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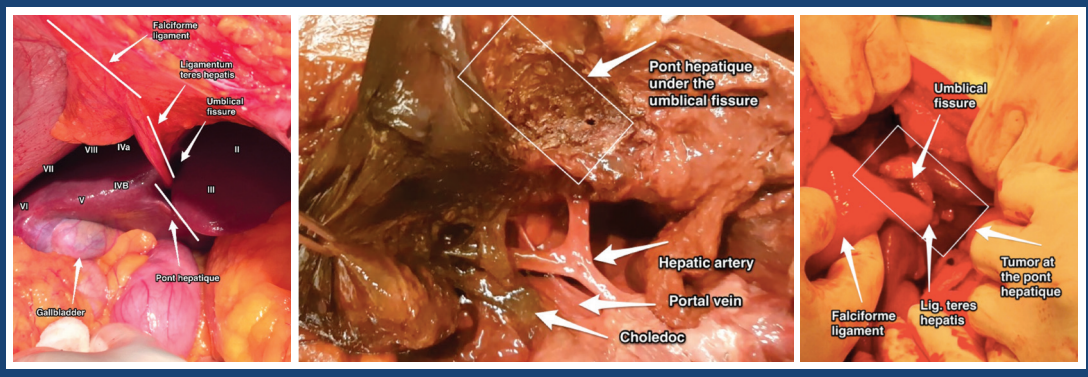

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Aims and Scope

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The journal is printed on acid-free paper.

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PRISMA for preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.) (http://www.prisma-statement.org/),

STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al, for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4.) (http://www.stard-statement.org/),

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State the importance and significance of your findings but do not repeat the details given in the Results section. Limit your opinions to those strictly indicated by the facts in your report. Compare your finding with those of others. Provide information on the limitations and strenghts of the study. No new data are to be presented in this section.

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Book;

Kohler G; Egelkraut H. In Kohler G and Egelkraut H (edts).Munchener Funktionelle Entwicklungsdiagnostik im zweitem und drittem Lebensjahr. Handanweisung. Munchen: Uni Munchen, Institut fur Soziale Paediatrie und Jugendmedizin; 1984.

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Editorial

Dear Colleagues,

I am very happy and enjoy to introduce the first issue of the "Journal of the Turkish German Gynecological Association (*J Turk Ger Gynecol Assoc*)" in the publishing year of 2019.

Dear Young Researcher and Authors,

I want to give you some basics of a manuscript preparation and general writing tips. Think about the message you want to give to readers. If that is not clear, misinterpretations may arise later. The most important information should be in the main text.

To begin it might be interesting to learn why reviewers accept manuscripts! Reviewers consider the following five criteria to be the most important in decisions about whether to accept manuscripts for publication:

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2) the quality of the writing style (i.e., that it is well-written, clear, straightforward, easy to follow, and logical);
3) the study design applied (i.e., that the design was appropriate, rigorous, and comprehensive);
4) the degree to which the literature review was thoughtful, focused, and up-to-date; and
5) the use of a sufficiently large sample.

Countless manuscripts are rejected because the discussion section is so weak that it's obvious the writer does not clearly understand the existing literature. For these statements to be true there are also reasons that reviewers reject manuscripts. The following are the top five reasons for rejecting papers:

1) inappropriate, incomplete, or insufficiently described statistics;
2) over-interpretation of results;
3) use of inappropriate, suboptimal, or insufficiently described populations or instruments;
4) small or biased samples; and
5) text that is poorly written or difficult to follow.

With these reasons for acceptance or rejection in mind, it is time to review basics and general writing tips to be used when performing manuscript preparation. There is a narrow line between speculation and evidence-based conclusions. A writer can speculate in the discussion — but not too much. ***Avoid Plagiarism and inadvertent lack of citations.***

Journal of the
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Gynecological Association

Editorial

Dear Researchers, Dear Authors,

There are many interesting articles in this particular issue. Our reputation is everywhere. We have to have much more effort to suspend this achievements. We have manuscripts from Iran and United Kingdom to Nigeria and from Germany and Indonesia to United States and India. I hope you will enjoy reading these manuscripts. As you know we have started **Video Article.** We are very excited about it. Please do not hesitate to send your interesting videos to this link.

As 2019 starts, I want to thank many authors who submitted manuscripts to *J Turk German Gynecol Assoc* during past years. I wish to extend my heartfelt gratitude and appreciation to everyone who dedicated and sacrificed their time to deliver expertise, effort, and contribution to this publication and evaluation process.

We are looking forward to receiving your valuable submissions, thank you in advance for your contributions.

Sincerely,

Prof. Cihat Ünlü, M.D.
Editor in Chief of *J Turk Ger Gynecol Assoc*
President of TGGF

The relationship between semen parameters in processed and unprocessed semen with intrauterine insemination success rates

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Abstract

Objective: To evaluate the relationship between semen parameters and intrauterine insemination (IUI) success rates.

Material and Methods: This retrospective study was conducted during a 4-year period (2011-2015) on the medical records of 350 couples admitted to the infertility center of Beast Hospital in Tehran. The participants' data such as age, duration of infertility, semen parameters [including volume, concentration, motility, normal morphology and total motile sperm count (TMSC)] before and after sperm processing, as well as the IUI results were extracted from the patients' records. Only the first IUI cycle of the couples was considered. The main outcome criterion for the IUI success was serum positive beta human chorionic gonadtotropin 14 days after IUI. The collected data were analyzed using the Mann-Whitney U test, chi-square, and Fisher's exact tests.

Results: The overall pregnancy rate for each couple was reported as 23.42% (82/350). There was no significant difference in the mean age of the couple and infertility duration between the groups who achieved pregnancy and those who failed. The two groups showed no significant differences in pre and post processing of semen parameters (including volume, concentration and TMSC). Sperm motility and normal sperm morphology before and after sperm processing were significantly different between the two groups, respectively (p=0.023 before sperm processing and p=0.032 after) (p=0.032 before sperm processing and p=0.007 after).

Conclusion: Sperm motility and normal sperm morphology have an effect in IUI success. (J Turk Ger Gynecol Assoc 2019; 20: 1-7)

Keywords: Intrauterine insemination, sperm parameters, pregnancy rate

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Introduction

Infertility is defined as the failure to conceive after one year of regular intercourse, without the use of contraceptives. Ten to fifteen percent of couples are infertile (1). The use of techniques such as intrauterine insemination (IUI) in conjunction with controlled ovarian stimulation have increased the hope for pregnancy in infertile couples. IUI is the first-line treatment, a non-invasive and cost effective procedure for the treatment of infertile couples and is performed by inserting a higher concentration of prepared sperms into the uterine cavity (2,3).

Semen analysis is the first step in the evaluation of male infertility because male factors account for 25 to 40% of infertility cases (4). In these assessments, semen characteristics including volume, sperm concentration, sperm motility, and normal sperm morphology are usually evaluated. The standard value of semen analysis that is accepted by the World Health Organization (WHO) 2010 is;

1. Volume: 1.5 mL,
2. pH: 7.2,
3. Sperm concentration: 20 million/mL or more,
4. Total motility (progressive and non-progressive): 40%,
5. Normal sperm morphology: 4% (5,6).

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In the literature, several semen parameters have been described in association with IUI results. There are controversial findings about the best evaluation method of semen analysis as a predictor of IUI success (7-9). Ruiter-Ligeti et al. (10) showed that semen processing significantly improved most of the sperm parameters. In a study by Basirat et al. (11), the presence of sperm progressive motility before semen processing was found to be the most important factor in predicting IUI outcomes (11). In contrast, Luco et al. (12) reported none of the pre or post processing semen analysis parameters considered to be predictors of pregnancy in couples undergoing IUI (12).

Numerous studies reviewed the effect of total motile sperm count (TMSC) on IUI success rates. There is still discrepancy on a reliable TMSC cut-off to predict IUI outcomes (13-15). Some reserchers found a significant decrease in pregnancy rates when the total motile sperm count was less than 10 million (14,16,17). On the contrary, others stated that the TMSC did not appear to be a predictor of IUI success (15). Xiao et al. (18) showed that a low TMSC on the day of IUI did not reduce the chance of pregnancy in couples that underwent IUI (18).

There are conflicting results and there is no consensus on semen parameters associated with IUI success (7,10,12,13). In the present study, our objective was to investigate the relationship between semen parameters and IUI success in couples referred to Beast Hospital Infertility Center.

Material and Methods

This retrospective study was performed over a 4-period from 2011 to 2015 using the medical records of 350 couples admitted at the infertility center of Beast Hospital in Tehran.

Couples who underwent IUI during the 4-year study period at this center and had one year or more primary infertility were enrolled in the study. Only the first IUI cycle of the couples was included in the study. The female partner had regular menstrual cycles and normal pelvic ultrasonography and at least one normal and open uterine tube in hysterosalpingography or laparoscopy.

Regardless of the cause of male infertility, all male partners who were candidates for IUI were included. They had normal semen analysis or one or two of the sperm parameters were below the values established by the WHO (2010). Both pre- and post-processing semen results were available.

Incomplete data regarding the pregnancy outcome or missing data on pre and post processing sperm parameters results were excluded. All pregnancies were confirmed with serum positive beta human chorionic gonadtotropin (β-hCG) 14 days after IUI. Demographic data such as the age of couple, duration of infertility, semen parameters before and after sperm processing, and also the IUI results were extracted from the patients' records.

The subjects under study were divided into two groups, those who achieved pregnancy and those who failed, and the two groups were compared.

Sperm preparation

Semen samples were collected from the male partners following 3-5 days of sexual abstinence by masturbation in sterile plastic containers at the infertility clinic. Liquefaction was performed at room temperature for 30 minutes. The initial analysis of semen parameters (volume, sperm count, sperm motility, sperm with normal morphology) was performed manually according to WHO guidelines (2010). The TMSC was calculated using the folowing formula:

Count (million/mL) × motility (% as a decimal fraction) × volume (mL)

Semen samples were prepared using the standard swim-up techniques. Each specimen was covered with double volume Ham's F10 medium (Merck, Germany) and warmed at 37 °C (99 °F) for 45 min. The top layer, which now contained the most active sperm, was suspended in the medium (centrifugation was performed at 2500 g for 5 min). After discarding the supernatant, the residual substance was washed with the medium (centrifuging for 5 min at 2500 g) and then the supernatant was discharged. The isolated fraction of motile sperm was diluted in 0.5-1 mL of the same preparation medium and incubated until the time of insemination. Ater the processing procedures, the sperm analysis was reevaluated and the TMSC was recalculated.

Insemination method

For all women, 50-100 mg clomiphene citrate was administered from the third day of menstruation for 5 days and human menopausal gonadotropins (75 to 150 units) was injected intramuscularly on days 6, 8, and 10. When at least one 18 mm follicle was detected under ultrasonography, hCG (5000-10000 IU) was injected intramuscularly. Thirty six hours later, 0.5-1 mL of the processed sperms, which was prepared only from fresh semen, was injected using a Wallace catheter very slowly for 3 minutes into the fundus of the uterus. The catheter was withdrawn very slowly and the patient then rested in the supine position for 30-45 minutes. Luteal phase support was provided with a 400 mg daily progesterone suppository, and 14 days after IUI, the serum β-hCG was measured to confirm pregnancy.

Statistical analysis

The SPSS software (version 22) was used to record all data. The results are presented as mean ± standard deviation (SD). Comparison between variables (female and male age,

duration of infertility, semen parameters) was performed using the Mann-Whitney test because data distribution according to the Kolmogorov-Smirnov test was not normal. Categorical variables were evaluated using the chi-square and Fisher's exact test. Statistical significance was accepted as $p<0.05$.

Results

A total of 350 IUI cycles were analyzed. The overall pregnancy rate per couple was 23.4% (82/350). A comparison of the demographic data between the groups who did and did not achieve pregnancy is shown in Table 1.

The mean (±SD) female age in the pregnant and non-pregnant groups was 28.68±4.14 and 29.25±5.20 (range, 19-48) years, respectively. The mean (±SD) male age was 33.01±5.41 years in the pregnant group and 32.59±4.78 years in the non-pregnant group (range, 21-49 years). As can be noted, there were no significant differences in the female or male ages among both groups (Table 1).

Table 2 shows the outcome of IUI (pregnancy rate) for the different female age groups.

Regarding the age of the female, patients were divided into four age groups as follows: <25 years, 25-29 years, 30-34 years, and >35 years.

Out of 82 pregnancies that occurred, 37 (45.1%) were achieved in the age group of 25-29 years, and 7 (8.5%) were achieved for the age of 35 years and over. However, according to the chi-square test, no significant correlation was found between female age and IUI success (p=0.578).

In addition, the two groups did not differ statistically for the duration of infertility (Table 1).

Table 3 shows the comparison between pre and post processing semen analysis parameters between the pregnant and non pregnant groups.

There was no significant difference in semen parameters including sperm volume, sperm concentration and TMSC before and after sperm processing between the two groups (Table 3).

TMSC was divided into four groups: $<1\times10^6$, $1\text{-}4.99\times10^6$, $5\text{-}10\times10^6$, and $>10\times10^6$.

Pregnancy rates for the subgroups of pre and post processing TMSC are compared in Table 4.

The highest pregnancy rate occurred in TMSC of over 10 million and the lowest pregnancy occurred in TMSC of under 1 million. However, there was no significant relationship between pregnancy rate and TMSC pre and post processing semen analysis (p=0.503 and p=0.761, respectively).

Only sperm motility and normal sperm morphology before and after sperm processing were significantly associated with pregnancy rates between the two groups (p=0.023 before sperm processing and p=0.032 after) (p=0.032 before sperm processing and p=0.007 after, respectively) (Table 3).

Discussion

In the literature, pregnancy rate after IUI has been reported differently and it was dependent on several female and male factors (7,8,13,14). The results of our study showed that the pregnancy rate with IUI was 23.4% for each couple (82/350). This is similar to the results of (23.5%) Sinha et al. (19) and is in line with other studies (15,20,21).

In some studies, female age was shown to be an important predictor factor of IUI success (8,21,22). Yousefi and Azargon (21) showed that with an increase of patients' age, the pregnancy rate decreased, thus in their study, most pregnancies with IUI were observed in patients aged under 35 years (21). In the study of Ghaffari et al. (23), a negative relationship between female age and IUI outcome was shown.

The age-related decline in female fertility is attributable to the reduction of ovarian reserve and the aging of the reproductive system (20,24,25). In our study, there was no significant difference regarding the mean age of the women in the

Table 2. Outcome of intrauterine insemination procedure for different female age groups

Age groups (years)	Females n (%)	Pregnancies n (%)	p value
<25	56 (16.0)	14 (17.1)	0.578
25-29	141 (40.3)	37 (45.1)	
30-34	111 (31.7)	24 (29.3)	
>35	42 (12.0)	7 (8.5)	
Total	350 (100)	82 (100)	

χ^2 test was used to determine significance; $p<0.05$ was considered statistically significant

Table 1. The participants' demographic data

Parameters	Pregnant n=82 (23.4%) mean ± standard deviation*	Non-pregnant n=268 (76.6%) mean ± standard deviation*	p value**
Female age (years)	28.68±4.14	29.25±5.20	0.508
Male age (years)	33.01±5.41	32.59±4.78	0.701
Infertility duration (months)	38.34±27.46	38.89±31.29	0.716

*Data are presented mean ± standard deviation; **p<0.05 was considered statistically significant. The Mann-Whitney U test was used for all variables

pregnant and non pregnant groups (p=0.508) (Table 1). We also compared pregnancy rates for different female age groups. Out of 82 pregnancies, 37 (45.1%) occurred for those aged between 25-29 years and only 7 (8.5%) occurred in women aged over 35 years (Table 2). However, the results of the present study are similar to the results of Basirat et al. (11), Koyun Ok et al. (14), Ganguly et al. (26), and Yildirim et al. (27) who failed to show a significant correlation between female age and IUI success (p=0.578). We believe that this is more likely due to the small population in our study. Sharma et al. (28) published a study showing that with an increase in male age, the fertility rate was reduced. In this study, there was no significant difference in the age of males between the pregnant and non-pregnant groups. This finding is in agreement with several studies (11,19,27,29).

The reports of some studies indicated that with the increase in the duration of infertility, the chance of pregnancy decreased, which is probability attributed to the increased age of patients (23,27,30). Yavuz et al. (31) found that the pregnancy rate in couples with a period of infertility of less than 6 years was 2.33 times higher than those with infertility problems for over 6 years. The results of our study are similar to those of other studies that found no significant association between the duration of infertility and IUI success (7,8,14,20,26).

Although several studies reported the effect of semen parameters on IUI success (7,10,14,32), Luco et al. (12) failed to indicate such a relationship. A lack of agreement exists about the best semen parameters that can predict the possibility of pregnancy after IUI (13,32,33). Ruiter-Ligeti et al. (10) evaluated the impact of semen processing on sperm parameters and pregnancy rates after IUI. They found that semen processing led to significant increases in most sperm parameters such as the percentage of motile sperm and forward sperm progression (10).

Zhao et al. (34) published a retrospective study showing that pre and post processing sperm motility were independent factors that affected pregnancy rates. Our results agree with several studies that showed that sperm motility significantly influenced pregnancy rates after IUI (p=0.023 before sperm processing and 0.032 after) (7,8,10,21,31).

The importance of sperm morphology alone to predict IUI results before or after sperm preparation is controversial. Some researchers found that sperm morphology in male infertility was not a prognostic factor in IUI success (12,35). In contrast, Aboutorabi et al. (36) showed that in comparison with the other semen parameters, normal sperm morphology before and after semen processing had higher sensitivity and specificity and was more effective in predicting IUI outcomes (36). Lemmens et al. (37) concluded that none of the sperm parameters had a direct association with IUI success, but sperm morphology ≤4% could contribute to IUI success. Our result demonstrated that normal sperm morphology was significantly associated with pregnancy rates (p=0.032 before sperm processing and 0.007 after). These results also confirm the findings achieved by Jellad et al. (8) and Kdous et al. (32)

Wiser et al. (13) published a study to design a model to predict IUI success. This model included all basic sperm

Table 4. Comparison of pregnancy rates with total motile sperm count before and after sperm processing

Before semen processing TMSC ($\times 10^6$)	Cases n (%)	Pregnancies n (%)	p value
<1	6 (1.7)	0 (0)	0.503
1-4.99	16 (4.6)	3 (3.7)	
5-10	25 (7.1)	4 (4.9)	
>10	303 (86.6)	75 (91.4)	
Total	350 (100)	82 (100)	
After semen processing TMSC ($\times 10^6$)			
<1	21 (6)	3 (3.6)	0.761
1-4.99	53 (15.2)	11 (13.4)	
5-10	82 (23.4)	18 (22)	
>10	194 (55.4)	50 (61)	
Total	350 (100)	82 (100)	

TMSC: Total motile sperm count; χ^2 test, Fisher's exact test was used to determine significance; p<0.05 was considered statically significant

Table 3. Sperm parameters in the pregnant and non-pregnant groups before and after semen processing

Parameters	Preprocessing mean ± standard deviation*			Postprocessing mean ± standard deviation*		
	Pregnant n=82 (23.4%)	Non-pregnant n=268 (76.6%)	p value**	Pregnant n=82 (23.4%)	Non-pregnant n=268 (76.6%)	p value**
Semen volume (mL)	3.09±0.82	3.09±0.68	0.960	0.7043±0.2457	0.6894±0.2415	0.625
Sperm count (10^6/mL)	88.25±34.90	86.85±37.43	0.977	29.78±14.26	28.35±15.23	0.444
Sperm motility (%)	0.4891±0.08991	0.4568±0.1183	0.023	0.9176±0.08137	0.8725±0.14925	0.032
Normal morphology (%)	0.3009±0.08598	0.2790±0.06151	0.032	0.7160±0.1197	0.6765±0.1377	0.007
TMSC	48.17±40.67	43.81±37.68	0.517	15.08±10.83	13.78±11.45	0.195

*Data are presented mean ± standard deviation; **p<0.05 was considered statistically significant; the Mann-Whitney U test was used for all variables; TMSC: Total motile sperm count

characteristics: sperm concentration (million/mL) × volume (mL) × motility (%) × morphology (%) and showed that the total motile normal sperm count was a more reliable criterion to predict IUI success.

The minimum of TMSC recommended by authors varies in different studies, and is reported to be between 0.8 to 10×10^6 (8,14,16,17,32). Tan et al. (38) discussed the predictive value of postwashed TMSC on IUI success. They showed that TMSC was an independent predictor, and to achieve statistically pregnancy rate after IUI, at least 0.5×10^6 or greater TMSC was needed (38). A "linear by linear" relationship between post-processsing TMSC and IUI sucess was observed in Koyun Ok et al. (14). Tournays (39) declared that the TMSC could predict pregnancy failure more than pregnancy success; when the TMSC is lower than 1 million, in vitro fertilization should be suggested (39). In contrast, Hassan et al. (15) evaluated the impact of both pre and post processing TMSC on pregnancy rates and showed that pregnancy rates following IUI were unaffected by TMSC. In the present study, we found no significant difference for TMSC between the groups who did and did not achieve pregnancy.

Pregnancy rates for subgroups of pre and post processing TMSC were compared and in this regard, most pregnancies observed were with a TMSC of more than 10 million and the lowest pregnancy rate was observed in TMSC under one million. It should be noted that we had very few subjects with TMSC under 10 million. However, it is difficult to determine the effects of TMSC on IUI outcomes at these levels of subjects. Our results are consistent with those of several studies (15,18,23) that found no significant relationship between TMSC and IUI success (pre $p=0.503$ and post $p=0.761$ semen processing). Similar to our findings, Zadehmodarres et al. (22), Koyun Ok et al. (14), and Kdous et al. (32) demonstrated that sperm concentration before and after preparation had no significant effect on IUI success (14,22,32). However, Dadkhah et al. (30) did find such a relationship.

There are few articles about the correlation of the volume of inseminated sperm with IUI success (14,23). Study by Ghaffari et al. (23) showed the influence of semen volume in predicting IUI success. In 2013, Koyun Ok et al. (14) evaluated the effect of low semen volume on pregnancy rates. In agreement with our study, no significant relationship was shown between semen volume and IUI outcomes.

Variations and inconsistencies in the literature concerning predictive factors for IUI sucess can be attributed to the heterogeneity of the studied populations, the small size of the study population, the method of using statistical tests, and the lack of prospective clinical studies. Besides, differences in the correct use of standard criteria for sperm preparation, injection techniques, ovulation induction regimens, reporting method, inadequate care for women after sperm injection, and lack of adequate education should not be neglected (21,37,40,41).

The principal limitation of this study is that it was a retrospective study. Data were collected from information previously registrated in the patients' records. No documents were available about the number of follicles and serum hormones such as follicle-stimulating hormone, luteinizing hormone, and anti-mullerian hormone. However, in this study we only included male factors in order to make the differences in sperm parameters more significant. In comparison with other studies, the population evaluated in our study was small and may not be adequate to achieve statistical significance for some parameters such as age and TMSC. Hence, larger prospective, randomized, controlled clinical studies are recommended. Another limitation is that clinical pregnancy was only defined as serum-positive β-hCG two weeks after IUI and sonography results were not recorded for the observation of a gestational sac and fetal heart rate in the patients' records. Considering the fact that the goal of infertility treatment is live births, it is recommended that in subsequent studies, pregnancy outcomes such as live births, stillbirth, abortion, and multiple pregnancies should be carefully investigated for infertile couples who undergo IUI.

The strength of this study is that it included all sperm parameters before and after processing and the whole process of sperm preparation was performed and reported in the same method by the same team.

The results of the present study indicate that there was a significant difference in sperm morphology and sperm motility before and after sperm processing between the pregnant and non-pregnant groups. Therefore, it seems that sperm motility and normal sperm morphology have a positive effect on IUI success.

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Ethics Committee Approval: *The research was approved by the Ethics Committee of the Deputy of Research and Technology Shahroud University on 25th January 2016 (Ethical code no: 182).*

Informed Consent: *Being a retrospective study, informed consent was not required per the IRB protocol.*

Peer-review: *Externally peer-reviewed.*

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

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Overcoming barriers to vaginal hysterectomy: An analysis of perioperative outcomes

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Abstract

Objective: To determine perioperative outcome differences in patients undergoing vaginal hysterectomy based on uterine weight, vaginal delivery, and menopausal state.

Material and Methods: Retrospective chart review of 452 patients who underwent vaginal hysterectomy performed by a single surgeon. Patients' age, vaginal delivery, uterine weight, previous pelvic surgery, previous cesarean delivery, removal of ovaries were compared, as well as estimated blood loss (EBL), operating room time (ORT), length of stay, intraoperative complications and postoperative complications. Multivariable logistic regression was used, and all data were analyzed at the level of $p<0.05$ statistical significance using SAS system software (SAS Institute Inc., Cary, NC), version 9.3.

Results: The mean age was 57.13±11.52 years and the median vaginal delivery was 2. The uterine weight range was 16.6-1174.5 g (mean 169.79±183.94 g). The incidences of blood transfusion and bladder injury were 3.03% and 0.66%, respectively. Factors shown to be associated with longer ORT included greater uterine weight, removal of ovaries, posterior repair, tension-free vaginal tape sling, prolapse, and EBL >500 mL ($p<0.001$). The factors associated with EBL >500 mL were greater uterine weight ($p=0.001$), uterine myomas ($p=0.016$) and premenopausal state ($p=0.014$). The factors associated with conversion to laparotomy were greater uterine weight ($p<0.001$) and premenopausal state ($p<0.001$).

Conclusion: Vaginal hysterectomy is a safe and feasible approach for patients desiring hysterectomy regardless of uterine weight and vaginal delivery. (J Turk Ger Gynecol Assoc 2019; 20: 8-14)

Keywords: Vaginal hysterectomy, perioperative outcomes, minimally invasive

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Introduction

Hysterectomy is the most frequent non-pregnancy-related major surgical procedure performed on women in the United States (US) (1,2). The most common benign indications include leiomyomas, endometriosis, and prolapse, followed by pelvic pain, dysfunctional uterine bleeding, adenomyosis, pelvic inflammatory disease, and obstetric indications (1,2). Evidence suggests that when deemed feasible, the vaginal approach is the safest route of performing hysterectomy for benign disease and is considered the gold standard approach (2-8). When compared with abdominal hysterectomy, it is associated with fewer complications, including urinary tract injury and infection, as well as better economic outcomes and perioperative outcomes including operating room time (ORT), length of hospital stay, and recovery time (3-8). In addition, multiple studies have shown no benefit of laparoscopic-assisted vaginal hysterectomy when compared with vaginal hysterectomy (9). Furthermore, vaginal hysterectomy was associated with shorter operative time and shorter hospital stay compared with total laparoscopic hysterectomy and laparoscopic-assisted vaginal hysterectomy (9).

Several studies comparing perioperative outcomes in vaginal hysterectomy versus robotically-assisted laparoscopic

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hysterectomy found that vaginal hysterectomy was associated with shorter operative time, overall comparable perioperative outcomes, and lower cost (10-15). Jacome et al. (11) reported a slight increase in "major" intraoperative complications with vaginal compared with the robotic surgical approach, although those "major intraoperative complications" were never defined and the statistical analysis was underpowered. Additionally, a study by Martino et al. (16) reported lower estimated blood loss (EBL), shorter hospital length of stay, and lower readmission rates in robotic-assisted laparoscopic hysterectomies when compared with all non-robotic surgical approaches including vaginal hysterectomy in their retrospective study of 2554 patients. Even though the American College of Obstetricians and Gynecologists has considered vaginal hysterectomy as the gold standard approach, vaginal hysterectomy is still largely underutilized as evidenced by US statistics, which show that 66% of hysterectomies performed for benign conditions are still being performed by the abdominal route, 22% vaginally and, 12% laparoscopically, with the rate of vaginal hysterectomy having steadily declined since its peak in 2002 (2,17).

Historically, physicians have used certain clinical criteria to exclude patients as candidates for vaginal hysterectomy, including large uterine size, a narrow vagina or narrow pubic arch, prior pelvic or abdominal surgery, and undescended or non-mobile uterus (18-20). Currently, there is a growing body of evidence that such rigid guidelines should not be used to limit the use of vaginal hysterectomy. Multiple studies have shown high success rates performing vaginal hysterectomy despite enlarged uteri (3,17,21,22). Furthermore, nulliparity has also been largely dispelled as a potential barrier for success of vaginal hysterectomy (2,5,6,8,17,23). Nulliparity used in this context refers to anatomic considerations such as narrow vaginal introitus, narrow pubic arch and/or lack of descensus, which have traditionally been associated with nulliparity.

Our study aims to examine factors associated with successful vaginal hysterectomy despite perceived challenges based on patient history and physical examination. We sought to determine if any differences in perioperative outcomes existed in patients undergoing vaginal hysterectomy based on uterine weight, parity, and menopausal state. We hypothesized that given an experienced surgeon, vaginal hysterectomy should remain the gold standard approach regardless of large uterus, nulliparity or menopausal status.

Material and Methods

This is a retrospective descriptive study of a prospectively collected database, with 452 patients' charts reviewed in total. All patients underwent vaginal hysterectomy by a single urogynecologist with a referral-based practice in a community academically-affiliated hospital between March 2003 and March 2016. The surgeon was assisted on all cases by OB/GYN residents in training. The most common indications for surgery included uterovaginal prolapse, abnormal uterine bleeding, and uterine leiomyoma, which accounted for 94% of the surgical indications.

Vaginal hysterectomy was performed by first entering the posterior cul de sac sharply followed by progressive clamping of the suspensory ligaments (uterosacral, cardinal, uteroovarian) with curved Heaney clamps and ligating with Vicryl sutures on both sides. McCall's culdoplasty was performed on all patients prior to closure of the vaginal cuff by placating the uterosacaral ligaments to the peritoneal surface prior to vaginal cuff closure. If salpingoophorectomy was performed, it was done so by grasping the adnexa with a Babcock clamp and using a Vicryl Endoloop to ligate the pedicle followed by transection of the adnexa.

Information was extracted from pre-operative patient histories, pathology reports, and operative reports. Variables studied include patient age, vaginal delivery, uterine weight, indication for surgery, previous pelvic surgery, previous cesarean delivery, and removal of ovaries. These variables were examined for statistically significant associations with perioperative complications, our primary outcome. For our study, we defined patients with uterine weight >250 g as having a "large uterus". Menopausal status was determined by patient history, referring to the absence of menses >1 year. Perioperative complications in our study were defined as EBL more than 500 mL, conversion to laparotomy, ureteral and bladder injuries, as well as post-operative complications during the 6 weeks following surgery, which includes bowel injury, vaginal cuff cellulitis, pelvic collections/abscesses, ureteral injury, bladder injury, and post-op fever.

All factors were explored using a multivariable logistic regression. For ORT analysis, multiple linear regression was used. All data were analyzed at a level of $p<0.05$ statistical significance using SAS system software (SAS Institute Inc., Cary, NC), version 9.3.

Results

The study population included a total of 452 patients. The mean age was 57.13±11.52 (range, 26-85) years, and the median number of vaginal deliveries was 2 (range, 0-8) (Table 1). The uterine weight range was 16.6-1174.5 g with a mean of 169.79±183.94 g (Table 1). The overall incidence of blood transfusions and bladder injuries were 3.03% and 0.66%, respectively (Table 3-5). Seven patients were converted to abdominal hysterectomy with a conversion rate of 1.5% (Table 2). The factors associated with conversion to laparotomy were greater uterine weight ($p<0.001$) and premenopausal

Table 1. Patient demographics and characteristics

Mean age	57.13±11.52 years
Mean vaginal delivery	2.59±1.65
Mean uterine weight	169.79±183.94 grams
Prior vaginal delivery	87.8% (n=397)
Post-menopausal status	59.1% (n=267)
• Prior abdominal and/or pelvic surgery • Dilation and curettage • Cesarean section • Tubal ligation • Laparoscopic ovarian cystectomy, salpingectomy, oophorectomy • Diagnostic laparoscopy • Cone biopsy/LEEP • Abdominoplasty • Anterior repair/TVT • Myomectomy • Appendectomy • Gastric bypass • Ex-lap • Cholecystectomy • Hernia repair	61.5% (n=278*) 16.8% (n=60) 14.5% (n=52) 32.7% (n=117) 8.7% (n=31) 1.9% (n=7) 1.1% (n=4) 1.9% (n=7) 5.6% (n=20) 3.1% (n=11) 7.2% (n=26) 1.7% (n=6) 1.4 % (n=5) 1.4% (n=5) 2.0% (n=7)
Bilateral ovaries and fallopian tubes removed	27.4% (n=124)
Prolapse present	62.6% (n=283)
LEEP: Loop Electrocautery Excision Procedure; TVT: Tension-free vaginal tape; *278 out of 462 patients had prior pelvic surgery. Many patients had more than one procedure and each individual procedure was noted in this section	

state (p<0.001). Conversion to laparoscopy was not chosen in these 7 cases due to physician preference. As stated above, all patients undergoing vaginal hysterectomy had uterosacral suspensions, including those who did not have hysterectomies for prolapse. There were 2 readmissions within 6 weeks post-op, including one for a bowel injury and one for a pelvic abscess. The patient with the bowel injury had history of multiple prior laparotomies and although the hysterectomy was able to be completed vaginally, the patient re-presented 2 week later with peritonitis and was found to have a small enterotomy in the sigmoid colon.

The factors associated with longer ORT were uterine weight, removal of ovaries, posterior repair, tension-free vaginal tape sling, prolapse, and EBL more than 500 mL (p<0.001). The factors associated with EBL more than 500 mL were uterine weight (p=0.001), uterine myomas (p=0.016), and premenopausal state (p=0.014). No significant difference was noted in the incidence of blood transfusions, bladder and ureteral injuries, as well as readmissions in patients regardless of uterine weight, vaginal delivery or menopausal status (Table 3-5).

Discussion

The objective of our study was to determine if perioperative differences existed in patients undergoing vaginal hysterectomy based on uterine weight, vaginal delivery, and menopausal state. We found that although greater uterine weight was associated with longer ORT and EBL more than 500 mL, no significant differences were noted in the incidence of blood transfusions, bladder/ureteral injury, or readmissions in patients regardless of uterine weight, vaginal delivery or menopausal state (Table 3-5). Although conversion to laparotomy was found to be associated with greater uterine weight, the overall incidence of conversion was 1.5%, which is exceedingly low for a cohort of this size. Our findings are in agreement with the current literature, which emphasizes that vaginal hysterectomy can be successfully performed with favorable perioperative outcomes in patients with characteristics previously perceived to be contraindications.

Benassi et al. (3) examined uterine weight as a risk factor for perioperative complications in patients undergoing vaginal hysterectomy (n=60) versus abdominal hysterectomy (n=59) for fibroid uteruses weighing 200-1300 g. The results were shorter ORT, shorter hospital stay, as well as lower incidence of post-operative fever and demand for post-operative analgesics in the vaginal hysterectomy group compared with the abdominal hysterectomy group. Darai et al. (22) similarly evaluated uterine weight as a risk factor for successful completion of vaginal hysterectomy. Eighty patients who were referred for abdominal hysterectomy were randomized to vaginal hysterectomy vs laparosopic-assisted vaginal hysterectomy. The inclusion criteria included uterine weight more than 280 g, as well as one or more commonly considered contraindications to vaginal hysterectomy such as prior pelvic surgery, history of pelvic inflammatory disease, moderat-to-severe endometriosis, adnexal masses or nulliparity without uterine descent. The investigators found that the complication rates were lower in the vaginal hysterectomy group compared with the laparoscopic-assisted vaginal hysterectomy group (15% and 37%, respectively) and vaginal hysterectomy was associated with shorter ORT.

Agostini et al. (23) examined nulliparity as a risk factor for increased perioperative complications. The study included 345 women without uterovaginal prolapse and without prior pelvic surgery undergoing vaginal hysterectomy for benign indications. Only 52 patients were nulliparous; however, the authors concluded that ORT and overall complication rate was higher in nulliparous patients. Additionally, Tohic et al. (24) evaluated 300 patients without previous vaginal delivery for success rates of planned vaginal hysterectomy and found

Table 2. Clinical information for patients converted to laparotomy

Patient	Age	Vaginal delivery	Prior VD	Menopausal status	Indication	Prior surgery	Uterine weight (g)	Reason for conversion
1	47	2	0	Pre	Menorrhagia	Cesarean section (2), hysteroscopic myomectomy, bilateral tubal ligation	1174.5	Large fibroid, could not bring down into surgical field
2	47	2	0	Pre	Menorrhagia	Cesarean section (2)	1022	Large fibroids, bleeding with uterine morcellation
3	45	0	0	Pre	Menorrhagia	None	1090.6	Large fibroids, could not bring down into surgical field
4	42	2	1	Pre	Menorrhagia	Cesarean section (1), abdominoplasty, cholecystectomy, ventral hernia repair	309	Uterus severely scarred and densely adhesed to rectus fascia
5	45	1	1	Pre	Fibroids	Dilation and curettage	1074	Large fibroids, could not bring down into surgical field
6	47	4	4	Pre	Menorrhagia	Bilateral tubal ligation	634	Large anterior fibroid on pubic bone, could not bring down into surgical field
7	43	2	1	Pre	Menorrhagia	Cesarean section (1), diagnostic laparoscopy, dilation and curettage	519.9	Large anterior fibroid on pubic bone, could not bring down into surgical field

VD: Vessel disease

Table 3. Perioperative complications and uterine weight

Complication	Total (n=452)	Uterus <250 g (n=358)	Uterus >250 g (n=87)	Uterine weight unknown (n=7)	p value
EBL >500 cc	11.7% (n=53)	8.1% (n=29)	27.6% (n=24)	-	<0.001‡
Blood transfusion	3.03% (n=11)	2.0% (n=7)	4.6% (n=4)	-	0.303‡
Bladder Injury	2.9% (n=13)	3.4% (n=12)	1.1% (n=1)	-	0.313‡
Hematoma	0.88% (n=4)	1.1% (n=4)	0.0% (n=0)	-	0.828‡
Post-op fever	2.0% (n=9)	1.4% (n=5)	3.4% (n=3)	n=1	0.821‡
Ureteral Injury	0.69% (n=3)	0.56% (n=2)	1.1% (n=1)	-	0.602‡
Conversion to laparotomy	1.5% (n=7)	0% (n=0)	8.0% (n=7)	-	<0.001‡
Mean length of stay (days)	0.88±0.85	0.87±0.88	0.92±0.66	-	0.198‡
Mean surgical time (mins)	100.66±34.35	97.72±31.13	118.78±42.07	-	<0.001‡

‡Multivariable logistic regression was used for all statistical analysis of these variables; EBL: Estimated blood loss

a 92.1% success rate; however, perioperative outcomes were not reported. In another study by Harmanli et al. (19) 75 women with the intention of undergoing vaginal hysterectomy by a single surgeon were included in the study. Fifty patients successfully underwent vaginal hysterectomies compared with 25 that failed. Although multiple factors were compared between the two groups, the investigators concluded that the only patient characteristic associated with an increased risk of failure for vaginal hysterectomy was the presence of a narrow pubic arch, which was determined clinically by the surgeon.

Figueiredo et al. (5) evaluated perioperative outcomes in 300 women without prolapse undergoing vaginal hysterectomy for benign indications. Vaginal delivery and prior pelvic surgery were the only risk factors evaluated, and only 7% of their cohort was nulliparous. They similarly concluded no significant differences in perioperative outcomes.

Table 4. Perioperative outcomes and menopausal status

Complication	Total (n=452)	Pre-menopausal (n=182)	Menopausal (n=267)	Menopausal status unknown (n=3)	p value
EBL >500 cc	11.7% (n=53)	21.4% (n=39)	16.5% (n=14)	-	<0.001‡
Blood transfusion	3.03% (n=11)	3.8% (n=7)	1.5% (n=4)	-	0.110‡
Bladder injury	2.9% (n=13)	3.8% (n=7)	2.2% (n=6)	-	0.121‡
Hematoma	0.88% (n=4)	1.0% (n=2)	0.75% (n=2)	-	0.697‡
Post-op fever	2.0% (n=9)	1.1% (n=2)	2.6% (n=7)	-	0.267‡
Ureteral injury	0.69% (n=3)	0.55% (n=1)	0.75% (n=2)	-	0.807‡
Conversion to laparotomy	1.5% (n=7)	3.84% (n=7)	0% (n=0)	-	0.002‡
Mean length of stay (days)	0.88±0.85	0.80±0.67	0.92±0.93	-	0.214‡
Mean surgical time (mins)	100.66±34.35	100.24±38.80	101.02±31.16	-	0.826‡
‡Multivariable logistic regression was used for all statistical analysis of these variables; EBL: Estimated blood loss					

Table 5. Perioperative complications and prior vaginal delivery

Complication	Total (n=452)	Prior VD (n=397)	No prior VD (n=50)	Prior VD unknown (n=5)	p value
EBL >500 cc	11.7% (n=53)	11.6% (n=46)	14.0% (n=7)	-	0.740‡
Blood transfusion	3.03% (n=11)	2.3% (n=9)	4.0% (n=2)	-	0.482‡
Bladder injury	2.9% (n=13)	2.8% (n=11)	4.0% (n=2)	-	0.655‡
Hematoma	0.88% (n=4)	1.0%(n=4)	0.0% (n=0)	-	0.474‡
Post-op fever	2.0% (n=9)	2.0% (n=8)	2.0% (n=1)	-	0.960‡
Ureteral injury	0.69% (n=3)	0.75% (n=3)	0.0% (n=0)	-	0.531‡
Conversion to laparotomy	1.5% (n=7)	1.0% (n=4)	6.0% (n=3)	-	0.043‡
Mean length of stay (days)	0.88±0.85	0.83±0.78	1.18±1.23	-	0.126‡
Mean surgical time (mins)	100.66±34.35	99.40±33.20	111.26±42.17	-	0.061‡
‡Multivariable logistic regression was used for all statistical analysis of these variables; VD: Vessel disease; EBL: Estimated blood loss					

Doucette et al. (4) examined vaginal hysterectomy success rates and perioperative complications in a group of 250 patients with large uterus weighing more than 180 g, and either no prior vaginal delivery or previous cesarean section or pelvic laparotomy. The study had three control groups that underwent either laparoscopic-assisted vaginal hysterectomy (n=250), vaginal hysterectomy (n=250) or abdominal hysterectomy (n=250). They concluded that large uterus, nulliparity, previous cesarean delivery, and pelvic laparotomy rarely constituted contraindications to vaginal hysterectomy, and vaginal hysterectomy was found to be associated with the least number of perioperative complications when compared with the laparoscopic-assisted vaginal hysterectomy and abdominal approaches.

In a study by Paparella et al. (20) the investigators prospectively enrolled 204 patients with benign indications for hysterectomy to undergo vaginal hysterectomy by a single experienced vaginal surgeon with an experienced laparoscopic surgeon available if needed for laparoscopic assistance or conversion. Each patient had one or more commonly considered contraindications to vaginal surgery, including prior pelvic surgery, history of pelvic inflammatory disease, moderate-to-severe endometriosis, adnexal masses or nulliparity with lack of uterine descent, and limited vaginal access. Patients were thus divided into five groups, corresponding to each of the commonly considered contraindications listed above. The perioperative factors being evaluated were identical to those evaluated in our study. Similarly to our study, they found no statistically significant differences in complication rates among the five groups of patients studied. However, this study excluded patients with prolapse. Two major limiting factors of this study were the lack of a control group for comparison of perioperative outcomes and the small patient sample size, which was less than half of that presented in our study.

Lastly, in addition to the literature comparing perioperative outcomes in patients with different pre-operative characteristics undergoing vaginal hysterectomy, there is also a substantial amount of literature comparing vaginal hysterectomy with other minimally invasive hysterectomy approaches such as laparoscopic hysterectomy, laparoscopic-assisted vaginal hysterectomy, and robotic-assisted laparoscopic hysterectomy (4,10-16,21,22,25,26). The conclusions of these studies are

mixed with regard to comparison of perioperative outcomes; however, it has consistently been noted that robotic-assisted laparoscopic hysterectomy is associated with longer ORT and higher costs of care.

The strengths of our study include the large cohort of cases over an extended period of time performed by the same surgeon with a wide variety of patient characteristics and outcomes examined. Currently, our study is the largest that we know of that evaluates and dispels multiple patient characteristics as risk factors for vaginal hysterectomy as opposed to other studies that mainly examined a single risk factor (3,19,22,23). Our findings are limited by the retrospective nature of the study, the lack of power given that many outcomes were infrequent, and lack of Pelvic Organ Prolapse Quantification scores, which prevented us from identifying the degree of prolapse in each patient studied. In addition, the fact that all cases were performed by a single surgeon limits the ability to generalize the results to all surgeons, because the results of a highly experienced surgeon are not likely to be replicated. Lastly, the surgeon being assisted by different residents in each case is also a limitation, given that assistance by a senior compared with a junior resident may have theoretically resulted in better outcomes.

In conclusion, we believe our study supports the literature that vaginal hysterectomy is a feasible and safe approach despite commonly perceived challenges to its success. We have demonstrated favorable and comparable perioperative outcomes in patients undergoing vaginal hysterectomy regardless of uterine size, vaginal delivery or menopausal status. Although barriers to increased use of vaginal hysterectomy have been identified, further randomized controlled trials are needed to evaluate the feasibility and efficacy of various interventions proposed to increase the use of the vaginal approach.

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Results of an internal audit on the survival of patients with uterine sarcoma

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Abstract

Objective: In the last 5 years there has been much discussion about the surgical procedure for uterine fibroids, and essentially, also uterine sarcoma. Still there exists no reliable presurgical diagnostic tool to differentiate between benign fibroids and uterine sarcomas. The aim of this study was to confirm the suspected association between intraoperative spread of tumor by morcellation and impaired outcomes in patients with sarcoma.

Material and Methods: After the local ethics commission positively reviewed the study protocol, the oncologic database of our university hospital was retrospectively reviewed for patients with uterine sarcomas over a time period of 13 years (2002-2015). Data was extracted from the medical files and survival information was collected by contacting the patient's general practitioners if last follow-up-status was older than 6 months. For the analysis, patients were split into two groups with either intrasurgical morcellation (M+) or no morcellation (M-) regarding information provided by the surgical report.

Results: Data on 57 patients with uterine sarcoma were available for further analysis. The median age and body mass index of the patients was 63 years and 27 kg/m², respectively. The sarcoma subtypes were 25 leiomyosarcoma, 19 carcinosarcoma, 9 endometrioid stroma sarcoma, 3 adenosarcoma, and one case without further differentiation. In the majority, no morcellation was performed (M- group, n=44) and 51 patients received open surgery (3 laparoscopic, 1 vaginal, and 2 incomplete surgeries). The median time of follow-up was 31 months. The disease-free survival was 50.5 months and the Cox regression analysis showed a hazard ratio of 3.06 [no significant difference between the two subgroups (p=0.079; 95% confidence interval (CI): 0.9-10.6)]. The overall survival was found as 62.2 months and the Cox regression analysis showed a hazard ratio of 3.216 with a statistically significant difference between the two subgroups (p=0.013; 95% CI: 1.3-8.1).

Conclusion: Despite the efforts to find a pre-surgical diagnostic tool, the clinical situation remains unsatisfactory. Overall sarcoma prevalence is low during the last 13 years at our university center, but morcellation occurred in a relevant portion of patients (13 of 57). If sarcoma is suspected or diagnosed then en-bloc resection of the uterus can prolong survival. Thus, morcellation of the uterus and not the surgical technique (en-bloc resection) is the prognostic factor and should be avoided in any suspicious case. (J Turk Ger Gynecol Assoc 2019; 20: 15-22)

Keywords: Sarcoma, uterine, hysterectomy, fibroids, risk factors

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Introduction

Uterine sarcomas are a rare malignant entity of the uterus (1,2) and are diagnosed in approximately 0.2-0.5% (2-5) of all cases of hysterectomies. The World Health Organization (WHO) classification differentiates between mesenchymal and mixed (mesenchymal and epithelial) tumors (6). Pure mesenchymal tumors are further differentiated into leiomyosarcomas (LMS), endometrial stromal sarcomas, and smooth muscle tumors of uncertain malignant potential, and mixed tumors are differentiated into adenosarcomas and carcinosarcomas (CS). CS along with mullerian mixed tumors, malignant mesodermal mixed tumors, and metaplastic carcinoma are considered a subclass of endometrial carcinoma (6). Generally, the prognosis of uterine sarcomas is unfavorable. Whilst the International Federation of Gynecology and Obstetrics (FIGO) stage Ia still has a 5-year survival rate of 84.3%, this dramatically decreases for stage II (43.6%), III (38.8%), and IV (19.8%) (7).

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Clinical symptoms of this heterogenic tumor group might include uterine enlargement, bleeding, and pelvic pain, and are therefore rather unspecific and also common in many other gynecologic diseases (e.g. uterine leiomyomas). Blood parameters (serum lactate dehydrogenase, carcinoembryonic antigen, CA125, CA19-9, and CA15-3 (3,8), or presurgical imaging [ultrasound (US), magnetic resonance imaging (MRI), computed tomography (CT)] has room for improvement (3,9,10). Two case series for MRI scans found a positive predictive value of 52% (11) (negative predictive value 100%) and a specificity of 92% (12) to presurgically identify uterine sarcoma. Even positron emission tomography-CT is not capable of differentiating between benign uterine leiomyomas and malignant uterine sarcomas (13). US elastography case reports on the differential diagnosis of fibroids and sarcoma are being published (14), reporting a 'typical' mosaic pattern in sarcomas compared with a homogenous pattern in fibroids.

Given the fact that myomas are a common finding in gynecologic patients, distinguishing between suspected malignant tumors and benign fibroids has great implications for clinical practice. Due to fertility aspects, hypermenorrhea, and urogynecologic symptoms, surgery in patients with fibroids is frequent. Surgical treatment of benign uterine leiomyoma is either focused on the removal of the myoma or the complete uterus. With increasing availability of laparoscopic equipment and surgical training, the number of open abdominal surgeries has decreased (15-17) over the last decades in favor of laparoscopic-assisted vaginal hysterectomy, total laparoscopic hysterectomy, or laparoscopic supracervical hysterectomy, which are offered to women who do not wish to bear children. A uterus-conserving approach is offered if family planning is not complete. The vaginal approach is limited by patient factors [e.g. body mass index (BMI), previous vaginal births/surgeries, size of uterus] and surgeons skills; however, the laparoscopic pathway is possible even with larger uterus size (18,19), increased BMI (20), offers rapid recovery, less blood loss (21) and a low complication rate (22). Laparoscopic surgery can be considered the standard surgical treatment of uterine leiomyomas, with large specimens often requiring morcellation to be removed through trocar insertion sites. This will increase the numbers of uterine sarcomas accidentally through morcellation.

During morcellation, small visible and microscopic parts of the tissue may be dispersed within the abdomen. This might lead to peritoneal dissemination of tumor tissue (23). Based on the increased numbers of laparoscopic surgeries with subsequent morcellations, the rate of uterine sarcomas accidentally being morcellated will also increase. Given the general poor prognosis of uterine sarcomas (3,7,24) and the lack of sufficiently reliable preoperative diagnostic procedures to identify uterine sarcomas, this article tries to answer if accidental morcellation of uterine sarcomas in abdominal, vaginal or laparoscopic surgery has a negative impact on patients in terms of increased recurrence rates and/or decreased survival.

Material and Methods

Our university cancer centre database has continuously collected data for all oncologic patients since 2002. This database was searched for patients with uterine sarcoma or CS including patients up to January 2016. Though the documentation input in the database is performed by well-trained and specialised personnel, the documenting of rare diseases might have been misclassified and not shown in the results. To maximise the results, the search was conducted by diagnosis or surgical procedure. The result list was then checked for agreement with the inclusion criteria. All patient files with a hysterectomy as surgical treatment at the certified gynaecologic oncology centre with age >18 years were included in this analysis. The available date were analysed retrospectively for tumour stage, histologic subtype, and route of surgery (open/laparoscopic or vaginal). The route of surgery was noted and patients were classified according to the surgical and pathology reports in uterine morcellation (M+) or en-bloc resection (M-). Morcellation in an intraabdominal bag was not performed. The disease-free survival (DFS) and overall survival (OS) were compared between these two groups. Living status and follow-up was provided by the routine annual cancer centre follow-up. If these data were not available, the patient's general practitioner was contacted. Ethics approval (308/2012) was given by the Local Ethic Committee of Ulm University.

Parameters for the statistical analysis using the SPSS software (IBM® SPSS® Statistics Version) were age at histologic confirmation of sarcoma (WHO classification), BMI, American Society of Anesthesiologists status, date and status of follow-up, primary tumour stage [tumour, node, metastasis (TNM), FIGO classification 2009], resection status (R0 or R1/2), receptor status (oestrogen, progesterone) and location of recurrence, as well as further treatments (e.g. radiotherapy, chemotherapy). Due to the small sample sizes, no analyses were performed based on the influence of morcellation regarding the different histologic subtypes.

Descriptive statistical analysis was used to determine average, median, standard deviation, minimum and maximum, likelihood, and percentiles. The OS/DFS were defined in months starting from the date of surgery to the last documented vital status/date of recurrence. Survival was analysed using Kaplan-Meier analysis, the log-rank test, and Cox regression. $P<0.05$ was considered statistically significant. Further multivariate testing for differences was performed using the Wilcoxon-Mann-Whitney test, univariate testing with the Fisher's exact test, and the Mann-Whitney U test.

Results

The database search identified 59 patients with sarcoma treated at Ulm University Hospital, Department of Gynecology and Obstetrics between 2002 and 2015. Two patients were excluded because no follow-up data were available. The average age of the remaining 57 patients was 63 years and their average BMI was 27 kg/m^2. The histologic subtypes were LMS (n=25), CS (n=19), endometrial stroma sarcoma (n=9), high-grade sarcoma (n=3), and sarcoma without further classification (n=1). Twenty-nine patients were not TNM classified and only clinically staged, 15 patients were pT1, 10 pT2, and 5 pT3 after surgery. Detailed information on the two subgroups is presented in Table 1. Hormone receptors were negative or unknown in the majority of the specimens. Table 2

Table 1. Patient and tumour details in the subgroups

			Group M-	Group M+	Total
Tumor size pT	pT1	Number, n	12	3	15
		% Within the subgroup	52.2%	60.0%	53.6%
	pT2	Number, n	10	0	10
		% Within the subgroup	43.5%	0.0%	35.7%
	pT3	Number, n	1	2	3
		% Within the subgroup	4.3%	40.0%	10.7%
p=0.029	Total	Number, n	23	5	28
		% Within the subgroup	100.0%	100.0%	100.0%
Lymphnodes pN	pN0	Number, n	12	0	12
		% Within the subgroup	80.0%	0.0%	75.0%
	pN1	Number, n	3	1	4
		% Within the subgroup	20.0%	100.0%	25.0%
p=0.25	Total	Number, n	15	1	16
		% Within the subgroup	100.0%	100.0%	100.0%
Metastasis M	M0	Number, n	17	3	20
		% Within the subgroup	89.5%	37.5%	74.1%
	M1	Number, n	2	5	7
		% Within the subgroup	10.5%	62.5%	25.9%
p=0.011	Total	Number, n	19	8	27
		% Within the subgroup	100.0%	100.0%	100.0%
Age		Median in years	65	56	63
p=0.045					
Histology	LMS	Number, n	18	7	25
		% Within the subgroup	40.9%	53.8%	43.9%
	ESS	Number, n	6	3	9
		% Within the subgroup	13.6%	23.1%	15.8%
	CS	Number, n	17	2	19
		% Within the subgroup	38.6%	15.4%	33.3%
	AS	Number, n	2	1	3
		% Within the subgroup	4.5%	7.7%	5.3%
	Other	Number, n	1		1
		% Within the subgroup	2.3%		1.8%
p=0.548	Total	Number, n	44	13	57
		% Within the subgroup	100%	100%	100%

TNM classification with subgroup morcellated (M+) and non-morcellated (M-); p values with exact Fisher test; TNM: (T) tumour size, (N) lymph nodes, (M) metastasis; LMS: Leiomyosarcoma; ESS: Endometrioid stroma sarcoma; CS: Carcinosarcomas; AS: Adenosarcoma; pT/pN: Pathologic classification of the tumour size or lymph node status

provides further patient and histologic details. It is noteworthy that our M+ subgroup had significantly larger tumours and patients with primary metastases.

The surgical access was abdominal in 51 patients, laparoscopic in 3 patients, and vaginal in one. Another two patients were considered incurable after the surgery had started. Three patients were started laparoscopically and converted to open abdominal surgery due to very large fibromas with adhesions (n=2) and once to repair a bladder lesion. Twenty-eight patients were considered R0, 5 patients had a microscopic tumour, and 24 patients could not be classified. Further details regarding the surgery are provided in Table 3. Further treatments included radiotherapy (n=11), chemotherapy (n=25), and no further therapy (n=10). Cause of death was known in 10 patients (sarcoma n=2, other causes n=8) with a further 15 patients deceased. The remaining 32 patients had a documented live status, who were used for further analysis. Disease recurrence was found in 20 patients. Recurrence occurred mostly as distant or a combination of distant and local metastases, followed by local and lymph node metastases. The uterus was removed without morcellation (M-) in 44 surgeries and 13 cases were considered morcellated (M+).

The DFS of all patients was 50.5 months and Cox regressions analysis showed a hazard ratio of 3.06 without any significant difference between the two subgroups [12.3 months (M+) vs 54.9 months (M-); p=0.079; 95% confidence interval (CI): 0.9-10.6]. The OS was found as 62.2 months. Thereby, Cox regression analysis showed a hazard ratio of 3216 and was statistically significantly different between the two subgroups [19.2 months (M+) vs 69.2 months (M-); p=0.013; 95% CI: 1.3-8.1]. DFS and OS are presented in Figure 1.

Table 2. Patient and sarcoma details

Variable		All sarcomas n=57	LMS n=25	CS n=19	ESS n=9	AS n=3	Other n=1
Age, years	Average	61	56	68	63	60	61
	Median	63	51	67	60	67	61
BMI, kg/m²	Average	27	24	28	27	29	29
	Missing	5	3	1	1	0	0
Tumour size pT, n (%)	pT1	15 (26.3%)	4 (16.0%)	8 (42.1%)	2 (22.2%)	1 (33.3%)	0 (0%)
	pT2	10 (17.5%)	1 (4.0%)	9 (47.4%)	0 (0%)	0 (0%)	0 (0%)
	pT3	3 (5.3%)	1 (4.0%)	2 (10.5%)	0 (0%)	0 (0%)	0 (0%)
	Missing	29 (50.9%)	19 (76.0%)	0 (0%)	7 (77.8%)	2 (66.7%)	1 (100.0%)
Lymph node metastasis pN, n (%)	pN0	12 (21.2%)	4 (16.0%)	6 (31.6%)	2 (22.2%)	0 (0%)	0 (0%)
	pN1	4 (7.0%)	0 (0%)	4 (21.1%)	0 (0%)	0 (0%)	0 (0%)
	Missing	41 (71.9%)	21 (84.0%)	9 (47.4%)	7 (77.8%)	3 (100.0%)	1 (100.0%)
Grading G, n (%)	G1	7 (12.3%)	3 (12.0%)	0 (0%)	2 (22.2%)	2 (66.7%)	0 (0%)
	G2	13 (22.8%)	12 (48.0%)	0 (0%)	1 (11.1%)	0 (0%)	0 (0%)
	G3	24 (42.1%)	4 (16.0%)	16 (84.2%)	4 (44.4%)	0 (0%)	0 (0%)
	G4	4 (7.0%)	0 (0%)	2 (10.5%)	1 (11.1%)	0 (0%)	1 (100.0%)
	Missing	9 (15.8%)	6 (24.0%)	1 (5.3%)	1 (11.1%)	1 (33.3%)	0 (0%)
Remaining tumor R, n (%)	R0	28 (49.1%)	8 (32.0%)	13 (68.4%)	4 (44.4%)	2 (66.7%)	1 (100.0%)
	R1	5 (8.8%)	2 (8.0%)	1 (5.3%)	2 (22.2%)	0 (0%)	0 (0%)
	Missing	24 (42.1%)	15 (60.0%)	5 (26.3%)	3 (33.3%)	1 (33.3%)	0 (0%)
Estrogen receptor, n (%)	Negative	19 (33.3%)	3 (12.0%)	9 (47.4%)	5 (55.6%)	2 (66.7%)	0 (0%)
	Positive	9 (15.8%)	3 (12.0%)	2 (10.5%)	2 (22.2%)	1 (33.3%)	1 (100.0%)
	Missing	29 (50.9%)	19 (76.0%)	8 (42.1%)	2 (22.2%)	0 (0%)	0 (0%)
P4 receptor, n (%)	Negative	17 (29.8%)	3 (12.0%)	8 (42.1%)	5 (55.6%)	0 (0%)	1 (100.0%)
	Positive	11 (19.3%)	3 (12.0%)	3 (15.8%)	2 (22.2%)	3 (100.0%)	0 (0%)
	Missing	29 (50.9)	19 (76.0%)	8 (42.1%)	2 (22.2%)	0 (0%)	0 (0%)

Time interval 2002-2015, from a comprehensive database of the cancer centre of Ulm University; LMS: Leiomyosarcoma; ESS: Endometrioid stromasarcoma; CS: Carcinosarcomas; AS: Adenosarcoma; Other sarcoma: Sarcoma without further classification/details; pT/pN: Pathologic classification of the tumour size or lymph node status; M-Status: Clinical/diagnostic proven metastasis; P4: Progesterone; BMI: Body mass index

Discussion

Laparoscopic resection of uterine fibroids has been under scrutiny in recent years due to the lack of a preoperative diagnostic tool for uterine sarcoma. Reliable data on sarcoma incidence, diagnosis, prognosis, and further treatment are still rare. Prognosis for patients with uterine sarcoma is generally poor with a 5-year survival of 50% (25-30) (M+ vs M-: median OS 10.8 vs 39.6 months or 5-y OS 46% vs 73%) (26,31). Differences exist among subtypes and type of resection for survival. Endometrial stroma sarcoma and complete resection seem to be beneficial for the patient (32-34). Even in our small retrospective analysis, the results are in line with existing data on the recurrence pattern with mostly distant recurrence (35). Further data were published showing a decrease in survival if sarcomas were morcellated (31,36-39). The morcellation resulted in a tissue spill on various intraabdominal organs such as ovaries, liver, and omentum, and it did not matter which surgical technique (vaginal, laparoscopic or open) was used (40). Seidman et al. (41) published a reduced OS in patients with morcellation and LMS, but could not show this in other subtypes of uterine sarcoma. Similar results were published by other authors (26,42,43). Our data contribute to these conflicting results; DFS is not significantly different between the two surgical study groups – though there is a statistical trend indicating a disadvantage for the morcellated group. However the M+ subgroup had significant larger tumours and patients with primary metastases. However, our analysis shows a significant difference for OS, contrary to data published by Morice et al. (38). In their analysis, 123 patients were closely followed up and no significant difference in the 6-month recurrence rate was found between the two treatment groups (M- vs M+). However, the database includes various histologic subtypes (i.e. LMS, CS and endometrial stroma sarcoma with low and high-grade cases). The cases series by Liu et al. (44) indicates that there might be a very aggressive biologic subgroup, yet to be identified, due to the peritoneal metastasis in both surgical groups.

Perri et al. (43) and George et al. (31) found a 3-fold increased risk for metastasis if the tumour was morcellated [hazard ratio (HR): 2.85; 95% CI: (1.05-7.5); HR: 2.95; 95% CI: (1.5-6.0)] (31,43), and a significantly shorter DFS (p=0.03 and p=0.002, respectively), which was similar to the results from Park et al. (45) who showed a significantly reduced OS and DFS in 56 patients with stage I and II LMS. Here, patients with a morcellation had more peritoneal and vaginal cuff metastasis.

Table 3. Surgical management, adjuvant therapy and outcome of patients with uterine sarcoma

Variable		All sarcomas n=57	LMS n=25	CS n=19	ESS n=9	AS n=3	Other n=1
Hysterectomy n (%)	Abdominal	51 (89.5%)	21 (84.0%)	19 (100.0%)	8 (88.9%)	2 (66.7%)	1 (100.0%)
	Laparoscopic	3 (5.3%)	2 (8.0%)	0 (0%)	0 (0%)	1 (33.3%)	0 (0%)
	Vaginal	1 (1.8%)	1 (4.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Aborted surgery	2 (3.5%)	1 (4.0%)	0 (0%)	1 (11.1%)	0 (0%)	0 (0%)
ASA score, n (%)	I	5 (8.8%)	4 (16.0%)	0 (0%)	1 (11.1%)	0 (0%)	0 (0%)
	II	21 (36.8%)	11 (44.0%)	4 (21.1%)	5 (55.6%)	1 (33.3%)	0 (0%)
	III	25 (43.9%)	7 (28.0%)	13 (68.4%)	2 (22.2%)	2 (66.7%)	1 (100.0%)
	Missing	6 (10.5%)	3 (12.0%)	2 (10.5%)	1 (11.1%)	0 (0%)	0 (0%)
Radiotherapy postoperative n (%)	No	10 (17.5%)	4 (16.0%)	3 (15.8%)	3 (33.3%)	0 (0%)	0 (0%)
	Yes	11 (19.3%)	5 (20.0%)	6 (31.6%)	0 (0%)	0 (0%)	0 (0%)
	Missing	36 (63.2%)	16 (64.0%)	10 (52.6%)	6 (66.7%)	3 (100.0%)	1 (100.0%)
Chemo-therapy postoperative n (%)	No	11 (19.3%)	4 (16.0%)	5 (26.3%)	2 (22.2%)	0 (0%)	0 (0%)
	Yes	25 (43.9%)	14 (56.0%)	9 (47.4%)	0 (0%)	1 (33.3%)	1 (100.0%)
	Missing	21 (36.8%)	7 (28.0%)	5 (26.3%)	7 (77.8%)	2 (66.7%)	0 (0%)
Recurrence, n (%)	No	14 (24.6%)	3 (12.0%)	6 (31.6%)	4 (44.4%)	1 (33.3%)	0 (0%)
	Yes	20 (35.1%)	11 (44.0%)	7 (36.8%)	0 (0%)	1 (33.3%)	1 (100.0%)
	Missing	23 (40.4%)	11 (44.0%)	6 (31.6%)	5 (55.6%)	1 (33.3%)	0 (0%)
Death, n (%)	No	31 (54.4%)	12 (48.0%)	10 (52.6%)	5 (55.6%)	3 (100.0%)	1 (100.0%)
	Yes	25 (43.9%)	12 (48.0%)	9 (47.4%)	4 (44.4%)	0 (0%)	0 (0%)
	Missing	1 (1.8%)	1 (4.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Time interval 2002-2015, from a comprehensive database of the cancer centre of Ulm University; LMS: Leiomyosarcoma; ESS: Endometrioid stroma sarcoma; CS: Carcinosarcomas; AS: Adenosarcoma; Other: Sarcoma without further classification/details; ASA: American Society of Anesthesiologists

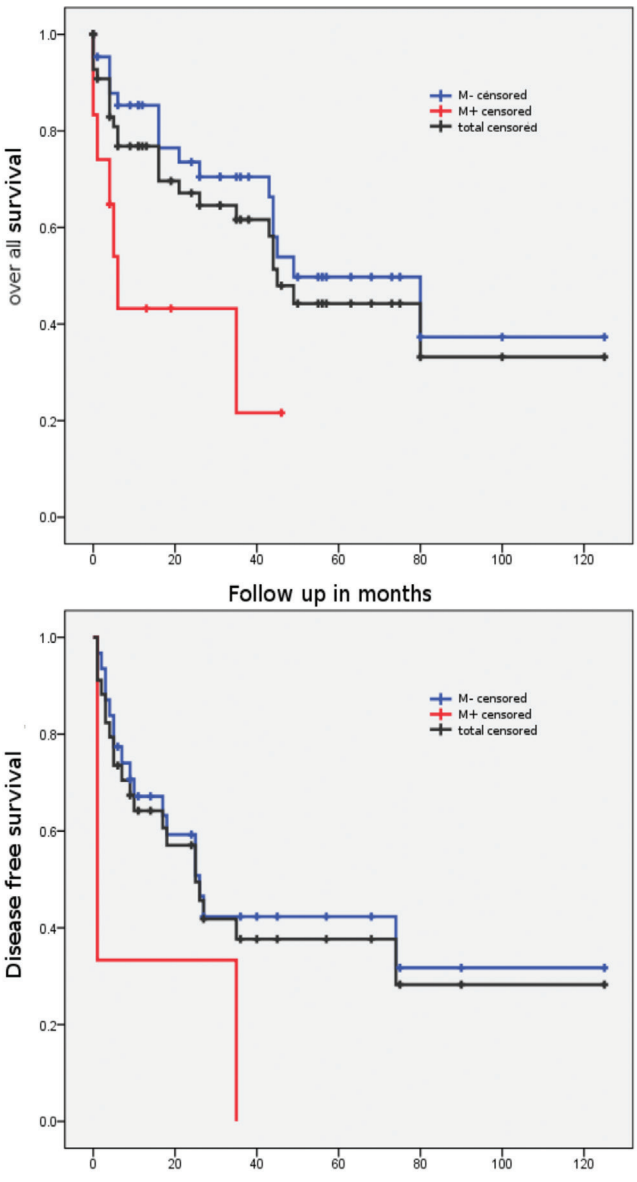

Figure 1. Disease-free survival and overall survival for all patients and the two subgroups. The disease-free survival difference M+/- is not statistically significant but should be considered clinically relevant. Patients with morcellation of the sarcoma (M+), no morcellation (M-)

The most current published data indicate that patients with uterine LMS may have a shorter DFS and OS. Due to the low numbers in our analysis, the DFS difference of 42.6 months was not statistically different, but still should be considered clinically relevant.

In early-stage low-grade endometrial stroma sarcoma, Park et al. (42) found a significantly shorter DFS but a longer, non-significant, 5-year OS for a morcellation subgroup. According to the authors the prolonged survival might be due to the more aggressive systemic therapy in case of morcellation and the short follow up. However, the incidence of accidental morcellation of uterine sarcoma seems to be low. In a large German monocentric retrospective study, the overall rate of uterine malignancies was 0.13% in more than 10,000 patients with morcellated uteri during laparoscopic-assisted supracervical hysterectomy. Thereby, the majority of malignancies were endometrial cancer (0.07%) with only 0.06% sarcomas [4 endometrial stromal sarcomas (0.04%) and 2 LMS (0.02%)] (46). As with any rare diseases, our retrospective database misses information on tumour classifications, follow-up, and most of all, the conclusions drawn from the analysis are restricted by the small number of cases. Unfortunately this also applies to most of the current literature regarding uterine sarcoma (47).

Only a few authors clearly differ between the subtypes of sarcoma (31,42,43). Other studies, like ours, included various subtypes in the analysis. Some tumour variables cannot be provided by the pathologist. For example, the sarcoma size cannot be measured on a morcellated uterus. Thereby, this factor is a limiting point in study analysis and is important for appropriate assessment of tumour stage, and further required adjuvant therapy and can impact the ability to identify pathologic features for the determination of the tumour entity. In summary, a retrospective database will always miss certain information on the tumour that might be vital for further analysis. However, a prospective randomised trial with a known uterine sarcoma and deliberate morcellation on basis of the current data is unethical. Accordingly, the only possible and ethical way to increase knowledge on these rare diseases is through retrospective studies.

Although this is a small, retrospective analysis, it includes all patients with uterine sarcoma over a time period of 13 years at a university hospital and investigates the impact of intraoperative morcellation. OS significantly differed between the intraoperative morcellation (M+) and whole-tumour resection (M-) subgroups. DFS also showed a clear, clinically relevant trend to impaired survival within the M+ group, but did not show a statistically significant difference. This is a common statistical issue with such small patient and follow-up numbers. Relapse mostly occurred as distant relapse. In contrast to some requests for abandoning morcellation in gynaecologic surgery, we recommend careful preoperative review and informed consent of intraoperative morcellation. This approach is in line with the Society of Gynecologic Oncology and the German Society for Gynecology and Obstetrics because purposeful use of morcellation allows less invasive surgery with reduced patients morbidity (48-50).

Although the overall numbers of patients treated with uterine sarcomas at our certified oncologic university centre is low, the rate of morcellated sarcomas (13 out of 57) underlies the

clinical relevance of the topic. To address the clinical demand for improved identification strategies, we are currently performing a prospective liquid biopsy study on all patients with suspected LMS and storing the drawn blood samples for further investigation in our biobank. Possible target markers include vascular endothelial growth factor and cell-free RNA with evaluation of their use as prognostic and predictive factors. Other studies are also investigating possible mutations in sarcomas for personalized systemic treatment options (51).

Our data support resection of the entire uterus if any malignancy including sarcoma is suspected or known. For patients and physicians, a reliable presurgical test to eliminate the risk of uterine sarcoma is urgently needed.

Ethics Committee Approval: *Ethics approval (308/2012) was given by the Local Ethic Committee of Ulm University.*

Informed Consent: *It was taken.*

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Comparing perioperative vaginal misoprostol with intraoperative pericervical hemostatic tourniquet in reducing blood loss during abdominal myomectomy: A randomized controlled trial

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Abstract

Objective: To compare the effectiveness of perioperative vaginal misoprostol with intraoperative pericervical hemostatic tourniquet in reducing blood loss during abdominal myomectomy.

Material and Methods: A randomized controlled trial involving women with uterine leiomyoma who underwent abdominal myomectomy was conducted at a tertiary facility in Nigeria. Participants were recruited after they gave informed consent and randomized into group I (single dose 400 μg vaginal misoprostol one-hour before surgery) and group II (intraoperative pericervical hemostatic tourniquet). Eighty participants (40 in each group) were recruited. Uterine size was measured in centimeters above the pubic symphysis, and blood loss estimation involved direct volume measurement and gravimetric methods. The main outcome measures were intraoperative blood loss, blood transfusion, and recourse to hysterectomy. Ethical approval and trial registration were obtained; the data were analyzed using the SPSS software version 21.0; $p<0.05$ was considered significant.

Results: Participants in group I had higher mean intraoperative blood loss (931.89±602.13 vs 848.40±588.85 mL, p=0.532), intra-operative blood transfusion rates (60 vs 55%; p=0.651) and mean units of blood transfused (1.30±1.20 vs 1.20±1.30; p=0.722) compared with group II. The mean uterine size (19.50±6.93 vs 20.05±6.98 cm; p=0.725) and number of fibroid nodules (11.25±7.99 vs 11.45±8.22; p=0.912) were comparable. The change in post-operative hematocrit was 2.66±2.21% vs 3.24±2.85% (p=0.315) and post-operation blood transfusion was 2.5 vs 5% (p=0.556). There was no recourse to hysterectomy in either of the study groups. While adverse effects of misoprostol occurred in 5 (12.5%) participants of group I.

Conclusion: The effectiveness of perioperative vaginal misoprostol is comparable to intra-operative hemostatic pericervical tourniquet in reducing blood loss during abdominal myomectomy. (J Turk Ger Gynecol Assoc 2019; 20: 23-30)

Keywords: Uterine leiomyoma, misoprostol, hemostatic tourniquet, abdominal myomectomy, hemostasis

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Introduction

Uterine leiomyoma is the most common benign genital tract tumor in women of reproductive age (1) and the most frequent reason for gynecologic consultation in most Nigerian hospitals (2,3). It is more common among black women (4) with an incidence of 3.0% to 29.3% (2,5). It may be asymptomatic with incidental discovery during pelvic examination or ultrasonography for other indications. Symptomatic uterine fibroid can adversely affect the quality of life, especially in low resource countries where patients often present late with huge masses and anemia (2,3,5). The definitive treatment for symptomatic leiomyoma is hysterectomy; however, for women who desire future fertility or preservation of the uterus, myomectomy is a common option (6). Abdominal myomectomy is often preferred to the laparoscopic route in the presence of large and multiple uterine leiomyoma (7).

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Intraoperative hemorrhage necessitating blood transfusion is the most common complication of abdominal myomectomy (4) and when uncontrollable, it may necessitate hysterectomy (8). The volume of blood loss at abdominal myomectomy depends on the uterine size, number, and location of the leiomyoma (7). Generally, the blood transfusion rate for abdominal myomectomy is 13.5 to 58.2% (4,9), with a 2% inadvertent hysterectomy rate following uncontrollable hemorrhage (6,9). Therefore, effective interventions to reduce blood loss remain desirable during myomectomy (10).

Methods of reducing hemorrhage during myomectomy include peri-operative vaginal misoprostol, intra-operative-myometrial vasopressin, intra-myometrial bupivacaine with epinephrine, intravenous tranexamic acid, gelatin-thrombin matrix, intravenous ascorbic acid, vaginal dinoprostone, loop ligation of the leiomyoma pseudo-capsule, fibrin sealant patch and per cervical tourniquet using a Foley catheter (3). However, each method has its limitations; therefore, controlling hemorrhage remains a major task for gynecologists (11).

The Foley catheter, often improvised as a tourniquet in low resource countries, is cheap and readily available (12); however, they require intermittent release intraoperatively to prevent the build-up of toxins and tissue ischemia, and may be impracticable to apply sometimes (11). Once the tourniquet is removed, there is bleeding from the raw myometrium and cavities with the possibility of increased blood loss and blood transfusion (13).

Misoprostol, in addition to its role in managing miscarriages, pre-induction cervical ripening, and induction of labor, prevention and treatment of primary postpartum hemorrhage has gained relevance in myomectomy (14). It increases myometrial contractions thereby reducing uterine artery blood flow to the uterus (15). Its heat stability and long shelf-life improves its availability in the tropics where huge leiomyoma are predominant, and the multiple routes of administration increases choices and acceptability (16). The peak plasma level of 400 μg of vaginal misoprostol is reached one to two hours after administration and is sustained for four hours, and the side effects are self-limiting (15,16).

Reports on misoprostol use to control blood loss in abdominal myomectomy showed a reduction in intra and post-operative blood loss, surgical time, and post-operative blood transfusion (6,15), but these were from developed countries. In practice, there are instances when application of the tourniquet is impracticable and another method is indicated. Therefore, aim of this study was to evaluate the effectiveness of vaginal misoprostol compared with hemostatic tourniquet in reducing hemorrhage during abdominal myomectomy.

Material and Methods

Study design

The study was a randomized controlled study conducted between June 2016 and May 2017 at the University of Ilorin Teaching Hospital - a tertiary health facility in North-central Nigeria with facilities for undergraduate and postgraduate medical training. The obstetrics and gynecology department has 170 beds, an average annual delivery rate of 2000 and 500 gynecologic admissions. Participants were women with symptomatic uterine leiomyoma who underwent abdominal myomectomy. The study evaluated the effectiveness of perioperative misoprostol administered vaginally compared with intraoperative pericervical hemostatic tourniquet in reducing blood loss during abdominal myomectomy.

The inclusion criteria were a diagnosis of uterine leiomyoma and a decision for abdominal myomectomy. Women who had other forms of myomectomy, allergy to prostaglandins, chronic medical disorders, previous uterine surgery (myomectomy, caesarean delivery) and anemia (hematocrit <10 g/dL at 24 hours preop) were excluded from the study. The primary outcome measures were estimated intraoperative blood loss and the need for intraoperative blood transfusion. The secondary outcome measures were intraoperative recourse to hysterectomy, post-operative hematocrit change, and adverse effects of misoprostol among group I participants.

Sample size determination

The sample size was calculated using a previously validated formula (17). The power was set at 95%. The standard normal deviate corresponding to 5% level of significance and the mean intraoperative blood loss for hemostatic tourniquet (18) and misoprostol (15) of 286.4±137.5 mL and 200.16±18.8 mL from previous studies with 10% attrition rate yielded a sample size of 40 participants for each group and a total 80 participants.

Study protocol

All women with symptomatic uterine leiomyoma were informed about the study; interested individuals were then screened using the eligibility criteria and eligible women were requested to provide written informed consent. Consenting participants were randomized into one of two groups to receive perioperative vaginal misoprostol (group I) or intraoperative pericervical hemostatic tourniquet (group II). To allow randomization, researchers prepared the management protocol for each group and sealed one protocol per envelope with a computer-generated number assigned. Randomization was performed by picking the numbered study envelopes sequentially and managing the participant based on the enclosed protocol. Participants were identified with the

randomization number until discharge from the hospital. All participants had standard preoperative evaluations including complete blood count; urinalysis; serum electrolyte; urea and creatinine; pelvic ultrasound scan for size, number and location of the leiomyoma; and hysterosalpingography. Other investigations were performed as indicated.

Group I participants received two tablets of 200 μg i.e. total of 400 μg misoprostol (Pfizer Limited, United Kingdom) administered into the posterior fornix of the vagina at least one hour before the onset of surgery. Group II participants had peri-cervical tourniquet using a Foley catheter size 18, which was firmly tied at the level of the cervico-isthmic junction of the uterus before the uterine incision. The time of tourniquet administration was recorded, and it was released not later than 45 minutes after its application. For those requiring multiple applications, the tourniquet was reapplied after a period of at least 15 minutes.

All procedures were performed in equal proportion by four consultant gynecologists of similar skill and experience, and estimation of blood loss was performed through the measurement of blood volume in the suction bottle; other losses were accounted for using gravimetric methods by mopping with pre-weighed abdominal mops and repeat measurements with a one-gram weight difference equivalent to 1 mL of blood (19). The maximum allowable blood loss (transfusion trigger) was calculated for each participant and intraoperative blood transfusion was commenced when this was exceeded (20). Blood transfusion was also commenced with cardiovascular instability from hemorrhage or signs of inadequate perfusion or oxygenation. All participants were monitored until hospital discharge. Participants in group I were evaluated for adverse effects of misoprostol [nausea, vomiting, diarrhea, elevated temperature (>38 °C), shivering] within one hour and 24 hours post-surgery. All participants had a hematocrit estimation at 24 hours post-surgery in addition to other routine post operation care procedures.

Ethical issues

Ethical approval was obtained from the ethical review committee of the University of Ilorin Teaching Hospital, Ilorin, Nigeria (ERCPAN/2015/09/1455; 10/09/2015) before commencement of the study. The trial was registered with the Pan African Clinical Trial Registry (www.pactr.org) with registration number PACTR201802003039106. Written informed consent was obtained from all participants in the study.

Statistical analysis

The data obtained from this study were analyzed using SPSS version 21.0. The chi-square, t-test, and Mann-Whitney U test were used to describe variables as appropriate. $P<0.05$ was considered significant.

Results

A total of 120 women were screened for eligibility in the study. Eighty (66.7% of the total screened) women participated in the study, 40 in each group. Figure 1 shows the flow chart for the trial. The mean age of the participants was 36.4±5.97 (range, 24-45) years; 47 (58.8%) were nulliparous, and 51 (63.8%) had no children. The common presenting symptoms were excessive/prolonged menstrual flow (n=50; 62.5%), abdominal swelling (n=46; 57.5%), inability to conceive (n=43; 53.75%), and 75 (93.7%) had multiple symptoms (Table 1).

There were similarities in the two groups in relation to mean uterine size (19.50±6.93 vs 20.05±6.98; p=0.725) and mean number of fibroid nodules (11.25±7.99 vs 11.45±8.22; p=0.912), as shown in Table 2. Intraoperatively, group I participants recorded higher values in mean intraoperative blood loss (931.89±602.13 vs 848.40±588.85 mL; p=0.532), blood transfusion [24 (60.0%) vs 22 (55.0%), p=0.651], and mean number of units of blood transfused (1.30±1.20 vs 1.20±1.30, p=0.655) than group II. Postoperatively, blood transfusion was performed in 1 (2.5%) patient and 2 (5.0%) patients in groups I and II, respectively, as shown in Table 3.

The mean preoperative hematocrit was 33.78±2.70 vs 34.56±0.53% (p=0.253), the mean post-operative hematocrit was 31.11±3.25 vs 31.32±3.36% (p=0.782), and the mean hematocrit change was 2.66±2.21 vs 3.24±2.85% (p=0.315) for groups I and II, respectively. Among the 34 participants [group I (n=16) and group II (n=18)] who did not receive intraoperative blood transfusion, the hematocrit change was similar ranging from 2 to 10.5%, but these were not statistically significant (Table 4). Adverse effects of misoprostol occurred in 5 (12.5%)

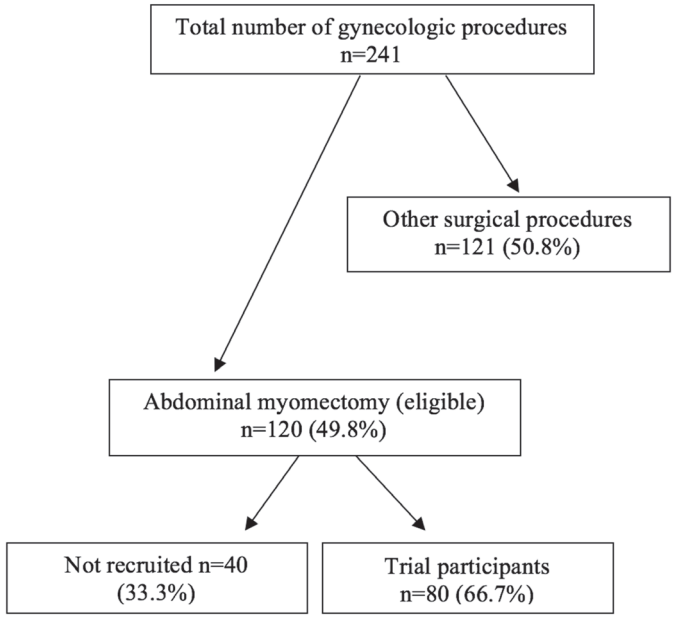

Figure 1. Flow chart of participants in the trial

Table 1. Sociodemographic characteristics of the study population

Variables	Freq (%) n=80
Age groups (years)	
≤25	2 (2.5)
26-30	14 (17.5)
31-35	17 (21.2)
36-40	30 (37.6)
≥41	17 (21.2)
Mean ± standard deviation	**36.4±5.97**
Marital status	
Single	8 (10.0)
Married	71 (88.8)
Divorced	1 (1.2)
Educational status	
None	6 (7.5)
Primary	13 (16.2)
Secondary	21 (26.3)
Tertiary	40 (50.0)
Parity	
0	47 (58.8)
1	20 (25.0)
2-4	12 (15.0)
≥5	1 (1.2)
Number of children alive	
0	51 (63.8)
1	17 (21.2)
2-4	11 (13.8)
≥5	1 (1.2)
Presenting symptom	
Irregular vaginal bleeding	2 (2.5)
Dysmenorrhea	12 (15.0)
Recurrent pregnancy losses	19 (23.8)
Recurrent abdominal pain	22 (27.5)
Inability to conceive	43 (53.8)
Abdominal swelling	46(57.5)
Excessive/prolonged menstruation	50 (62.5)
Single symptom	5 (6.3)
Multiple symptoms	75 (93.7)

patients of group I, II (40.0%) of whom experienced multiple adverse effects (Table 5).

Discussion

In this study, the mean intra-operative blood loss, rate of intra-operative blood transfusion, and number of units of

Table 2. Intra-operative events of participants in the two groups

Variable	Group I n=40 (%)	Group II n=40 (%)	χ^2/ MWU	p value
Uterine size (weeks)				
8-12	8 (20.0)	5 (12.5)		
14-18	13 (32.5)	16 (40.0)		
20-24	9 (22.5)	7 (17.5)		
26-30	9 (22.5)	9 (22.5)		
32	1 (2.5)	3 (7.5)	2.253	0.689
Mean ± standard deviation	**19.50±6.93**	**20.05±6.98**	**-0.353^T**	**0.725**
Anesthesia				
Regional	22 (55.0)	22 (55.0)		
Spinal	6 (15.0)	6 (15.0)		
Epidural	8 (20.0)	8 (20.0)		
Combined spinal-epidural	8 (20.0)	8 (20.0)		
General anesthesia	18 (45.0)	18 (45.0)	0.000	0.999
Skin incision				
Pfannenstiel	20 (50.0)	21 (52.5)		
Midline infra-umbilical	9 (22.5)	7 (17.5)		
Midline infra-umbilical with supra-umbilical extension	11 (27.5)	12 (30.0)	0.318	0.853
***Location of fibroids**				
Sub-serous	35 (87.5)	33 (82.5)	0.392	0.754
Intramural	39 (97.5)	39 (97.5)	0.513	0.474
Submucosa	20 (50.0)	21 (52.5)	0.05	0.823
Number of fibroid				
Sub-serous	1.67±2.08	2.67±2.42	0.000	0.999
Intramural	7.47±6.34	7.73±6.80	-0.170	0.865
Submucosa	0.90±1.15	0.93±1.31	-0.910	0.928
Mean ± standard deviation	**11.25±7.99**	**11.45±8.22**	**-0.110^T**	**0.912**
Duration of surgery (minutes)				
<60	52.00±4.24	51.40±5.89	0.128	0.903
60-120	92.75±18.93	92.32±19.75	0.078	0.938
>120	146.36±23.01	152±31.54	-0.508	0.617
Mean ± standard deviation	**109.48±34.90**	**102.13±38.76**	**0.891^T**	**0.376**

MWU: Mann-Whitney U test; χ^2: Chi-square test; T: Independent standard t-test; *Some participants had fibroid masses in multiple locations

Table 3. Pre-operative, intra-operative, and post-operative intravenous fluid and blood transfusion management

Variable	Group I n=40 (%)	Group II n=40 (%)	χ^2/T	p value
Estimated blood loss (mL)				
<500	11 (27.5)	12 (30.0)		
500-<1000	16 (40.0)	18 (45.0)		
1000-<1500	9 (22.5)	5 (12.5)		
1500-<2000	1 (2.5)	2 (5.0)		
>2000	3 (7.5)	3 97.5)	1.637	0.802
Mean ± standard deviation	**931.89±602.13**	**848.40±588.85**	**0.627[T]**	**0.532**
Blood transfusion				
No	16 (40.0)	18 (45.0)		
Yes	24 (60.0)	22 (55.0)	0.205	0.651
Number of units				
0	16 (40.0)	18 (45.0)		
1	2 (5.0)	5 (12.5)		
2	18 (45.0)	11 (27.5)		
3	2 (5.0)	3 (7.5)		
4	2 (5.0)	3 (7.5)	4.383	0.223
Mean ± standard deviation	**1.30±1.20**	**1.20±1.30**	**0.358[T]**	**0.722**
Post-operation blood transfusion				
No	39 (97.5)	38 (95.0)		
Yes	1 (2.5)	2 (5.0)	0.346	0.556
Number of units				
0	39 (97.5)	38 (95.0)		
1	1 (2.5)	2 (5.0)		
Mean ± standard deviation	**0.05±0.22**	**0.03±0.16**	**0.582[T]**	**0.562**

χ^2: Chi-square test; T: Independent samples T test

blood transfused were higher among participants who had perioperative vaginal misoprostol compared with those who had intra-operative pericervical hemostatic tourniquet, although these were not statistically significant. However, the change in post-operative hematocrit and rate of post-operation blood transfusion were higher in women who had intra-operative pericervical hemostatic tourniquet, but again, these were not statistically significant. None of the participants in the study had recourse to hysterectomy, and the adverse effects of misoprostol were minimal and self-limiting.

The strength of the study is that it compared perioperative misoprostol with hemostatic tourniquet, which is uncommon in the literature, the randomized design, and the objective measurement of blood loss. The limitations included the small sample size and the limited study area.

Misoprostol has been reported to be effective in reducing blood loss in myomectomy following comparison with placebo (21-23) or other agents (24). The mean blood loss following misoprostol administration in this study was higher than in reports from Egypt (574±194.8 mL) (23), Iran (458±287 mL) (22), and Turkey (472±77 mL) (21). A review of the methodology showed that these studies with lower blood loss had lower mean uterine sizes of <24 weeks (23), 8.7±4.6 weeks (22), and 15.7±2.6 weeks (21) compared with 19.50±6.93 in this study. This may explain the higher blood loss in our study because blood loss during myomectomy has been shown to be proportional to uterine size. In addition, the number of fibroid nodules is related to blood loss, which explains the lower blood loss in the Turkish study with mean number of leiomyoma of 5.5±1 (21) compared with 11.25±7.99 in this study. Blood loss estimation remains central during abdominal myomectomy. In the Turkish (21) and Iranian (22) studies, the recorded blood loss was measured from the blood in the suction bottle, whereas this study assessed other losses in addition to the suction bottle, using a gravimetric method.

Different studies used different dosing regimens for misoprostol in myomectomy. A study from Iran used 200 μg of vaginally administered misoprostol three hours prior to surgery (22)

Table 4. Comparison of levels and changes in hematocrit among participants

Hematocrit (%)	Group I n=40 (%)	Group II n=40 (%)	χ^2/MWU	p value
Pre-operation				
≥30-33	20 (50.0)	18 (45.0)		
>33-36	14 (35.0)	11 (27.5)		
>36-39	5 (12.5)	6 (15.0)		
>39	1 (2.5)	5 (12.5)	3.223	0.359
Mean ± standard deviation	33.78±2.70	34.56±0.53	-1.153[T]	0.253
Post-operation				
≤30	16 (40.0)	20 (50.0)		
>30-33	15 (37.5)	12 (30.0)		
>33-36	9 (22.5)	6 (15.0)		
>36-39	0 (0.0)	1 (2.5)		
>39	0 (0.0)	1 (2.5)	3.378	0.497
Mean ± standard deviation	31.11±3.25	31.32±3.36	-0.277[T]	0.782
Mean hematocrit change	2.66±2.21	3.24±2.85	-1.012	0.315
Hematocrit change among participants who were not transfused	n=16	n=18		
% change	6 (37.5)	4 (22.2)		
≤3	1 (6.3)	2 (11.1)		
4-6	6 (37.5)	5 (27.8)		
7-9	3 (16.7)	7 (38.9)	2.382	0.666
>9				

χ^2: Chi-square test; MWU: Mann-Whitney U test; [T]: Independent standard t-test

compared with 400 μg of vaginal misoprostol administered one hour prior to surgery in this study. This raises a future research question on the effect of dose and time interval from administration of misoprostol to commencement of surgery on blood loss. Another study evaluated the effect of multiple doses and reported greater blood loss (200.16±18.8 vs 101.4±25.5 mL) (15) for single and two doses, respectively, but more adverse effects of misoprostol with multiple dosing. The concern of researchers remains the possible additive adverse effects of misoprostol with multiple dosing (15), which necessitated single dosing in this study. However, further comparison was limited by the smaller mean uterine size and number of leiomyomas (15.33±8.48 weeks and 2.91±4.24 leiomyomas) in a previous study (15) compared with this study.

Table 5. Adverse effect profile of misoprostol among group I participants*

Variable	Frequency n=40 (%)
Nausea	
Yes	3 (7.5)
No	37 (92.5)
Vomiting	
Yes	1 (2.5)
No	39 (97.5)
Shivering	
Yes	3 (7.5)
No	37 (92.5)

*Some participants experienced more than one adverse effect; - There were no cases of diarrhea or pyrexia among participants

The intra-operative blood transfusion rate of 60% in this study was higher than in previous reports with 15.3% (21) and 24% (23); some studies reported no blood transfusion requirement (15,22). This may be attributed to the larger uterine sizes, presence of multiple uterine fibroids, and greater mean blood loss in this study. There is no consensus on the time to initiate blood transfusion during myomectomy. In this study, intraoperative blood transfusion was commenced when the calculated maximum allowed blood loss for the patient was reached or evidence of cardiovascular instability from hemorrhage. However, another study employed a loss of 2000 mL as indication for blood transfusion (22).

In this study, the mean pre-operative and post-operative hematocrits and changes in hematocrit were not statistically significant. This emphasizes the comparative effectiveness in reducing blood loss by the two methods compared. In most studies that compared misoprostol with placebo, the misoprostol group had post-operative hemoglobin values that were

significantly higher than those found in the placebo group (21-23). This validated the effectiveness and superiority of misoprostol, which is an active agent over placebo in such studies.

The adverse effects of misoprostol experienced by participants in this study compared to those in previous reports; they were self-limiting and included nausea, vomiting, diarrhea, shivering, and fever (15,21-23). They either required no intervention or simple interventions to alleviate symptoms such as covering the patient with blankets for shivering.

Other researchers compared misoprostol with other agents in reducing blood loss in myomectomy. A comparison of the effectiveness of the administration of a single preoperative dose of vaginal misoprostol with intraoperative oxytocin infusion on blood loss during abdominal myomectomy reported statistically significantly lower blood loss (401±48 vs 589±49 mL) in the misoprostol group (24). Also, a study that compared rectal misoprostol plus perivascular vasopressin with perivascular vasopressin alone reported statistically significantly lower blood loss (334 vs 623 mL) in the former group (25). This implies that misoprostol compares favorably with other agents, depending on the locally available alternatives in a number of settings.

The estimated blood loss from the tourniquet group in this study was higher than that reported by Ikechebelu et al. (11) in Nnewi, Nigeria (515.7±292.81 mL). A possible explanation is the difference in blood loss estimation in the studies. A comparison of tourniquet and no-tourniquet use recorded a significant reduction in blood loss in the tourniquet group (11,18), yet tourniquet use produced greater blood loss when compared with other hemostatic techniques such as vasopressin or preliminary uterine artery ligation (25,26). However, there is paucity of data regarding comparisons of tourniquet use and misoprostol in reducing blood loss during abdominal myomectomy.

In summary, this study suggests comparable effectiveness in reducing blood loss during abdominal myomectomy for peri-operative vaginal misoprostol and intra-operative hemostatic peri-cervical tourniquet. This is recommended for routine use especially in instances where application of the tourniquet is impracticable due to significant pelvic adhesions and leiomyoma in the broad ligament, uterine isthmus or cervix.

Ethics Committee Approval: *Ethical approval was obtained from the Research and Ethics Committee of the University of Ilorin Teaching Hospital, Ilorin, Nigeria.*

Informed Consent: *A written informed consent was obtained from all study participants.*

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In patients with advanced ovarian cancer, primary suboptimal surgery has better survival outcome than interval suboptimal surgery

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Abstract

Objective: It is known that optimal or complete cytoreduction is the most important factor in patients with advanced ovarian cancer. The aim of this study was to examine the results of patients who did not undergo optimal cytoreduction and to examine subgroup analysis based on neoadjuvant chemotherapy (NAC).

Material and Methods: Patients with advanced ovarian cancer and suboptimal surgery were retrospectively reviewed.

Results: A total of 99 patients with a median age of 59.0 years (range, 22-87 years) were studied. The median follow-up time was 39±32.7 months, 81 patients (81.8%) died and 18 patients (18.2%) were alive. The five-year survival rate was 27.6%. Of the patients, 37 (37.4%) were underwent surgery after NAC, 62 (62.3%) were primary. More patients with NAC died within 3 years compared with those without NAC (83.9% vs 56.0%) (p=0.015). Patients with NAC had less tumor spread (presence of visible tumor in the upper abdomen during surgery) (29.7% vs 72.6%; p<0.001) and had less overall survival times when compared with patients who underwent primary surgery [median 22.3±1.2; 95% CI: (19.9-24.7) vs (37.5±11.2); 95% CI: (15.4-59.5) months; log rank test p=0.055]. The relationship between overall survival and factors such as age, NAC, presence of metastasis in the upper abdomen, and tumor histology (serous vs. non-serous) were analyzed using univariate cox regression analysis. Of these factors, only NAC was close to significant, but it did not reach significance (p=0.055).

Conclusion: NAC reduces tumor burden before surgery in advanced ovarian cancer. The prognosis of patients who are not eligible for optimal surgery despite NAC is worse than in patients who do not receive NAC. (J Turk Ger Gynecol Assoc 2019; 20: 31-6)

Keywords: Primary surgery, neoadjuvant chemotherapy, cytoreductive surgery, survival

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Introduction

Epithelial ovarian carcinoma has the highest mortality among gynecologic cancers (1). The 5-year survival rate is around 30% (2). An important reason for this poor prognosis is that most patients' disease is diagnosed at advanced stages (3). The standard approach in the treatment of patients with advanced ovarian cancer is debulking surgery for optimal or complete cytoreduction, followed by adjuvant chemotherapy with paclitaxel and carboplatin (4-9). The goal is to achieve optimal cytoreduction (less than 1 cm of residual disease), but some patients cannot undergo optimal cytoreduction due to medical comorbidities, experience of the surgeon, intraoperative problems, and disseminated invasive tumor, especially.

Clinical reports provided differing figures about achievable patient rates for optimal debulking surgery. In a large study (1325 patients), the optimal debulking rate was reported as 65% for primary surgery and 74% for surgery after neoadjuvant chemotherapy (NAC) (10). In a randomized controlled trial, Vergote et al. (11) reported their optimal operation rate as 41% in patients who underwent primary surgery and 80% in

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surgery after NAC. In patients who are not eligible for optimal surgery, administering NAC before surgery is considered as an alternative treatment approach (11-13). After NAC, surgical morbidity and postoperative mortality rates are lower and optimal cytoreduction is more likely (11,14-16). However, 10-20% of patients who have undergone surgery even after NAC cannot undergo optimal cytoreduction (11,17,18).

In this study, we reviewed patients with advanced-stage ovarian cancer who could not undergo optimal surgery (residuel tumor >1 cm). We calculated the survival times of these patients and analyzed the relationship between survival duration and age, presence of tumors in the upper abdomen, NAC, tumor histology, and we performed subgroup analysis based on NAC.

Material and Methods

This retrospective study included 99 patients who underwent suboptimal surgery for advanced stage (International Federation of Gynecology and Obstetrics stage IIIC-IV) epithelial origin ovarian cancer at same center between 2002 and 2013. Patients who underwent suboptimal cytoreduction according to the operation report were selected. The age of the patients, whether NAC was taken, and tumor histology were recorded. According to the operation reports, the presence of visible tumor in the superior part of the liver and diaphragmatic serosa during laparatomy, whether lymphadenectomy was performed, and the number of lymph nodes removed were recorded. The association of these factors with survival was analyzed using univariate Cox analysis.

Patients

Patients were initially evaluated for gynecologic examination, tumor markers (CA125 and CA19.9) and imaging studies (mostly magnetic resonance imaging). Positron emission tomography examinations were performed in patients as required, and computed tomography was performed in addition to pulmonary evaluation. According to these evaluations, primary debulking surgery was planned for patients who were predicted as being eligeble for optimal surgery. Patients not eligible for primary optimal debulking surgery were deferred for interval debulking surgery after NAC. The current co-morbidity of the patient and the spread of the disease especially (such as liver parenchymal involvement, lung metastasis) was taken into consideration while choosing surgery or NAC. NAC was given after pathologic confirmation of the disease. The standard treatment protocol was 3-6 cycles of paclitaxel 175 mg/m2 and carboplatin (area under curve: 5-6) for 3 weeks. Patients underwent cytoreductive surgery after NAC. At the end of the operation, presence of residual tumor greater than 1 cm was accepted as suboptimal operation.

All patients received adjuvant chemotherapy after surgery. The total (before and after surgery) dose was planned to be 6 to 9 cures. Overall survival (OS) was defined as the time from the first treatment until death or last visit.

Permission of the local ethics committee was not sought because this study was planned as a retrospective review. However, all patients gave informed consent, which allowed our center to use their clinical data for scientific trials.

Statistical analysis

The Statistical Package for the Social Sciences for Windows version 21 (IBM Corporation, NY: USA, 2012) was used to perform all analyses. Univariate Cox regression analysis was used to investigate the survival- related criteria. Survival distributions were estimated using the Kaplan–Meier analysis. Statistical significance was determined using the log-rank test. P values less than 0.05 were considered significant.

Results

The study consisted of a total of 99 patients with a median age of 59.0 years (range, 22-87 years). The clinicopathologic features of the patients are presented in Table 1.

The median follow-up time was 39±32.7 months. Eighty-one patients (81.8%) died and 18 patients (18.2%) were alive. The five-year survival rate was 27.6%. Of the patients, 37 (37.4%) underwent surgery after NAC, and 62 (62.3%) were primary. The comparative analysis of patients who underwent surgery after NAC and primary surgery is shown Table 2.

Patients with NAC had more deaths within 3 years compared with those without NAC (83.9% vs 56.0%) (p=0.015) (Table 4). Patients with NAC had less tumor spread (presence of visible tumor in the upper abdomen during surgery) (29.7% vs 72.6%; p<0.001) and had less overall survival times when compared with patients who underwent primary surgery [median 22.3±1.2; 95% CI: (19.9-24.7) vs (37.5±11.2); 95% CI: (15.4-59.5) months; log-rank test p=0.055] (Figure 1). The relationship between OS and factors such as age, NAC, presence of metastasis in the upper abdomen, and tumor histology (serous vs non-serous) was analyzed using univariate Cox regression analysis. Of these factors, only NAC was close to significant, but did not reach significance (p=0.055) (Table 3).

More patients with NAC died within 3 years compared with those without NAC (83.9% vs 56.0%) (p=0.015). The distribution of deaths based on the first 3 years and after is presented in Table 4.

Discussion

In this study, we evaluated survival outcomes of patients with advanced-stage ovarian cancer who could not undergo optimal cytoreduction. Optimal surgery is the most important prognostic factor in survival. Therefore, a good prognosis cannot

Table 1. Clinical features of patients

Total number of patients	**99**
Age, years	
Median (minimum-maximum)	59.0 (22-87)
Mean ± standard deviation	58.6±13.7
Neoadjuvant chemotherapy	
Yes	37
No	62
Level of Ca125 (U/mL), (minimum-maximum)	33-9652
33-499	23
500-1999	35
2000-9652	16
Missing	25
Residual tumor at diaphragm/liver	
Yes	56
No	43
Lymphadenectomy (pelvic ± paraaortic)	21
Lymph nod metastasis	9
Inguinal lymphadenectomy	2
Removed lymph node count	
Median (minimum-maximum)	14 (3-29)
Follow-up time (months), mean ± standard deviation	39±32.7
Histology	
Serous	80
Carcinosarcoma	5
Clear cell	4
Undifferentia	1
Mixed subtypes	9
Postoperative exitus (within 30 day)	
Surgery after NAC	1
Primary surgery	4
Last status	
Alive	18
Died	81
Median survival (months)	29.4±4.9; 95% CI: 19.6-39.1
3-year overall survival	45.4%
5-year overall survival	27.6%
NAC: Neoadjuvant chemotherapy	

be expected in these patients. In the study, 81 patients (81.8%) died and only 18 patients (18.2%) were alive during a median follow-up of 39 months. The median OS time was 29 months. Some of these patients had received NAC and the prognosis of these patients was worse (22 vs 37 months, median) (Table 3). The death ratio was found higher, especially within 3 years, in the NAC group (Table 4). In fact, the tumor burden during surgery was less in patients who received NAC but this was not positively reflected in survival (presence of residual tumor in the upper abdomen 29.7% vs 72.6%, p<0.001).

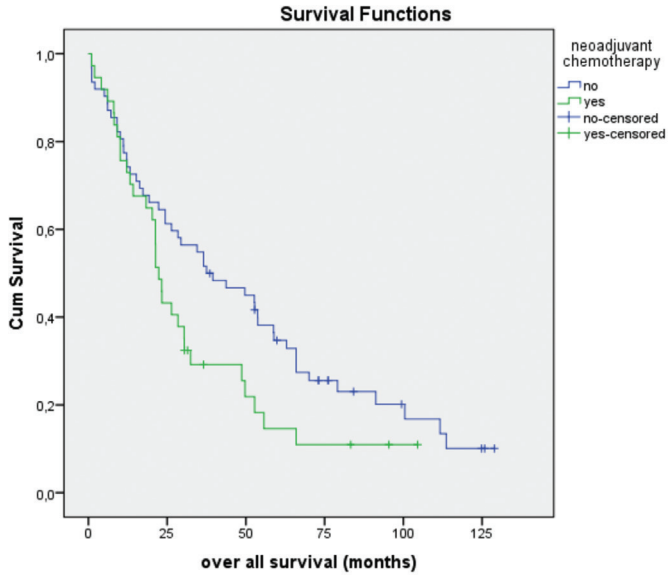

Figure 1. Overall survival graph of patients receiving and not receiving neoadjuvant chemotherapy

Table 2. Comparative analysis of patients with operated after NAC and primary surgery

Characteristic	**Surgery after NAC (n=37)**	**Primary surgery (n=62)**	**p value**
Age, mean ± standard deviation	61.9±12.4	56.5±14.2	0.085
CA125, mean ± standard deviation	1257±1530	1840±2331	0.102
Lymphadenectomy	1	20	**<0.001**
Nodal metastasis	-	9	-
Presence of residual tumor at diaphragm/liver, % (n)	29.7 (11)	72.6 (45)	**<0.001**
Postoperative died (within 30 days)	1	4	0.647
Median overall survival (months)	22.3±1.2 95% CI: 19.9-24.7	37.5±11.2 95% CI: 15.4-59.5	**0.055**
3-years survival	29.2%	54.8%	**0.020**
Death within 3 years, % (n)	70.2 (26)	45.1 (28)	**0.015**
Total death, % (n)	83.8 (31)	80.6 (50)	0.695
NAC: Neoadjuvant chemotherapy			

In the literature, there are studies comparing patients receiving NAC and patients not receiving NAC. Some survival of patients who received NAC. According to the recently published Danish retrospective cohort study in which 1734 patients were evaluated, survival was found to be lower than in the primary surgery group in patients with stage IIIC ovarian cancer who underwent surgery after NAC (29.4 months, 33.7 months;

Table 3. Analysis of survival related factors by univariate Cox analysis

Characteristic	n	Survival (months) median ± standard error	95% CI	p value
Age (years)				
≤60	54	43.7±9.1	25.8-61.5	0.147
>60	45	22.3±2.0	18.3-26.2	
NAC				
Yes	37	22.3±1.2	19.9-24.7	0.055
No	62	37.5±11.2	15.4-59.5	
Metastasis of diaphragm/liver				
Yes	56	28.4±6.2	16.5-44.2	0.429
No	43	30.4±7.0	16.1-39.1	
Histology				
Serous	80	29.4±5.9	17.8-40.9	0.643
Non-serous	19	28.3±13.9	3.0-39.1	

NAC: Neoadjuvant chemotherapy; CI: Confidence interval

Table 4. Distribution of 81 deaths in the first three years and after

	Neoadjuvant chemotherapy		Total deaths (n)	p value
	Yes	No		
First three years, n (%)	26 (83.9)	28 (56.0)	54	**0.015**
After three years, n (%)	5 (16.1)	22 (44.0)	27	
Total deaths, n	31	50	81	

p=0.057) (10). In their study, patients who had no residual tumor at the end of surgery were also compared and survival was found to be significantly lower in the NAC group (36.7 and 55.5 months; p=0.002). In addition, long-term survival (more than two years) was significantly lower in their study. According to the authors, treatment with NAC may impair long-term survival. In the study of the European Organization for Research and Treatment of Cancer, 55971 patients with stage III ovarian cancer had better survival in the primary surgery group compared with the NAC group (19). In a Surveillance, Epidemiology and End-Results data study in which 6844 patients were evaluated, NAC increased the risk of death by 16% for patients with stage III disease at two years (20). Rosen et al. (21) reported that 7-year survival was significantly better in the primary surgery group than in the NAC group (8.6% vs 41%; p<0.0001). In a meta-analysis involving 835 patients, NAC in lieu of primary cytoreduction was associated with inferior OS compared with initial surgery (22). In another study, Ren et al. (23) reported worse survival in the neoadjuvant group in a study involving 408 patients.

There are different opinions as to why the survival of patients with ovarian cancer who receive NAC is worse than in patients who undergo surgery without NAC. However, these groups are not similar enough to compare. Primary debulking surgery is planned for patients who have been predicted as being eligible for optimal surgery. Patients not eligible for primary optimal debulking surgery are deferred to interval debulking surgery after NAC. This indicates that patients were selected for surgery upfront if they were deemed "debulkable", whereas those who received NAC appeared not to be candidates for complete debulking. One cannot draw any conclusions about the difference in outcome because these two cohorts have different disease burden and biology, which is expected to be worse in patients who are not candidates for primary surgery. An another proposed idea is that NAC has a deceptive effect on intraoperative evaluation. Due to the effect of chemotherapy on the tissue, the tumoral area may be missed, and difficulty of resection of potentially resectable tumor tissues may have a negative effect (24,25). Another sugestion is that NAC induces the emergence of chemotherapy-resistant tumor cells in stem cell colonies over time. There are reports that NAC increases the risk of platinum resistance over time (26-28). It is important at this point to consider platinum resistance in the selection of patients for NAC. Currently, platinum resistance is not tested in patient selection and there is no such recommendation in guidelines. It may be useful to develop and apply *in vivo* chemosensitivity testing, which may show primary platinum resistance (29). Another hypothesis is that delayed debulking surgery may also adversely affect survival (30).

The contribution of NAC to survival is not clear in the literature, currently. According to the results of randomized controlled trials, the general consensus suggests a similar survival rate between primary surgery and interval surgery after NAC (11,31-34). NAC improves the feasibility of optimal surgery by decreasing tumor spread (16). However, optimal surgery may not be possible despite NAC. In the study of Fagö-Olsen et al. (10) 180 of 515 patients who received NAC did not undergo surgery (predominant reason was that the tumor was considered to be unresectable) and the median OS of these patients was 14.3 months. The authors reported that it was controversial as to whether these patients recovered from unnecessary surgery or that they were deprived of the possible advantage of surgery.

The present study has some limitations such as the low number of patients and its retrospective design. In addition, all patients were those with advanced ovarian cancer who underwent suboptimal surgery, but residual tumor burdens may be different.

This study evaluated a group of patients with advanced ovarian cancer who underwent surgery for optimal cytoreductive surgery but underwent suboptimal surgery. Even with NAC,

some patients may not be feasible for optimal surgery. The prognosis of these patients is poor. It is controversial as to why chemotherapy does not contribute to survival despite tumor burden reduction. In vitro studies on the relationship between chemotherapeutic agents and tumor cells may be informative.

Ethics Committee Approval: *No ethical approval has been sought because this was a retrospective study.*

Informed Consent: *Written informed consent was obtained from patients who participated in this study.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Concept - A.K., S.T., P.S., H.S., Y.S.; Design - A.K., S.T., P.S., H.S., Y.S.; Supervision - S.T.; Materials - A.K., P.S.; Writer: A.K., S.T., P.S., H.S., Y.S.*

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Iodine deficiency in pregnant women at first trimester in Ankara

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Abstract

Objective: Iodine deficiency in pregnant woman in Ankara was shown in previous studies. We aimed to conduct a study in a tertiary center to investigate the need for iodine replacement in our population.

Material and Methods: This was a single tertiary center, non-interventional, retrospective, cross-sectional study. Data were retrieved retrospectively from 440 women who were in the first trimester in gestational age. Maternal iodine status, thyroid-stimulating hormone (TSH) levels and T4 levels were examined. Urinary iodine concentration (UIC) was calculated based on the Sandell-Kolthoff reaction, which is a colorimetric method. We excluded patients with previous or current thyroid disease. Thyroid hormones and TSH were measured using chemiluminescence immunoassays.

Results: Iodine deficiency prevalence (urinary iodine <150 μg/L) was 84.7% in first trimester of pregnancy in our population. The median UIC was 81.6 (1-450) μg/L, indicating iodine insufficiency. All the patients declared iodized salt use. None of the patients were taking iodine replacement. The mean TSH level was 1.53±1.27 mIU/L, (0.01 mIU/L-14.74 mIU/L) and the mean T4 level was 12.51±5.01 mIU/L (7.09 mIU/L-23.7 mIU/L). The TSH levels of 56 patients were higher than 2.5 mIU/L. According to these results, 12.72% of the patients had subclinical hypothyroidism based on serum TSH and free thyroxine levels. Isolated hypothyroxinemia was present in one patient.

Conclusion: Our study demonstrated that pregnant women still develop iodine deficiency in Ankara despite mandatory iodine salt use. Iodized salt use does not provide enough iodine supplement, especially in pregnant women. Iodine supplementation has been shown to enhance neurologic development and psychomotor performance. We suggest that iodine should be a part of routine laboratory evaluation at the first prenatal visit for its importance in early pregnancy. Also, iodized salt use education should be provided to women to eradicate iodine deficiency. Iodine supplements should be recommended to all pregnant women in addition to iodized salt. (J Turk Ger Gynecol Assoc 2019; 20: 37-40

Keywords: Iodine deficiency, pregnancy, first trimester

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Introduction

Iodine deficiency is still a serious public health problem all over the world despite combative efforts (1). In previous studies, iodine deficiency status was determined by calculating urinary iodine concentration (UIC) in school age children (2). If the median results of urinary iodine levels were below 100 μg/L, it could be concluded that iodine intake is insufficient in the whole population (3). The World Health Organization (WHO) suggest classification for UIC, which is enough between 150-249 μg/L, insufficient if below 150 μg/L, and excessive above 250 μg/L (3). Iodine status is important in pregnancy because of its importance of maternal thyroid hormone production for fetal central system maturation (4). Severe iodine deficiency was found to be associated with mental retardation, decreased brain development, and low intelligence (5,6). Physiologic changes in pregnancy such as increased glomerular infiltration and the developing fetal thyroid gland increases the need for iodine beginning in the early weeks of pregnancy. The WHO recommends 250 μg/L iodine intakes for pregnant and lactating women (7). Iodine deficiency may cause diffuse or nodular goiter, hypothyroidism, and hyperthyroidism. Although there are approved treatment modalities for hypothyroidism and hyperthyroidism in pregnancy, treatment of subclinical hypothyroidism is still controversial. A recent meta-analysis showed that subclinical hypothyroidism is

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relevant to lower intelligence and motor scores in children (8). In some studies, subclinical hypothyroidism was reported to relate with increased risk for low birth weight, premature delivery, fetal distress, and fetal growth restriction (9,10). Subclinical hypothyroidism should be treated with 50 μg/daily levothyroxine (LT4) before conception or during gestation (11,12). Iodine status can be assessed through measurement of UIC, thyroid size, thyroglobulin, and neonatal serum thyroid-stimulating hormone (TSH) (13,14). UIC indicates current iodine nutrition, on the other hand, other methods reflect long-term iodine status. Iodination of salt is the first choice for iodine replacement (15,16). After recognizing iodine deficiency from tudies in Turkey, the Ministry of Health has obliged companies to iodinate table salt and sell it in proper storage since 1994. It has been shown that a decade of mandatory iodine prophylaxis was enough to eradicate goiter among school children (16). Ankara was shown to be an iodine-sufficient region of Turkey (median UIC in school age children; 135 μg/L), after mandatory iodization of salt (16). Herein, we aimed to show the iodine status in pregnant women in Ankara and to clarify the need for iodine replacement with iodine supplementation.

Material and Methods

The present study was conducted in a tertiary center, between January and July 2016. Four hunded sixty women who presented to hospital for the first visit of pregnancy were retrospectively analyzed. The mean age of the pregnant women was 27.8±5.71 years. The median gestational age of the patients was 7 weeks (6-10 weeks). Patients were evaluated for fasting blood and urine samples in this routine first trimester visit. TSH, free triiodothyronine (T3), and free thyroxine (FT4) levels were assessed from the serum. Immunochemiluminescent assays performed on an automated analyzer (Advia Centaur XP; Siemens) were used to measure levels of TSH, free T3, and FT4. The UIC was determined using a colorimetric method based on the Sandell-Kolthoff reaction as recommended by the WHO and the International Council for Control of Iodine Deficiency Disorders, using Fisher reagents (17). The analytical sensitivity was 2 μg/L. The coefficient of variation was <5% for the measurement range. A single-spot urine analysis was taken from the patients in the morning (between 09.00 and 12.00 hours) and stored in de-iodized I tubes at -40 °C. UIC was measured using the spectrophotometric method described by Sandell-Kolthoff. The coefficient of variation in the range investigated was <5%. Normal serum T3 and T4 values for nonpregnant women were 3.99-6.71 pmol/L and 7-15.96 pmol/L, respectively. The results showed inter- and intra-assay coefficients of variation <5% for the measurement range. Ensuring the Quality of Iodine Procedures and Center for Disease Control programme have been performed quarterly in our laboratuary since 2000. Laboratory external control reports have shown a success rate of 85-90%. Patients were excluded if they were on thyroid medication or were known to have thyroid diseases such as thyroiditis or hypo-hyperthyroidism. Twenty patients were excluded due to these criteria, so the study was concluded with 440 patients.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences software [SPSS, version 15.0; standard deviation or, if not normally distributed, as medians (ranges)]. Statistical analysis was performed using parametric (v2 - and Student's t-tests) or nonparametric (Fisher's exact and Mann-Whitney U) tests, when appropriate. Values for $p<0.05$ were accepted as statistically significant.

Ethics

The study was approved by the Ethics committee of Ankara University School of Medicine (approval no: 12-568-16).

Results

Four hundred forty pregnant women whose ages were between 17 and 45 (27.86±5.71) years were enrolled for the study before 12 weeks of gestation. The median gestational age was seven weeks. We found that the median UIC was 81.6 μg/L (1-414 μg/L) in pregnant women, which was described as insufficient iodine intake according to the WHO criteria. UIC was below 150 μg/L in 373 women (86.7%); 9 (2.04%)

Table 1. Urinary iodine concentration in pregnant women

Reference ranges for median UIC (μg/L)	Number of pregnant women	TSH mean range (mIU/L)
<50	149 (33.8%)	1.47±1.34
<100	286 (65%)	1.46±1.21
<150	373 (84.7%)	1.49±1.33
150-249	58 (13.18%)	1.36±0.80
250-499	9 (2.04%)	1.50±1.12
UIC: Urinary iodine concentration; TSH: Thyroid-stimulating hormone		

Table 2. Thyroid values of study population

	*Normal range	Mean ± SD	Median (range)
T3 (pmol/L)	3.99-6.71	4.67±0.60	4.7 (3.3-6.33)
T4 (pmol/L)	7-15.96	13.99±2.68	13.95 (7.09-23.07)
TSH (mIU/L)	0.1-2.5	1.53±1.27	1.37 (0.01-23.7)
TSH: Thyroid-stimulating hormone; T3: Triiodothyronine; T4: Thyroxine; SD: Standard deviation; *TSH normal ranges calculated from non-pregnant population			

women had UIC above than 250 μg/L, and only 58 women (13.24%) had adequate iodine intake. UIC in the study group is shown in Table 1. UIC were below 50 μg/L in 149 patients (33.6%). None of the patients had UIC levels higher than 500 μg/L. The prevalence of iodized salt consumption was 100%. Of the 440 patients, 56 (12.72%) patients' TSH levels were found to be higher than 2.5 mIU/L with normal FT4, which was diagnosed as subclinical hypothyroidism. One patient (0.22%) had isolated hypothyroxinemia with low FT4 (<7 pmol/L) and normal TSH concentrations. Thyroid values are shown in Table 2. We found no significant correlation between TSH and urinary iodine. (Spearman's correlation coefficient r=-0.009, p=0.874). Patients with subclinical hypothyroidism were treated with 50 mcg LT4. Isolated hypothyroxinemia was treated with only iodine replacement. Also, patients with iodine deficiency were given iodine replacement.

Discussion

Iodine deficiency is still a public health problem in Turkey (18). Despite the provision of mandatory iodinized salt, studies showed mild-to-severe iodine deficiency in the pregnant population (19). UIC levels have been accepted as a good indicator for assessing iodine status (18). Although studies in school age children showed enough iodine intake after mandatory iodized salt, it does not precisely represent iodine status in pregnant women (20). In our study, we found that iodine deficiency was still high in the pregnant population. The median UIC levels were found as 81.67 μg/L, and were below 50 in 33.6% of patients, and this was in a city that was found to be iodine sufficient in previous studies (19). Iodine deficiency is known to have an adverse effect on fetal development (20). Iodine is the essential component of T4 and T3. Proper iodine replacement is necessary for appropriate development of the fetus (3). Thyroid hormone is essential for normal maturation of the central nervous system (21). The fetus is completely dependent on maternal T4 during the first trimester of pregnancy. The production of TSH by the fetal pituitary gland start from week 18-22 of gestation, the production of fetal T4 starts from week 22-24. Severe iodine deficiency was found to be associated with fetal hypothyroidism, mental impairment, and increased neonatal and infant mortality (22). Hynes et al. (23) showed that even mild iodine deficiency had long-term adverse impacts on fetal neurocognition and these adverse effects could be reversed by replacement in childhood. Rydbeck et al. (24) also showed that birth weight and length increased by 9.3 g [95% confidence interval (CI): 2.9-16] and 0.042 cm (95% CI: 0.0066-0.076), respectively, for each 0.1 μg/L increase in maternal UIC (24). Bath et al. (21) also conducted a study known as Avon Longitudinal Study of Parents and Children in 1040 pregnant woman in their first trimester. They compared children's intelligence quotient (IQ) scores at the age of 8 years and reading ability at 9 years, and they found that children whose mothers had UIC levels less than 150 mg/g in pregnancy had lower IQ scores and reading accuracy (21). Oral et al. (25) showed that 90% of pregnant women were lacking iodine in their pregnancy in İstanbul, which is defined as an iodine-sufficient city and the salt iodization program was not an efficient for the pregnant population. Oguz Kutlu and Kara (19) assessed pregnant women who were in their second trimester in Ankara and they also found that 72.8% of woman had iodine deficiency. Despite mandatory iodized salt use, iodine deficiency can be explained by inconvenient storage or consumption of iodized salt. Erdoğan et al. (18) showed that only 56.5% of people consumed iodinised salt at home, which is lower than the WHO recommedation of 90%, to eradicate iodine deficiency. Anaforoğlu et al. (26) also showed that 64.9% of patients used salt inappropriately in the cooking process and only 25% of patients used proper containers for iodized salt (27). The limitations of this study include the patients' knowledge about iodized salt and their socioeconomic status. In addition, this was a single center study in the capital city of Turkey, which may not reflect the status of rural areas. In this study, we found that iodine deficiency has not been eradicated despite mandatory iodized salt use, similar to the literature. Iodine status should be assessed in pregnant women, and proper iodine replacement should be advised to patients even before pregnancy. To be successful in the eradication iodine deficiency, from salt iodinization to the cooking process, every step must be checked. One mistake in these steps results in inadequate iodine intake. Iodized salt use education may be given to pregnant women as a part of pregnancy education class. Attention should be given while buying salt, in order to not to take incorrect salt types. Proper iodine replacement should be given to all pregnant woman along with appropriate iodinised salt use.

Ethics Committee Approval: *Ethics Comitee Approval Number: 46004091-302.14.06/E.32516.*

Informed Consent: *Retrospective study.*

Peer-review: *Externally peer-reviewed.*

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Role of erythropoietin and its receptor in the development of endometriosis in rats

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Abstract

Objective: Besides its hematopoietic function, erythropoietin (EPO) may protect tissues from degenerative disorders. As such, EPO and its receptors were revealed in nonhematopoietic cells, including stromal and endometrial epithelial cells. However, the role of EPO in endometrial disorders is still unknown. Here, we aimed to examine the role of EPO and its receptor activation in the development of endometriosis in rats.

Material and Methods: Animals were treated with EPO, darbepoietin (the synthetic form of EPO) or EPO's receptor activator, methoxy polyethylene glycol-epoetin beta (MIRCERA), after development of endometriosis. Endometriosis was induced by estrogen-administration following surgical attachment of endometrial surface on the inner abdominal wall. Treatments were started 3 weeks after induction of endometriosis and continued for the following 3 weeks. For the analysis of recurrence of endometriosis, additional analyses were conducted 3 weeks after cessation of treatments.

Results: As compared with vehicle-treated animals, lesion size was reduced significantly and recurrence of endometriosis was not observed in all treatment groups. Histopathologic examination revealed that EPO and darbepoietin were more effective than MIRCERA- and vehicle-treated animals.

Conclusion: Here we provide evidence that EPO is a promising candidate for the treatment of endometriosis. Our histopathologic results in particular indicate that EPO is more effective than its receptor activator MIRCERA in the development endometriosis. (J Turk Ger Gynecol Assoc 2019; 20: 41-6)

Keywords: Endometriosis, darbepoietin, erythropoietin, MIRCERA, receptor activator

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Introduction

Endometriosis is defined as an etiologically unknown gynecologic condition resulting from the displacement of cells of the endometrium toward outside the uterine cavity (1). Endometrial cells normally constitute the lining of the uterine cavity and are regulated by sex hormones. Although endometrial cells appear outside the uterus in endometriosis, they still respond to hormonal changes in a similar fashion, like the cells found inside the uterine cavity (2). Endometriosis generally occurs in reproductive years and it is found in 6-10% of women (3). The two main symptoms of endometriosis are

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infertility and pain; the severity of the latter depends on the menstrual cycle and it is one of the most common causes of secondary dysmenorrhea (1,4).

It is largely believed that endometriosis develops from irregularities seen in molecular cascades, where estrogen, progesterone and several prostaglandins are involved (5). One of the key pathologic features of endometriosis is inflammation, which is associated with rising levels of proinflammatory cytokines, such as interleukin (IL)-6, IL-8, and tumor necrosis factor (TNF)-α (6). Elevated levels of such cytokines would increase the adhesion of endometrial tissue onto peritoneal surfaces. Excessively synthesized estrogen and prostaglandins, and resistance against progesterone would have been used as clinically important starting points in order to develop therapeutic strategies for endometriosis (7).

Recent studies showed that erythropoietin (EPO), which is an important molecular regulator in the activation, proliferation, and differentiation of the cells of erythroid lineage, has been found to be involved in estrogen-dependent angiogenesis in the mouse uterus (8). It has also been demonstrated that EPO levels were increased in the peritoneal fluid of patients with endometriosis. As such, EPO and its receptor expressions were revealed in nonhematopoietic cells, including neurons, stromal cells, and human and mouse endometrial epithelium (9-11). It was revealed that EPO improves the proliferation and inhibits the apoptosis of trophoblast and decidual cells in early human pregnancy (10-12). In addition, it has been shown that EPO protects myocardial tissue (13), lung (14), and neuronal tissue (10,11), and participates in the recovery and remodeling of neuronal tissue after brain injury (15). As such, EPO is a promising candidate for the treatment of degenerative disorders. It is routinely administrated in patients with anemia with renal insufficiency (16); this hematopoietic factor is considered very potent and safe.

In this context, we aimed to investigate the role of EPO treatment and its receptor activation in endometriosis in rats. In addition to the use of EPO, we also used darbopoetin alpha (DARBE), which is a synthetic form of EPO, and methoxy polyethylene glycol-epoetin beta (MIRCERA), a long-acting EPO receptor activator, in order to assess their possible effects on the pathogenesis of endometriosis.

Material and Methods

Animal model

Forty female non-pregnant and non-ovariectomized nulligravid Sprague Dawley albino rats weighing 200-250 g were chosen for the study. They were bred for 3 to 4 months at the Experimental Research Centre. The rats were fed ad libitum and individually caged in a controlled environment (21 °C temperature and 60% humidity) with a 12-hour light/dark cycle. This study was approved by the Experimental Animals Ethics Committee (approval number: 2013/291) and the experiments were performed in compliance with the international guidelines on the ethical use of animals. The animals (10 per group) were randomly divided into 4 groups and treated with vehicle (control); EPO [for the second 3-week period, EPO (100 IU/kg) was applied intraperitoneally three times per week], DARBE (for the second 3-week period, DARBE was administered intraperitoneally once per week in 0.50 μg/kg) or MIRCERA (for the second 3-weeks period, MIRCERA was injected intraperitoneally once per week in 0.1 μg/kg).

Experimental design and surgical procedures

All rats were anesthetized with an intramuscular administration of 60 mg/kg of ketamine (Ketalar; Eczacıbaşı İlaç Sanayi, Levent, İstanbul, Turkey) and 6 mg/kg of xylazine hydrochloride (Rompun; Bayer İlaç Sanayi, Şişli, İstanbul, Turkey).

Before starting each surgical procedure, the animals were weighed, and the weight data were statistically evaluated.

In order to induce the endometrial foci, the uterine horns were removed from the cranial cervix, specifically, the upper bifurcation uterine region, approximately 0.5 cm caudal to the ovaries. The parametrial tissues covering the uterine horns were also removed. Each individual uterine horn was divided into two sections to get four separate tissue pieces. Each of these tissues possessing cylindrical shapes were longitudinally opened to create a linearly-shaped surface. These tissues were sutured with non-absorbable polypropylene 6-0 suture such that endometrial surfaces faced the inner abdominal wall. These four tissue pieces were implanted into a vascular area, two on the left and two on the right on the abdominal wall. Sterile saline solution was applied to the peritoneal cavity to prevent moisture loss. The midline abdominal incision was sutured using 3-0 silk sutures. The skin incision was closed in a continuous interlocking manner using 3-0 silk sutures. The sutures were supported through the use of Tensoplast adhesive bandaging (Smith & Nephew, New Zealand) for keeping the rats away from the sutured area.

After inducing endometrial foci in all animals, estrogen (50 μg/kg) was administered twice a week for 3 weeks for the induction of endometrial foci. At the end of the first 3-week period, estrogen treatment was stopped for all groups and surgery was performed for all animals at the end of every 3-week period for 9 weeks. These surgical procedures were performed in order to assess the dimensions of the endometriotic foci in millimeters, and to randomly take one of the foci by biopsy for histopathologic analysis. The study was completed at the end of the nine weeks, and the animals were sacrificed by decapitation under anesthesia in order to evaluate recurrence of the pathology.

Histopathologic examination

At the end of the ninth week, all animals were sacrificed in order to harvest all the endometriotic foci for histopathologic assessment. Histopathologic examination and scoring were performed by a pathologist who was blinded to the groups, and average scores were calculated when more than one lesion was observed in the same rat (17,18).

Tissue was fixed in 10% formaldehyde and paraffin embedded. Four-micrometer-thick tissue sections were cut and stained with hematoxylin-eosin and visualized using a Nikon Eclipse light microscope. The presence of endometrial epithelium and stroma in the ectopic focus, endometrial glands, and blood vessels were used to determine the full-blown endometriosis histopathologically. Tissue sections were scored as follows: 0: Absence of endometrial epithelium; 1: Endometrial epithelial cells seen occasionally; 2: Endometrial epithelial cells well conserved; 3: Well-conserved endometrial epithelial cells and endometrial glands.

Volumetric analysis of the endometrial foci

The dimensions of the endometrial foci were calculated according to the prolate ellipsoid formula below:

$$\text{Volume } (mm^3) = 0.52 \times \text{length} \times \text{width} \times \text{height}$$

Statistical analysis

Data were evaluated using one-way ANOVA followed by LSD tests. Data are presented as mean ± standard error mean values. Throughout the study, p values <0.05 were considered significant.

Results

In the control group, no endometriotic lesions were observed in only one rat and this rat was excluded from the study because it died in the fifth week of the study. The rest of the experimental animals remained alive until they were sacrificed.

Body weights of all experimental animals were measured before inducing endometrial foci and every surgical procedure at the first, second and third 3-week periods. No statistically significant difference was found between and within all groups (data not shown).

In order to evaluate the lesion sizes, the prolate ellipsoid formula was used. As expected, at the end of the first 3-week period (after stopping estrogen administration), the sizes of the endometriotic foci were very similar between all groups and no statistically significant differences were detected (Figure 1). On the other hand, after treating animals with the previously mentioned molecules (at the end of the second 3-week period), the lesion sizes in groups 2 (EPO), 3 (DARBE) and 4 (MIRCERA) were found to have decreased remarkably with respect to group 1 (control) (Figure 1). However, the lesion size was significantly decreased only in EPO treated animals ($p<0.05$). At the end of the third 3-week period (no treatment), the lesion sizes in all experimental groups were significantly lower. When a comparison of lesion sizes was made between the second and third 3-week period, the decrease in lesion sizes of group 2 (EPO) ($p<0.01$) and group 4 (MIRCERA) ($p<0.01$) seemed to be more pronounced than that of group 3 (DARBE) ($p<0.01$) in the third 3-week period as compared with the controls (Figure 1).

Histopathologic assessments showed that the scores of group 2 (EPO) ($p<0.01$) and group 3 (DARBE) ($p<0.01$) were significantly lower compared with the control group at the

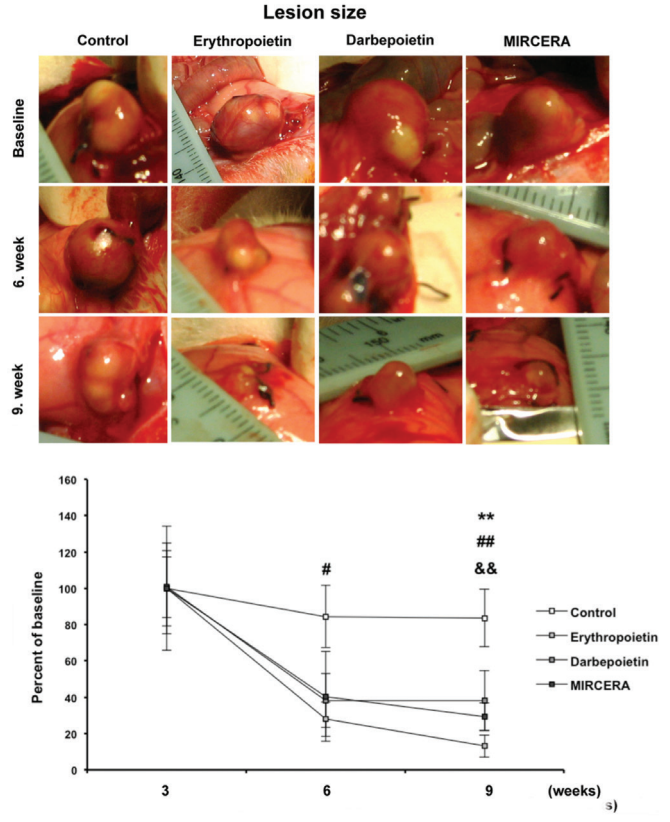

Figure 1. Effect of erythropoietin. Darbepoietin and MIRCERA on lesion development after induction of endometriosis. At the end of the first 3-weeks period (after stopping estrogen administration; baseline). Sizes of endometriotic foci are very similar between all groups and statistically significant differences have not been detected. In all treatment groups reduced lesion size was observed and the end of 6 weeks. No recurrence of lesions were observed 9 weeks after starting the experiment. Data are mean ± standard error mean values

MIRCERA: Methoxy polyethylene glycol-epoetin beta; ##p<0.01/#p<0.05 erythropoietin compared with control; **p<0.01 darbepoietin compared with control; &&p<0.01 MIRCERA compared with control

end of the second 3-week period. Scores of all experimental groups, on the other hand, were lower than the control group at the end of the third 3-week period. P values were less than 0.01 in EPO-, DARBE- and MIRCERA-treated animals as compared with the controls (Figure 2).

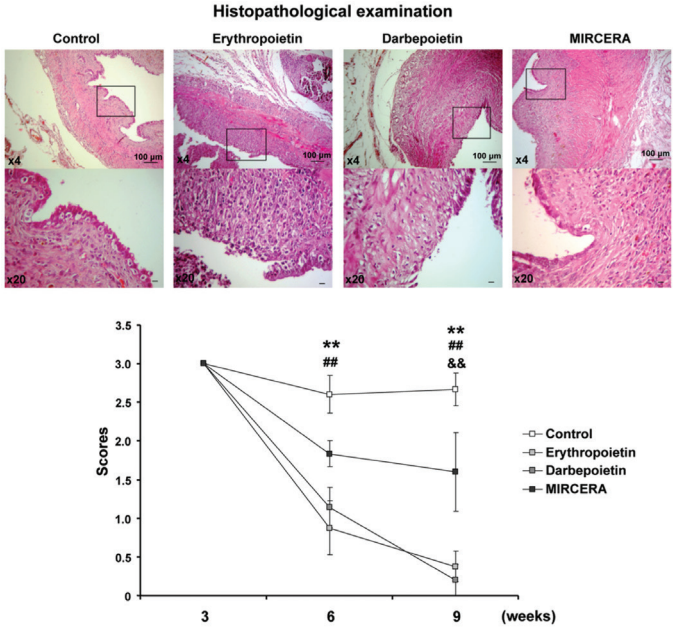

Figure 2. Histopathologic examination. Histopathologic examinations revealed that MIRCERA was less effective on the development of endometrial foci as compared with erythropoietin and darbepoietin

MIRCERA: Methoxy polyethylene glycol-epoetin beta; $^{\#\#}p<0.01$ erythropoietin compared with control; $^{**}p<0.01$ darbepoietin compared with control; $^{\&\&}p<0.01$ MIRCERA compared with control

Discussion

Endometriosis is a widely-occurring clinical situation seen in women with symptoms of pelvic pain and infertility. Although there are several treatment protocols for the situation, an effective cure does not exist.

EPO is an important molecule, synthesized mostly in the kidneys, liver, brain and uterus (19). In the kidneys, EPO synthesis and release is regulated by peritubular cells, whereas in the liver, hepatocytes and Kupffer cells are the main source and regulators of EPO production (20). It has been largely believed that neonatal anemia seen in early periods after birth may be caused by the reduction or complete loss of EPO synthesis and secretion from the placenta (21). It is also known that hypoxia is the primary stimulant for EPO production and its release, and hypoxia-inducible factor-1 is the main molecule in this pathway (22).

In addition, it was shown that oxidative stress was one of the key components in the pathophysiology of endometriosis. Accordingly, scientific research for the effective treatment of endometriosis has been focused on the reduction of oxidative stress (23). In recent studies, the antioxidant activity of EPO was revealed. It was shown that EPO has the capacity to act as a biologic antioxidant, a highly potent scavenger of hydoxyl radicals, which provides a mechanistic basis encouraging proof-of-concept studies in inflammatory disorders (24-26). In parallel with these studies, free radical scavengers such as melatonin have been found to cause a reduction of endometriotic lesions with its antioxidant properties (24). In another study, endometriotic lesions of rats decreased in size when melatonin was applied (25). Furthermore, EPO activates PI3K/Akt signaling pathways as a leading candidate with its role in cell metabolism and survival. In contrast, Matsuzaki et al. (26) demonstrated that intraperitoneal EPO concentration increased in women with endometriosis. It was a clinical study and it is not clear whether the increased EPO level was a part of the endogenous repair process after endometriosis.

We aimed to demonstrate the effects of exogenously-administrated EPO, DARBE, and MIRCERA on the treatment of endometriosis. We hypothesized that EPO and other agents could exert a therapeutic efficacy via their negative-feedback effect on EPO receptors, which have already been shown to play a critical role in the development of endometriosis. In this respect, we used a surgically-induced endometriosis model in rats and after induction, estrogen was administrated in order to accelerate the lesion formation, as described previously (18). In our EPO-administrated group of rats, the volumes of endometriotic foci and the histopathologic scores were both found to be decreased ($p<0.05$ for both). Furthermore, when the lesions were re-evaluated after 3 weeks of EPO treatment, the reduction in lesion sizes was still apparent and statistically significant. The decrease in lesion sizes and non-recurrence after stopping EPO injections led us to consider that exogenously-applied EPO could be used effectively in endometriosis.

DARBE is a structurally similar molecule to EPO but its half-life is approximately 3 times longer (~25 hours) (27). In our study, when DARBE was administrated for 3 weeks, a decrease in the sizes of endometriotic lesions was apparent but not statistically significant. However, even three weeks after stopping DARBE treatment, lesion sizes did not increase and the shrinkage of the endometriotic foci became statistically significant ($p<0.05$). In evaluating the histopathologic scores of the samples simultaneously, we revealed that the histopathologic scores were also lower during and after the DARBE treatment ($p<0.05$ for both measurements).

In the recurrence evaluation of the endometriotic lesions three weeks after the drug-free period, the decrease of the histopathologic scores after DARBE treatment was more pronounced with respect to the decrease of scores after EPO treatment. This would be related to the longer half-life of DARBE.

The third molecule used in this study was MIRCERA, which is an activator of the EPO receptor, and its half-life is approximately 133 hours (28). When treating rats with MIRCERA, the reduction of the endometriotic lesions was macroscopically apparent but not statistically significant. The decrease in the lesion sizes continued after stopping MIRCERA treatment (period for recurrence evaluation) and this reduction was also statistically significant ($p<0.05$). Histopathologic assessment showed that the scores were lower than the control group but there was no statistical significance; during recurrence evaluation, on the other hand, the histopathologic scores were significantly lower than the control group ($p<0.05$).

It is difficult to estimate what caused the discordance between the histopathologic and macroscopic evaluations; however, if we take a closer look at the total lesion size and histopathologic scores, it is easy to demonstrate that the most effective agents were EPO and DARBE. Not surprisingly, we have shown that DARBE was therapeutically superior to EPO in decreasing the recurrence rate. This is likely due to the relatively long-lasting effect of DARBE in comparison with EPO.

As compared with EPO, MIRCERA exerts different activity at the receptor level, which is defined as a slow association and rapid dissociation from the EPO receptor. Although there are strong data suggesting the antioxidant and anti-inflammatory activity of DARBE and EPO, there are still insufficient preclinical and clinical data to indicating the strong antioxidant effect of MIRCERA (29-31). To the best of our knowledge, there have been very few studies in other disciplines that have suggested the free radical scavenger effect of MIRCERA. Taken together, it is not unreasonable to assume that the therapeutic failure of MIRCERA could be partly attributed to its low anti-oxidant activity which needs to be confirmed with further comparative studies on the antioxidant effect of EPO, DARBE and MIRCERA. In the light of these observations, endometriotic lesions in rats were found to be decreased in size when EPO, DARBE, and MIRCERA were administrated. Moreover, these molecules seemed to reduce the recurrence rate of lesions after the treatment period. It is probable that the mechanism of action of these molecules could be related to the antioxidant properties of EPO itself and/or molecular pathways in which EPO might play its role. It should also be emphasized that large-scale clinical investigations on women with endometriosis are needed to be implemented before these three molecules can begin use in the treatment of endometriosis.

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Ethics Committee Approval: *All applicable international, national, and/or institutional guidelines for the care and use of animals were followed. This study was approved by the Experimental Animals Ethics Committee (with approval number: 2013/291) and the experiments were performed in compliance with the international guidelines on the ethical use of animals.*

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

Ovarian cancer: Pathogenesis and current recommendations for prophylactic surgery

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Abstract

Ovarian cancer is one of the most common gynecologic cancers, and one of the leading causes of cancer-associated female mortality in the world. Currently, no widely accepted pathogenesis is available, which may explain the entire disease. Early detection and primary prevention of ovarian cancer are difficult, mostly due to its heterogeneous nature. Risk factor modification based on epidemiologic data has not significantly reduced the incidence of ovarian cancer. Currently, prophylactic surgical methods have been proposed as the most effective preventive measures for both the high-risk or low-risk populations. Understanding the existing pathogenesis theories and the surgical options available may alter physician's perspectives and facilitate better decision making. (J Turk Ger Gynecol Assoc 2019; 20: 47-54)

Keywords: Ovarian cancer, primary prevention, salpingectomy, salpingo-oophorectomy

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Introduction

Ovarian cancer is one of the most prevalent gynecologic cancers in Indonesia, associated with high mortality rates (1,2). Difficulties in early detection contribute to the high mortality rate. Most patients (>75%) are diagnosed at a more advanced stage (stage III/IV), with a 5-year survival rate less than 30% (3,4).

Until recently, various preventive and early detection methods for ovarian cancer have not achieved satisfying results, which is partly due to its heterogeneous nature (5,6). Previously, primary ovarian cancer prevention was concerned with risk factor modification and encouraging protective factors, according to epidemiologic data, such as the use of oral contraception. Unfortunately, these modifications have not significantly reduced the incidence of ovarian cancer (7,8).

Currently, an alternative method has been proposed for ovarian cancer prevention. Prophylactic salpingectomy has been considered the most effective ovarian cancer prevention (9). In 2010, The British Columbia Ovarian Cancer Research Group (OVCARE) started the campaign for prophylactic salpingectomy implementation in hysterectomy and female sterilization. This approach is supposed to reduce the incidence of ovarian cancer as much as 20-40% in the next 20 years (8). This method is not popular yet in Indonesia. Through this review, we aim to provide a new insight and detailed overview of the role of salpingectomy for ovarian cancer prevention.

Epidemiology of Ovarian Cancer

Ovarian cancer ranks as the fifth leading cause of malignancy-associated mortality in females (10,11). In 2008, an estimated 225,500 women were diagnosed as having ovarian cancer worldwide, and in 2012 it was estimated that there were 238,700 new cases, and 151,900 women died of ovarian cancer (12). In general, ovarian cancer is more common in developed countries than developing countries with the highest incidence in Northern Europe (13.3 per 100,000 per year) and the lowest incidence in North Africa (2.6 per 100,000 per year). In Asia, the estimated incidence of ovarian cancer in China is 3.2 per 100,000 per year (12). In Indonesia, there are no national data on the incidence of ovarian cancer, but in 2002 it was estimated that 829 new cases were diagnosed (2). The incidence of ovarian cancer increases with age, with a peak incidence at the age of 50-60 years (3,4).

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Risk Factors for Ovarian Cancer

Studies showed that women with early menarche (age <12 years) and late menopause (age >50 years) were at higher risk for ovarian cancer due to a higher number of ovulatory cycles. Women with early menarche and late menopause are at a risk of 1.1 to 1.5 times and 1.4-4.6 times higher for ovarian cancer, respectively. Conversely, breastfeeding, pregnancy, and the use of oral contraceptive pills, which suppress ovulation, are protective factors for ovarian cancer (5,13). Epidemiologic studies have shown a link between the incidence of endometriosis and ovarian cancer through an uncertain mechanism (14).

One of the most important risk factors for ovarian cancer is a genetic factor. Genetic predisposition is found in 10-15% of cases of ovarian cancer. BRCA1 and BRCA2 gene mutations are associated with ovarian and breast cancer (5). BRCA1 and BRCA2 were first discovered in 1994 and 1995, and to date are the genes that have the strongest influence with ovarian cancer incidence (15). BRCA1 is an oncosuppressor gene on chromosome 17q21, and BRCA2 is located on chromosome 13q (5). Deletion or insertion of these genes causes the codon to stop prematurely and the protein produced becomes shorter. The genes also play a role in the chromatin remodeling process, thus their mutation causes uncontrolled cell growth. Mutations of BRCA1 and BRCA2 are associated with the risk of ovarian cancer at 50% and 20%, respectively (15).

Pathogenesis of Ovarian Cancer

To date, no widely accepted pathogenesis of ovarian cancer has been described. One of the biggest problems in uncovering the pathogenesis of ovarian cancer is the heterogeneous nature of ovarian cancer, comprising various histologic types with different behaviors and characteristics (16). Although 40% of ovarian tumors are nonepithelial types, only 10% of ovarian cancers are nonepithelial (17,18).

Incessant Ovulation Theory

Initially, all ovarian cancers were thought to originate from the epithelium of the ovarian cell surface. During ovulation, these surface epithelial cells experience physical trauma, which is repaired immediately. During a woman's life cycle, ovulation occurs repeatedly, which causes repetitive trauma to the epithelium, ultimately causing cellular DNA damage. Epithelial cells that have undergone DNA damage are very susceptible to change, which facilitates invagination to the cortical stroma. This invagination eventually becomes trapped and forms a sphere of epithelial cells in the stroma called cortical inclusion cysts. While inside the ovary, the epithelial cells are exposed to ovarian hormones that stimulate cell proliferation, which in turn transforms into cancer cells (3,7).

This theory is consistent with epidemiologic data where the number of ovulatory cycles is associated with the risk of ovarian cancer. The weakness of this theory is that it cannot explain the pathogenesis of various histologic types of ovarian cancer and prognostic differences (19). Histologically, the ovarian surface epithelium (mesothelium) has no similarity to serous, endometrioid, mucinous, clear cells or transitional cells (6). In addition, this theory also contradicts the fact that in patients with polycystic ovary syndrome who experience a decrease in the ovulation cycle, the risk of developing ovarian cancer is higher (3,7).

Fallopian Tube Theory

Previously, most researchers believed that ovarian cancer originated from the ovary itself. Thus, only a few tried to look for ovarian cancer precursor lesions elsewhere (6). It was reported that epithelial dysplasia was found at a high incidence in the Fallopian tubes (50%) of women with BRCA1/2 gene mutations undergoing prophylactic salpingo-oophorectomy. This epithelial dysplasia resembled high-grade serous ovarian carcinoma, which they called tubal intraepithelial carcinoma (TIC). Other studies also found similar histology characteristics of ovarian cancer and high-grade serous peritoneal cancer, regardless of BRCA status. Studies that examined the contralateral ovary of patients with ovarian cancer showed either normal histology or morphologic changes that did not resemble high-grade serous neoplasm characteristics (3,6). Based on these studies, it can be concluded that the fallopian tube would likely be the location of the ovarian cancer precursor lesions, which eventually spread to the adjacent ovary.

TP53 gene mutation is also obtained in TIC. In normal fallopian tubes, immunohistochemical examinations revealed that TP53 expressions in the secretory cells were identical to TP53 mutations in serous ovarian cancer. Nevertheless, not all TP53 mutations become cancerous. TP53 expression is thought to be a response that shows DNA damage in tubal epithelial cells due to exposure to cytokines and oxidants. About 50% of TP53 mutations eventually become cancerous (7,16).

Almost all TICs (70-90%) are found in the fimbria region, which is the distal part of the fallopian tube. Although initially controversial, this theory began to be accepted by experts. Fimbriae located very close to the ovary are exposed to the same environmental stressors as the ovary. In addition, fimbriae are also rich in blood vessels that facilitate metastasis to the ovaries through the bloodstream (6).

Two-Pathways Theory

This theory was originally proposed by Kurman and Shih (3) in 2004, who sought to integrate the histological, clinical and genetic findings of ovarian cancer. They divided ovarian cancer

into 2 types, namely type I and type II. Type I ovarian cancer consists of low-grade serous, mucinous, endometrioid, clear cell, and transitional histology types. Meanwhile, type II ovarian cancer consists of high-grade serous, undifferentiated and carcinosarcoma histology types (Figure 1) (3).

Precursor lesions are thought to originate in the ovary in type I ovarian cancer. In this, ovarian cancer grows slowly, tends to be benign, usually affects only the ovary in the diagnosis, and is genetically stable (19). Ovarian tumors undergo a series of morphologic changes on an ongoing basis and become ovarian cancer after surpassing the intermediate (borderline) phase. The pathogenesis of type I ovarian cancer is through the traditional pathway: ovarian surface epithelial inclusion cysts that receive proliferation stimulation from the environment, eventually transforming them into cancer cells. The most common genetic changes in type I ovarian cancers are KRAS and BRAF mutations, both of which can activate the oncogenic pathway MAPK (3,6,7).

In contrast to type I ovarian cancer, precursor lesions of type II ovarian cancer are thought to originate from outside the ovary, one of which is from the fallopian tube. Type II ovarian cancers tend to grow more aggressively, are genetically unstable, and are usually diagnosed at a more advanced stage. The majority of type II ovarian cancers exhibit TP53 gene mutations (50-80%), also overexpression of HER2/neu (10-20%) and AKT (12-18%) genes. Nearly half of all type II ovarian cancers are associated with BRCA1/2 gene mutations. Type II cancer cell precursors may originate from the fallopian tube, where a combination of TP53 mutations and environmental stressors such as inflammatory cytokines and reactive oxygen species cause secretory epithelial cells in the fallopian tubes to undergo neoplastic changes. Researchers showed that TP53 mutations were associated with lower parity, thus, ovulation was still considered the risk factor of TP53 gene mutation (3,19). In general, this theory is considered more capable of explaining the pathogenesis of ovarian cancer than other theories. However, it still lacks an understanding of the cancer development of non-ovarian origin (19).

Prophylactic Surgical Methods for Ovarian Cancer

Primary prevention of ovarian cancer was mostly achieved by modifying risk factors and protective factors for ovarian cancer, based on epidemiologic data. For example, the use of oral contraceptives for at least 5 years reduces the risk of ovarian cancer by 50%. The same goes for parity, which reduces the risk of ovarian cancer by 50% when compared with nulliparity. However, these modifications have not shown a significant impact on the incidence of ovarian cancer in general. In addition, advocating the long-term use of oral contraceptives may increase the risk of breast cancer and thromboembolism (6,8). Clinical signs and symptoms of ovarian cancer are often non-specific and appear in a more advanced stage. No screening method has been proven effective in reducing the incidence of ovarian cancer, including periodic gynecologic examination, ultrasound study, and serum marker measurement. Calculating the possibility of ovarian cancer using CA125 may be useful. However, a single measurement may not be of value, thus serial testing is needed. Unfortunately, the rise in CA125 is not

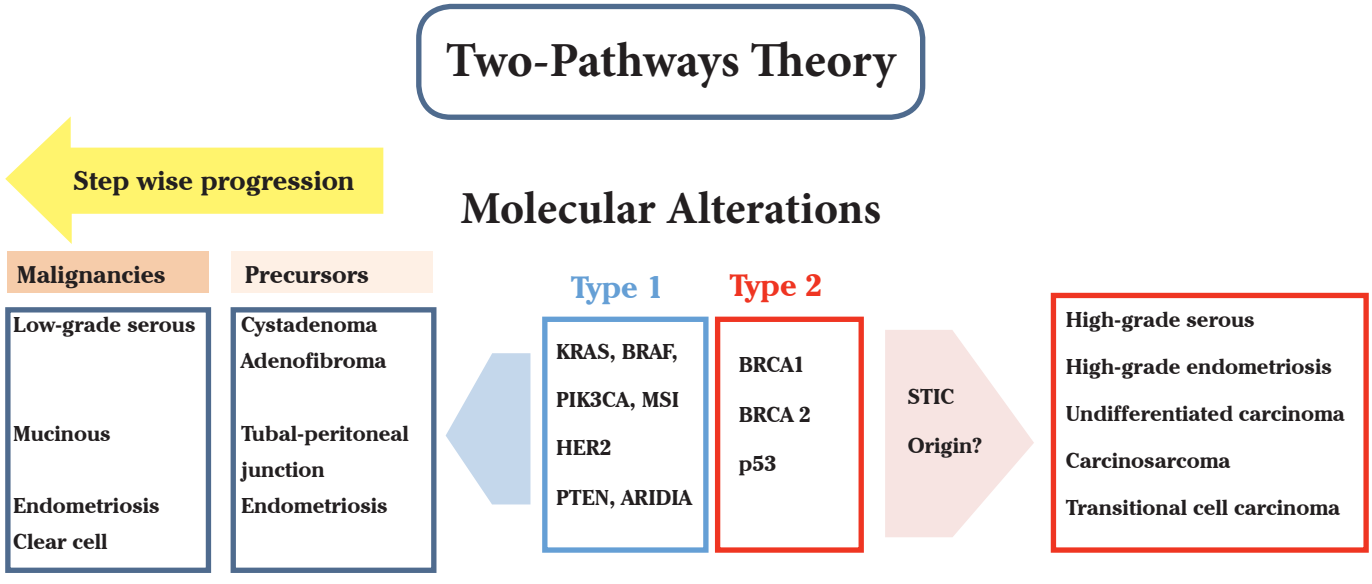

Figure 1. The two-pathways theory of ovarian cancer
STIC: Serous tubal intraepithelial carcinoma

only associated with ovarian cancer, and there is no consensus on a threshold value to prompt surgical intervention for patients (4,20).

Currently, prophylactic surgical methods (either salpingectomy or salpingo-oophorectomy), have been proposed as a more effective primary prevention (6). In the past, prophylactic surgery was only intended for women at high risk of ovarian cancer, such as those with BRCA1/2 gene mutation. However, many studies suggest that not all ovarian cancers are related to genetic factors, thus prophylactic surgery is also considered useful for women in the general population. The fallopian tube, which is currently considered the initial location of ovarian cancer, has led to a trend shift from salpingo-oophorectomy to salpingectomy. The number of adverse effects caused by oophorectomy for young women also supports this tendency (7,21).

To reduce the incidence of ovarian cancer, it is estimated that 100 prophylactic salpingectomies should be performed to prevent 1 case of ovarian cancer (21). However, to date, prophylactic salpingo-oophorectomy is still considered the most effective preventive measure, and is associated with low incidence of surgical complications (9). In 2010, OVCARE began a campaign to perform prophylactic surgery at the time of hysterectomy or female sterilization procedures. It was estimated that the approach would reduce the incidence of ovarian cancer by 20-40% in the next 20 years (8).

Salpingectomy is a simple procedure and can be performed simultaneously with or without a hysterectomy, for example in sterilization procedures. However, salpingectomy may disrupt blood flow to the ovary, impairing ovarian function, which is certainly not desired by young patients (8,9,22). Salpingectomy does not cause significant surgical risk and adds only minimal time. This procedure can be implemented during hysterectomy for benign disease, tubal sterilization, and other abdominal or pelvic surgery that gives access to gynecologic organs. However, salpingectomy during tubal sterilization may not be as popular because it is more difficult when compared with other techniques (20). Salpingectomy should include the total resection of the fallopian tube from the most distal fimbriae to the proximal portion up to the utero-tubal junction, without severing the collateral vasculature from mesosalpinx (23). Care must be taken in performing salpingectomy to avoid potential vascular compromise to both ovaries. When carefully executed, there is no significant decrease in ovarian function indicated by serum anti-mullerian hormone and follicle-stimulating hormone measurements (24). Salpingectomy adds 16 minutes to the operating time with hysterectomy, and 10 minutes in a sterilization procedure (20). Prophylactic salpingectomy is clearly an improvement in the efforts to prevent ovarian cancer. Nevertheless, the fallopian tube theory may not be the only pathogenesis of ovarian cancer. Hence, prophylactic salpingectomy may not prevent all ovarian cancers (22).

Prophylactic Surgical Methods in BRCA1/2 Genes Mutation

Women with BRCA1 and BRCA2 mutations have a higher risk of ovarian cancer at the age of 70 years at 39-46% and 10-27%, respectively. The Society of Gynecologic Oncology recommends genetic testing for individuals with a high tendency for familial cancer (a first-degree or several close relatives with an inherited predisposition, a close relative carrying known BRCA1 or BRCA2 mutations, and a close relative with male breast cancer) (25). It is important to identify women at high risk, including the presence of BRCA mutation in the family, early-onset breast cancer, ovarian cancer at any age, male breast cancer, and Ashkenazi Jewish ancestry (26). Women with a first-degree relative with ovarian cancer have a three to four-fold increased risk of developing ovarian cancer (27).

One study showed that 54% of women with ovarian cancer and BRCA1 mutation were diagnosed before the age of 50 years, unusually diagnosed before the age of 40 years, and rarely before 30 years. Bilateral salpingo-oophorectomy should be considered for women with BRCA mutation after the age of 40 years once childbearing is complete because the onset of the disease is mostly after 40 years of age (26,28). Bilateral salpingo-oophorectomy reduces the risk of ovarian cancer by 75-96% and breast cancer by 50% when undertaken before menopause. The risk of primary peritoneal cancer after prophylactic surgery is reported as 2-4% (28).

The best timing for salpingo-oophorectomy in high-risk women is still controversial. It is agreed that the procedure must be performed as soon as possible given the potential of ovarian cancer. On the other hand, it may increase the risk of systemic complications in young women. Salpingo-oophorectomy is more effective if undertaken before menopause, but will lead to premature menopause in reproductive-aged women (7,22). Some authors recommend prophylactic salpingo-oophorectomy at the age of 40 or when reproductive function preservation is not desired (15,21). Women with BRCA mutations should be offered prophylactic surgery when childbearing is complete. The timing of surgery should also consider the age at onset of cancer in family members (29). Oophorectomy is associated with a rapid decline in serum estrogen and androgens, leading to postmenopausal symptoms and increased risk of various health problems (30). Prophylactic salpingo-oophorectomy is not without risk, however. Bilateral oophorectomy increased the risk of mortality associated with cardiovascular disease. In addition, this action can also increase the risk of parkinsonism, dementia, and osteoporosis (21,22,31). Studies reported that the risk of mortality due to cardiovascular disease was

increased when performed before the age of 45-47.5 years (28,32). Premenopausal oophorectomy increases the risk of osteopenia and osteoporosis, and also causes a 20% decrease of trabecular bone, 18 months after surgery. The procedure is also associated with an increased risk of osteoporosis when performed before the age of 45 years. Thus, baseline bone density and follow-up every 1-2 years are recommended. The risk of cognitive impairment is greatest when oophorectomy is undertaken before the age of 49 years. Overall all-cause mortality was higher in women who underwent oophorectomy before the age of 45 years (33). Counseling should include the risk of death from ovarian cancer and the potential medical morbidities related to premature menopause (34).

Short-term sexual function seems to be less affected by oophorectomy, although studies are limited. In more than 50% of women, menopause-specific quality of life and sexual satisfaction were lower at 5 years after surgery (28). However, impairment of quality of life and sexual function in women who undergo bilateral salpingo-oophorectomy recover to baseline by 6 and 12 months (35). These adverse effects can be reduced by using hormone replacement therapy to some extent, but long-term use may decrease the benefit of oophorectomy on the breast as cancer prevention. Controversies regarding the risk-benefit comparison of oophorectomy exist. From the epidemiologic point of view, ovarian cancer is a far less common cause of female death (14,800 deaths/year) when compared with coronary heart disease (350,000 deaths/year) and hip for the actual (66,000 deaths/year) in the United States of America (USA). Also, around 10% of dementia in women is associated with a history of bilateral oophorectomy. These data conflict with the benefit of performing bilateral oophorectomy because preventing these problems (commonly associated with oophorectomy) seems much more important than preventing ovarian cancer due to their higher incidence. Patient's age and family history are strong determinants for suggesting oophorectomy. Women with a known genetic predisposition should be recommended salpingo-oophorectomy after childbearing age (30).

Salpingectomy may be an option to avoid the adverse effects of oophorectomy. Histopathologic analysis of adnexa resected from BRCA-positive women revealed 4-17% had a cancerous lesion; 57-100% of cases were found in the distal portion of the fallopian tubes, characterized by an increase in the nuclear-cytoplasmic ratio, loss of nuclear polarity, nuclear pleomorphism, and loss of ciliated cells. This pathology is termed serous TIC (STIC). This lesion is found in almost 60% of patients with ovarian cancer, which indicates that the majority of cases are of tubal origin. It is estimated that 80-90% of BRCA-related ovarian cancers originate from the fallopian tube. Thus, only performing salpingectomy in BRCA-positive women may reduce the likelihood of having ovarian cancer as much as salpingo-oophorectomy, with the lowest risk of long-term complications. For young patients who wish to undergo prophylactic surgery, salpingectomy alone may provide more time to conceive via in vitro fertilization (36). Complete salpingectomy is preferred compared with fimbriectomy, although most BRCA-associated tubal lesions were found in the distal portion of the fallopian tube. The risk of ovarian cancer after hysterectomy with salpingectomy is 0.1-0.75% and the benefits of ovarian preservation decrease significantly after the age of 65 years (23). The risk of having repeat surgery for gynecologic problems after salpingectomy (with or without hysterectomy) is 0.89-5.5%, and the risk of developing ovarian cancer after hysterectomy with salpingectomy is reported as 0.1-0.75%. Therefore, salpingectomy alone or delayed oophorectomy can be a considerable choice for young patients (30). However, the effectiveness of salpingectomy alone is yet to be proven, and the benefit as a breast cancer prevention cannot be achieved (Finch, 2009). Considering the possibility of the ovarian origin of ovarian cancer, oophorectomy may still benefit women (7,21,22).

The timing for prophylactic salpingectomy remains controversial. One may suggest that surgical prevention may be of more benefit if conducted at an earlier age. Some authors propose that salpingectomy should be performed after the age of 35 years in high-risk women (37). Unfortunately, currently, there is no large prospective study assessing the relationship between age-related risk reductions among women undergoing prophylactic surgery.

Thus, for women with BRCA1/2 gene mutations, there are three options of prophylactic surgical procedures: (1) bilateral salpingo-oophorectomy, (2) salpingectomy alone, and (3) salpingectomy with delayed oophorectomy. A Markov Monte Carlo risk simulation study aimed at assessing the advantages of these options found that prophylactic salpingoopherectomy was the most effective strategy for the prevention of ovarian cancer. There are no data regarding the impact of two-staged surgery on quality of life, the percentage of women who decline the second surgery or delay the procedure long after natural menopause, and the overall impact on ovarian cancer incidence in this population (37). However, salpingectomy with delayed oophorectomy showed the best quality of life (21,22).

Prophylactic Surgical Methods in General Population

In the general population, the lifetime risk of ovarian cancer is estimated to be around 1.4%. To date, there have been no recommendations for prophylactic surgical methods in the low-risk general population. For the low-risk population, oophorectomy is rarely recommended before the age of 40 years and highly recommended for women aged over 55 years

(30). Prophylactic surgery has been implemented in several gynecologic procedures, such as sterilization and hysterectomy. Hysterectomy is the most common gynecologic procedure. In the USA, it is estimated that 600,000 hysterectomies are performed each year, and 55% are accompanied by bilateral salpingoopherectomy (7). Women who undergo hysterectomy without accompanying salpingectomy are at 7.8% higher risk of developing a disorder that ultimately requires salpingectomy, such as hydrosalpinges, infection, benign tumors, and ovarian cancer (8,21,38). When salpingectomy was integrated in the hysterectomy procedure aimed for benign gynecological cases, it caused an increase in the number of salpingectomies 20 times in Canada. In addition, the method of female sterilization by salpingectomy is also recommended due to its protective effect against ovarian cancer compared with tubal ligation alone (22,39,40). For women in the general population who are undergoing hysterectomy, sterilization or pelvic and abdominal surgery, the decision to include ovarian cancer prevention should be made after detailed informed consent, including the risk and benefit of each procedure. Careful history taking, risk factor assessment, systemic and gynecologic disease evaluation should also be made. Low-risk women with certain gynecologic conditions (severe endometriosis, chronic pelvic inflammatory disease, ovarian neoplasm, and chronic pelvic pain) or medical conditions that may complicate repeat surgery (cardiopulmonary and hepato-renal disease, immunosuppression and morbid obesity) should consider prophylactic surgery. The rate of repeat surgery for various gynecologic indications ranges between 2.5% and 7.6% (29). In women aged 40 years and over, implementation of prophylactic surgery during hysterectomy and general surgery that permit access to the gynecologic organ may prevent ovarian cases by 5.2% and 10.9%, respectively. However, the decision of gynecologic or abdominal surgery should not be affected by the intention for salpingectomy (30).

Technically, the addition of a salpingectomy during hysterectomy does not increase the risk of complications and only slightly increases the duration of surgery (31). Salpingectomy performed during hysterectomy only increases the duration by about 16 minutes, and salpingectomy for female sterilization only increases the duration of surgery by 10 minutes compared with other procedures. No increased risk for blood transfusion need, prolonged hospital care, and postoperative re-admission have been reported (8,21,41).

Understanding the benefits of performing salpingectomy would encourage physicians to provide sufficient information regarding the procedure and may facilitate the patient's decision making (22). In a Canadian survey involving obstetrics and gynecology specialists found that majority of physicians (68%) had been well-educated on the benefits of prophylactic salpingectomy and had or would add the procedure when performing a hysterectomy (38). Recent research showed that prophylactic salpingectomy procedures did not impair ovarian function. Morelli et al. found no significant differences in the levels of anti-mullerian hormone, follicle-stimulating hormone, the number of antral follicles, and the average diameter of the ovaries taken before surgery and 3 months after surgery (9,24). The American College of Obstetrics and Gynecology issued its opinion regarding prophylactic salpingectomy as a preventive measure of ovarian cancer as follows (40):

1. The surgeon and patient should discuss the potential benefits of the removal of the fallopian tubes during a hysterectomy in women at population risk of ovarian cancer who are not having an oophorectomy.
2. When counseling women about laparoscopic sterilization methods, physicians can communicate that bilateral salpingectomy can be considered a method that provides effective contraception.
3. Prophylactic salpingectomy may offer physicians the opportunity to prevent ovarian cancer in their patients.
4. Randomized controlled trials are needed to support the validity of this approach to reduce the incidence of ovarian cancer.

Kwon et al. (23) conducted a study using Markov Monte Carlo simulation models to assess the economic impact of prophylactic surgery during hysterectomy and sterilization in the general population. They found that hysterectomy with salpingectomy was less costly than hysterectomy alone or hysterectomy with bilateral salpingo-oophorectomy. However, hysterectomy with bilateral salpingo-oophorectomy was more effective in preventing ovarian cancer. They also found that even though salpingectomy for sterilization was more costly than tubal ligation, it was more effective at preventing ovarian cancer (23). Despite all the evidence that supports the role of prophylactic salpingectomy in preventing ovarian cancer, it has not yet become a guideline for the ovarian cancer prevention. Large-scale research is still required in the future (8,21).

Ovarian cancer is a heterogeneous disease, which consists of various histologic characteristics, with unclearly described pathogenesis. The fallopian tubes are thought to be the main location of the precursor lesions of most ovarian cancers, thus, prophylactic efforts are now directed towards surgical procedures for both the tubes and/or ovaries. In high-risk populations with BRCA1/2 gene mutations, salpingo-oophorectomy shows better effectiveness and is recommended for women aged over 40 years or when childbearing is complete. In young women, salpingectomy can be performed either alone or combined with late oophorectomy near the onset of natural menopause. In the low-risk general population, prophylactic salpingectomy still lacks a solid basis, but it may be offered

during gynecologic procedures such as hysterectomy and female sterilization, or various pelvic and abdominal surgeries that allow access to the gynecologic organ.

Further research to validate the role of prophylactic surgery for ovarian cancer must be conducted, involving a larger and more diverse population. However, given the possible protective effects, the authors recommend that the available information should be delivered such that patients can choose whether to undergo prophylactic surgical procedures.

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Management of fibroids prior to in vitro fertilization/ intracytoplasmic sperm injection: A pragmatic approach

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Abstract

Fibroids are relatively common in women undergoing in vitro fertilization (IVF) treatment due to their high prevalence in women. It is generally accepted that submucosal fibroids are deleterious to IVF outcomes and their removal is beneficial. Evidence from relatively low quality studies on the impact of intramural fibroids on IVF outcome is also suggestive of a detrimental impact. The majority of published studies included women with relatively small intramural fibroids and women with cavity-distorting fibroids were usually excluded, hence it is quite likely that the detected impact in the systematic reviews is an underestimation. Evidence of benefit is scarce for the removal of noncavity-distorting intramural fibroids. It is quite likely that numbers needed to treat for this purpose would be very high for small fibroids but lower for larger fibroids. This would need to be taken into account when decisions are made on myomectomy and potential benefits should be weighed against the associated morbidity, cost, and delay in fertility treatment. Whilst there is a need to perform prospective randomised studies in this field, a pragmatic approach that takes prognostic factors into account to estimate the magnitude of the possible impact of the fibroid(s) and potential benefit of removal is likely to lead to better reproductive outcomes. (J Turk Ger Gynecol Assoc 2019; 20: 55-9)

Keywords: Fibroids, leiomyoma, in vitro fertilization, assisted reproductive technology

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Introduction

Fibroids are common in women in their reproductive years and are frequently detected in women who are about to undergo treatment with assisted reproductive technologies (ART). Although many fibroids are completely harmless and have no clinical significance, 10-15% of white women and 30-40% of black women between the ages of 35 to 39 years have been found to have clinically relevant fibroids (uteri nine weeks gestation size or larger, at least one submucosal fibroid or at least one fibroid of ≥4 cm) (1). As a result, questions are inevitably raised by physicians and couples about the possible detrimental impact of fibroids on the planned ART or whether removal of fibroids would be expected to be beneficial in improving the ART outcome. The published literature on the impact of fibroids on fertility/fertility treatment outcome and potential benefit of fibroid removal is marred by a number of problems. The majority of studies are observational and are prone to selection bias. It is quite likely that women with larger and more 'significant' fibroids undergo surgery and are excluded from these studies. In addition, there are a large number of confounding parameters that are difficult to control in fibroid-related studies; fibroids come in all different numbers, sizes, and locations. Studies set out to diligently study the impact of intramural fibroids to ensure that uterine cavity distortion is excluded with a high quality or reliable test. This has resulted in exclusion of a large subgroup of women who have intramural fibroids with cavity distortion and the published systematic reviews do not provide a clear outcome analysis for this group. As a result, recommendations from professional

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organisations end up representing the opinion of the people who write them, sometimes with conflicting views even in the same document.

A number of meta-analyses since 2007 reported different conclusions despite mostly including the same studies (2-7). This is likely to be the result of differences in the methodology of reviews and inclusion/exclusion criteria that were used. In this article, the evidence from the published literature will be critically analysed in an attempt to provide guidance to physicians as to how fibroids can be managed in women undergoing in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) treatment.

Evidence from Meta-Analyses

We will look at six major reviews that analysed the impact of fibroids on reproductive outcomes (2-7). Three of these reviews included studies that investigated the impact of all-type fibroids on both spontaneous pregnancies and IVF treatment outcomes (2-4), and the other three specifically addressed studies that assessed the impact of intramural fibroids that did not distort the uterine cavity on the outcome of IVF treatment (5-7).

Somigliana et al. (2) conducted a number of meta-analyses on the published literature related to fibroids and reproduction. In one of these, they assessed 16 articles on IVF outcomes and fibroids. Two studies, which included submucosal fibroids, showed that the presence of these fibroids significantly reduced pregnancy [odds ratio (OR): 0.3, 95% confidence interval (CI): 0.1-0.7] and delivery rates (OR: 0.3, 95% CI: 0.1-0.8). Intramural fibroids (seven studies) caused a small but significant detrimental impact of intramural fibroids on conception (OR: 0.8, 95% CI: 0.6-0.9) and delivery (OR: 0.7, 95% CI: 0.5-0.8) rates following IVF/ICSI treatment. Studies showed that subserosal or intramural/subserosal fibroids did not significantly reduce IVF/ICSI outcomes. They noted that the average diameter of fibroids in the included studies was rarely above 3 cm and that the detrimental impact emerging from the published articles may have been an underestimation of the real impact. They based this opinion on the finding that the negative impact was seen in women with fibroids >4 cm (8). Somigliana et al. (2) highlighted a nonrandomised comparative study by Bulletti et al. (9) who found higher cumulative clinical pregnancy (33% vs 15%) and delivery (25% vs 12%) rates after one to three cycles of IVF treatment in women who underwent myomectomy for intramural fibroids >5 cm compared with those who decided against myomectomy.

Klatsky et al. (3) included three studies on submucosal fibroids and IVF outcomes. This showed a significant reduction in implantation (OR: 0.39, 95% CI: 0.24-0.65) and clinical pregnancy rates (OR: 0.44, 95% CI: 0.28-0.70) and increase in miscarriage rates (OR: 3.89, 95% CI: 1.12-13.27). Nineteen studies compared IVF outcomes in women with intramural fibroids of 1-8 cm with those of controls without fibroids. Most studies included women with relatively small fibroids of 2-3 cm. The meta-analysis by Klatsky et al. (3) showed a significant decrease in implantation (OR: 0.79, 95% CI: 0.71-0.88) and clinical pregnancy rates (OR: 0.84, 95% CI: 0.74-0.95) and increase in miscarriage rates (OR: 1.82, 95% CI: 1.43-2.30). Klatsky et al. (3) did not analyse the impact of subserosal fibroids on IVF outcomes.

Pritts et al. (4) analysed 23 studies, which mostly gave IVF/ICSI related outcomes. Four of these studies on submucosal fibroids showed significantly reduced clinical pregnancy (OR: 0.36, 95% CI: 0.18-0.74), implantation (OR: 0.283, 95% CI: 0.12-0.65), and ongoing pregnancy/live birth rates (OR: 0.32, 95% CI: 0.12-0.85) and increased miscarriage rates (OR: 1.678, 95% CI: 1.37-2.05). Twelve studies that included outcomes related to intramural fibroids showed lower clinical pregnancy rate (OR: 0.81, 95% CI: 0.70-0.94), ongoing pregnancy/live birth (OR: 0.70, 95% CI: 0.58-0.85), and implantation rates (OR: 0.68, 95% CI: 0.59-0.80), and higher miscarriage rates (OR: 1.75, 95% CI: 1.23-2.49) compared with control women without fibroids. When only prospective studies or studies that assessed uterine cavity distortion with hysteroscopy or sonohysterography were included, the implantation rates remained significantly lower in women with intramural fibroids, but clinical pregnancy rates were no longer significantly different. Two studies that assessed the clinical pregnancy rates and one that gave the ongoing/live pregnancy rates showed that myomectomy for intramural fibroids did not improve the outcomes compared with controls with in situ fibroids. This review did not show a significant impact of subserosal fibroids.

Sunkara et al. (5) published an analysis of 19 studies on the impact of non-cavity distorting intramural fibroids on IVF outcomes. They found significant reductions in live birth rates (OR: 0.79, 95% CI: 0.70-0.88) and clinical pregnancy rates (OR: 0.85, 95% CI: 0.77-0.94) in women with fibroids compared with women without fibroids. Implantation and miscarriage rates were not statistically different. The studies included in this article had data from women with fibroids of 0.4-8.0 cm, the majority being less than 5 cm.

Metwally et al. (6) conducted a further analysis of the effect of intramural fibroids on ART treatment using published studies that included an aged-match control group, analysed intramural fibroids separately (not grouping them together with subserosal fibroids), and excluded submucosal fibroids by assessing the endometrial cavity using an objective method (hysteroscopy or sonohysterography). With this approach, no differences in live births, clinical pregnancy or miscarriage rates were found between women with and without fibroids. However, inclusion of studies with less strict criteria suggested lower clinical pregnancy rates (OR: 0.60, 95% CI: 0.42-0.87),

whilst live birth and miscarriage rates were still similar. Importantly, four studies that gave the size of fibroids included women with fibroids sized of 5 cm or less.

Wang et al. (7) recently performed an updated meta-analysis of the impact of noncavity-distorting fibroids on the outcomes of IVF. The authors included 28 studies comprising 9189 IVF cycles, including the 19 studies included in the meta-analysis by Sunkara et al. (5). Seven of these were prospective trials and 23 studies controlled for compounding factors such as the woman's age. This meta-analysis demonstrated significantly reduced clinical pregnancy [risk ratio (RR): 0.86, 95% CI: 0.80-0.93], live birth (RR: 0.81, 95% CI: 0.73-0.91) and implantation rates (RR: 0.90, 95% CI: 0.81-1.00) and increased miscarriage rates (RR: 1.27, 95% CI: 1.08-1.50). Separate analysis of prospective studies only and outcome of first cycle IVF confirmed the detrimental impact of noncavity-distorting fibroids on clinical pregnancy and live birth rates.

It appears that, despite some degree of differences in the conclusions of these systematic reviews, the common finding is that the presence of fibroids has a detrimental impact on the outcome of IVF. It is generally accepted that submucosal fibroids do have a detrimental impact on fertility outcome. However, the quality of evidence to support this is weak and the significance of benefit of submucosal fibroid removal was brought into question in a Cochrane review (10).

Importance of Fibroid Size

A common feature in the majority of studies is that they included only women with relatively small intramural fibroids, probably because women with larger fibroids were excluded and underwent a myomectomy. Hence, the published literature is very likely underestimating the impact of intramural fibroids, particularly larger fibroids.

Only a few studies attempted to assess the impact of fibroid size. Oliveira et al. (8) found that a detrimental impact was seen in the presence of relatively larger fibroids. The clinical pregnancy rates were lower after IVF/ICSI in women with intramural or subserosal fibroids of 4.1-6.9 cm compared with women with no fibroids or fibroids ≤4 cm. There was no difference in pregnancy rates between the control group and women with fibroids ≤4 cm. Women with fibroids of ≥7 cm were excluded.

Another retrospective study of impact of fibroids that did not distort the cavity found that delivery rates were lower in the presence of fibroids >2.85 cm, whilst there was no detrimental impact in the presence of smaller fibroids (11).

A more recent retrospective matched cohort study showed that fibroids ≥30 mm had a deleterious effect on live birth rates, whereas this effect was not seen in the presence of fibroids <30 mm (12).

Impact of Fibroid Removal

Evidence on the potential benefit of removal of fibroids prior to IVF/ICSI for women with fibroids is relatively scarce. A retrospective case controlled study of women with submucosal fibroids undergoing IVF using own or donated eggs showed that hysteroscopic or abdominal myomectomy for submucosal fibroids normalised the cycle outcomes. In this group of women, implantation and ongoing pregnancy rates were similar to the controls who had no fibroids, suggesting that the detrimental impact of submucosal fibroids is eliminated by fibroid removal (13).

A comparative non-randomised study assessed the potential benefit of myomectomy for intramural fibroids prior to IVF (10). One hundred sixty-eight women with at least one fibroid >5 cm were allowed to choose between myomectomy and expectant management prior to IVF. Submucosal fibroids were excluded. In the 84 women who had a myomectomy, clinical pregnancy (33% vs 15%, $p<0.05$) and delivery (25% vs 12%, $p<0.05$) rates were significantly better compared with the other 84 women who did not have surgery after one to three cycles of IVF treatment.

Hysteroscopic myomectomy is a relatively safe procedure with minimal surgical morbidity. However, it can cause intrauterine adhesions, which could lead to a reduction in fertility and chances of success with fertility treatment. Special attention should be paid to treatment of multiple and large submucosal fibroids. Hysteroscopic removal of large fibroids is more challenging and multiple fibroid removal is more likely to cause intrauterine adhesions.

Abdominal myomectomy is a major operation that can cause significant morbidity, especially in the presence of multiple and large fibroids. Potential long-term harm of postoperative pelvic adhesions on spontaneous conception is well recognised but the impact of myometrial trauma or intrauterine adhesions after abdominal myomectomy on IVF is less well recognised. At the same time, questions still remain on its effect on fertility and outcome of ART due to the absence of convincing evidence.

When an abdominal myomectomy is indicated, the potential benefits of the laparoscopic approach against open myomectomy have been well established (14). In comparison with traditional open myomectomy, the laparoscopic approach is associated with less postoperative pain and fever, and shorter hospital stay at the expense of longer operating times in a number of randomized clinical trials (15). Other potential advantages of the laparoscopic approach include a shorter recovery time with a quicker return to activities of daily living (16).

There will be a need to delay pregnancy after myomectomy to allow the uterine wall to heal. This is relatively short after hysteroscopic myomectomy because it does not involve a

myometrial incision, but needs to be long enough for the fibroid bed to 'recover' and be covered with endometrium. However, women are usually advised to avoid pregnancy for at least three months after abdominal myomectomies, resulting in delays in the planned IVF treatment. This may potentially be an issue for older women, particularly for those with reduced ovarian reserve. This delay may, however, be overcome by performing IVF before myomectomy and freezing the embryos for transfer after the recovery period. One potential problem with this approach is difficulties with access to the ovaries due to fibroids.

Conclusions and a Pragmatic Approach to Management of Fibroids Prior to IVF/ICSI

There is overall consensus that submucosal fibroids have a detrimental impact on the chances of success with IVF/ICSI. Furthermore, there is some evidence of the benefit of myomectomy for submucosal fibroids to improve ART outcomes. For this reason, we make every effort to remove all submucosal fibroids in our practice. It is usually possible to remove all type 0 and I fibroids hysteroscopically (17). We administer gonadotropin releasing hormone treatment for 2-3 months when the fibroid is ≥4 cm to reduce the likelihood of two-stage procedures. We also aim to remove single type II submucosal fibroids <4 cm hysteroscopically; some 3-4 cm type II fibroids require a two- stage approach. For type II fibroids of ≥4 cm, we give serious consideration to abdominal myomectomy (laparoscopic when possible, open in the presence of numerous fibroids). We pay special attention to reducing the risk of intrauterine adhesions in the presence of multiple submucosal fibroids, including removal of fibroids on opposing walls in different sessions.

Subserosal fibroids are unlikely to have an impact on ART outcomes, except when they cause difficulties with ovarian access for egg collection. For this reason, the majority of subserosal fibroids are left alone during IVF cycles.

The management of noncavity-distorting intramural fibroids prior to IVF/ICSI is less straightforward. Current evidence suggests a detrimental impact of the presence of these fibroids; however, this is based on relatively low quality studies that show significant variability in selection criteria and outcome measures. This is not unexpected considering that fibroids come in different numbers, sizes, locations, and consistencies. There is a clear need to perform prospective randomised studies on this subject, but this is likely to be difficult due to a high number of confounding factors that would be difficult to stratify.

A major problem with the published studies that were analysed in the meta-analyses is that they included women with relatively small intramural fibroids, probably because women with larger fibroids and those with fibroids that distort the cavity undergo myomectomy. Therefore, the real impact of these fibroids on IVF outcomes is likely to be larger. An additional problem is that there is a shortage of evidence regarding benefit of removing noncavity-distorting intramural fibroids. However, abdominal myomectomy (laparoscopic or open) is relatively frequently performed for these fibroids. It is likely that the numbers needed to treat (NNT) for this purpose would be lower for larger fibroids but very high for small fibroids. This point would need to be weighed against the associated morbidity, cost, and delay in treatment when decisions are made on myomectomy.

In our practice, we take the number and size of fibroids, the overall size of the uterus, history of previous surgery, and ovarian accessibility into account when we counsel patients who have intramural fibroids that do not distort the cavity prior to IVF treatment. We try to avoid surgery in the presence of fibroids <5 cm when the uterine cavity is regular. We tend to offer surgery first to women with intramural fibroids ≥7 cm, but proceed with IVF treatment without surgery in the presence of fibroids of 5-6 cm in the first IVF attempt. We usually offer surgery for fibroids of 5-6 cm if the woman had one or two failed IVF attempts. This approach aims to keep the NNT as low as possible per additional pregnancy achieved.

If there are difficulties with ovarian accessibility due to fibroids, we prefer surgery before IVF. We usually wait for three months before proceeding with IVF postoperatively, but in older women with reduced ovarian reserve, we proceed with IVF earlier and freeze embryos for delayed transfer.

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What is your diagnosis?

A 42-year-old lady, para 2 with 2 living issues, presented to us with symptoms of continuous bleeding per vaginum for 15 days following two months of amenorrhoea. She had associated left lower abdominal pain. Her vitals were stable and on per abdominal examination a 16-18 weeks size abdominopelvic mass, firm in consistency, irregular, tender with restricted mobility was palpable. On per vaginal examination, the uterus was irregularly enlarged to 16-18 weeks' size. A 5×5-cm firm, irregular, tender mass was palpated in the left fornix. This mass could not be demarcated separately from the uterus. Cervical motion tenderness was elicited. On ultrasound, an irregularly enlarged 14-16 weeks' size uterus with multiple myomas was seen, largest 10×9×9 cm at the left cornua, with intramural and sub-serosal component. The left ovary could not be seen separately from the mass. The right ovary was normal in size and location. Urine pregnancy test and serum beta human chorionic gonadotropin were found to be negative. With suspicion of chronic ectopic pregnancy, the patient was planned for a laparotomy. Intraoperatively, around 200 mL hemoperitoneum was found. Uterus was 14-16 weeks' size enlarged, with multiple fibroids. A large 10×10 cm irregular friable mass with blood clots was observed at the left cornua extending into the left adnexa. The left tube and ovary were adhered to the mass and were not seen separately. Right tube and ovary was normal (Figure 1). In view of multiple fibroids, total abdominal hysterectomy with bilateral salpingo-oophorectomy was performed (Figure 2).

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Answer

Total abdominal hysterectomy with bilateral salpingo-oophorectomy was performed and a sample was sent for histopathologic examination. The histopathology report suggested leiomyosarcoma involving the myometrium and left ovary, with French Federation of Comprehensive Cancer Centers histologic grade 2 (total score: 1+2+1=4). Here, the primary tumour extends beyond the uterus ($pT2NxM_{not\ applicable}$) and regional lymph nodes cannot be assessed (pN_x). Postoperative period was uneventful and patient was discharged in a satisfactory condition after 4 days. She was referred to the radiotherapy department for further management. The patient is doing well 6 months post-operatively.

Uterine leiomyosarcoma is a rare uterine malignancy, originating from smooth muscle of the uterine wall. The median age of occurrence of leiomyosarcomas is 43 to 53 years. The incidence of sarcomas in patients undergoing surgery for leiomyomas has been observed to be around 0.23% (1). Leiomyosarcoma is the commonest histopathologic variant of uterine sarcomas (2). The presenting symptoms include heavy menstrual bleeding, pelvic pain or pressure and occasionally an abdominopelvic mass. We report a case of a 42-year-old female who presented with irregular menstrual cycles, pelvic pain, and bleeding per vaginum, and was later diagnosed as having leiomyosarcoma of the uterus.

Ectopic pregnancy is considered to be a great mimic in gynecology (3) and chronic ectopic pregnancy poses a challenge because of its subtle symptoms and wide range of clinical presentation. A rare case report by Sinha et al. (4) describe a case of chorioadenoma destruens mimicking ruptured ectopic pregnancy. A case report by Sakamoto et al. (5) reported gestational choriocarcinoma with uterine serosal metastasis mimicking ruptured ectopic pregnancy. Ogu et al. (6) reported a case of submucous uterine fibroid mimicking ruptured ectopic gestation. Primary ovarian choriocarcinoma mimicking ectopic pregnancy has been reported by Heo et al. (7). In a study by Leitao et al. (8), the percentage of ovarian metastasis secondary to uterine leiomyosarcoma was 5.4%. However, the incidence of ovarian metastasis in a case of uterine leiomyosarcoma in India is not well documented. The most common mode of spread in leiomyosarcoma is

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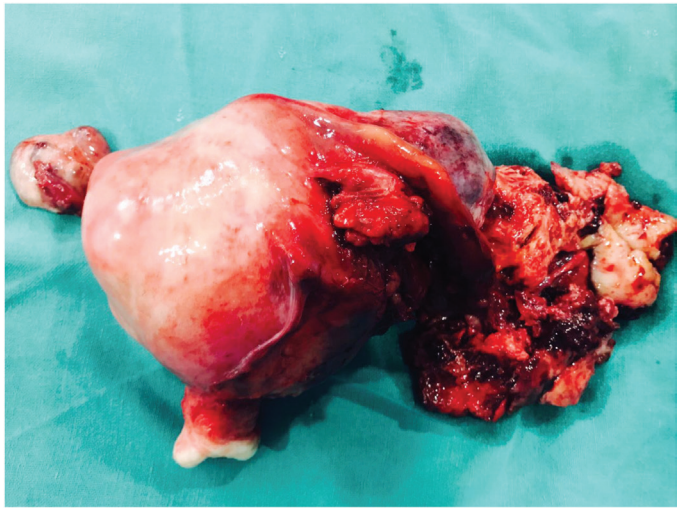

Figure 1. Uterus with bilateral tubes and ovaries showing leiomyosarcoma involving the right ovary, mimicking chronic ectopic pregnancy

hematogenous with lymphatic spread being rare, and hence lymph node dissection may be omitted in leiomyosarcoma where its therapeutic and diagnostic value is questionable (9).

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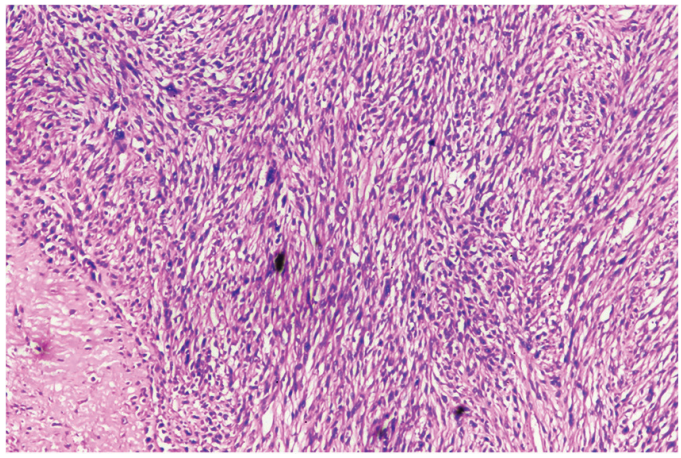

Figure 2. Showing fascicles of spindle cells with necrosis, marked nuclear pleomorphism and increased mitoses showing features of leiomyosarcoma

Comparative surgical resection of the ligamentum teres hepatis in a cadaveric model and a patient with ovarian cancer

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Abstract

Resection of all tumor implants with the aim of maximal cytoreduction is the main predictor of overall survival in ovarian carcinoma. However, there are high risk sites of tumor recurrence, and the perihepatic region, especially the point where the ligamentum teres hepatis enters the liver parenchyma under the hepatic bridge (pont hepatique), is one of them. This video demonstrates the resection of the ligamentum teres hepatis both in a cadaveric model and in a patient with ovarian cancer. (J Turk Ger Gynecol Assoc 2019; 20: 62-3)

Keywords: Pont hepatique, umbilical ligament, liver, ovarian cancer, cytoreduction

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Introduction

The falciform ligament divides the liver into the right and left lobes on the antero-superior part of portoumbilical fissure where the ligamentum teres hepatis (umbilical ligament of liver/round ligament of liver) attaches to the visceral surface. Due to the distribution pattern of the portal vein and hepatic veins, the liver is divided into eight functional segments (1). The umbilical fissure exists between liver segments III and IVb, and the umbilical ligament lies there. The liver parenchyma over this structure varies in thickness, and in some patients the umbilical ligament will be completely visible, which allows broad exposure until its entrance into the liver. Paul Sugarbaker defined this parenchyma surrounding the umbilical ligament as the 'pont hepatique/hepatic bridge,' which creates a tunnel (2,3).

Mucinous ovarian or gastrointestinal carcinoma, appendiceal carcinoma, mesothelioma or a serous ovarian cancer may have a widely disseminated recurrence on the peritoneal surfaces. The complicated surgical anatomy of the liver and perihepatic tissues limits the easy detection of tumor implants; eventually, good exposure of the abdominal cavity is needed to excise all the visible tumor implants, especially on high-risk fields such as the end part of the ligamentum teres hepatis under the hepatic bridge (4).

There is no risk of injuring any structures while cutting the hepatic bridge. However, if the ligament is deeply attached to the bottom of the liver parenchyma, while dissecting the end point, care should be taken not to damage the left hepatic artery or the left hepatic duct over the hepatoduodenal ligament, which is covered by the peritoneal lining of lesser sac (3,5). Routine resection of the ligamentum teres hepatis may increase morbidity (6); however, in patients with peritoneal carcinomatosis, the base of the ligamentum teres hepatis should be observed under the hepatic bridge because it is a continuation of peritoneal tissue.

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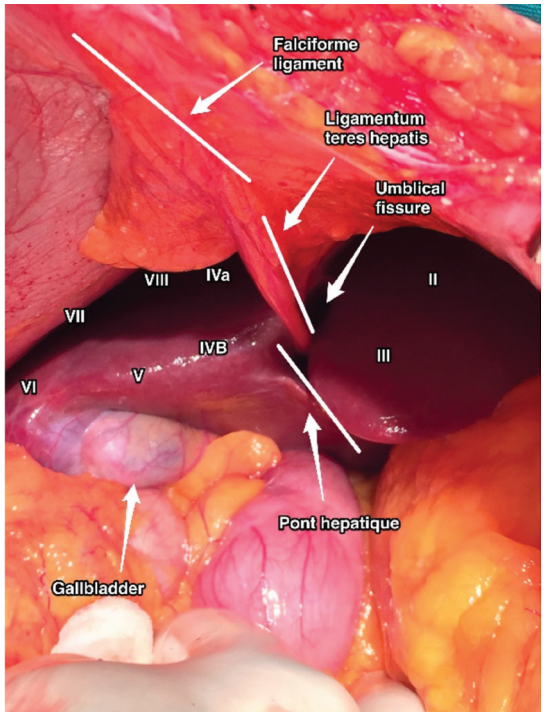

Figure 1. Localization of the pont hepatique and hepatic segmentation with the anatomic structures of the falciform ligament and ligamentum teres hepatis

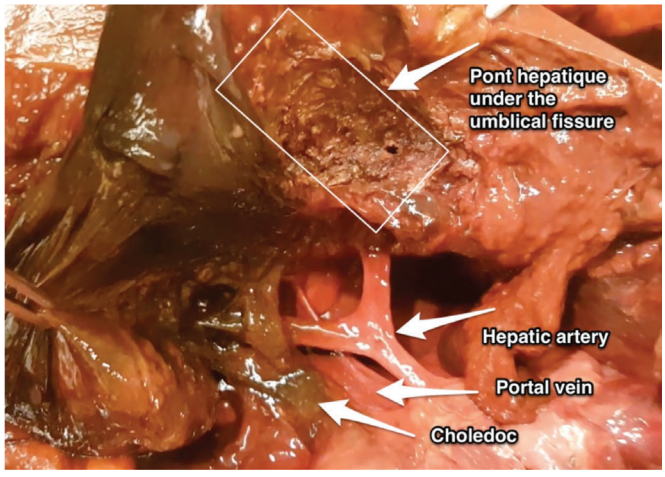

Figure 2. Cut end of the ligamentum teres hepatis over the liver parenchyma superior to hepatoduodenal ligament (choledoc, portal vein and hepatic artery)

This video consists a cadaveric surgical demonstration of ligamentum teres hepatis resection over the portoumbilical fissure and a live patient video of 56 years old woman who had a recurrent high-grade serous ovarian cancer with widespread peritoneal implants. There were tumor implants at the perihepatic region on the umbilical ligament, which were resected.

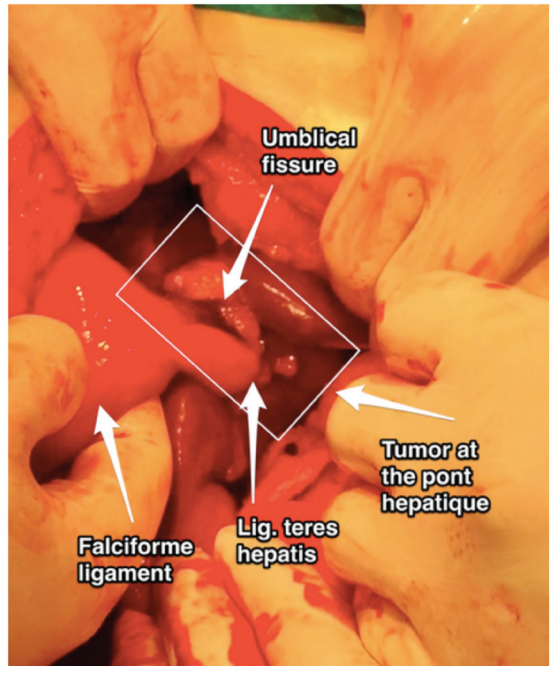

Figure 3. Tumor implants at the ligamentum teres hepatis and pont hepatique

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ERRATUM

Erratum to: 2016 TAJEV/Oral Presentation

A missing supplement abstract article on online version was reported by the author.
Abstract OP-148 is included in this erratum.

Missing supplement abstract of S75 is given below:

[OP-148]

Infertility Associated with the Familial Mediterranean Fever

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Familial Mediterranean Fever (FMF) is an autosomal recessive, systemic, autoinflammatory disease that affects the serous membrane (peritoneum, pleura, pericardium). It is common among Mediterranean populations (Jews, Arabs, Turks and Armenians). FMF is characterized by recurrent fever and inflammation of serous membranes, leading to abdominal pain, joint pain and chestpain. The most important complication of FMF is amyloidosis, which eventually leads to kidney failure. Sympoms of the disease usually occur during the first decade of life in more than 80% of patients. MEFV gene, responsible for the disease, located on chromosome 16P (13.3) codes synthesis of a protein called pyrin. M680I is common among Armenians and Turks and is associated with more severe form of the relapsing fever in early childhood which may be the only presentation of familial Mediterranean fever. It mainly presents in patients of Mediterranean descent as recurrent, self-limiting episodes of aseptic peritonitis accompanied by fever that last for 24-72 hours. Colchicine is the “gold-standard” medication and it prevents FMF attacks and systemic amyloid deposition. And we commonly forget, it is a cause of infertility both man and woman. We present the case of a 28-year-old FMF patient woman, gravida 0, parity 0 infertile female patients who was admitted the our department with desire of pregnancy. She said, she admitted to an other hospital for this complaint and as a result of her test performed reported, she has an ‘uterine septatus+tubal occlusion to right side’, previously. She knows that own disease about 13 years and she does not use Colchicine regularly. She didn’t have any external physical examination findings related to FMF. This marriage is her husband’s second and he has one child from previous marriage and his spermiogram was normally. Our ultrasonographic assessment was shown us, she didn’t have any uterus and bilateral ovarian pathologic evidence and both size was normally, endometrial cavity was regular and we didn’t monitorized any intrauterin septum. We performed Saline Infusion Sonography (SIS) in examination room, we watched the fundus-seated polipoid mass (11 mm*7mm). We couldn’t achieve her prior histerosalpingography (HSG) results and films, and so, after this situation HSG was taken by us again, and it showed us, the right fallopian tube is completely occluded. After these findings we planned the Diagnostic/ Operative Laparoscopy and Hysterescopy (+chromopertubation). We have seen that the common peritoneal defects and adhesions, right fallopian tube was severely stuck to the peritoneum. And then we started to adhesiolysis, results of operations, we have seen transition of methylene blue from both tubal ostia. We continued processing with hysteroscopy and we’ve excised polyps (11*7mm) in the fundus. And in the meantime, we have not seen any uterine shape anomaly. In this case, we would like to remind the FMF, among the causes of can not be explained women infertility. Peritoneal defects and adhesions which is caused by FMF, can be seen as a simple oclusion on the HSG, but in this case it should not be forgotten that there may be extensive adhesions and should not be avoided from resorting to laparoscopy.

Keywords: Familial Mediterranean Fever, intertility, adhesion and peritoneal defects.

CONGRESS CALENDER

INTERNATIONAL MEETINGS

(for detailed International Meeting please go website:
http://www.medical.theconferencewebsite.com/conferences/obstetrics-and-gynaecology)

March 14-16, 2019	**4th European Congress on Intrapartum Care: Making Birth Safer 2019, Torino, Italy**
March 17-22, 2019	**Obstetrics and Gynecology 56th Annual Update 2019, Boston, MA, United States**
March 24-29, 2019	**American College of Osteopathic Obstetricians and Gynecologists 86th Annual Conference 2019, New Orleans, United States**
March 31-April 3, 2019	**Society of Gynecologic Surgeons 45th Annual Meeting 2019, Arizona, United States**
April 3-5, 2019	**National Perinatal Association Annual Clinical Conference 2019, Rhode Island, United States**
April 3-6, 2019	**18th World Congress of the Academy of Human Production 2019, Dublin, Ireland**
April 3-7, 2019	**Pacific Coast Reproductive Society 68th Annual Meeting 2019, Indian Wells, United States**
April 4-6, 2019	**20th Annual National Conference on Foetal Monitoring 2019, New Orleans, United States**
April 11-14, 2019	**Japan Society of Obstetrics and Gynaecology 71st Annual Congress 2019, Nagoya, Japan**
April 12-14, 2019	**Survival Skills for Today's Gynecologist 2019, Manhattan, United States**
April 13-17, 2019	**International Society for Gynecologic Endoscopy and European Society Gynecological Endoscopy South African Conference 2019, Cape Town, South Africa**
May 3-6, 2019	**American College of Obstetricians and Gynecologists 67th Annual Clinical Meeting 2019, Nashville, United States**
May 8-11, 2019	**Expert Fetal Medicine 2019, London, United Kingdom**
May 16-18, 2019	**Society of Endometriosis and Uterine Disorders 5th Congress 2019, Montreal, Canada**
May 21-23, 2019	**British Society for Gynaecological Endoscopy 29th Meeting 2019, Newport, United Kingdom**
May 29-June 1, 2019	**10th International Dip Symposium on Diabetes, Hypertension, Metabolic Syndrome & Pregnancy 2019, Florence, Italy**

CONGRESS CALENDER

NATIONAL MEETINGS

(for detailed International Meeting please go website:
http://www.kongre2019.com)

March 1-3, 2019	**Uluslararası Hipokrat Tıp ve Sağlık Bilimleri Kongresi, Ankara, Turkey**
March 7-10, 2019	**14. Uludağ Jinekoloji ve Obstetrik Kış Kongresi, Bursa, Turkey**
March 13-17, 2019	**6. MESGE ve 8. Ulusal Jinekolojik Endoskopi Kongresi, Antalya, Turkey**
March 27-30, 2019	**7. Uluslararası Fetal Hayattan Çocukluğa İlk 1000 Gün Anne Çocuk Beslenme Kongresi, İstanbul, Turkey**
March 29-31, 2019	**7. Acıbadem Kadın Doğum Günleri, İstanbul, Turkey**
April 5-7, 2019	**Karadeniz Jinekoloji ve Obstetrik Kongresi, Samsun, Turkey**
April 11-14, 2019	**3. Uluslararası EXPERMED Kongresi, Cyprus**
April 18-19, 2019	**3. Uluslararası Kadın Çocuk Sağlığı ve Eğitimi Kongresi, Trabzon, Turkey**
April 18-21, 2019	**ÇİSED 4. Ulusal Cinsel Sağlık Kongresi, Antalya, Turkey**
April 24-28, 2019	**17. Ulusal Jinekoloji ve Obstetrik Kongresi, Antalya, Turkey**
April 25-27, 2019	**2. Uluslararası İstanbul Ebelik Günleri, İstanbul, Turkey**
October 2-6, 2019	**Obstetrik ve Jinekoloji Zirvesi "Tartışmalı Konular", Antalya, Turkey**