association between quality of life and severity of PMS symptoms has been reported in the literature[10,11]. The majority of women in reproductive age have at least one symptom of dysmenorrhea and/or PMS[12-16]. We wanted to address the impact of the symptoms of menstrual disorders on the academic performance of female students. Similar to our results, several other studies also reported that menstrual disorders caused school absenteeism, defects in social life, and a decline in academic performance[17-19]. Absenteeism varied in a range of 18.6% to 80.6% among university students in previous studies[16,20,21].

The retrospective diagnosis of PMS is a limitation of this study. However, because there is not an objective diagnostic criterion of PMS[22], it is difficult to evaluate its accurate prevalence. Further studies should be designed prospectively via providing the participants with the charts for PMS symptoms for at least for three consecutive months. Hence, we would like to ask experts to prepare an up-to-date objective universal guideline.

Intriguingly, highly educated women are hesitant to disclose their menstrual disorders and even their absenteeism being due to dysmenorrhea or/and PMS symptoms to their instructors[23]. Even more remarkably, medical and nursing school students, who are expected to have a higher awareness of these disorders, were also reluctant to share the fact that their absenteeism was due to menstrual disorders. Sharing and presenting to a gynecology clinic or for emergency care was also low among the students. This makes one think that most women consider

Table 3. Severity of the premenstrual syndrome symptoms (n=251)

	None (%)	Mild (%)	Moderate (%)	Severe (%)
1. Depressed, sad, "down" or "blue" feeling of worthless or guilty	11 (4.4)	66 (26.3)	92 (36.7)	82 (32.7)
2. Anxious, tense, "keyed up" or on edge	9 (3.6)	47 (18.7)	96 (38.2)	99 (39.4)
3. Mood swings/sensitive to rejection	8 (3.2)	34 (13.5)	98 (39.0)	111 (44.2)
4. Angry or irritable	7 (2.8)	44 (17.5)	85 (33.9)	115 (45.8)
5. Less interested in usual activities	30 (12.0)	74 (29.5)	103 (41.0)	44 (17.5)
6. Lack of concentration	53 (21.1)	66 (26.3)	87 (34.7)	45 (17.9)
7. Lethargic, tired, fatigued or of energy	3 (1.2)	52 (20.7)	85 (33.9)	111 (44.2)
8. Increased appetite or food cravings	42 (16.7)	58 (23.1)	81 (32.3)	70 (27.9)
9. Insomnia/hypersomnia	46 (18.3)	65 (25.9)	77 (30.7)	63 (25.1)
10. Overwhelmed, unable to cope	37 (14.7)	61 (24.3)	76 (30.3)	77 (30.7)
11. Breast tenderness, breast swelling, bloated sensation, weight gain, headache, joint or muscle pain, or other physical symptoms	11 (4.4)	64 (25.5)	99 (39.4)	77 (30.7)
12. Reduced productivity or inefficiency at work, school, home or in daily routine	31 (12.4)	64 (25.5)	100 (39.8)	56 (22.3)
13. Less participation in hobbies or social activities	38 (15.1)	76 (30.3)	97 (38.6)	40 (15.9)
14. Interference in relationships with others	23 (9.2)	74 (29.5)	98 (39.0)	56 (22.3)

menstrual disorders as natural and do not seek a remedy, rather the try to manage with temporary solutions or to live with it. On the other hand, the lack of seeing a physician due to menstrual disorders also causes a delay in diagnoses for conditions underlying secondary dysmenorrhea, such as endometriosis[24].

Current treatment options for dysmenorrhea include non-hormonal medical therapy such as acetaminophen and non-steroidal anti-inflammatory drugs, hormonal treatment such as contraceptive pills or progestin regimens[25]. Complementary and alternative treatment options can be recommended, such as exercise, transcutaneous electrical nerve stimulation, acupuncture and acupressure, behavioral interventions, topical heat, and dietary supplements[25]. Most of the respondents improved their coping mechanisms with dysmenorrhea in an unusual way in our study. Some of them reported benefiting from these strategies; however, mostly, they were temporary. Analgesic usage was very common among participants (92.6%). Only 10% of the students were on oral contraceptive pills. Most of the students used alternative methods while managing with their symptoms such as hot packs (63.4%), hot showers (56.6%), rest (34.8%), herbs (14.8%), exercise (9.7%), and hobbies (8.2%).

Conclusion

Symptoms of dysmenorrhea and PMS are frequently neglected by college students. The symptoms can vary widely among women. Quality of life can be affected more than estimated, and even being a female can be regarded as a misfortune by the affected population. Considering the reluctance to disclose menstrual disorders, healthcare providers should be aware of the fact and ask women about such symptoms in routine visits. Thereby, the symptoms of PMS and dysmenorrhea ignored by women, which affect the quality of life, can be identified, and awareness can be increased. Besides, education for adolescents can be an efficient method to increase awareness and prevent delays in diagnosis.

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The authors would like to thank the Koç University's Female Students for their participation.

Ethics

Ethics Committee Approval: This study was approved by Koç University Institutional Review Board (IRB) (2017. 216. IRB3.119).

Informed Consent: Participants were required to provide online informed consent in order to proceed to the questionnaire. Identification information was not collected.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: E.B., Ş.Y., K.Y., B.A., Design: E.B., Ş.Y., K.Y., B.A. Data Collection or Processing: E.B., Ş.Y., B.A., Analysis or Interpretation: E.B., Ş.Y., B.A., Literature Search: E.B., Ş.Y., B.A., Writing: E.B., Ş.Y., B.A.* E.B., Ş.Y.: The authors contributed equally.

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Asymptomatic trocar site hernias: An underestimated complication of laparoscopy

Asemptomatik trokar bölgesi hernileri: Laparoskopinin azımsanan komplikasyonu

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Abstract

Objective: To estimate the exact incidence of trocar site hernia (TSH) through sonographic examination and to evaluate the predisposing risk factors of TSH.

Materials and Methods: Three hundred patients who underwent laparoscopic surgery for benign gynecologic indications were included in this study and called back for a follow-up visit. All patients underwent an ultrasound evaluation for the detection of TSH. Risk factors for TSH formation were investigated.

Results: Twenty-five (8.3%) TSHs were diagnosed among 300 postoperative laparoscopies. The highest rate of TSH development among the surgeries was found in tubal ligation cases with 19%. Parity ≥3 [odds ratio (OR), 3.13; 95% confidence interval (CI): 1.21-8.09; p=0.018], and not closing fascia (OR: 6.74; 95% CI: 2.72-16.70; p<0.001) were statistically significant risk factors for the development of TSH in multivariate analysis.

Conclusion: The prevalence of TSH is higher than previously reported, and ultrasonographic examination is adequate for detecting subclinical types of this complication.

Keywords: Complications, laparoscopy, port site hernia, trocar, trocar site hernia

Öz

Amaç: Bu çalışmanın temel amacı sonografik inceleme ile trokar bölgesi hernisinin (TSH) kesin insidansını tahmin etmek ve TSH'nin predispozan risk faktörlerini değerlendirmektir.

Gereç ve Yöntemler: Benign jinekolojik endikasyonlar için laparoskopik operasyon geçiren 300 hasta çalışmaya dahil edildi ve tekrar takip ziyareti için çağırıldı. Tüm hastalara TSH saptanması için ultrason değerlendirmesi yapıldı. TSH oluşumu için risk faktörleri araştırıldı.

Bulgular: Üç yüz laparoskopik ameliyat sonrasında yirmi beş (%8,3) TSH tanısı kondu. Operasyonlar arasında en yüksek TSH gelişimi oranı %19 ile tubal ligasyon olgularında bulundu. Çok değişkenli analizde parite ≥3 [olasılık oranı (OR), 3,13; %95 güven aralığı (GA), 1,21 ila 8,09; p=0,018] ve kapatılmamış fasya (OR: 6,74; %95 GA: 2,72 ila 16,70; p<0,001) TSH gelişimi için istatistiksel olarak anlamlı risk faktörleri idi.

Sonuç: TSH prevalansı daha önce bildirilenden daha fazladır ve ultrasonografik inceleme bu komplikasyonun subklinik tiplerini tespit etmek için yeterlidir.

Anahtar Kelimeler: Komplikasyonlar, laparoskopi, port alanı hernisi, trokar, trokar alanı hernisi

Introduction

Trocar site hernia (TSH) is defined as an incisional hernia (IH) occurring after laparoscopic procedures at the trocar incision site[1]. TSH is a rare surgical complication with an estimated incidence ranging between 0.6% and 5.2%[2-5]. However, because available data are based only on symptomatic patients and clinically diagnosed cases, the actual incidence is probably underestimated. The overall incidence might be higher if asymptomatic patients are routinely screened using a more effective diagnostic tool such as ultrasonography (USG).

Most TSHs are asymptomatic, but they can occasionally lead to severe morbidity and mortality, such as bowel strangulation and necrosis[5]. Thus, early detection of subclinical TSH before the occurrence of severe complications is essential. Many

PRECIS: When ultrasonography was used for diagnosis, it was observed that the frequency of trocar site hernia development was higher than previously reported.

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factors have been implicated as predisposing to TSH formation. Advanced age, obesity, diabetes mellitus and wound infection were identified as patient-related risk factors[1,5-7]. Moreover, trocar size, design, and insertion technique; port location; duration of surgery; fascial incision enlargement; and fascial closure were suggested as technical factors for the occurrence of TSH[1,8-10].

When the literature on this subject is examined, it is seen that information about prevalence and risk factors of TSH, especially in the female population, is still limited and contradictory.

The primary objective of this study was to estimate the exact incidence of TSH by sonographic examination and to evaluate the predisposing risk factors of TSH.

Materials and Methods

This study was conducted in University of Health Sciences Turkey, Bursa Yüksek İhtisas Training and Research Hospital, Clinic of Obstetrics and Gynecology. After receiving approval of the ethics committee, medical records of 491 patients who underwent laparoscopic surgery between May 2016 and July 2018 in our clinic were retrospectively scanned.

All patients undergoing a laparoscopic surgical procedure for benign gynecologic indications during the study period with a minimum follow-up of 12 months were included in the study. The exclusion criteria of the study were determined as follows: age <18 years old, previous history of midline laparotomy, pregnancy after the procedure, a subsequent abdominal surgical procedure except for IH repairs, use of the open technique or palmar point for entering the abdomen, conversion to laparotomy, malignancy, and refusal to give informed consent. Also, we excluded any patients who underwent laparoscopic surgery before or after the index procedure.

Finally, 300 patients were included in the study and called back for a follow-up visit. The average time between the surgery and the patient's sonographic evaluation with USG was 16 (range, 12-29) months. Written informed consent was obtained from all participants. All patients underwent a clinical examination. Furthermore, all participants underwent an ultrasonographic evaluation for the detection of TSH. The ultrasonographic diagnosis of TSH was defined as any discontinuation of the fascial layer (Figure 1). Clinical and sonographic examinations were performed by a single physician and a single radiologist. A 9L-D linear broad-spectrum transducer with the GE Health Care Logic S7 expert model USG was used.

Laparoscopic surgeries were performed by different surgeons working in our institution. Three or four-port sites were generally used for the procedures, one of which was 10/12 mm cutting trocar for the camera, and two or three were the lateral 5-mm cutting trocars. Initially, a 10 or 12 mm trocar was inserted with the closed technique to the umbilical location. Lateral trocars were placed approximately 6-8 cm from the midline and 4-5 cm above the symphysis. At our institution, the decisions for the type of abdominal entry (direct trocar or Veress needle), closure of umbilical port site (only skin or fascia and skin), and the placement of drain are based on the clinical judgment of the operative surgeon. If a drain was inserted, it is aimed to be removed within 1-2 days in cases without problems.

All patients received prophylactic antibiotherapy (1 to 2 g cefazolin was administered intravenously 15 to 60 minutes prior to skin incision). Skin sutures were removed at day 7-10.

For each patient enrolled in the study, the hospital and follow-up records were reviewed for the following data: pre-operative age in years, weight in kilograms and height in meters, body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared), gravida, parity, type II diabetes [defined as blood glycemia >126 mg/dL and/or glycated hemoglobin (HbA1c) >7% and/or use of oral hypoglycemic agents and/or insulin], presence of chronic constipation, smoking status (defined as positive when actively smoking), type of abdominal access, fascia enlargement to remove material, closure of umbilical 10/12 mm trocar fascia, surgical duration, drain placement, and the presence of wound infection (defined as a positive culture and/or presence of infection according to the physician's opinion).

Statistical Analysis

Data were analyzed using the IBM SPSS V23 (SPSS, Inc., Chicago, IL). The Shapiro-Wilk test was used to examine the compatibility of data to normal distribution. The independent samples t-test was used to compare the parameters according to the presence of TSH. The chi-square test was used to evaluate the correlation between categorical data and TSH. Independent risk factors for the development of TSH were analyzed using univariate and multivariate logistic regression analysis. A p-value of <0.05 was considered as statistically significant.

Results

There were 25 (8.3%) TSHs among 300 patients who underwent laparoscopic surgery. Of the 25 patients with TSH, 23 had a

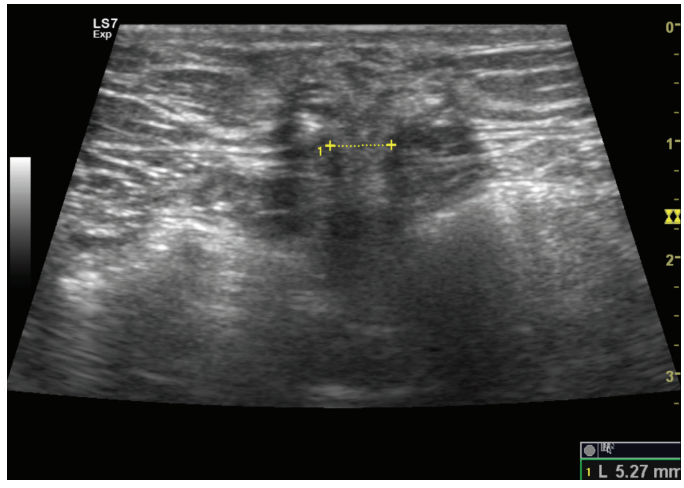

Figure 1. Ultrasound image showing herniation of omentum through the defect at the 10 mm trocar site

herniation at the umbilicus, and two had herniation at the extra-umbilical sites. The TSHs were asymptomatic in 23 patients (92% of all TSHs). Five were detected by physical examination and confirmed by ultrasound, whereas 18 patients had normal abdominal examination findings and were diagnosed as having TSH with USG.

Two patients have already undergone hernia repair surgery for symptomatic TSH in the 8th and 10th postoperative months, respectively. The first of these patients was a 31-year-old who underwent bilateral tubal ligation and developed wound infection in the postoperative period. She was admitted to the hospital eight months after surgery due to TSH containing omentum tissue in the umbilical region. The second case was a 38-year-old patient who underwent cystectomy. In this case, the cyst material was removed from the left lower quadrant, but fascia was not enlarged, and the drain was inserted from the same site. Ten months after the surgery, she was admitted to hospital with gastrointestinal symptoms and was immediately taken to the operating room due to the detection of intestinal herniation from the trocar site in the left lower quadrant.

The most frequent surgeries performed during the study period were cystectomy (33%), hysterectomy (25.3%), and tubal ligation (19.3%), respectively. The highest rate of TSH development among the procedures was found in tubal ligation cases with 19%. The rate of patients with a parity number of three or more was highest in the group undergoing tubal ligation (75.9%). Patient data and surgery types are presented in Table 1.

The gravida and parity of patients who developed hernia (3.4±1.58 vs 2.53±1.64; p=0.011 and 3±1.38 vs 2.15±1.53; p=0.008, respectively) were significantly higher. The fascia closure rate was significantly lower in patients with TSH compared with those without TSH (40% vs 82.2%; p<0.001, respectively). Characteristics of patients with and without TSH are presented in Table 2.

There were no statistically significant differences between patients with and without TSH regarding age (42.12±10.15 vs 40.64±11.11; p=0.520), BMI (28.44±4.26 vs 27.05±4.94; p=0.175), presence of comorbidities (p=0.410 for diabetes mellitus and p=0.665 for chronic constipation), preoperative hemoglobin values (12.13±5.88 vs 11.89±1.44; p=0.838), and surgical duration (58.6±36.98 vs 65.05±33.41; p=0.360). Likewise, in terms of hernia development, no statistically significant difference was found between the following parameters: presence of previous surgery, smoking status, trocar entry technique, and fascial incision enlargement (p>0.05).

Parity ≥3 and the absence of fascia closure were statistically significant risk factors for the development of TSH in both univariate and multivariate analyses (Table 3). Wound infection was found to have a significant effect on TSH formation in multivariate analysis. There was no significant association with not placing a drain and TSH formation in the multivariate analysis.

Discussion

Data on the frequency of TSHs show a wide distribution in the relevant literature. The lack of consensus regarding the definition

Table 1. Patient data and types of surgery

Operations	n	TSH n (%)	Age (y) mean ± SD	BMI (kg/m²) mean ± SD	Parity ≥3 n (%)	Fascia closed n (%)	Duration of operation (min) mean ± SD
Cystectomy	99	5/99 (5.1%)	34.09±8.89	25.42±4.28	13/99 (13.1%)	86/99 (86.9%)	57.02±14.03
TLH ± BSO	76	7/76 (9.2%)	52.21±8.31	29.83±4.87	42/76 (55.3%)	47/76 (61.8%)	102.37±15.78
BTL	58	11/58 (19.0%)	37.53±4.50	26.84±3.81	44/58 (75.9%)	43/58 (74.1%)	26.72±5.58
Myomectomy	23	1/23 (4.3%)	38.57±5.28	25.22±5.44	2/23 (8.7%)	21/23 (91.3%)	110.43±30.34
Salpingectomy	19	0	35.89±7.41	25.89±3.88	3/19 (15.9%)	16/19 (84.2%)	42.63±11.23
USO/BSO	14	0	55.29±9.42	31.60±5.29	7/14 (50.0%)	12/14 (85.7%)	46.79±20.63
Other	11	1/11 (9.1%)	33.18±6.40	26.80±5.02	3/11 (27.3%)	11/11 (100%)	34.09±15.14
Total	300	25/300 (8.3%)	40.76±11.03	27.17±4.90	114/300 (38%)	236/300 (78.7%)	64.52±33.70

TSH: Trocar site incisional hernia, SD: Standard deviaton, BMI: Body mass index, BSO: Bilateral salpingoopherectomy, BTL: Bileteral tubal ligation, TLH: Total laparoscopic hysterectomy, USO: Unilateral salpingoopherectomy, min: Minute

of TSH among studies might influence the reported prevalence. TSH is a type of IH that occurs after laparoscopic surgery at the trocar incision site. IH was defined as any abdominal wall gap or defect in the proximity of the postoperative scar by most of the studies[11-13]. However, some of these studies included a protrusion of abdominal contents in the definition[14]. In this study, we defined hernia as any defect in the fascia layers in the trocar entry site because we aimed to detect all asymptomatic cases. Tonouchi et al.[1] first classified three types of TSHs according to the cause and the onset time. The early-onset type of hernia occurs by the dehiscence of anterior and posterior fascial plane and peritoneum in the early postoperative period. The late-onset type of hernia occurs by the dehiscence of anterior and posterior fascial plane, with peritoneum providing the hernia sac; they appear several months after surgery. Small intestinal obstruction is not seen, and it manifests as an asymptomatic swelling. This special type of hernia is due to the dehiscence of the whole abdominal wall immediately after surgery, with intestine and/or omentum protruding without a sac[1]. All our cases except two symptomatic were thought to represent the late-onset type.

In many studies, the frequency of TSH is reported as between 0.6% and 5.2%[2-5]. According to these publications, the frequency of TSH of 8.3% in our study is significantly high. However, most of these studies focused on hernia cases that required symptomatic or surgical repair. Also, in studies involving asymptomatic cases, hernia diagnosis was made primarily with physical examination findings. In studies where additional imaging modalities were used for diagnosis other than physical examination, higher hernia identification rates were reported[10,15,16]. In the study of Christie et al.[10] evaluating TSH development after robot-assisted urologic surgery, all patients underwent radiologic imaging (computed tomography), and the incidence of TSH was reported as 7.7%. In the literature, there are three studies that evaluated patients who underwent bariatric surgery with an imaging modality, and the incidence of TSH was approximately 24.5%[17-19]. In our study, the patients were invited to our clinic for re-evaluation after a minimum of 12 months and a maximum of 29 months after surgery. The incidence of TSH detection is significantly higher when the follow-up period is longer than 12 months, and when an imaging modality is used[7].

Generally, there is worldwide variability in the abdominal entry techniques as well as port site closures, and our institution is no different. Some surgeons prefer the Veress needle, whereas others perform the direct trocar technique. Likewise, there is no consensus among surgeons regarding the closure of trocar entry points. In many studies, it is emphasized that leaving the

Table 2. Characteristics of patients with and without trocar site incisional hernia

Variable	Patients without TSH (n=275)	TSH (n=25)	p
Age (years)	40.64±11.11	42.12±10.15	0.520†
BMI (kg/m²)	27.05±4.94	28.44±4.26	0.175†
BMI >30 kg/m²	66 (24%)	8 (32%)	0.518*
Gravida	2.53±1.64	3.4±1.58	**0.011†**
Parity	2.15±1.53	3±1.38	**0.008†**
Parity ≥3	97 (35.3%)	17 (68%)	**0.003***
Diabetes mellitus	19 (6.9%)	3 (12%)	0.410*
Chronic constipation	17 (6.2%)	2 (8%)	0.665*
Smoking	35 (12.7%)	3 (12%)	0.999
Previous abdominal surgery	59 (21.5%)	2 (8%)	0.180*
Preoperative hemoglobin values (g/dL)	12.13±5.88	11.89±1.44	0.838†
Direct trocar access	77 (28%)	7 (28%)	0.288*
Fascial incision enlargement	37 (13.5%)	1 (4%)	0.223*
Fascia was not closed	49 (17.8%)	15 (60%)	**<0.001**
Duration of operation (min)	65.05±33.41	58.6±36.98	0.360†
Drain placement	181 (65.8%)	11 (44%)	**0.050***
Wound infection	6 (2.2%)	2 (8%)	0.137*

Data are expressed as number (percentage) or mean ± SD, SD: Standard deviation, BMI: Body mass index, TSH: Trocar site incisional hernia, *: chi-square test, †: Student's t-test, min: Minute

Table 3. Univariate and multivariate logistic regression analysis for development of trocar site incisional hernia

Variable	Univariate		Multivariate	
	OR (95% CI)	p	OR (95% CI)	p
Parity ≥3	3.90 (1.62-9.36)	**0.002**	3.13 (1.21-8.09)	**0.018**
Fascia was not closed	6.92 (2.93-16.31)	**<0.001**	6.74 (2.72-16.70)	**<0.001**
No drain	2.45 (1.071-5.61)	**0.034**	2.24 (0.90-5.56)	0.083
Wound infection	3.90 (0.74-20.42)	0.107	9.96 (1.47-67.48)	**0.019**

OR: Odds ratio, CI: Confidence interval

fascia open is the most important factor in the development of TSH, and closure of the fascia is recommended in trocar site incisions of 10 mm and over[1,5,20,21]. In the first systemic review of TSH, Tonouchi et al.[1] indicated that surgical technique-related factors rather than patient-related factors were of primary importance in the formation of TSH, and reported that large trocar diameter, open facial defects, and stretching of port sites were strictly related to TSH formation. They suggested the closure of the facial defects of umbilical or extra umbilical areas where trocar diameters of 10 mm and over were used as well as the closure of the fascial defect in the case of active manipulation from the 5-mm port during lengthy procedures. In a systemic review compiled by Helgstrand et al.[6] 96% of TSHs were reported to occur in trocar locations with 10 mm and larger diameter trocars, and 82% were in the umbilicus; it was suggested to close the facial defects of trocars with a diameter of 10 mm and over. Also, in many studies, it has been reported that 12-mm cutting trocars caused higher rates of hernia formation compared with 10-mm bladeless trocars[22,23]. In our study, 92% of the detected hernias occurred at the port entry points of 10-12 mm trocars. Moreover, in more than half (60%) of our patients who developed hernias, fascial closure was not performed. Our findings also support the literature suggesting the closure of the trocar sites over 10 mm. In the systemic review published by Karampinis et al.[7] in 2019, contrary to expectations, a higher incidence of TSH was found in studies that routinely performed fascial closure in patients who underwent laparoscopic bariatric procedures. However, this result did not reach statistical significance. In our study, we also observed that fascial closure was performed in 40% of hernia cases. This result may be due to the fact that the surgeries were performed by different surgeons with different experiences and skills; therefore, fascia closure may not be effectively performed.

The role of sex in the development of TSH is conflicting in the literature[5,6,8]. It is evident that a condition that may lead to laxity and fascial defects, especially in the anterior abdominal wall, such as pregnancy and labor, may be an important risk factor for hernia development. The data on the effect of parity on hernia development in the literature are minimal. It is known that relaxation and damage occur in the abdominal wall and fascial structures due to childbirth[8]. This damage in the umbilical region may cause fascial defects in the following years. In a study involving 2.100 cases, 18% of patients had a fascial defect in the anterior abdominal wall during laparoscopy[24]. Considering factors such as age, BMI, and surgical time, tubal ligation cases were in a low-risk group for hernia development. However, TSH development rate per surgery was found to be significantly higher in these patients in our study. This finding cannot be explained only by the low fascia closure rate. We believe that the high parity number in tubal ligation cases indicates that parity is an important risk factor for TSH development.

To the best of our knowledge, there are no studies examining the relationship between drain insertion and TSH development in the literature. In this study, we aimed to evaluate whether drain insertion decreased the development of TSH by reducing intraabdominal pressure. Although drain insertion resulted in fewer cases of TSH in our study, this finding did not reach statistical significance. On the other hand, drain use may contribute to the formation of hernia by causing infection. Evidence regarding the relationship between closed suction drain (CSD) and surgical site infection (SSI) in the obstetrics and gynecology literature is conflicting[25]. A few studies suggested an increased risk of SSI associated with drain placement but usually associated with open drainage and not the use of CSD[25]. We also believe that short-term closed drainage does not play an important role in the development of infection. The data of both this study and current studies are insufficient to determine the effect of drain insertion on TSH development. We believe that prospective randomized studies on this subject are necessary to clarify this issue.

Although many studies have reported that age and BMI might be risk factors for the development of TSH, such a relationship has not been reported in other publications[5-8,26]. Especially in studies evaluating patients who underwent bariatric surgery, obesity has been reported to be an important risk factor for TSH due to the high intraabdominal pressure and the full thickness of the preperitoneal area, which causes a challenge for closure and increase in wound infection[17,18]. Likewise, being aged over 60 or 70 years has been reported to be associated with increased TSH[8,15,27]. Our study population was relatively younger and had a lower weight average than the published literature reporting increased risk, and no relationship was found between age or BMI and TSH development. It could be explained by the fact that our study group did not have the extreme values stated in the literature regarding the mentioned factors.

Contrary to previous studies reporting the association between surgical duration and TSH, surgical duration did not differ between the patients who had TSH[8,27]. Moreover, the highest TSH rate was observed in tubal ligation cases with the shortest surgical duration. The fact that tubal ligation cases had higher values in terms of parity, which was determined as an important risk factor for TSH also in this study, may have masked the effect of surgical time.

In a recently published study, excessive manipulation of the trocar site to remove specimens during surgery was reported to be an important risk factor for TSH formation[28]. The authors also suggested avoiding conditions that increased abdominal pressure such as coughing within 2 weeks after surgery. In our study, the port site for specimen removal was not mentioned in the surgical notes. Likewise, we did not have any data on the exposure of patients to conditions that might increase intra-abdominal pressure in the early postoperative period.

Study Limitations

Our study has limitations. The missing data in the medical records is the structural limit of our study; we were unable to control or evaluate many factors that could affect hernia development, such as the use of different brands and sizes (10 or 12 mm) of trocars. The performed surgeries have technical variations because different surgeons performed the procedures. Differences in entering the abdomen (e.g. trocar insertion angle, excessive manipulations) and closure techniques may have influenced the outcomes. Also, the structure and the size of our sample may not be sufficient to determine the effect of individual factors, such as age, BMI, wound infection, and comorbidities.

The strength of our study is the diagnostic method we use in diagnosing TSH. Regardless of the physical examination findings, the evaluation of all patients using USG enabled us to diagnose all asymptomatic or subclinical cases. Thus, we believe that the frequency of TSH detected in our study reflects the true prevalence of this complication. Also, contrary to the relevant literature, which mostly includes general surgery and urology patients, the data of our study, which consists of only female cases, can provide predictions about the risk of TSH in common basic gynecologic procedures. Another important finding of our study is the high rate of TSH in young women with high parity. We believe that the high parity, which has not been sufficiently evaluated in studies published to date, should be considered as an important risk factor for hernia development regardless of the type of surgery.

Conclusion

Our findings suggest that the prevalence of TSH is higher than previously reported, and an ultrasonographic examination is sufficient for identifying subclinical types of this complication.

Ethics

Ethics Committee Approval: The study was reviewed by the Ethics Committee of University of Health Sciences Turkey, Bursa Higher Specialization Training and Research Hospital, (approval number: 2011-KAEK-25 2019/01-01) and was conducted under the ethical standards described in an appropriate version of the 1975 Declaration of Helsinki, as revised in 2000.

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

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: E.Ü., F.N.T., Design: E.Ü., F.N.T., S.T., Data Collection or Processing: E.Ü., F.N.T., S.T., Analysis or Interpretation: E.Ü., Writing: E.Ü., F.N.T.

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The impact of morbid obesity on survival of endometrial cancer

Morbid obezitenin endometriyal kanserli hastaların sağkalımına etkisi

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Abstract

Objective: Morbid obesity is identified as patients with a body mass index more than 40 kg/m^2. Obesity is known as a risk factor for endometrial cancer due to the increase of the deposited estrogen. This study was conducted to evaluate the effect of morbid obesity on the survival of endometrial cancer.

Materials and Methods: The archival records and pathologic reports of patients with endometrial cancer who underwent surgery and were followed up in Çukurova University Gynecologic Oncology Center between January 1996 and December 2018 were reviewed, retrospectively. Data regarding body mass index and survival was reported in 520 patients. These patients were stratified into two groups according to their body mass index, <40 and ≥40 kg/m^2. The groups' clinic, pathologic features, and survival rates were compared.

Results: There were 146 patients in the morbidly obese group and 374 patients in the obese group. The mean age of the groups was 58.5 and 56.2 years, respectively. The mean follow-up time was 51.6 months. Comorbidities were significantly higher in the morbidly obese group. The five-year disease-free and overall survival rates were 78.3% and 85.3% in the morbidly obese group, and 81.6% and 90.1% in the obese group, respectively. Although the groups' clinical and pathologic features were homogeneously distributed, disease-free and overall survival rates were significantly different (p=0.053 and p=0.054, respectively).

Conclusion: Morbidly obese patients with endometrial cancer were associated with 2.7-fold increased risk of death and 1.7-fold increased risk of recurrence compared with those who had body mass index <40 kg/m^2. It is important to deal with the frequent comorbidities in this special group, which could be simply altered by lifestyle changes. Morbidly obese patients with endometrial cancer should be encouraged in lifestyle changes and consulted by dieticians and endocrinologists.

Keywords: Morbid obesity, endometrial cancer, survival

Öz

Amaç: Morbid obezite, vücut kitle indeksi 40 kg/m^2'den fazla olan hastaları tanımlar. Obezite, yağ dokusunda depolanan östrojenin artışı nedeniyle endometriyum kanseri için bir risk faktörü olarak bilinir. Bu çalışma, endometriyal kanserin sağkalımı üzerine morbid obezite etkisini değerlendirmek için planlanmıştır.

Gereç ve Yöntemler: Çukurova Üniversitesi Jinekolojik Onkoloji Birimi'nde Ocak 1996 - Aralık 2018 tarihleri arasında opere edilen ve takip edilen endometriyum kanserli olgularının arşiv kayıtları ve patolojik raporları retrospektif olarak incelendi. Bu hastalardan vücut kitle indeksi ve sağkalım ile ilgili tam verilerine ulaşılabilen 520 olgu çalışmaya dahil edildi. Hastalar vücut kitle indeksleri <40 ve ≥40 şeklinde iki gruba ayrıldı. Grupların kliniği, patolojik özellikleri ve sağkalım oranları karşılaştırıldı.

Bulgular: Morbid obez hasta grubunda 146 ve vücut kitle indeksi <40 kg/m^2 olan grupta 374 hasta vardı. Grupların yaş ortalaması sırasıyla 58,5 ve 56,2 idi. Ortalama takip süresi 51,6 aydı. Komorbiditeler, morbid obez grupta anlamlı derecede yüksekti. Beş yıllık hastalıksız ve genel sağkalım oranları, morbid obez grupta sırasıyla; %78,3 ve %85,3, vücut kitle indeksi <40 kg/m^2 olan grupta %81,6 ve %90,1 idi. Grupların klinik ve patolojik özelliklerinin homojen olarak dağılmış olmasına rağmen, hastalıksız ve genel sağkalım oranlarının anlamlı derecede farklı olduğu görülmüştür (sırasıyla, p=0,053 ve p=0,054).

Sonuç: Morbid obez endometriyal kanserli hastalar, vücut kitle indeksi <40 kg/m^2 olanlara göre 2,7 artmış ölüm riski ve 1,7 artmış nüks riski ile ilişkiliydi. Yaşam tarzındaki değişimlerle kolayca değiştirilebilecek olan ve bu özel grupta sıkça görülen komorbiditelerle baş etmek son derece önemlidir. Morbid obez endometriyal kanserli hastalar yaşam tarzı değişiklikleri için teşvik edilmeli ve diyetisyenler ile endokrinologlara konsülte edilmelidir.

Anahtar Kelimeler: Morbid obezite, endometriyum kanseri, sağkalım

PRECIS: Although there are limited studies on the effect of obesity on long-term outcomes of endometrial cancer, morbid obesity has not been considered separately in most of them. We address this issue herein.

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Introduction

Endometrial carcinoma is the most seen gynecologic cancer in the developed world[1]. Based on epidemiologic and histologic evidence, endometrial cancer has been historically stratified into two types[2]. Endometrioid type (type 1), which comprises about 80% of the cases, is an unopposed estrogen-dependent endometrial cancer type[2,3]. It has been supposed that the estrogen deposited in the adipose tissue leaves the endometrium layer under continuous hormonal exposure[4]. Hence, the relation of obesity with endometrial cancer risk, particularly the endometrioid type, has been emphasized since the dualistic identification[2-5]. Therefore, the growing incidence of endometrial carcinoma in the last decades is presumably due to the rising obesity levels[6]. The World Health Organization (WHO) defined obesity as patients with body mass index (BMI) more than 30 kg/m^2 and morbid obesity as ≥40 kg/m^2 [7]. It has been reported that up to 81% of the endometrial cancer' patients are obese and 19% to 36% of them are morbidly obese[6]. Inadequate activity and obesity-linked medical comorbidities in these patients were supposed to contribute in the management complexity and to negatively affect long-term outcomes[6,8]. Even though this special population is characterized with the low-grade, early-stage, and good prognostic endometrioid type endometrial cancers, their mortality seems to be higher compared with their normal weight (kg) counterparts[5,8-10]. However, the underlying reason and mechanism for this condition is uncertain. In other words, it is not clear whether obesity itself has a negative prognostic influence on endometrial cancer or its comorbidities that lead to such a result[3,5]. Furthermore, there are insufficient studies on the issue, focusing on morbidly obese patients (BMI ≥40 kg/m^2) with endometrial cancer. In the present study, the impact of morbid obesity on the survival of endometrial cancer was investigated.

Materials and Methods

The archival records and pathologic reports of patients with endometrial cancer who underwent surgery and were followed up in Çukurova University Gynecologic Oncology Center between January 1996 and December 2018, were reviewed, retrospectively. Data regarding BMI and survival was reached in 520 patients. These patients were stratified into two groups according to their BMI, <40 and ≥40. BMI [kg/height (m)]^2 was calculated and classified regarding to the WHO guidelines. Thus, patients with BMI ≥40 kg/m^2 were identified as morbidly obese. The groups' clinic, pathologic features, and survival rates were compared. Compared variables included age, comorbidities, surgical approach, surgical procedure, perioperative and postoperative complications including wound infections, hospitalization time, tumor size, histologic type, stage, grade, myometrial invasion, retroperitoneal lymph node (LN) involvement, yielded LN count, lymphovascular space invasion, adjuvant treatments, and follow-up data.

This study was performed in accordance with the ethical standards of the Helsinki Declaration. Ethical approval was not obtained for this study because of its retrospective nature. A informed consent was obtained routinely.

The main surgical procedures were total hysterectomy-bilateral salpingo-oophorectomy (via laparotomy or laparoscopy) with or without pelvic and para-aortic lymphadenectomy according to the intraoperative frozen section result. Intraoperative frozen section was applied for all included cases, and a decision whether to pursue lymphadenectomy was taken based on its results. Lymphadenectomy was not performed in patients with stage 1a, International Federation of Gynecology and Obstetrics (FIGO) grade 1-2, and <2 cm tumors (low-risk factors). Lymphadenectomy (± omentectomy) was considered in the presence of any of the following: endometrioid adenocarcinoma grade 3, tumor diameter >2 cm, ≥50% myometrial invasion, stage >1a or non-endometrioid histologies. Adjuvant therapies (brachytherapy, external beam radiotherapy and/or chemotherapy) were kept in view for patients with ≥ intermediate risk factors. All specimens were assessed by gynecologic pathologists. Comorbidities were accepted as any concomitant chronic disease. The FIGO 2009 staging guideline for endometrial cancer was used[11]. Stage of cases operated before 2009 was rearranged according to this recent staging system. Grade was also identified according to the 1988 FIGO grading system[11,12]. The period between the date of the histopathologic diagnosis and recurrence was identified as disease-free survival (DFS). Overall survival (OS) was considered to be the time between the date of the histopathologic diagnosis and date of death from any cause.

Statistical Analysis

Data were analyzed using the SPSS software version 23.0 (IBM, Armonk, NY, USA). Descriptive analyses are presented as mean ± standard deviation, number and percentage. Normally distributed continuous variables were analyzed using Student's t-test. Categorical data were analyzed using the chi-square test or Fisher's Exact test. Survival analysis was realized using the Kaplan-Meier method and the differences in the survival curves were calculated through the log-rank test. The significance of multiple variables was assessed using the Cox proportional hazard model. P-values were considered significant at the level <0.05.

Results

The groups' characteristics are summarized in Table 1. Unlike age, comorbidities and LN dissection, all clinical, surgical, and pathologic variables were identical between the groups. The mean age of the morbidly obese group and obese group was 58.5±10 years and 56.3±10.7 years, respectively (p=0.033). The rate of comorbidities was significantly higher in the morbidly obese group compared with the obese group (64.6% vs 53.2%, respectively, p=0.020).

More than half of the patients in both groups underwent laparoscopic surgery, 55.5% of the patients with morbid obesity and 54.8% obese group. No difference between the groups was observed with respect to the surgical approach (p=0.895). Wound infections were developed in 6.3% of the morbidly obese group and in 3.5% of the obese group.

Table 1. Patients' characteristics

Variables		Body mass index		p
		<40	≥40	
Age (mean ± SD)		56.29±10.7	58.52±10.0	0.0033
		n (%)	n (%)	
Comorbidities	**No**	174 (46.8)	51 (35.4)	0.020
	Yes	198 (53.2)	93 (64.6)	-
Surgical approach	**LT**	168 (45.2)	65 (44.5)	0.895
	LS	204 (54.8)	81 (55.5)	-
Intraoperative complications	**No**	361 (97.0)	141 (96.6)	0.203
	Bleeding	6 (1.6)	2 (1.4)	-
	Urinary injury	1 (0.3)	3 (2.1)	-
	Intestinal injury	3 (0.8)	0 (0.0)	-
	Others	1 (0.3)	0 (0.0)	-
Postoperative complications	**No**	355 (95.4)	133 (92.4)	0.564
	Infection	13 (3.5)	9 (6.3)	-
	Urinary complications	0 (0.0)	0 (0.0)	-
	Intestinal complications	2 (0.5)	1 (0.7)	-
	Others	2 (0.5)	1 (0.7)	-
MI	**No**	205 (55.0)	106 (72.6)	<0.001
	Pelvic	39 (10.5)	14 (9.6)	-
	Pelvic + Paraaortic	129 (34.6)	26 (17.8)	-
Histopathology	**Endometrioid**	283 (76.1)	119 (81.5)	0.182
	Non-endometrioid	89 (23.9)	27 (18.5)	-
Grade	**1**	196 (60.7)	79 (58.5)	0.578
	2	104 (32.2)	49 (36.3)	-
	3	23 (7.1)	7 (5.2)	-
Stage	**Uterus confined (stage 1-2)**	317 (85.4)	127 (87.0)	0.650
	Extrauterine spread (stage 3-4)	54 (14.6)	19 (13.0)	-
MI	**<50**	242 (69.7)	91 (65.9)	0.416
	≥50	105 (30.3)	47 (34.1)	-
LVSI	**No**	249 (68.2)	94 (65.3)	0.326
	Yes	116 (31.8)	50 (34.7)	-
LND involvement	**Negative**	310 (89.9)	124 (93.9)	0.163
	Positive	35 (10.1)	8 (6.1)	-
Adjuvant treatments	**No**	226 (61.6)	88 (61.1)	0.922
	Yes	141 (38.4)	56 (38.9)	-

LT: Laparotomy, LS: Laparoscopy, SD: Standard deviation, LND: Lymph node dissection, MI: Myometrial invasion, LVSI: Lymphovascular space invasion

However, there was no significant difference between the groups according to the intraoperative and postoperative complications including wound infections. Pelvic and para-aortic lymphadenectomy was performed less frequently in the morbidly obese group compared with the obese group (17.8% vs 34.6%, respectively). However, it should be noted that comparable lymphadenectomy ratios of both groups were recorded when pelvic LN dissection was performed exclusively (9.6% and 10.5%, respectively).

Endometrioid type endometrial cancer was found in 81.5% of the morbidly obese group and 76.1% the obese group. With respect to the histopathologic type, no significant difference was determined between the groups (p=0.182). There was also no difference regarding to grade distribution between the groups (p=0.578). Most cases of both groups were confined to the uterus, 87% of the morbidly obese group and 85.4% of the obese group, without a significant difference (p=0.650). The myometrium was invaded less than 50% in 65.9% and 69.7% of the morbidly obese group and obese group, respectively. No significantly difference was detected between the groups in terms of myometrial invasion (p=0.416). The ratio of lymphovascular space invasion was also not significantly different between the groups; 34.7% in the morbidly obese group and 31.8% in the obese group. The involved LN rate was 6.1% in the morbidly obese group and 10.1% in the obese group, with no significant difference (p=0.163). Furthermore, there was no significant difference between the groups concerning adjuvant treatments (p=0.922) (see Table 1).

The mean follow-up period was 51 months. The 5-year OS of the morbidly obese group and obese group was 85.3% and 90.1%, respectively (p=0.054). The 5-year DFS of the morbidly obese group was 78.3% and 81.6% in the obese group, and this difference was relatively significant (p=0.053). The survival curves of the groups are demonstrated in Figure 1. Significant variables determined with the univariate analysis were assessed using a Cox regression hazard model (Table 2). Comorbidities, stage, and BMI were detected as independent prognostic factors for OS. For DFS, only myometrial invasion and BMI were found to be independent prognostic factors. Patients with endometrial cancer who were morbidly obese were associated with 2.7-fold (1.11-6.58; p=0.028) increased risk of death and 1.7-fold (1.02-3.07; p=0.042) increased risk of recurrence compared with those who had a BMI <40 kg/m^2.

Discussion

Obesity, and morbid obesity in particular, is a growing issue around the world. Obesity is a well-known predisposing factor for several metabolic diseases, as well as various malignancies[4,13]. It was reported that compared with the normal-kg population, patients with BMI >40 kg/m^2 were associated with a 60% higher risk of death from all cancers[8,9]. Additionally, obesity was considered as a risk factor for recurrence in various malignancies such as breast, colon, and prostate cancers[14]. The robust association between obesity and endometrial cancer risk has been emphasized in many studies[3,4,14]. It was reported that patients with morbid obesity had a 9-fold increased risk for endometrial cancer as compared with the normal-kg population[4]. However, even though there are limited studies in which the effect of obesity on the long-term outcomes of endometrial cancer were evaluated, morbid obesity was not taken into account separately in most of them. In the current study, the impact of morbid obesity on the survival of the endometrial cancer was exclusively investigated. Herein, we found a tendency toward lower DFS (p=0.053) and OS (p=0.054) in patients with morbid obesity compared with those with a BMI <40 kg/m^2. Furthermore, morbid obesity was detected to be an independent prognostic factor for both DFS and OS.

In a prospective cohort study with more than 900,000 participants, the relative risk of death from endometrial cancer for patients with BMI 30-34 and >40 kg/m^2 was recorded as 2.53 and 6.25, respectively[9]. Arem and Irwin[3] reported that worse survival was noticed in four studies included in their review, and risk was greatest (1.86-2.76) in women with morbid obesity. In a Gynecologic Oncology Group study, von Gruenigen et al.[14] determined that obesity was related to an increased risk of mortality but not increased recurrence

Table 2. Multivariate analysis of age adjusted overall survival and disease-free survival

Covariates	HR (95% CI)	
	OS	DFS
Grade 1	Ref	Ref
Grade 2	0.330 (0.086-1.264)	0.668 (0.269-1.659)
Grade 3	0.555 (0.177-1.738)	0.516 (0.210-1.270)
Comorbidities	**8.379 (2.400-29.259)**	1.574 (0.935-2.650)
LVSI	0.725 (0.247-2.135)	0.826 (0.395-1.729)
Adjuvant treatments	1.556 (0.416-5.823)	1.147 (0.511-2.577)
MI	2.236 (0.708-7.068)	**2.328 (1.030-5.263)**
Histology	1.982 (0.750-5.241)	1.361 (0.716-2.589)
LN involvement	0.623 (0.135-2.880)	2.502 (0.711-8.797)
Stage	**3.394 (1.008-11.426)**	1.143 (0.400-3.262)
BMI	**2.709 (1.115-6.579)**	**1.770 (1.020-3.071)**
No LND	Ref	Ref
Pelvic LND	1.339 (0.453-3.959)	1.508 (0.723-3.143)
PPALND	2.220 (0.609-8.096)	0.877 (0.328-2.345)
Surgical route	0.546 (0.218-1.367)	1.017 (0.586-1.765)

HR: Hazard ratio, CI: Confidence interval, OS: Overall survival, DFS: Disease-free survival, LVSI: Lymphovascular space invasion, MI: Myometrial invasion, LN: Lymph node, BMI: Body mass index, LND: Lymph node dissection, PPALND: Pelvic-paraaortic lymph node dissection

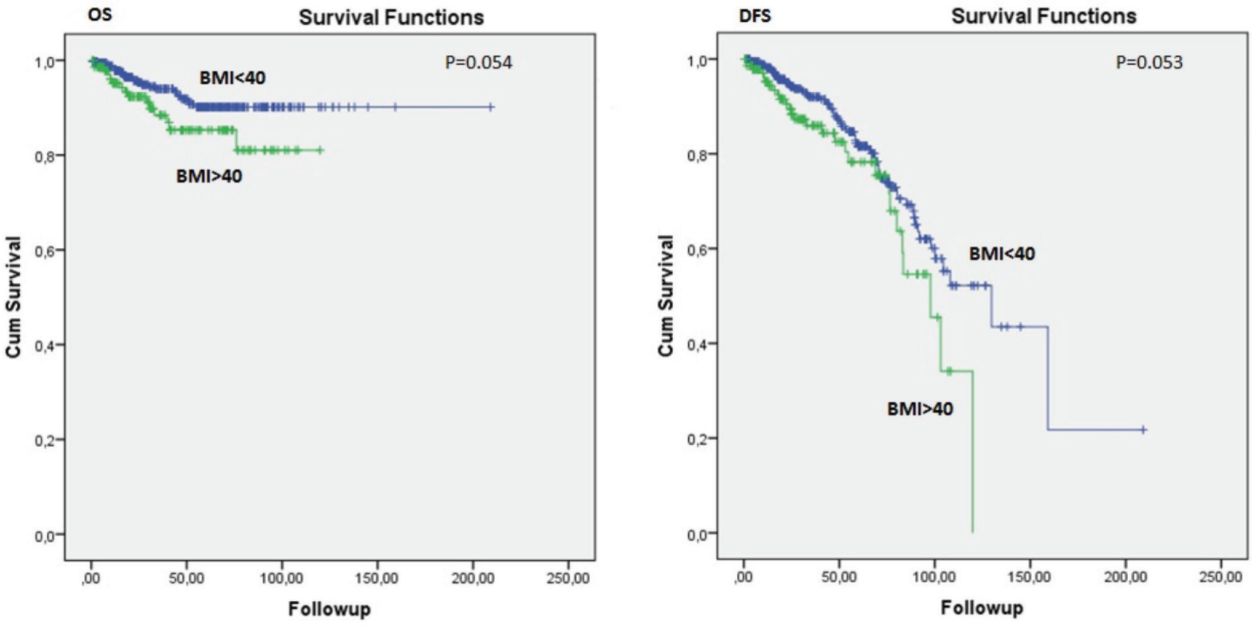

Figure 1. Survival curves of the groups

DFS: Disease-free survival, OS: Overall survival, BMI: Body mass index

rates in patients with early-stage endometrial cancer. Also, the ancillary data analysis of the Gynecologic Oncology Group LAP2 study illustrated that obesity was linked to all-cause mortality but not cancer-specific mortality[5]. By contrast, in our study, morbidly obese patients with endometrial cancer were compared with obese patients with endometrial, not only with the normal-kg women with endometrial cancer. In other words, solely morbid obesity was the point of our study, likely leading to the difference with the abovementioned studies concerning DFS. In addition, all women, regardless of disease stage, not only patients with early-stage endometrial cancer, were included in our study.

Several arguments have been proposed to explain the rationale of the association between obesity and mortality in women with endometrial cancer[15]. Medical conditions such as hypertension, diabetes, and cardiovascular diseases, the increased surgical complexity, operation time, and blood loss were suggested as influencers in this relationship[3,16-18]. Moreover, physiologic alterations including chronic inflammation, insulin resistance, changes in lipid and hormone profiles in patients with obesity were offered as mediators for this association[3,19]. Conversely, some studies failed to demonstrate a relationship between obesity and endometrial cancer prognosis[3,13]. It would not be fair to attribute the worse survival in these patients to the obesity-linked tumor prognostic features because endometrial cancer tends to be with favorable grade and histology in obese women. However, it should be remembered that this association could harbor multiple confounders such as age, patient, and tumor characteristics[15]. Temkin et al.[13] stated that BMI was not an independent prognosticator for survival of endometrial cancer, and the attributed favorable potency was because of younger age, low grade, and early stage of the tumor, not due to obesity itself. Furthermore, it was shown in some studies that BMI was not an independent predictor for endometrial cancer stage[13,15,20]. Therefore, LN evaluation should not be omitted thanks to the favorable-disease-argument in women with obesity. However, serious technical difficulties of lymphadenectomy in patients with morbid obesity should be kept in mind. In our study, pelvic lymphadenectomy was comparable between the groups, but para-aortic LN dissection was significantly lower in the morbidly obese group compared with the obese group. Despite the relative high rate of lymphadenectomy in both groups of our study, no difference between them was detected in terms of per- and postoperative complications, and these findings were commensurate with some literature studies, but not with others[21].

Beyond the association between obesity and survival, there is robust evidence of increased quality of life of patients with endometrial cancer made through lifestyle alterations such as physical activity, kg, and diet[3,22]. Higher health-related quality of life was reported in patients who followed more dedicated lifestyle recommendations[22-24].

Study Limitations

The retrospective nature and its potential biases are the main weaknesses of our study. However, the limitation the study population to women with morbid obesity, the large cohort from a single academic cancer center, surgery and evaluation of all cases by the same team of gynecologic oncologists and

gynecologic pathologists, and the long follow-up period were the main strengths.

Conclusion

Patients with endometrial cancer who were morbidly obese tended to have worse OS and DFS compared with women who were obese (BMI <40 kg/m^2). BMI >40 kg/m^2 was determined to be an independent prognostic factor for both OS and DFS. Stage and comorbidities were also detected as independent prognosticators for OS. Keeping in mind that comorbidities and BMI are modifiable factors, efforts in this population should be focused on medical optimization and lifestyle alterations, particularly kg loss.

Ethics

Ethics Committee Approval: Ethical approval was not obtained for this study because of its retrospective nature.
Informed Consent: A informed consent was obtained routinely.
Peer-review: Externally peer-reviewed.

Author Contributions

Concept: A.B.G., G.K., Design: M.A.V., D.G., Data Collection and Processing: G.K., Ü.K.G., Analysis or Interpretation: A.B.G., G.K., Ü.K.G., D.G., M.A.V., Literature Review: A.B.G., G.K., Ü.K.G., Writing: A.B.G., G.K., Ü.K.G.
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Prevelance of upper extremity lymphedema and risk factors in patients with mastectomy: Single-center, observational, cross-sectional study

Mastektomili hastalarda üst ekstremite lenfödem prevelansı ve risk faktörleri: Tek merkezli, gözlemsel, kesitsel çalışma

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Abstract

Objective: Upper extremity complaints are frequently encountered in breast cancer. It was aimed to investigate the pain, extremity pain, and limitation of motion, lymphedema prevalence, severity, risk factors and quality of life in patients with breast cancer followed by mastectomy in our center.

Materials and Methods: The study included 67 patients with mastectomy. The presence of lymphedema, lymphedema duration, and grade of lymphedema were recorded. Grip strength was measured on both hands using a dynamometer; arm, shoulder and hand problems were evaluated using the disabilities of the arm, shoulder, and hand. Quality of life was assessed using the World Health Organization Quality of Life scale-short form.

Results: The presence of lymphedema was 23.9%; the most common was international society of lymphology grade 1 (76.1%); the median lymphedema duration was 12 (range, 3-72) months. Radical/modified radical mastectomy (58.2%) was the most common type of surgery. Median pain score in the affected extremity according to the visual analogue scale was 2 (minimum: 0/maximum: 7); the presence of shoulder pain was 40.3%; shoulder movement limitation was 7.5%.

Conclusion: It was found that lymphedema had a negative effect on quality of life by affecting shoulder, arm, and hand functions even in the early stages. The recognition of risk factors and signs of upper extremity complications in breast cancer survivors will contribute to rehabilitation success.

Keywords: Breast cancer, lymphedema, rehabilitation

Öz

Amaç: Meme kanserinde üst ekstremite şikayetlerine sıkça rastlanmaktadır. Merkezimizde meme kanseri sonrası hastalarda ağrı, ekstremite ağrısı ve hareket kısıtlılığı, lenfödem prevalansı, ciddiyeti, risk faktörleri ve yaşam kalitesinin incelenmesi amaçlandı.

Gereç ve Yöntemler: Çalışmaya mastektomi operasyonu yapılan 67 hasta alındı. Katılımcıların lenfödem varlığı, lenfödem süresi, lenfödem derecesi kaydedildi. Dinamometre ile her iki elde kavrama gücü ölçüldü; kol, omuz ve el sorunları kol, omuz ve el özürlülükleri kullanılarak değerlendirildi. Yaşam kalitesi, Dünya Sağlık Örgütü Yaşam Kalitesi ölçeği-kısa formu ile değerlendirildi.

Bulgular: Lenfödem varlığı %23,9 idi; en yaygın olanı uluslararası lenfödem topluluğu grade 1 (%76,1) idi; median lenfödem süresi 12 aydı (3-72 ay). Radikal/modifiye radikal mastektomi (%58,2) en sık görülen cerrahi tipti. Etkilenen ekstremitede görsel analog skalaya göre ağrı ortanca= 2 cm (minimum: 0/maksimum: 7 cm); omuz ağrısı varlığı %40,3 idi; omuz hareket kısıtlılığı %7,5 idi.

Sonuç: Lenfödemin erken dönemde bile omuz, kol ve el fonksiyonlarını etkileyerek yaşam kalitesini olumsuz yönde etkilediği bulundu. Meme kanseri sağkalımlarında risk faktörlerinin ve üst ekstremite komplikasyon belirtilerinin tanınması rehabilitasyon başarısına katkıda bulunacaktır.

Anahtar Kelimeler: Meme kanseri, lenfödem, rehabilitasyon

PRECIS: Upper extremity lymphedema in patients with mastectomy.

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Introduction

Lymphedema is a localized tissue swelling caused by the excessive retention of lymphatic fluid in the interstitial space and is caused by impaired lymphatic drainage. It is classified as primary or secondary. Primary lymphedema is caused by developmental lymphatic vascular anomalies; secondary lymphedema is acquired and is caused by an underlying cause, such as systemic disease, trauma, or surgery. This progressive chronic disease has serious effects on the quality of life of the affected person. It mimics other conditions that cause extremity swelling and is often misdiagnosed. There is no definitive cure for lymphedema. However, with proper diagnosis and management, progression and possible complications can be prevented[1,2].

In the near future, developing countries will face a rapid increase in the number of individuals in the elderly population. In the next 20 years, the average age will reach 50 years and individuals aged over 65 years will form a significant part of society. The incidence of breast cancer increases with age, the risk of breast cancer reaches 0.44% at age 30 years, 3.82% at age 70 years, and 10% at the age of 80 years[3]. Recent studies have noted that a large portion of older patients do not receive conventional treatment for breast cancer. They are frequently treated with breast conservation, omitting axillary dissection, radiation therapy, and chemotherapy[4]. The development of upper extremity lymphedema following axillary lymph node (LN) dissection in patients with breast cancer is reported in 16-40% of cases. Lymphedema may develop in 3.5% of cases following sentinel LN biopsy alone[5]. Regional LN dissection is an important risk factor for the development of upper extremity lymphedema in patients with breast cancer, but there are insufficient tools to accurately measure the risk of lymphedema in individuals. Body mass index (BMI), the extent of axillary surgery, the number of LNs, and the width of the nodal radiation can be counted among the affecting risk factors[6,7]. Lymphedema adversely affects the quality of life in young women of active working age who are treated for breast cancer[8].

The prevalence of lymphedema in patients with surgical breast cancer is high and difficult to treat. There is limited literature information about additional risk factors such as LN dissection and BMI, infection, and radiation in its formation[1-8]. The aim of this study was to investigate the pain, extremity pain and limitation of motion, lymphedema prevalence, severity, risk factors, and the effect on quality of life in patients with breast cancer followed by mastectomy in our center.

Materials and Methods

The study was planned prospectively and as cross-sectional reasearch. The study included 67 patients with mastectomy who were followed up in the oncology outpatient clinic. Participants' age, BMI, smoking, education level, breast cancer diagnosis time, histopathologic type, tumor stage, surgical procedure, postoperative time, number of positive LNs, affected arm, dominant hand, upper extremity diameter difference, presence of lymphedema, lymphedema duration, grade of lymphedema, history of infection in the affected extremity, shoulder pain on the affected side, severity of pain [visual analogue scale, (VAS) 0-10], and presence of shoulder movement limitation were recorded. The presence of lymphedema was determined objectively according to the diameter difference in extremity circumference measurements, which were defined as standard in both arms. Patients without lymphedema were accepted as grade 0. Grip strength was measured in both hands using a dynamometer (kg); arm, shoulder, and hand problems in the affected extremity were evaluated using the disabilities of the arm, shoulder, and hand (DASH) and Tampa scale for kinesiophobia (TSK). Quality of life was assessed using the World Health Organization Quality of Life scale-short form (WHOQOL-bref). Neuropathic symptoms such as dysesthesia and anesthesia were not questioned.

The inclusion criteria were: (1) having undergone mastectomy over the age of 18 years for unilateral breast cancer. The exclusion criteria were (1) a history of cognitive dysfunction, (2) upper extremity orthopedic surgery or trauma, (3) bilateral involvement, and (4) a history of neuropathic or myopathic disease that might cause muscle weakness. Data were recorded by the same experienced physician. The study was approved by the local Medical Research Ethics Committee (protocol no: 2019/185). Informed and written consent was obtained from all participants.

Outcome Measures

Clinical Stage of Lympedema

The clinical stage of lymphedema was determined according to the International Society of Lymphology (ISL). Patients without apparent symptoms were graded as stage 0 because all patients who underwent axillary LN dissection were considered to have impaired lymph transport.

Stage 0: A latent or subclinical condition in which limb swelling is not yet evident.

Stage I: An early accumulation of fluid that subsides with limb elevation.

Stage II: Tissue swelling that is not reduced by limb elevation alone. Pitting is manifested in earlier stage II, but the limb may or may not pit in later stage II because excess fat and fibrosis supervene.

Stage III: Lymphostatic elephantiasis in which pitting can be absent and trophic skin changes, such as acanthosis, further deposition of fat and fibrosis, and watery overgrowths, have developed.

Upper Extremity Diameter Measurements

Lymphedema of the upper extremity was evaluated using the circumferential method. The circumferential upper extremity measurements were performed with the arm abducted at 30°, starting at the level of the carpometacarpal joint, every 5 cm

proximal to this point along both extremity[9]. Interextremity volume difference was defined as edema.

DASH Questionnaire

DASH is a self-report questionnaire that detects physical function and symptoms in people with musculoskeletal disorders of the upper extremity. DASH has 30 items, and each item is scored on a Likert scale from 1 to 5 where 1 reflects 'no difficulty' and 5 'severe difficulty.' Scores are transformed to a 0-100 scale with higher DASH scores indicating greater disability. This instrument assesses physical functions, symptoms, and social functions. The optional four items related to work or sports activities were not used for this study[10]. The Turkish validity and reliability study of DASH has been conducted by Duger et al.[11].

Grip Strength

The grip strength of the upper extremities was measured using a handheld kg (model 5030J1, Sammons Preston Rolyan, Bolingbrook, IL, USA) in the standardized recommended position by American Society of Hand Therapy, with a rest period of 20 seconds; three trials were performed and the mean values were recorded.

TSK

Kinesiophobia is a term that was introduced by Miller, Kori and Todd in 1990 at the Ninth Annual Scientific Meeting of the American Pain Society, and it describes a situation where "A patient has an excessive, irrational, and debilitating fear of physical movement and activity resulting from a feeling of vulnerability to painful injury or reinjury." TSK is a 17-item questionnaire used to assess the subjective rating of kinesiophobia or fear of movement. The original questionnaire was developed to "discriminate between non-excessive fear and phobia among patients with chronic musculoskeletal pain." Several studies have found the scale to be a valid and reliable psychometric measure. As the score increases, the severity of kinesiophobia increases[12,13].

WHOQOL-BREF

WHOQOL-BREF produces scores for four domains related to quality of life: physical health, psychological, social relationships and environment. It also includes one facet on overall quality of life and general health. WHOQOL-BREF provides a valid and reliable alternative to the assessment of domain profiles using the WHOQOL-100. It is envisaged that the WHOQOL-BREF will be most useful in studies that require a brief assessment of quality of life, for example, in large epidemiologic studies and clinical trials where quality of life is of interest[14].

Statistical Analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows version 20.0 software (IBM Corp., Armonk, NY, USA). The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov test) to determine whether they were normally disturbed. Analysis of the characteristics of patients was performed using descriptive studies. Analysis of variance was used to compare the groups. Spearman test was used for correlation analysis. A multiple linear regression model was used to identify independent predictors of lympedema presence. A p-value 0.05 was considered as statistically significant.

Results

The study included 67 women with a median age of 50.4±11.2 years median =36 months who had been diagnosed and usergone surgery for breast cancer. The sociodemographic data of the participants are summarized in Table 1. The presence of lymphedema was 23.9%; the most common was ISL grade 1 (76.1%); the median lymphedema duration was 12 (range, 3-72) months. The majority of the participants were primary school graduates (40.3%). Radical/modified radical mastectomy (58.2%) was the most common type of surgery. The mean number of positive LNs was 13.2±11.5. The median tumor stage was 2 (range, 1-4) and 62.6% were invasive ductal carcinoma. The most frequently involved side was the right arm with a rate of 55.2%. The median pain in the affected extremity according to the VAS scale was 2 (minimum: 0/maximum: 7); the rate of shoulder pain was 40.3%; the rate of shoulder movement limitation was 7.5%; and the mean DASH score was 65.1±20.8. The mean general health score was 6.4±1.6; physical health score was 23.2±4.8; psychological health score was 22 (11-29); social health score was 10.5±2.2; environmental health score was 28.9±5.1; and total WHOQOL score was 89.3±12.7. The mean TSK was 40.4±7.7. Only three patients had a history of infection (4.5%) in the affected extremity.

When we divided the groups into 4 groups according to ISL lymphedema grading, the patients' number distributions were not homogeneous (grade 0, n=51; grade 1, n=7; grade 2, n=8; grade 3, n=1), pain (VAS) in the affected extremity (p=0.01); shoulder pain (p=0.05); limitation of movement in the shoulder (p<0.001); WHOQOL total score (p=0.01); physical health score (p=0.09); psychological health score (p=0.07); social health score (p=0.08); and environmental health score (p=0.01) were significantly different between the groups (Table 2).

Advanced age was positively correlated with the number of positive LNs extracted and DASH score, and was negatively correlated with hand grip strength hand and social health score. The duration of diagnosis was positively correlated with the duration of lymphedema and negatively correlated with the social health score. The VAS score of the affected extremity was positively correlated with lymphedema duration, WHOQOL total score, and DASH, and was negatively correlated with general health, physical, psychological health score, hand grip stregth. Lymphedema duration was positively correlated with VAS score, social and total WHOQOL score, and negatively with hand grip strength. The number of positive LNs extracted was positively correlated with postoperative duration and TSK,

Table 1. Descriptive characteristics of the study group

Parameter	n=67 n/%/mean ± SD/median (min-max)
Age (year)	50.4±11.2
BMI (kg/m^2)	30±4.6
Smoking	1/1.5
Education level	
Illiterate	16/23.9
Elementary school	27/40.3
Secondary school	1/1.5
High school	14/20.9
Postdoc/university	9/13.4
Duration of diagnosis (months)	36 (range, 3-240) months
Stage of breast cancer	2 (1-4)
Type of the surgery	
Breast conserving	22/32.8
Radical mastectomy	39/58.2
Number of positive lymph node	13.2±11.5
Invasive ductal carsinoma	42/62.6
Postoperative duration (months)	36 (2-240)
Affected extremity	
Right	37/55.2
Left	30/44.8
Dominant hand	
Right	61/91
Left	6/9
Difference of diameter (cm)	0 (0-9)
Presence of lymphedema	16/23.9
Grade of lymphedema	
0	51/76.1
1	7/10.4
2	8/11.9
3	1/1.5
History of infection	3/4.5
Duration of lymphedema (months)	12 (3-72)
Pain of the affected extremity (VAS: 0-10 cm)	2 (0-7)
Shoulder pain	27/40.3
Limitation of shoulder movement	5/7.5
Grip strength (right) (kg)	18.7±6
Grip strength (left) (kg)	19.1±6.8
DASH score	65.1±20.8
WHOQOL score (total)	89.3±12.7
General health score	6.4±1.6
Physical health score	23.2±4.8
Psychologicalhealth score	22 (11-29)
Social health score	10.5±2.2
Environmental health score	28.9±5.1
TSK	40.4±7.7

SD: Standard deviation, BMI: Body mass index, DASH: Disabilities of the arm, shoulder, and hand, TSK: Tampa scale for kinesiophobia, WHOQOL: World Health Organization Quality of Life scale, TSK: Tampa scale for kinesiophobia, VAS: Visual analog scale, min: Minimum, max: Maximum

and negatively correlated with hand grip strength. Postoperative duration was positively correlated with lymphedema duration and negatively correlated with social health score. The difference in diameter between extremities was negatively correlated with psychological health score.

Hand grip strength was negatively correlated with DASH and TSK, and positively correlated with general health, physical health, social health, environmental health, and total WHOQOL scores. DASH score was positively correlated with TSK, and negatively correlated with general health, physical health, psychological health, social, environmental and total WHOQOL scores. BMI was negatively correlated with general health and psychological health. Lymphedema grade was positively correlated with extremity diameter difference and duration of lymphedema, and negatively correlated with psychological, environmental health, and total WHOQOL scores. Statistically significant correlation results only are summarized in Table 3.

Multiple logistic regression analysis showed that the number of extracted positive LNs (beta=0.575; p=0.10); DASH score (beta=-0.266; p=0.013); total WHOQOL score (beta=3.712; p=0.001); and the duration of breast cancer diagnosis (beta=-2.257; p=0.031) were found to be significant predictors of lymphedema presence.

Discussion

Breast cancer is one of the most common cancers among women. Upper extremity lymphedema is the riskiest and most frequent complication that occurs following breast cancer surgery (20%), causing irreversible and functional, psychological, and social problems[15]. It is proportional to axillary surgery and radiation. Sentinel LN biopsy is the option for elective axillary LN dissection in patients with clinical node-negative early-stage breast cancer. Other risk factors are obesity and infection. Minimizing axillary surgery and radiation reduces the risk. Early physical therapy, weight loss, skin and

Table 2. Analytic characteristics of the groups accroding to grade of the lymphedema

Parameter	Lymphedema grade 0 n=51 n/%/mean/median	Lymphedema grade 1 n=7 n/%/mean/median	Lymphedema grade 2 n=8 n/%/mean/median	Lymphedema grade 3 n=1 n/%/mean/median	p
Age (year)	49.3±10.9	54.5±14.1	50.5±8.5	73	0.14
BMI (kg/m^2)	29.6±4.7	29.6±3.4	32.9±5.1	31.02	0.31
Smoking	1	0	0	0	0.96
Education					
Illiterate	11/21.6	2/28.6	2/25	1	
Elementary school	23/45.1	3/42.9	1/12.5	0	0.66
Secondary school	0	0	1/12.5	0	
High school	10/19.6	0	4/50	0	
Postdoc/university	7/13.7	2/28.6	0	0	
Duration of diagnosis (months)	38.1±41.2	9.4±4.9	51±21	48	0.17
Stage of breast cancer					
Stage 1	2 (1-3)	2 (2-4)	2 (1-3)		
Stage 2	17/33.3	0	2/25	0	0.75
Stage 3	10/19.6	1/14.3	3/37.5	0	
Stage 4	9/17.6 6/11.8	0 4/57.1	2/25 0	0 0	
Type of the surgery					
Breast conserving	19/37.3	1/14.3	2/25	0	0.98
Radical mastectomy	30/58.8	4/57.1	6/75	1	
Number of positive lymph node	13.4±11.6	8.7±15.5	14.7±9.3	-	0.7
Postoperative duration (months)	36 (2-240)	5 (3-12)	51±21	48	0.12
Pain of the affected extremity (VAS: 0-10 cm)	0 (0-7)	0 (0-7)	4 (0-5)	7	0.01*
Shoulder pain presence	1	1/14.3	6/75	19/37.03	0.05*
Affected extremity					
Right	28/54.9	4/57.1	5/62.5	1	-
Left	23/45.1	3/42.9	3/37.5		
Dominant hand					
Right	49/96.1	5/71.4	6/75	1	-
Left	2/3.9	2/28.6	2/25		
Limitation of shoulder movement	4/7.8	0	0	1	<0.001*
Grip strength (right) (kg)	19.1±5.8	17.5±8.1	18.4±5.6	12	0.64
Grip strength (left) (kg)	19.4±6.8	17.7±7.6	20.3±6	7	0.29
DASH score	63.7±22.5	68.2±15.2	73.3±6.9		0.54
WHOQOL score (total)	90.9±11.8	93±17.9	75.5±4.8		0.01*
General health score	6.5±1.7	7±1	5.8±0.7		0.47
Physical health score	23.8±4.8	22.8±4.8	19.3±1.8		0.09*
Psychologicalhealth score	23 (11-29)	21 (17-25)	18 (17-23)		0.07*
Social health score	10.7±2.1	11.2±2.9	8.6±1.2		0.08*
Environmental health score	29.4±4.7	31±6.4	23.3±.1		0.01*
TSK	40.8±8	37.3±2.8	39.8±7.4		0.74

BMI: Body mass index, DASH: Disabilities of the arm, shoulder, and hand, TSK: Tampa scale for kinesiophobia, WHOQOL: World Health Organization Quality of Life scale, TSK: Tampa scale for kinesiophobia, VAS: Visual analog scale, *: p>0.05, statistically difference, ANOVA test

Table 3. Correlation analysis of the parameters (*only statistically significant results)

		rho	p
Age	Number of positive lymph node	0.351	0.012
	Duration of lympedema	0.602	0.05
	Grip strength right	-0.5	<0.001
	Grip strength left	-0.459	<0.001
	DASH score	0.287	0.035
	Social health score	-0.284	0.041
Duration of diagnosis→	Duration of lymphedema	0.893	<0.001
	Social health score	-0.465	0.001
VAS score→	Duration of lymphedema	0.771	0.005
	General health score	-0.317	0.021
	Physical health score	-0.454	0.001
	Psychological score	-3.654	0.008
	Total WHOQOL score	0.534	0.001
	DASH score	0.546	<0.001
	Grip strength right	-0.342	0.005
	Grip strength left	-0.335	0.006
Duration of lymphedema→	VAS score	0.771	0.005
	Social health score	0.781	0.038
	Total WHOQOL score	0.781	0.038
	Grip strength right	-0.726	0.011
Number of positive lymph node→	Postoperative duration	0.334	0.017
	Grip strength right	-0.278	0.048
	TSK	0.329	0.047
Postoperative duration	Duration of lymphedema	0.852	0.001
	Social health score	-0.569	<0.001
Difference of extremity diameter→	Psychological score	-0.325	0.019
Grip strength right→	DASH score	-0.385	0.004
	General health score	0.370	0.006
	Physical health score	0.465	<0.000
	Social health score	0.352	0.011
	Environmental score	0.438	0.001
	Total WHOQOL score	0.406	0.003
	TSK	-0.326	0.0027
Grip strength left→	DASH score	-0.303	0.026
	Physical health score	0.379	0.005
	Social health score	0.300	0.003
	Environmental score	0.459	0.001
	Total WHOQOL score	0.356	0.01

Table 3. Continued

		rho	p
DASH score→	General health score	-0.414	0.002
	Physical health score	-0.501	0.001
	Psychological health score	-0.499	<0.001
	Social health score	-0.283	0.042
	Environmental health score	-0.312	0.024
	Total WHOQOL score	-0.549	<0.001
	TSK	0.521	<0.001
BMI→	General health score	-0.293	0.033
	Psychological health score	-0.303	0.029
Grade of lymphedema	Difference of extremity diameter	0.984	<0.001
	Duration of lymphedema	0.878	<0.001
	Psychological health score	-0.367	0.007
	Environmental health score	-0.291	0.036
	WHOQOL total score	-0.351	0.011

BMI: Body mass index, DASH: Disabilities of the arm, shoulder, and hand, TSK: Tampa scale for kinesiophobia, WHOQOL: World Health Organization Quality of Life scale, TSK: Tampa scale for kinesiophobia, VAS: Visual analog scale, *: p<0.05, statistically significance

nail care after surgery are cornerstones of treatment in early-stage lymphedema. Late-stage lymphedema may benefit from plastic surgery[16]. Women with breast cancer also report upper extremity symptoms (shoulder pain, limitation of motion in the shoulder, paresthesia, axillary web syndrome, loss of strength) at rates ranging from 10-64%[17,18]. In our study, the frequency of shoulder pain was close to half of the patients and limitation of motion in the shoulder was one-sixth. Pain in the affected extremity was median 2 (VAS: 0-10 cm). Pain, shoulder pain, and limitation of motion in the shoulder were significantly high in the presence of lymphedema and in the affected extremities in advanced grades, and was found to be a positive predictor of lymphedema.

As the number of positive LNs increases, we see that postoperative time and kinesiophobia increase and hand grip strength decreases. This can be explained by the fact that the presence of lymphedema is more common in patients with high LN numbers. In determining the presence of lymphedema, the positive LN number, breast cancer diagnosis time, DASH score showing shoulder, arm and hand functions, and quality of life were found to be important determinants. Accordingly, the high number of extracted LNs and long duration of diagnosis increases the risk of developing lymphedema. In addition, upper limb function and quality of life are negatively affected in these individuals as expected. As the degree of lymphedema increases, we see that the presence and severity of pain in the shoulder (VAS), mobility limitation, and negative effects on quality of life subparameters increase. Accordingly, lymphedema negatively affects the affected limb functions. In the early diagnosis of lymphedema, questioning pain and limitation of motion on the involved side can be a guide for early diagnosis. The symptoms persist for a long time, and even those with mild lymphedema may develop moderate or severe lymphedema. Breast cancer-associated lymphedema can be a transient or permanent condition. Early diagnosis of lymphedema and initiation of a home program including appropriate exercises affect quality of life in patients with breast cancer[19]. In our study, quality of life scores in patients with breast cancer were negatively affected by the duration between diagnosis and surgery, BMI, diameter difference, extremity pain, shoulder pain, DASH, and hand grip strength.

Mastectomy seems to be multifactorial in the etiology of lymphedema. However, it appears that even certain known risk factors do not provide information on the development of lymphedema. In the study by Penn et al.[20], more LN metastases, weight gain, and extremity diameter difference were observed as risk factors for the development of persistent lymphedema. In our study, the duration of lymphedema, the number of positive LNs, DASH score, and the duration of breast cancer diagnosis were positive predictors of the presence of lymphedema. BMI and diameter difference were not significant. Despite negative sentinel LN biopsies up to 7 years postoperatively, patients present with arm and shoulder symptoms that affect daily life[21]. The development of lymphedema can be as short as 3 months and can be seen after years. Therefore, hand, arm and shoulder symptoms should be followed closely and lymphedema should be detected in the early period.

Secondary lymphedema in cancer treatment is characterized by progressive fibroadipous tissue accumulation, increased

infection, and malignancy risk. To date, it has been thought to be associated with impaired collateral lymphatic formation after surgical injury. However, chronic inflammation-related fibrosis plays a key role in recent publications. Lymphatic damage is associated with a chronic immune response (T helper cell) that causes fibrosis and lymphatic leakage, decreased lymphatic pumping, and impaired collateral lymphatic formation[22].

Physical therapy modalities such as self-massage, manual lymphatic drainage, therapeutic physical exercises, compression bandage, elastic compression garments, kinesio tape, pneumatic compression, ultrasonic, electrostatic, extracorporeal shock wave therapy, electrical muscle stimulation and laser therapy are used in the treatment of postmastectomy lymphedema. Although recent studies have not shown superiority over one another, combined therapies in advanced stage lymphedema are recommended[23-27]. There are serious developments in alternative and new surgical approaches in the management of lymphedema[28]. Methods such as physical activity, acupuncture, healing touch, hypnosis, and music therapy, yoga, tai chi, visual reality, and cognitive behavior therapy are also used in cancer pain[29].

Obesity appears to be a risk factor for the development of lymphedema after breast cancer and mastectomy, and preoperative measures should be taken[30,31]. Therefore, it is important how the percentage of total fat and BMI affect the measurements that determine lymphedema. For this purpose, tissue dielectric constant method is used for accurate detection of lymphedema associated with breast cancer treatment[32]. In our study, BMI was not significantly different in patients with lymphedema, but BMI was negatively correlated with psychological and general health scores. Obesity adversely affects general and psychological health.

Various imaging methods can be used in the diagnosis and treatment of lymphedema. Ultrasound is also helpful in revealing extremity differences in the diagnosis of upper extremity lymphedema[33]. In the study by Kilmartin et al.[34], low-level laser therapy in patients with lymphedema has been shown to reduce beneficial effects in breast cancer symptoms and emotional stress. Axillary reverse mapping (ARM) and sentinel LN dissection often involve common and associated lymphatic drainage pathways. According to recent studies, the combination of sentinel LN biopsy and ARM is promising to prevent the development of lymphedema after surgery[35].

According to the study the lymphoedema impact and prevelance - international study in Turkey, most of the Turkish patients were recruited from specialist lymphedema services and were found to be women, housewives, and had secondary lymphedema because of cancer treatment. The duration of lymphedema was commonly <5 years and most of them had ISL grade 2 lymphedema. Cellulitis, infection, and wounds were uncommon. The majority of patients received no treatment or advice before. Most of the patients had impaired quality of life and decreased functionality, but psychological support was neglected. Although most had social health security access to lymphedema centers, access seemed difficult because of distance and cost[36]. According to the data of our center, our participants consisted of obese, primary school educated, non-smoking women in their 50s. The median breast cancer was stage 2 and the majority had undergone radical/modified radical mastectomy. The time after diagnosis and surgery was similar (median 3 years). All of the histopathologic findings were invasive ductal carcinoma. The majority of the patients were ISL grade 0 or 1 lymphedema. The Infection rate was low in the affected extremity. A reduction in hand grip strength was observed in patients with both early and advanced grade lymphedema.

Upper extremity lymphedema affects work and sometimes careers. Workplace adaptations can be useful[37]. Similar to our study, in the study by Chachaj et al.[38] factors such as upper extremity pain (shoulder and arm), pain in the operated breast, difficulty in arm movements, dermatolymphangitis and a history of chemotherapy were found to be associated with high DASH and low-quality life scores. Lymphedema severity, young age, BMI, and lymphedema localization were not associated with poor outcomes. As expected, the severity of lymphedema was positively correlated with diameter difference and lymphedema duration, and was negatively correlated with quality of life scores. Accordingly, high severity of lymphedema negatively affects the quality of life.

Zou et al.[39] found that lymphedema might occur at the earliest 1 month after surgery and this incidence has increased over time, especially observed in the first year in their study. In our study, the mean duration of lymphedema after surgery was 36 months (the earliest 3 months, the latest 240 months). In the same study, axillary LN dissection, radiotherapy, modified radical mastectomy, positive number of axillary LNs and BMI were found to be independent risk factors for the development of lymphedema. Giray and Akyüz[40] showed that shoulder instability caused caregiver burden and decreased quality of life.

It is very important in the management for early breast cancer by selecting the most suitable surgery mode for every individual patient to cure their disease and to satisfy the patient psychologically. Conservation should be preferred prior to reconstruction whenever possible. The choice of breast conserving surgery and radical mastectomy/modified radical mastectomy in patients with breast cancer is determined by the decision of the physician or patient. In our study, the radical mastectomy/modified radical mastectomy ratio is 58.2% and is compatible with the general literature[41,42]. Several factors explain why some women do not develop lymphedema after axillary LN dissection. The reduced lymphatic flow mechanism by the lymphatics alone cannot explain the late onset and selected protected areas (such as hands). Quantitative lymphoscintigraphy indicates that the drainage of the lymphatic flow in the subcutis (where edema is most common)

is slower and that the subfascial muscle compartment has a higher lymph flow than the subcutis. Lymphatic congestion lymphoscintigraphy showed the association of edema with decreased contractility in arm lymphatics. Swelling increases as the active lymphatic pump weakens[43].

Kinesiophobia is an irrational fear that is linked to the belief in susceptibility to injury. It is associated with lower physical activity levels. Kinesiophobia adversely affects the compliance of older patients to rehabilitation programs[44]. According to our study, kinesiophobia was not significantly different between the groups; TSK was positively correlated with hand grip strength and the number of positive LNs. As seen, kinesophobia is found high in patients whose shoulder, arm and hand functions are more affected. These patients may also develop kinesiophobia to protect the affected extremities from trauma.

Study Limitations

In this study, chemotherapy or radiotherapy protocols were not taken into consideration. Data originates from a single center, which restricts generalization. In some patients, some questionnaires could not be completed due to low education levels. The majority of our study group consisted of patients with tumor stage 0 or 1. The limited number of patients with advanced stage lymphedema is another limitation of the study.

Conclusion

In summary, lymphedema is a chronic, progressive condition caused by imbalance in lymphatic flow. Secondary lymphedema is common in the treatment of breast cancer. Early detection of lymphedema during routine examinations will be useful for treatment management and prevention of complications. In our study, it was found that lymphedema had a negative effect on quality of life by affecting shoulder, arm, and hand functions, even in the early stages. Early diagnosis and raising awareness of well-known risk factors for lymphedema should be new targets of treatment.

Ethics

Ethics Committee Approval: The study was approved by the local Medical Research Ethics Committee (protocol no: 2019/185).

Informed Consent: Informed and written consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Author Contributions

Surgical and Medical Practices: T.T.K., G.A., Concept: T.T.K., G.A., Design: T.T.K., Data Collection or Processing: M.E.K., T.T.K., Analysis or Interpretation: T.T.K., Literature Search: T.T.K., Writing: T.T.K.

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How to perform and interpret the lung ultrasound by the obstetricians in pregnant women during the SARS-CoV-2 pandemic

SARS-CoV-2 pandemisinde gebeler akciğer ultrasonunun obstetrisyenler tarafından yapılması ve yorumlanması

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Abstract

Objective: Evidence for the use of lung ultrasound scan (LUS) examinations in coronavirus 2019 pneumonia is rapidly growing. The safe and non-ionizing nature of LUS drew attention, particularly for pregnant women. This study aimed to contribute to the interpretation of LUS findings in pregnant women for the obstetricians.

Materials and Methods: LUS was performed to pregnant women suspected of or diagnosed as having Severe Acute Respiratory syndrome coronavirus-2 (SARS-CoV-2) in the first 24 hours of admission. Fourteen areas (3 posterior, 2 lateral, and 2 anterior) were scanned per patient for at least 10 seconds along the indicated anatomical landmarks. The scan was performed in supine, right-sided and left-sided positions, respectively. Each area was given a score between 0 and 3 according to the specific pattern.

Results: In this study, 21 still images and 21 videoclips that enabled dynamic and real-time evaluation were provided. Pleural line assessment, physiologic A-lines, pathologic B-lines, light beam pattern, white lung pattern, and specific patterns for quick recognition and evaluation are described.

Conclusion: The potential advantages and limitations of LUS and its areas of use for obstetricians are discussed. LUS is a promising supplementary imaging tool during the SARS-CoV-2 pandemic. It is easy to perform and may be feasible in the hands of obstetricians after a brief didactic course. It may be a first-line imaging modality for pregnant women.

Keywords: Lung ultrasound, pregnancy, SARS-CoV-2, COVID-19

Öz

Amaç: Koronavirüs 2019 pnömonisinde akciğer ultrason taraması (LUS) muayenesinin kullanımına ilişkin kanıtlar hızla artmaktadır. LUS'nin güvenli ve iyonlaştırıcı olmayan doğası, özellikle hamile kadınlar için dikkat çektmektedir. Bu çalışma, gebe kadınlarda kadın doğum uzmanları için LUS bulgularının yorumlanmasına katkıda bulunmayı amaçlamıştır.

Gereç ve Yöntemler: LUS, başvurudan sonraki ilk 24 saat içinde Şiddetli Akut Solunum Yolu sendromu koronavirüsü 2 (SARS-CoV-2) şüphesi olan veya tanısı konan gebe kadınlara uygulandı. Belirtilen anatomik işaretler boyunca hasta başına on dört alan (3 posterior, 2 lateral ve 2 anterior) en az 10 saniye tarandı. Tarama sırasıyla sırt üstü, sağ taraflı ve sol taraflı pozisyonlarda gerçekleştirildi. Her bölgeye, spesifik örüntüye göre 0 ile 3 arasında bir puan verildi.

Bulgular: Bu çalışmada, dinamik ve gerçek zamanlı değerlendirmeyi mümkün kılan 21 fotoğraf ve 21 video klip sunulmuştur. Plevral çizgi değerlendirmesi, fizyolojik A-çizgileri, patolojik B-çizgileri, ışık huzmesi paterni, beyaz akciğer paterni ve hızlı tanıma ve değerlendirme için spesifik paternler tanımlanmıştır.

Sonuç: Akciğer ultrasonunun potansiyel avantajları ve sınırlamaları ve doğum uzmanları için kullanım alanları tartışılmıştır. Akciğer ultrasonu, SARS-CoV-2 salgını sırasında umut verici bir yardımcı görüntüleme aracıdır. Kısa didaktik kursun ardından obstetrisyenlerin elinde yapmak kolaydır ve uygulanabilir. Hamile kadınlar için ilk basamak görüntüleme yöntemi olabilir.

Anahtar Kelimeler: Akciger ultrasonu, gebelik, SARS-COV-2, COVID-19

PRECIS: Lung ultrasound is feasible and relatively easy to perform for obstetricians to be used during the COVID-19 pandemic.

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Introduction

Chest computed tomography (CT) is the gold standard in the diagnosis of coronavirus diseases-2019 (COVID-19) pneumonia. The prominent features of COVID-19 are subpleural, ground-glass consolidative pulmonary opacities[1,2]. However, CT is relatively expensive, not feasible for monitoring and patients admitted to the intensive care unit, has an ionizing radiation nature and carries the risk of transmission during transportation[3].

By contrast, lung ultrasound scanning (LUS) is easy to perform, has a non-ionizing nature, and has the advantages of bed-side application and thus is well suited for monitoring patients[2-5]. Its interpretation is accepted as relatively easy because it is mainly based on pattern recognition and provides real-time dynamic images[5,6]. LUS has been traditionally used by non-radiologists as an adjunctive imaging tool[4]. Pulmonologists, emergency medicine physicians, thoracic and cardiac surgeons often benefit from LUS in the management of traumatic conditions and intraoperative situations[7]. Obstetricians also use ultrasound liberally in their routine clinical practice. Practically, the examination of the maternal lungs immediately after obstetric sonographic evaluation could be feasible for obstetricians, basically to ascertain the presence or absence of normality and specific patterns, and thus to determine the need for further multidisciplinary management[4].

The attenuation of sound waves by the lung and bone tissues limits the use of LUS in the diagnosis of central lung diseases; therefore, LUS mainly targets artifacts that originate from peri-pulmonary lesions to reach a diagnosis[8]. Changes in the lung parenchyma following COVID-19 pneumonia begin in the distal regions and progress proximally[3]. Lesions are mostly located in the posterior and inferior fields of both lungs[8]. This feature makes LUS non-inferior to CT in the pandemic setting compared with other respiratory disorders. The pathologic progression of pneumonia of COVID-19 provides credibility to a surface imaging modality such as LUS[3]. Herein, it was aimed to provide a didactical, pictorial review to assist obstetricians in the multidisciplinary management of pregnant women suspected or diagnosed as haing COVID-19 infection.

Materials and Methods

In this educational, non-systematic pictorial review, all lung images and videoclips were obtained with a dedicated machine [Esaote S.p.a., Italy; Manufactured by: Eizo Nanao Corp., Model: EA720] for use in pregnant women with suspicion or diagnosis of COVID-19. A 1-8-MHz convex transducer was used on the regular obstetric preset.

Fourteen areas (3 posterior, 2 lateral, and 2 anterior) were scanned per patient for at least 10 seconds along the indicated anatomical landmarks[9]. The scan was performed in supine, right-sided and left-sided positions, respectively (Figure 1). Where applicable, scanning from the intercostal space was preferred.

Each area was given a score between 0 and 3 according to the specific pattern[9]. The pattern with a continuous and regular pleural line and horizontal artifacts, referred to as A-lines, was classified as score 0. The pattern with an indented pleural line and sporadic vertical white areas below the point of discontinuity in the pleural line, referred to as sporadic B-lines, was classified as score 1. The pattern with a broken pleura, small consolidated areas below the discontinuity, and multiple vertical white areas that reached the bottom of the field of view, referred to as multiple B-lines, was classified as score 2. The pattern with a severely broken pleura and a dense and largely extended white lung pattern with or without larger consolidations was classified as score 3. At the end of the procedure, the highest score obtained for each area was noted (e.g. landmark 1, score 0; landmark 2, score 1; and so on)[5].

Local Instutional Ethical Board and National Scientific Research Board approved the study. Written consent was obtained from all patients underwent lung ultrasound.

Figure 1. Lung ultrasound examination following a fetal assessment in supine and sided positions

Results

In this study, six figures and three videos for score 0 (Figure 2-7, Video 1-3), five figures and three videos for score 1 (Figure 8-12, Video 4-6), 5 figures and seven videos for score 2 (Figure 13-17, Video 7-13), four figures and four videos for score 3 (Figure 18-21, Video 14-17) were provided and explained in detail. In addition, four featured videos were added showing pleural effusion, the co-existence of scores 0 and 1, and perihepatic and pericardial effusions (Video 18-21). The clinical characteristics and outcomes of the patients were not in the scope of this study and were therefore not presented.

LUS Findings

The ribs and their posterior shadowing can be seen when the probe is positioned longitudinally. Transverse positioning of the probe on the intercostal spaces should be preferred, where applicable.

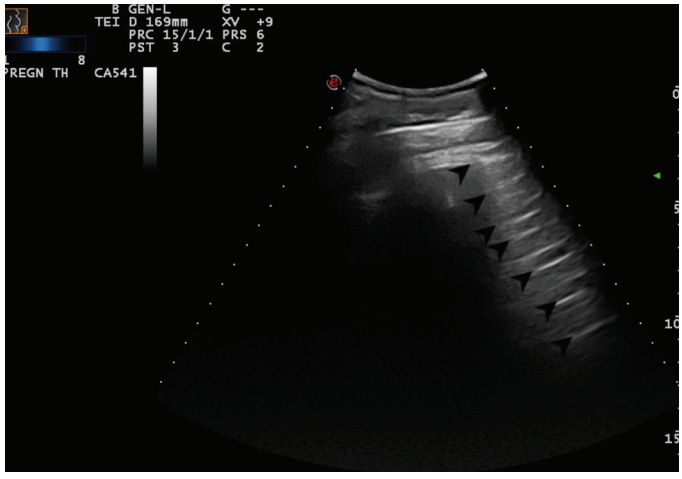

Figure 2. Regular pleural line. Arrows indicate physiological A-lines at regular intervals. Convex transducer positioned in the intercostal space (Scored 0)

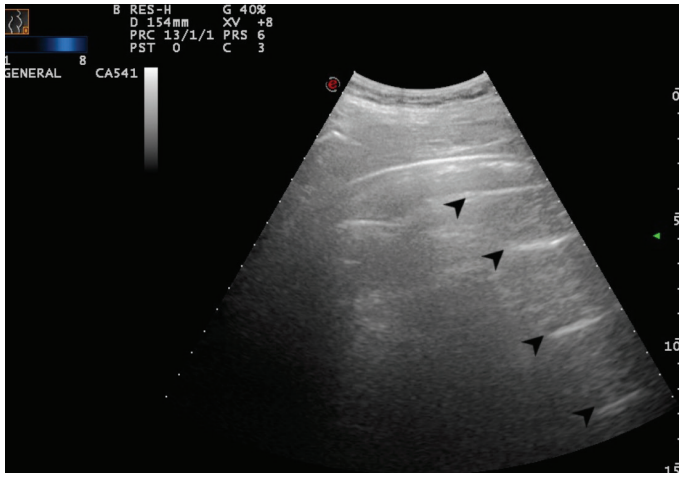

Figure 3. Regular pleural line. Arrows indicate physiologic A-lines at regular intervals (Scored 0)

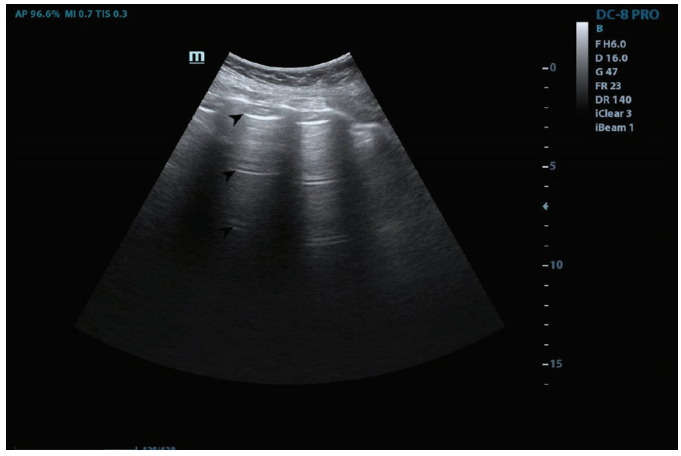

Figure 4. Normal LUS pattern with the convex transducer positioned longitudinally. Arrows indicate physiologic A-lines at regular intervals (Scored 0)

LUS: Lung ultrasound scanning

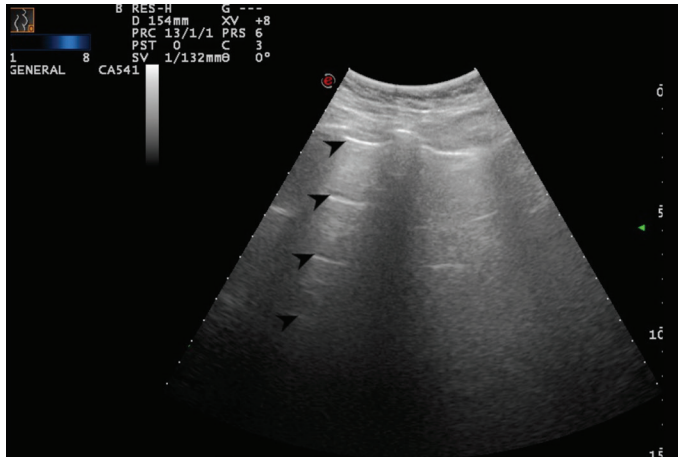

Figure 5. Normal LUS pattern with the convex transducer positioned longitudinally. Arrows indicate physiologic A-lines at regular intervals (Scored 0)

LUS: Lung ultrasound scanning

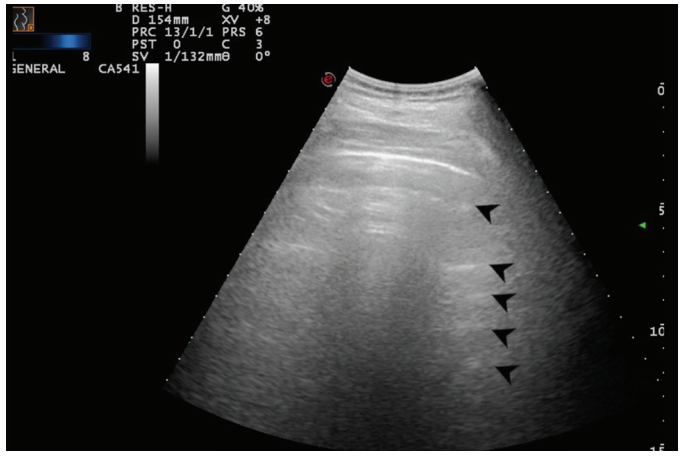

Figure 6. Regular pleural line. Arrows indicate physiologic A-lines at regular intervals (Scored 0)

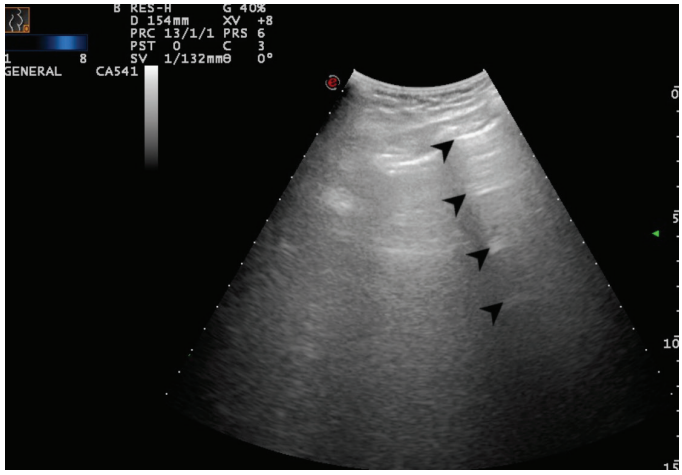

Figure 7. Regular pleural line. Arrows indicate physiologic A-lines at regular intervals (Scored 0)

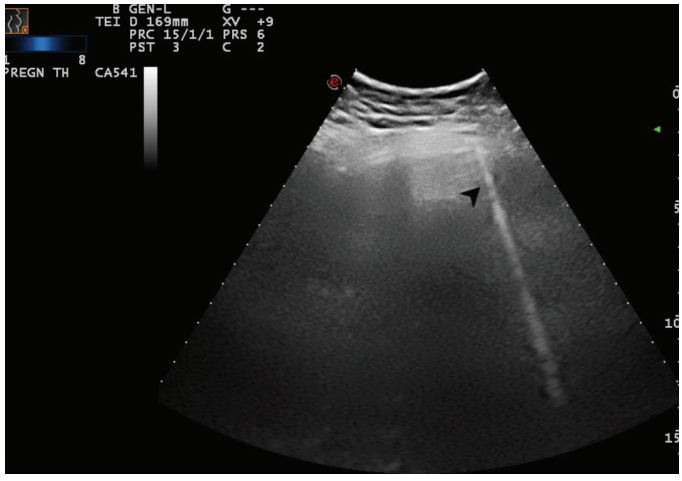

Figure 8. The arrow indicates a sporadic B-line arising from the intended pleural line (Scored 1)

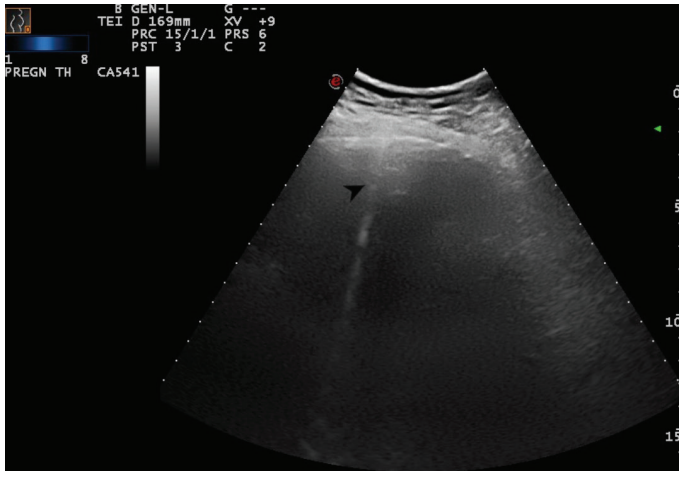

Figure 9. The arrow indicates a sporadic B-line arising from the intended pleural line (Scored 1)

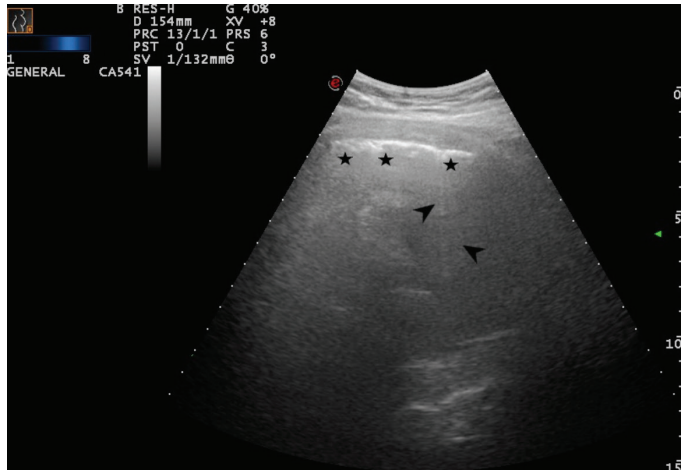

Figure 10. The arrow indicates a sporadic B-line arising from the intended pleural line. Stars indicate the thickened and intended pleural line (Scored 1)

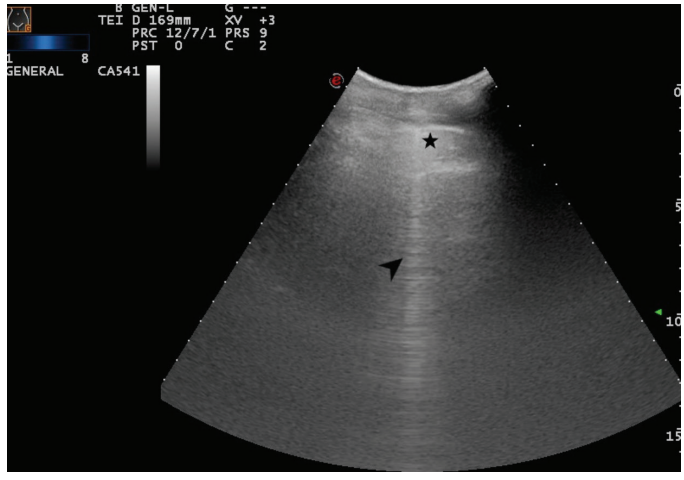

Figure 11. The arrow indicates a sporadic B-line arising from the intended pleural line. Star indicates the thickened and intended pleural line (Scored 1)

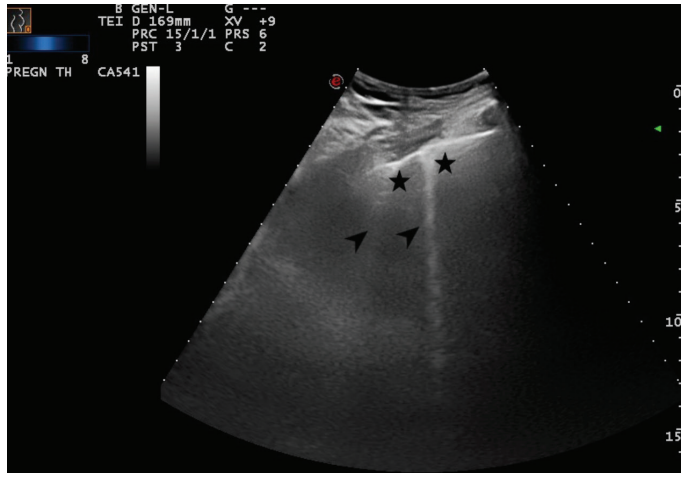

Figure 12. The arrow indicates a sporadic B-line arising from the intended pleural line. Stars indicate the thickened and intended pleural line (Scored 1)

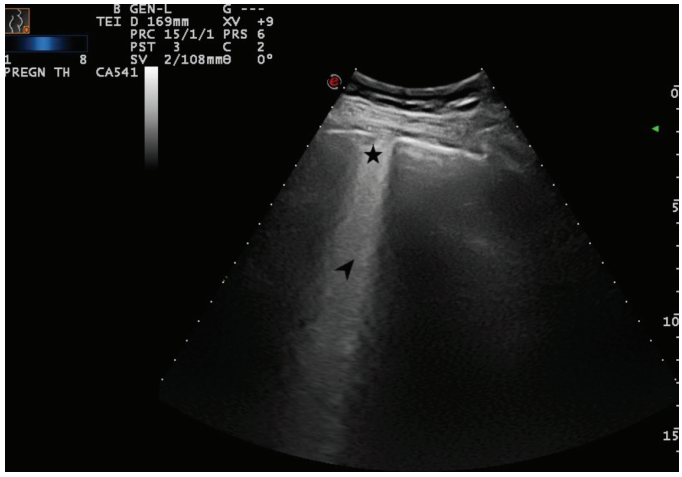

Figure 13. A broken pleural line and small consolidated area (indicated with star) below the irregularity and a large bright vertical area (indicated with arrow) can be seen (Scored 2)

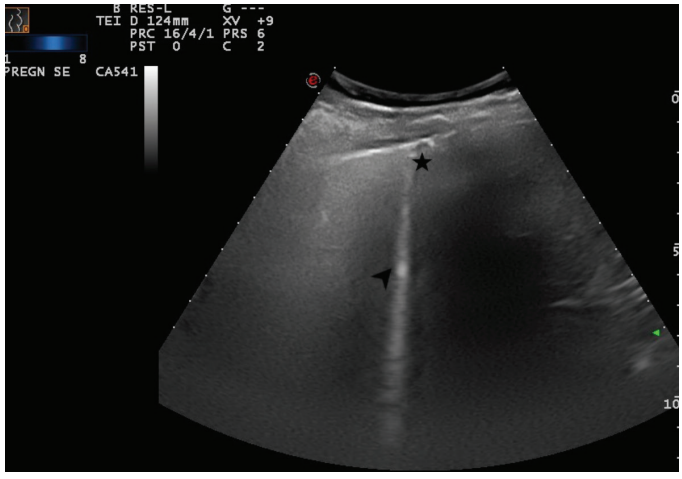

Figure 14. Star indicates a subpleural consolidation area and arrow indicate a B-line that reaches the bottom of the screen (Scored 2)

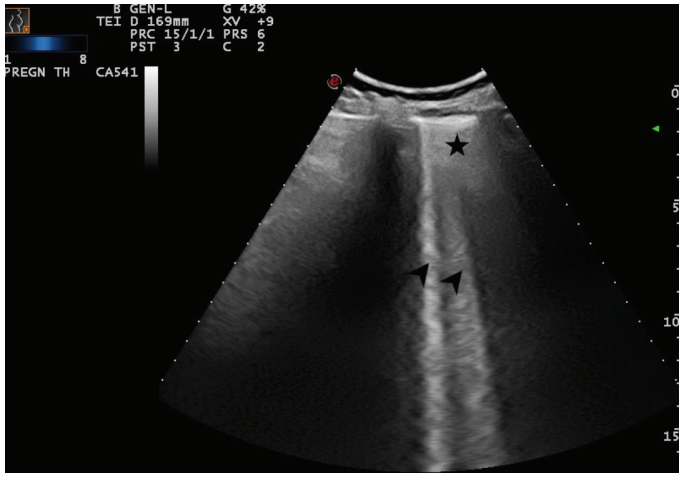

Figure 15. Arrows indicate multiple B-lines and the star indicates a broken and thickened pleural line (Scored 2)

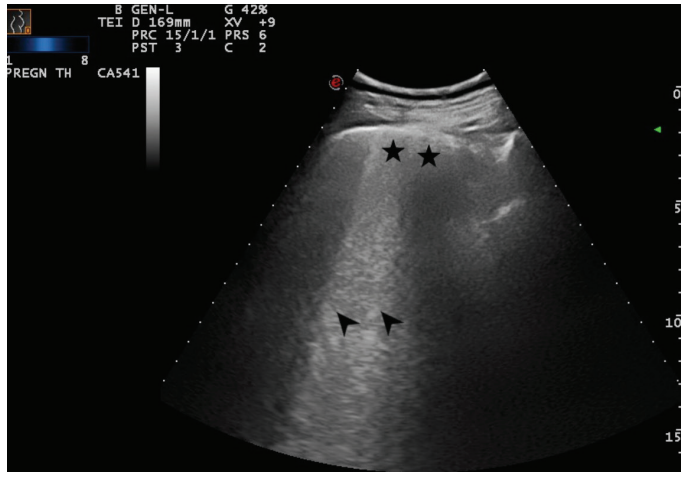

Figure 16. Arrows indicate multiple B-lines and stars indicate a broken and thickened pleural line (Scored 2)

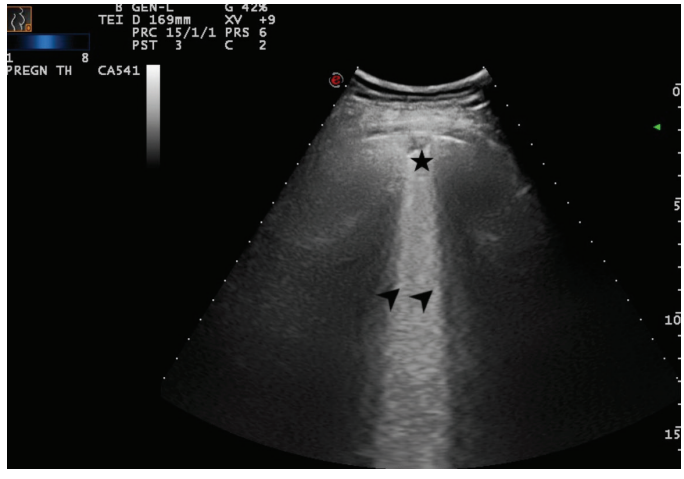

Figure 17. Arrows indicate multiple B-lines and star indicates a sub-pleural effusion and broken pleural line (Scored 2)

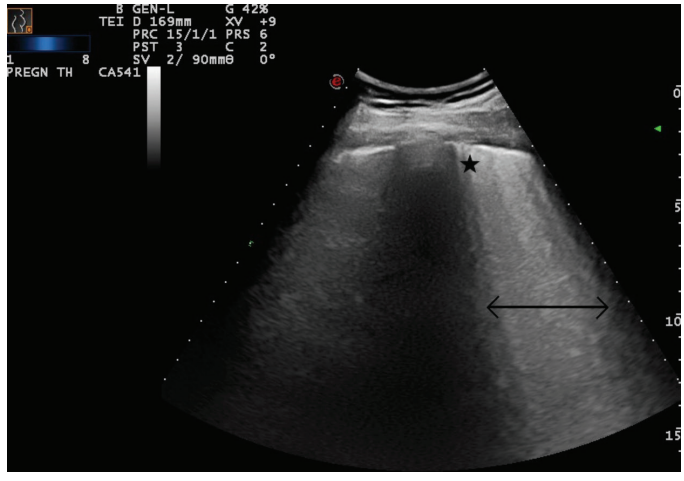

Figure 18. Double-headed arrow indicates a largely extended white lung pattern with small subpleural consolidation area as indicated with a star (Scored 3)

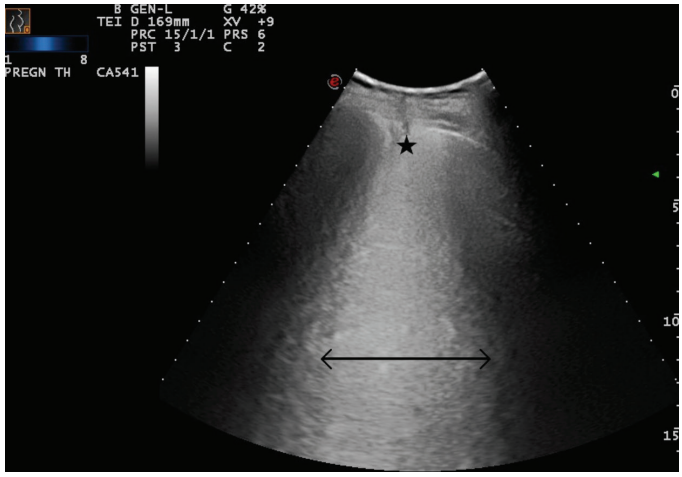

Figure 19. Double-headed arrow indicates a largely extended white lung pattern. The star indicates a severely broken pleural line and a small subpleural consolidation area (Scored 3)

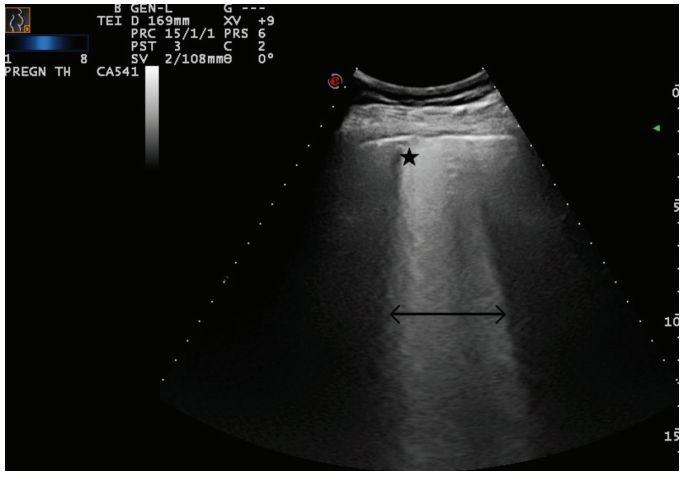

Figure 20. Double-headed arrow indicates a largely extended white lung pattern. The star indicates a severely broken pleural line and a small subpleural consolidation area (Scored 3)

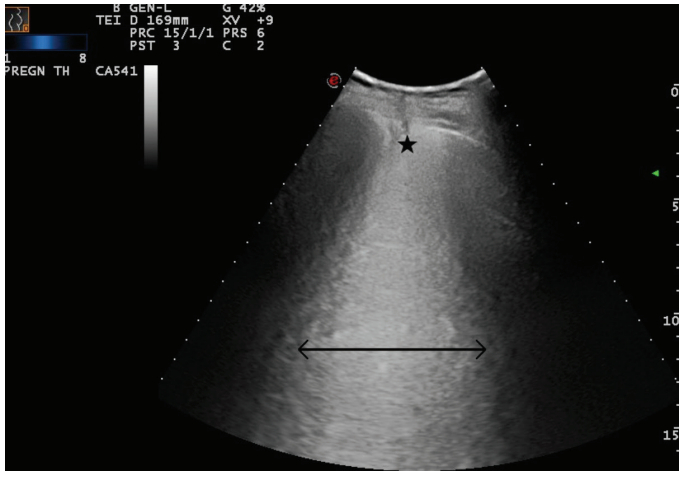

Figure 21. Double-headed arrow indicates a largely extended white lung pattern. The star indicates a severely broken pleural line and a small subpleural consolidation area (Scored 3)

Pleural line assessment: Attention should be paid to the sliding, thickness, and irregularities (e.g. unsmooth, discontinuous or interrupted, indentation, broken pleura) of pleural line and subpleural effusion, if they exist.

The visceral and parietal parts of pleura slide over each other in backward and forward directions with respiratory movements called the normal sliding sign[10]. The sliding sign is absent in some clinical conditions such as pneumothorax.

The subpleural consolidations appear as an irregular hypoechoic area. Small patchy, strip or nodule consolidations can often be observed as a subpleural lesion.

In the COVID-19 infection, pleural thickening and subpleural effusion were found to be about 1-2 mm and 2-3 mm, respectively, which can change as the disease progresses[8].

A-lines: These represent repetitive reverberation artifacts and commonly appear as horizontal, parallel lines at regular intervals[7]. These lines represent a normal inflated peripheral lung when combined with a normal pleural sliding sign[4].

B-lines: These lines are well-defined vertical hyperechoic artifacts arising from the pleural line and reach the bottom of the screen[4]. These lines move with the pleural line during respiration and may erase A-lines[7]. Sporadic/coalescent or multiple B-lines can be seen and the density and combination of the pathologic signs may be correlated with the probability of disease[11].

Sometimes, fewer than three B-lines between two adjacent ribs may be seen in 30% of normal lungs[7,10]. However, possible false-positive cases should also be approached with great caution in the pandemic settings and should be considered as a possible pathologic condition until proven otherwise.

There are also false vertical lines including C-, E- and Z-lines, which can commonly be mistaken for B-lines. However, for obstetricians working in the COVID-19 pandemic setting, discriminating those from pathologic B-lines may not be clinically relevant because they refer to specialist's (such as radiologist and pulmonologist) considerations to differentiate from underlying diseases. In addition, they are mainly differentiated with B-lines concerning their synchronous movements with inspiration and expiration. Basically, an obstetrician should pay attention to the synchronized vertical lines that move with respiration.

Light beam pattern: A specific pattern that consists of a shining band-form artifact spreading down from a large portion of a regular pleural line and often has an on-off effect with respiration that may also have normal A-lines visible in the background[11]. This pattern was proposed to reflect the acute phase of ground-glass opacities during the early spread of the active COVID-19 pneumonia[11].

White lung pattern: This pattern corresponds to the increased density of the lung parenchyma in which physiologic A-lines and other vertical artifacts including B-lines are erased[4].

Pleural effusions and air bronchograms, which are the reflection of air-filled bronchus in the context of opacity

are rarely seen in COVID-19 infections and should lead physicians to superinfections or other differential diagnoses[12].

Discussion

Obstetricians should be responsive during the Severe Acute Respiratory syndrome coronavirus-2 pandemic because they are the frontline physicians for the pregnant population[13] and should be ready for the second wave or the next epidemics or pandemics caused by other viruses. The use of LUS for pregnant women in the hands of obstetricians can make a difference during such exceptional and critical situations[14]. This pictorial study can be used for the training of obstetricians in the pandemic setting and encourage the liberal use of LUS.

LUS cannot be a substitute for chest CT; however, it has certain advantages over CT as an adjunctive method in the diagnosis and management of respiratory involvement of COVID-19 infection, particularly for pregnant women[4,5,8]. The sensitivity and specificity of LUS in several clinical conditions range between 81% and 97%, and between 95% and 100%, respectively[7,15]. Authors postulate that LUS should be the first choice of imaging method in pregnant women suspected of having COVID-19 infection. However, LUS findings should be evaluated with the patient's background because they are not always specifically attributable. More importantly, mild LUS findings (score 1) in an asymptomatic woman should be approached cautiously. For example, A-lines that are known as physiologic artifacts can represent abnormal signs in atelectasis, asthma, chronic obstructive pulmonary disease, and pneumothorax[16]. Similarly, B-lines can represent normal signs in healthy patients when they are fewer than three and do not reach the bottom of the screen[16].

We have previously shared our clinical experience in eight cases showing that the use of LUS immediately after the fetal assessment can positively affect the clinical management of pregnant women infected with COVID-19[5]. As physicians without formal radiology residency training, we organized a brief course that consisted of a didactic lecture and hands-on ultrasound examinations supervised by experts[17]. This approach has been previously tested and found that LUS is feasible following theoretical training combined with still images taken from pregnant women infected with COVID-19[6,18]. The interobserver agreement between obstetricians with different levels of experience on still-images and videoclips of LUS was found as good[17].

Conclusion

LUS is a promising non-invasive, safe, and easily learned and performed imaging tool that can be used in pregnant women suspected of having COVID-19 pneumonia following an initial fetal assessment. This technical pictorial study can encourage the reasonable learning of LUS for obstetricians in the pandemic setting.

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Ethics

Ethics Committee Approval: Local Instutional Ethical Board and National Scientific Research Board approved the study.
Informed Consent: Written consent was obtained from all patients underwent lung ultrasound.
Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.Y., M.A.M., P.B., C.Y., Concept: M.Y., E.K., N.T., Design: M.Y., A.B.T., K.S., C.K., M.Y., Data Collection or Processing: M.A.M., P.B., C.Y., E.A., Analysis or Interpretation: M.Y, E.K., M.Y.; Literature Search: M.A.M., A.B.T., K.S., E.A., M.Y., C.K., Writing: M.Y., M.A.M., N.T.
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Case Report / Olgu Sunumu

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An unusual cause of female secondary infertility: Hypospadias

Kadında sekonder infertilitenin nadir bir olgusu: Hipospadias

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Abstract

Female hypospadias is a very rare congenital anomaly and its impact on fertility has not yet been clearly defined. A 21-year-old woman with hypospadias was admitted with secondary infertility, dyspareunia, and urge symptoms. She was successfully treated with vaginal flap urethroplasty and broad spectrum antibiotics. Postoperatively, her symptoms resolved and she conceived spontaneously and aborted at her 17th gestational week following premature rupture of membranes suggesting infection. She then conceived spontaneously again and delivered a healthy term baby 30 months after the operation. Female hypospadias may cause chronic pelvic infections, urge symptoms, sexual dysfunction, hence infertility with time. After achieving normal anatomy by vaginal flap urethroplasty, treatment of chronic infections allows restoring normal urologic and sexual functions, and fertility.

Keywords: Female hypospadias, female infertility, urethroplasty, sexual dysfunction, urinary tract infection

Öz

Kadın hipospadiası çok nadir görülen bir doğuştan anomalidir ve doğurganlık üzerindeki etkisi henüz net bir şekilde tanımlanamamıştır. Yirmi bir yaşında bir hipospadias olgusu sekonder infertilite, disparoni ve urge inkontinans semptomları ile başvurdu. Hasta vajinal flep üretroplasti ve geniş spektrumlu antibiyotiklerle başarıyla tedavi edildi. Ameliyat sonrası şikayetleri düzeldi, kendiliğinden gebe kaldı ve enfeksiyona bağlı olduğu düşünülen erken membran rüptürünün ardından 17. haftada düşük yaptı. Daha sonra tekrar kendiliğinden gebe kaldı ve ameliyattan 30 ay sonra sağlıklı bir bebek doğurdu. Kadın hipospadiası kronik pelvik enfeksiyonlara, urge inkontinans semptomlarına, cinsel fonksiyon bozukluğuna ve dolayısıyla zamanla infertiliteye neden olabilir. Normal anatomiyi vajinal flep üretroplasti ile oluşturduktan sonra üretroplasti kronik enfeksiyonların tedavisi normal ürolojik ve cinsel fonksiyonların ve doğurganlığın geri kazanılmasını sağlar.

Anahtar Kelimeler: Kadın hipospadias, kadın infertilitesi, üretroplasti, cinsel disfonksiyon, üriner trakt enfeksiyonu

Introduction

Female hypospadias, in particular among adults with no other genitourinary abnormalities, is a very rare clinical entity, with the urethral meatus located at any site on the anterior vaginal wall from just above the introitus up to the vaginal fornix[1].

In hypospadias, urination into the vagina adversely affects the normal vaginal flora and favors cervico-vaginal infections, which may even lead to chronic or intermittent endometritis and infertility. Conversely, washing the vaginal secretions out of the vagina by urine would also cause vaginal dryness and hence dyspareunia which further contributes to the risk of infertility[2].

In this paper, we report a 21-year-old woman with secondary infertility who presented with symptoms of dyspareunia, recurrent urinary tract infections, and urge symptoms. Her physical examination revealed hypospadias, and she was successfully treated with vaginal flap urethroplasty and delivered a healthy term baby.

Case Report

A 21-year-old woman was admitted with severe dyspareunia, vaginal dryness, pelvic pain, and recurrent urinary tract infections. She had a healthy 6-year-old child as a result of sexual abuse but she did not describe any perineal trauma related with that. The patient was continent but reported severe urge symptoms. Her mother had worked as an agricultural laborer. Cervical cytology, vaginal culture and pelvic organs on transvaginal ultrasonography and hysterosalpingography were normal. The husband did not report any signs related to infertility and his spermiogram

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was normal. A physical examination revealed a urethral meatus located just above the hymenal ring and the vagina was prominently dry. On cystoscopy, chronic cystitis was diagnosed. Magnetic resonance imaging revealed grade 1 ureteropelvic ectasia. Female Sexual Function index (FSFI) was obtained from the patient[3]. Vaginal flap urethroplasty was performed. The surgical technique was as follows: A 16-French Foley catheter was inserted into the urethra. The anterior part of the hymenal ring and vaginal mucosa was incised with reverse U-shaped incision and dissected with its submucosa cephalad. The perineal mucosa anterior to the hymen was incised using railway shaped incisions on both sides of the catheter up to the point where normal urethral meatus was supposed to be located. This incised mucosa was mobilized and the flaps were sutured using separated sutures over the catheter to each other and to the original urethral meatus. The hymenal remnants of the other flap prepared from the hymenal ring and its continuing vaginal mucosa were extirpated. The prepared triangular vaginal flap edges were sutured at the midline to elongate the flap and a strip shape was obtained. The vaginal strip was then positioned over the neo-urethra and sutured to the neo-urethral meatus and to the intact perineal mucosa on both sides of the railway shaped incisions, tension-free. The 1-cm long spindle-shaped uncovered defects on each side of the neo-urethral meatus were closed using single sutures. For all sutures, 3/0 delayed absorbable material was used (Figure 1).

The patient was treated with broad spectrum antibiotics postoperatively. After two months of sexual abstinence, her initial symptoms were all resolved and her FSFI scores improved gradually at her 6th, 12th, and 24th month follow-ups postoperatively. At her 14th postoperative month, she conceived spontaneously but aborted at her 17th gestational week following prematurely ruptured membranes and a bum-curettage was performed. She was then re-treated with broad spectrum antibiotics and she again conceived spontaneously. Then she delivered a term healthy 2900 g baby by elective cesarean section 16 months after the abortion.

Discussion

The etiology of hypospadias is obscured in the majority cases. A multi-factorial explanation and the implication of genetic susceptibility and environmental pollutants remain a plausible working hypothesis[4]. In the presented case, the mother of the patient was an agriculture laborer, which suggests a possible *in utero* exposure to phytoestrogens or insecticides showing an anti-estrogenic effect as the etiologic factor.

Hypospadias results in urination into the vagina and hence, as in the presented case, causes recurrent urinary tract infections and disturbed normal vaginal flora, which play pivotal roles in the prevention of pelvic infections and infertility[2].

Urine also washes the physiologic secretions out of the vagina and leads to vaginal dryness, which contributes to dyspareunia. In this case, the patient's sexual functions gradually returned to normal after the operation as shown by the improvement in all items of the FSFI test in the 24-month follow-up (Table 1).

Female hypospadias is an unusual cause of infertility. In this case, the patient conceived her first pregnancy at age 14 years. Later, she conceived spontaneously after the operation but aborted following premature rupture of membranes. Following broad spectrum antibiotherapy she conceived again and delivered a healthy baby at term. This course of the patient's medical data suggests an ascending pelvic infection secondary to impaired vaginal flora and cervicovaginitis as the cause of the infertility.

In this case, a female patient with hypospadias with urinary symptoms, sexual dysfunction, and infertility was treated successfully through urethroplasty surgery with vaginal flap.

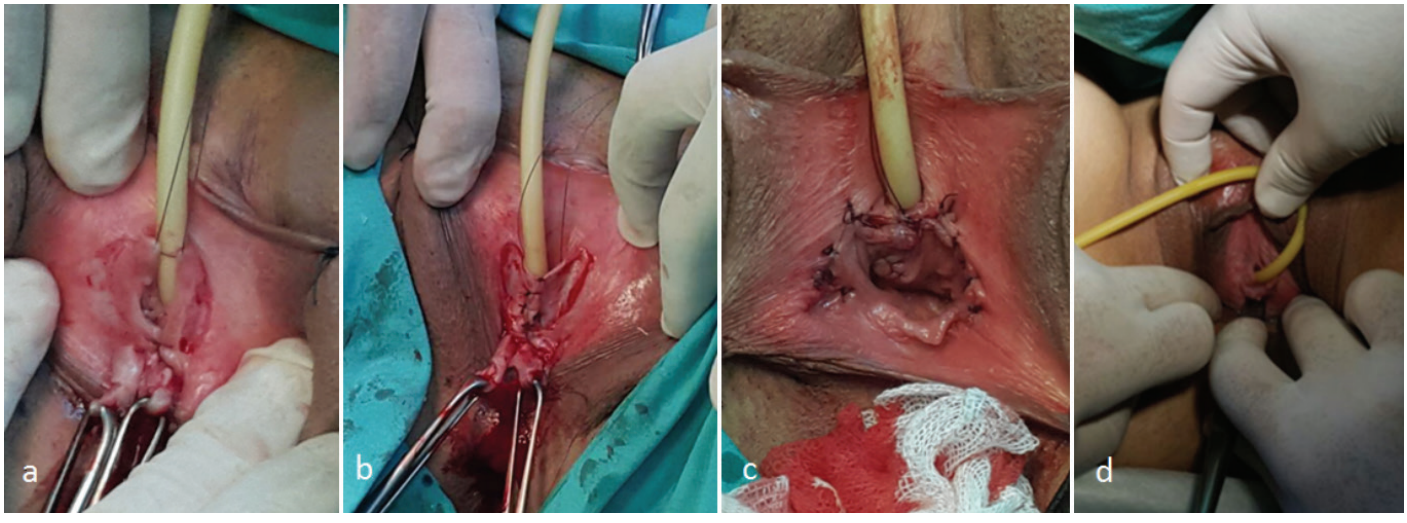

Figure 1. Urethroplasty operation. a) Perineal mucosa on both sides of the catheter, b) The incised mucosa was mobilized and sutured over the catheter, c) The vaginal strip was positioned and fixed over the neo-urethra, d) Two months postoperatively

Table 1. FSFI scores of the patient pre-operatively and 6, 12 and 24 months post-operatively. The gradual improvement of the scores is prominent

FSFI Domains	Items	Factor	Preop.	6th Mo	12th Mo	24th Mo
Desire	1, 2	0.6	1.8	5.4	6	6
Arousal	3, 4, 5, 6	0.3	2.1	4.5	5.7	5.7
Lubrication	7, 8, 9, 10	0.3	2.1	4.8	4.8	5.1
Orgasm	11, 12, 13	0.4	1.2	3.6	4.8	5.2
Satisfaction	14, 15, 16	0.4	2.4	4.8	5.2	6
Pain	17, 18, 19	0.4	1.2	4.8	6	6
Total score	-	-	**10.8**	**27.9**	**32.5**	**34**

FSFI: Female Sexual Function index, Preop: Preoperative

Ethics

Informed Consent: An informed consent has been received from the patient.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: N.T., Design: N.T., Data Collection or Processing: M.A.S., M.Y., G.T., Analysis or Interpretation: N.T., M.A.S., M.Y., G.T., Literature Search: N.T., M.A.S., M.Y., G.T., Writing: N.T.

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