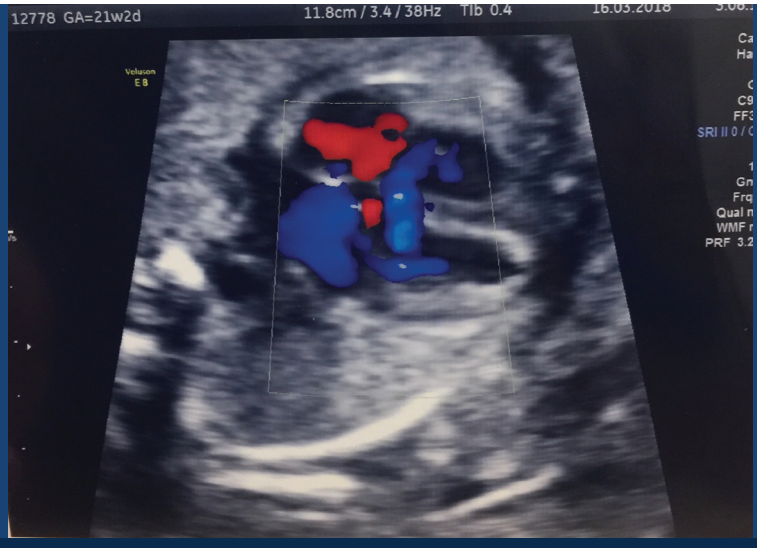
ISSN 1309-0399 • EISSN 1309-0380

TURKISH-GERMAN GYNECOLOGICAL EDUCATION and RESEARCH FOUNDATION

Journal of the Turkish-German Gynecological Association



Volume 19
Issue 2
June
2018

Cover Picture: Peri-membranous VSD. From archieve of Yildirim G.

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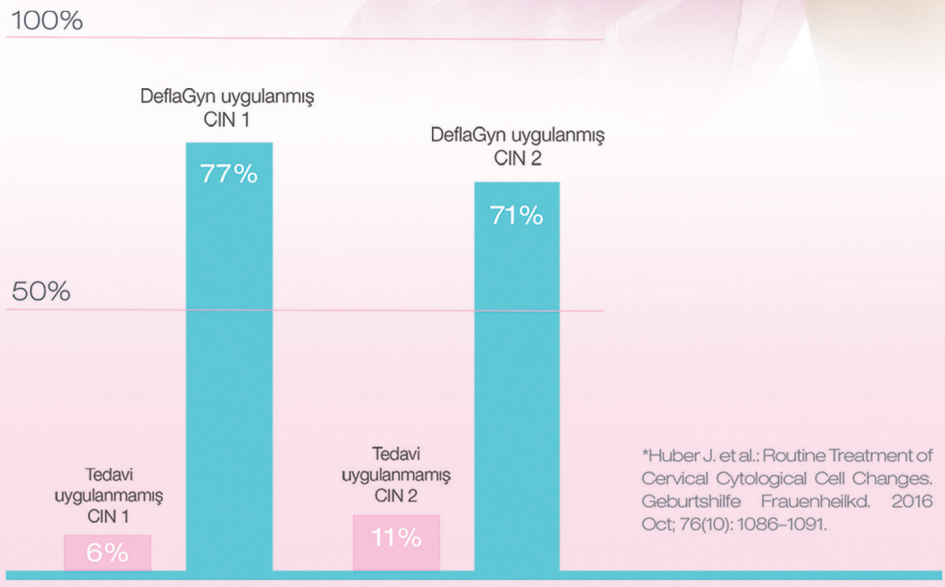

*Huber J. et al.: Routine Treatment of Cervical Cytological Cell Changes. Geburtshilfe Frauenheilkd. 2016 Oct; 76(10): 1086–1091.

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Published by Turkish German Gynecology Education Research Foundation. / Türk Alman Jinekoloji Eğitim Araştırma ve Hizmet Vakfı tarafından yayınlanmaktadır.
Abdi İpekçi Cad. 2/7 34367 Nişantaşı, İstanbul, Turkey

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Printing at: Özgün Ofset Ticaret Ltd. Şti.
Yeşilce Mah. Aytekin Sk. No: 21 34418 4. Levent, İstanbul, Turkey
Phone: +90 (212) 280 00 09
Printing Date: June 2018
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▶ **Trikomonal vajinit**,

▶ **Mikst vajinal enfeksiyonların**

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Contents

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Editorial

Dear Colleagues,

It is my great pleasure to present you the second issue of Journal of the Turkish-German Gynecological Association (*J Turk Ger Gynecol Assoc*) in the publishing year of 2018.

Our submission traffic is also progressing in a healthy way. Due to *J Turk Ger Gynecol Assoc*'s increasing international popularity and visibility, the number of international submissions we receive has almost tripled over the past 12 months and it is nice to see the quality of submissions is also rising.

Increasing submission numbers and the quality of these submissions makes our jobs as editors easier and harder at the same time. With each new issue of *J Turk Ger Gynecol Assoc*, we are trying to further increase the quality of our content. We are glad to see that this consistency in quality has translated well into our readership numbers. Number of hits we have received on PubMed has almost doubled over the past 12 months. Thank you for your interest.

Research is a fundamental aspect of academic life. In most journals, however, the quality of the publications varies. Some papers are not clearly written, have poorly described methods, or use tools of low validity and reliability in spite of the Journal Impact Factor (JIF). The JIF has emerged as a tool for ranking, evaluating, categorizing, and comparing scientific journals. The Institute for Scientific Information (ISI), a component of Thomson Scientific, was behind this development.

Journal Impact Factor (JIF) has been used in assessing scientific journals. Other indices, h- and g-indices and Article Influence Score, have been developed to overcome some limitations of JIF. Impact factor is a commonly used indicator for evaluating the performance of a scientific journal. There are some difficult and easier ways to help improve a journal's impact factor. The most difficult—but at the same time likely the most consistent—way is to publish high quality articles (Aydıngöz Ü, Diagn Interv Radiol 2010; 16: 255-256).

- Journals should find referees (i.e., reviewers) who have already published in journals with an international scope.
- Journals published in countries where English is not a native language should be printed in full-text English.
- Journals should prepare guidelines for their reviewers and find ways to ensure their use.
- Publishers with monetary resources should consider giving awards (e.g., "Outstanding Reviewer of the Year") to attract and/or motivate reviewers.
- English-language check by native English-speaking experts should be part of the procedures an accepted article should pass through.
- Once an article is accepted for publication, a full-text HTML and/or PDF version should be prepared ahead of print and a digital object identifier (DOI) number should be assigned for the article.

Journal of the
Turkish-German
Gynecological Association

Editorial

• Titles and abstracts of articles should be tailored to render them high visibility on the Internet search engines while preserving their intended meaning.

• Review articles in general have a higher likelihood of earning citations. Priority should be given to review articles on dedicated subjects of interest to wide masses of prospective authors. Soliciting review articles from experts on the field should be a priority task for editors, although it can be very challenging to acquire them.

• Article evaluation times should be decreased to the possible minimum. An effective online system for referees has to be established.

I am very glad and satisfied to say that The **XII. Turkish German Gynecologic Congress**, held in "Elexus Hotel" in Kyrenia, **Turkish Republic of Northern Cyprus** (TRNC) between the dates of **April 27th and May 1st, 2018** with a great success. With more than a thousand registered participants, 2 Live Surgery Sessions, 1 Panel, 4 Keynote Lectures, 122 Lectures, 6 Precongress Courses, 3 Satellite Symposiums, 214 Oral Presentations, 148 Poster Presentations and 32 Video Presentations. This was made possible with your invaluable scientific contributions. I would like to thank to all participant once again for coming to **Cyprus** to share their expertise with us. We have had a tremendously positive feedback from the congress participants on the quality of the scientific presentations and the organization of the congress.

Finally, you will read many interesting and good paper in this issue. Papers from all over the world help to us increase our index scores. I am looking forward to see your scientific collaboration with us.

Sincerely,

Prof. Cihat Ünlü, M.D.

Editor in Chief of *J Turk Ger Gynecol Assoc*

President of TGGF

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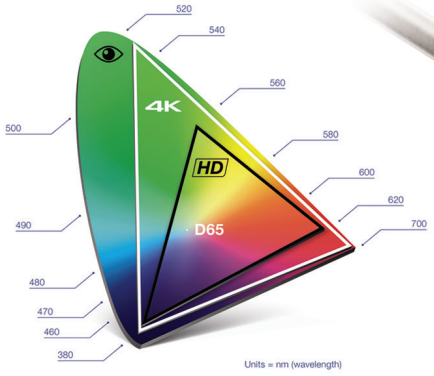

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Do pregnancy rates differ with intra-uterine insemination when different combinations of semen analysis parameters are abnormal?

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Abstract

Objective: To evaluate the relationship of one or a combination of semen analysis parameter results on insemination outcomes.

Material and Methods: A retrospective analysis was performed to evaluate the effect on pregnancy rates in relation to one or more abnormal semen analysis parameters based on the 2010 World Health Organization semen analysis guidelines.

Results: Nine hundred eighty-one couples underwent 2231 intrauterine insemination cycles at the Stanford Fertility and Reproductive Medicine Center. In our study, the pregnancy rates ranged from 11-25% when an individual or combined semen analysis parameters were analyzed. Similar pregnancy rates were found when one, two, and in most cases three parameters were abnormal. When a single parameter was abnormal among volume, concentration, and motility, pregnancy rates were mainly unaffected. There was the exception of total sperm count where pregnancy rates were diminished when counts were below 39 million (p=0.04).

Conclusion: Clearly, total sperm in the specimen and not the concentration of sperm per milliliter was the critical factor for predicting pregnancy. Therefore, a reorganization of semen analysis reports should be done emphasizing the total amount of sperm present and de-emphasizing concentration of sperm. (J Turk Ger Gynecol Assoc 2018; 19: 57-64)

Keywords: Artificial insemination, pregnancy rate, semen analysis

Received: 21 July, 2017 **Accepted:** 16 March, 2018

Introduction

Infertility is the failure to conceive following twelve months of unprotected intercourse (1). Studies suggest that infertility affects 10 to 15% of the reproductive population (1). Male factor infertility is responsible for up to 50% of infertility cases (1). Male factor infertility is diagnosed primarily based on the results of at least two semen analyses performed 90 days apart. A semen analysis consists of a wide range of parameters including: volume, sperm concentration, progressive motility, and morphology. The total motile sperm count (TMSC) is calculated by multiplying the total sperm in the specimen by the percentage of motile sperm and is felt to be an essential predictor of intrauterine insemination (IUI) success (2).

When faced with severe male factor infertility, although there exists a lack of randomized control trials, the consensus is to offer in vitro fertilization (IVF) with intracytoplasmic sperm injection (ICSI) (3). Others argue that IVF should not be considered for routine use (3) and question its cost-effectiveness for most cases of male factor infertility (3). In these cases, it is argued that IUI should be the first-line treatment instead (3,4).

Most male partners of couples presenting for infertility will have one or more abnormal parameters in their semen analysis. Many have studied the effect of single parameters in relation to pregnancy and fertilization outcomes (5-8), or combining some of these parameters into the TMSC (9-12). However, there exists a lack of literature on whether a combination of parameters or any specific parameter (except for TMSC) would allow for

These data were presented at the 2015 ESHRE eeting, and selected as a finalist for a poster prize.

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Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.2017.0082

lower pregnancy rates with IUI. Therefore, the objective of this study was to evaluate the effect on pregnancy rates with one or more abnormal semen analysis parameters based on the 2010 World Health Organization (WHO) semen analysis guidelines.

Material and Methods

A retrospective analysis was performed on 2.5 years of data collected at an American University. A total of 981 couples underwent 2231 IUI cycles. The original database contained information regarding evaluation of semen quality on the day of insemination. Subjects at the clinic are 40% Caucasian, 7% African American, 33% Asian, and 20% Hispanic. The biochemical pregnancy rate was 14%, the clinical pregnancy rate was 82%, and the ectopic pregnancy rate was 4%.

Semen quality was classified on the day of insemination based on the 2010 WHO semen criteria. Criteria used were 1.5 mL, 15 million/mL, minimum count per specimen 39 million, and forward motility 32%. If Kruger strict morphology was less than 4% in two samples, the patients were treated with IVF and ICSI. These patients were not included in this study. It should also be noted that strict morphology is not traditionally calculated on each specimen being used for insemination because preparation would kill some of the sample required for use, possibly affecting pregnancy rates. It should also be noted that total motility was not calculated by the computer semen analyzer and was therefore unavailable for comparison. The 2010 WHO criteria also list a minimum total motility of 40% in the specimen as criteria of normality. However, forward motility of 32% was used because this and not total percent motility was available in the processing report. The specimens were compared based on the presence of all criteria being normal or one or more being abnormal.

The evaluation and examination of patients: The couples enrolled in this study had at least one year of either primary or secondary infertility with their current partner. All couples underwent a comprehensive evaluation including medical history and physical examination, documentation of ovulation or an assessment for the lack thereof, as well as a semen analysis using Kruger strict morphology. All patients had at least one patent fallopian tube on either hysterosalpingogram or laparoscopy with chromopertubation. Ovulation was evaluated with a luteal phase progesterone >3 ng/mL, basal body temperature charts, urinary luteinizing hormone (LH) kits with regular cycles every 21 to 35 days, or regular periods every 21 to 35 days with a clear history of premenstrual molimina. All women had serum prolactin and thyroid-stimulating hormone levels in the normal range of the assay used before starting treatment. Women were included if they were anovulatory with inducible ovulation, if they had a serum follicle-stimulating hormone levels <12 IU/L on basal and clomiphene citrate challenge testing (if performed), a baseline follicle count of greater than 8 on endovaginal ultrasonography or stage 1-2 endometriosis on laparoscopy with at least one patent and undamaged fallopian tube. All women were evaluated with hysterosalpingography or hysteroscopy, and any intra-cavitary pathology including polyps, fibroids, and synechiae were corrected before initiating treatment. Any patients with four or more myometrial fibroids of 1 cm or greater in diameter, or one leiomyoma of 5 cm or greater in the uterine muscle, underwent surgical resection and appropriate recovery before initiating the insemination cycle.

Couples did not have, women with bilaterally blocked fallopian tubes, decreased ovarian reserve, stage 3 or 4 endometriosis, recurrent pregnancy loss (2 or more miscarriages), two previous ectopic pregnancies or anovulation and folliculogenesis was not successfully induced. Donor frozen IUI semen results were excluded because only post-processing parameters were available for these samples, and the donor was unlikely to be infertile. Only partners' fresh sperm specimens were included in the analyses.

Seven percent of patients were treated with natural cycle IUI, 54% were treated with clomiphene IUI, 3% were treated with letrozole IUI, and 36% received gonadotropin IUI. Gonadotropin injections were performed daily starting on cycle day 2 or 3 and titrated to develop 2 to 3 mature follicles in patients aged under 40 years, and 2 to 5 follicles in women aged over 40 years. Clomiphene citrate (50 or 100 mg daily) and letrozole (5 mg daily) were administered orally for five days starting on cycle day 2 to 4. Serial sonography was performed to monitor folliculogenesis as per standard protocols.

Semen collection, analysis, and processing: Individuals were asked to refrain from ejaculation for two to four days before the collection of the specimen. Specimens were produced with masturbation, either in a collection room at the fertility clinic or at the patient's home. To be collected at home, the sample had to be delivered within thirty minutes of production while being kept warm (i.e., placement of the receptacle in an axilla).

Freshly ejaculated sperm was allowed to liquefy before semen analysis. Liquefied semen was thoroughly mixed before an aliquot was placed on a standard count slide (Leja Products BV, Nieuw-Vennep, the Netherlands) for the pre-processing analysis. The slide was placed on a 37 °C stage of an IVOS computer-assisted semen analyzer (Hamilton Thorn Biosciences, Beverly, MA). At least three random fields were evaluated for each analysis. Intra and inter-assay coefficients of variation of the parameters were less than 10% in all cases, pre- and post-processing.

Following the initial semen analysis, the sample was processed by first placing up to 4 mL of raw semen on a differential density gradient column consisting of 1 mL of 40% PureSperm and 1 mL

of 80% PureSperm (Nidacon, Molndol, Sweden). The gradient was centrifuged for 20 minutes at 350 × g, and subsequently, the 40% layer and the seminal plasma fraction were removed from the test tube, leaving the 80% layer undisturbed. Approximately 6-8 mL of sperm-washing medium and 5% HAS (Cooper-Sage, Trumbull, CT) was added to the 80% layer and centrifuged for 10 minutes at 550 × g. The sperm pellet was then reconstituted to approximately 0.5 mL. The analysis of an aliquot of the processed sample was performed as previously described using the IVOS computer-assisted semen analyzer.

IUI and beta-human chorionic gonadotropin (β-hCG) assay: IUI was performed approximately 24-hours (+/- 3 hours) after detection of a spontaneous urinary LH surge, or 36-hours (+/- 1 hours) after 10.000 IU β-hCG injection (Pregnyl, Merck, West Orange, NJ), (Novarel, Ferring Pharmaceuticals, Inc., Tarrytown, NY) or 250 mcg Ovidrel injection, (Merck-Serono Laboratories, Rockland, MD). hCG was administered when a transvaginal ultrasound revealed the largest follicle had a mean diameter of ≥18 mm. The insemination was performed in a sterile fashion, using a flexible plastic catheter with the patient in the dorsal lithotomy position. The patient remained supine for at least ten minutes after the end of the insemination.

Serum β-hCG levels were analyzed 15 to 17 days after IUI to determine pregnancy status. Blood samples were assayed on an Immulite 2500 (Diagnostic Products Corporation, Los Angeles, CA) for a quantitative measurement of β-hCG. The Immulite uses a solid-phase two-site chemiluminescent immunometric assay with a sensitivity of 1 mIU/mL and a calibrated range to 5000 mIU/mL. Intra- and inter-assay coefficients of variation were each less than 7%. Most normal singleton pregnancies have levels in the range of 50 to 100 mIU/mL at this gestation. However, a level higher than five mIU/mL was considered positive for pregnancy.

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences 11.0 (SPSS, Inc., Chicago, IL). Continuous variables were evaluated for normal distribution using the Kolmogorov-Smirnov test. Any variables that were not normally distributed were logarithmically transformed to obtain normality. Results are reported as mean value ± standard deviation (SD). Categorical variables were evaluated with likelihood ratios. Likelihood ratios were calculated as:

$$LR+ = \frac{\text{sensitivity}}{1 - \text{specificity}}$$

which is equivalent to;

$$LR+ = \frac{Pr\ (T+/D+)}{Pr\ (T+/D-)}$$

or "the probability of a person who falls into a grouping of the semen analysis having a pregnancy divided by the probability of a person who does not fall into the semen grouping having a pregnancy." Here "T+" or "T−" denotes that the classification into the semen analysis grouping is positive or negative, respectively. Likewise, "D+" or "D−" denotes that the pregnancy is present or absent, respectively. T-tests were used to compare for continuous variables. Levine's test for equality of variances was used to determine which p value to accept. Significance was taken as a $p \leq 0.05$.

Ethical approval

The university's Human Subjects Research Ethics Committee approved this study (IRB number 95940). The authors have no conflict of interest.

Results

Baseline data of the cohort are provided in Table 1. An initial comparison without controlling for other semen analysis results was made to determine any single abnormal factor that gave lower pregnancy rates. Those with and without a pregnancy were classified based on volume <1.5 mL or not, concentration <15 mil/mL or not, <32% forward motility or not, and <39 million sperm in the specimen. The results are presented in Table 2. Data are presented as mean values and SDs in the pregnant and not pregnant groups. The p-values for the likelihood ratio (one-sided, because it was hypothesized that abnormal results would have lower pregnancy values) are also presented comparing pregnancy rates in the groups that were normal or abnormal for the given parameter. As expected, the parameters were significantly different when comparing those grouped based on a parameter being abnormal or not. Among the parameters, only total sperm in specimens with <39 million gave lower pregnancy rates.

Next, semen analysis results were categorized based on the presence of one or more abnormal parameters, and precisely what parameters were abnormal. This gave the ability to control for confounding effects. At this stage, comparison was performed using volume (less than or greater than 1.5 mL), concentration (less than or greater than 15 mil/mL), and forward motility (less than or greater than 32%). For this comparison, it was elected to exclude total sperm count

Table 1. The baseline characteristics of subjects

	n=981
Maternal age (Years)	37±6
Duration of infertility (Years)	24±14
Previous pregnancies	1.2±1.2
Number of mature follicles	2.4±1.3
Maximum day 3 serum FSH (IU/L)	7.9±2.4
FSH: Follicle-stimulating hormone	

because this value is not traditionally presented in a standard semen analysis reports. The results are presented in Table 3. Pregnancy rates are shown comparing all parameters in the normal group. As can be noted, none of the parameters or combination of these parameters predicted lower pregnancy rates when compared with normal specimens. Although two of the groups comprised few patients, given the trends in the total results, it is unlikely that the small numbers were the cause of lack of significance. The semen parameters for these seven groupings are presented in Table 4 for patients with and without pregnancies.

We made a comparison using total sperm count of less than or at least 39 million as well as volume and motility as predictors of pregnancy when compared with the normal group for all 3 because total sperm count in the specimen was the only factor that seemed to be associated with pregnancy rates. These results are shown in Table 5. There are fewer comparisons performed than in Table 3 because we did not repeat any comparisons already presented. Consideration of sperm concentration was not performed. It should be noted than only the groups with total counts less than 39 million, motility less than 32%, and volume less than 1.5 mL had a lower pregnancy rate. Even the group with low total count and motility but normal volume was not associated with pregnancy outcome, even though this group's results were equivalent to a low TMSC by the 2010 WHO parameters. Table 6 presents the semen analysis parameters from this group.

Discussion

Semen analysis has been the subject of debate for many years. It is unclear whether applying parameters found in a fertile population to an infertile population is valid (13,14,32). However, to this day, semen analysis remains the primary objective measure of male factor infertility. For this reason, this study was performed to determine the relationship between abnormal semen parameters and pregnancy rates in couples undergoing IUI. Our study is the first of its kind, making it unique in nature, using the 2010 WHO parameters.

Table 2. Comparisons of pregnancy rates and parameters in the groups abnormal for any of the listed criteria according to the 2010 World Health Organization semen analysis criteria without controlling for other semen analysis parameters

Parameters	Abnormal WHO parameter	Normal WHO parameter	p (comparing abnormal and normal WHO levels)	Likelihood ratio (for pregnancy) p value
Volume (mL)	0.9±0.3 (n=306)	3.2±1.5 (n=1925)	**≤0.0001**	0.28
Concentration (million/mL)	9.8±3.5 (n=250)	59.0±42.4 (n=1991)	**≤0.0001**	0.11
Motility (%)	19.3±8.2 (n=570)	58.1±15.3 (n=1661)	**≤0.0001**	0.11
Total sperm count (millions)	24.1±10.0 (n=364)	177.2±142.3 (n=1867)	**≤0.0001**	**0.04**

Data represented as mean ± standard deviation. Abnormal and normal World Health Organization levels based on 2010 recommendations. Statistically significant differences are in bold.
WHO: World Health Organization

Table 3. A comparison of data and pregnancy rates when one or more of the traditionally reported semen parameters are abnormal

Parameters	Pregnancy rate	n	Pregnancy rate p value
All 3 normal	20.9%	1384	-
Low volume others normal	24.8%	170	0.24
Low concentration others normal	17.4%	99	0.39
Low motility others normal	19.2%	316	0.48
Low volume and low concentration, motility normal	13.2%	8	0.54
Low volume and low motility, concentration normal	15.9%	55	0.42
Low motility and low concentration, volume normal	18.8%	180	0.56
All 3 abnormal	11.9%	17	0.33

Pregnancy rate is compared with the groups with all 3 parameters normal for the calculation of the p value. P value is two-sided. The reference is the 2010 World Health Organization semen analysis normal parameter recommendations.

The results demonstrate that if a single parameter is abnormal among those traditionally used to evaluate semen analysis, then pregnancy rates are unaffected with the exclusion of total sperm count less than 39 million in the specimen (Table 2). The data would be stronger if abnormal Kruger-Tyberg strict morphology data were available. However, because these patients are treated with IVF and ICSI at the center, conclusions cannot be drawn related to morphology. It remains important to note that the total quantity of sperm in the specimen affects pregnancy rates while other factors do not. Furthermore, pregnancy rates remain acceptable at 16% (p=0.4, Table 5).

Studies have found that TMSC was among the most important predictive factors of successful pregnancy rates (12,15-22). In Table 5, an evaluation of the parameters used to calculate TMSC is presented. When the total count and motility were low (which equates with a measure of low TMSC), pregnancy rates were 18% and remained unaffected when compared with the normal group. This likely occurred because if measured then the TMSC would be abnormal once the level was below 12.48 million sperm. Most of the studies listed above only found decreased pregnancy rates when the TMSC was less than 10 million (17-19,21) or 5 million (15,16,20,22), which is well below the normal parameters quoted in the 2010 WHO guidelines.

The value of TMSC in IUI nevertheless remains debated. Khalil et al. (16) in a retrospective study found that a TMSC of 5 million or higher was associated with higher pregnancy rates. In a descriptive retrospective cohort study by Kleppe et al. (23) based on 895 cycles in 273 couples, the cumulative pregnancy

Table 4. Preprocessing semen characteristics on the day of intrauterine insemination for the 7 different groupings

Parameters	Volume (mL)	Concentration (millions/mL)	Motility (%)	Total motile sperm count (million)
All 3 normal	3.1±1.4	66.4±43.3	59.4±15.0	122.3±111.2
Low volume others normal	0.9±0.2	70.3±40.0	57.2±15.1	36.2±34.3
Low concentration others normal	3.8±1.6	10.8±3.0	44.2±10.3	18.1±10.9
Low motility others normal	3.3±1.6	31.2±18.4	20.2±8.0	20.8±35.2
Low volume and low concentration, motility normal	1.0±0.2	7.8±4.3	49.0±13.9	3.8±2.2
Low volume and low motility, concentration normal	0.9±0.3	37.2±18.9	18.2±9.1	6.1±5.9
Low motility and low concentration, volume normal	3.5±2.2	9.6±3.6	17.3±7.9	5.8±5.6
All 3 abnormal	0.8±0.2	8.6±3.2	17.8±8.7	1.1±1.1
Mean ± standard deviation. The reference is the 2010 World Health Organization semen analysis normal parameter recommendations.				

Table 5. Comparison of pregnancy rates based on total sperm count in specimen, volume and motility

Parameters	Pregnancy rate	n	p value
All 3 normal	21%	1402	-
Low total sperm others normal	16%	81	0.29
Low total sperm and volume, motility normal	23%	66	0.70
Low total sperm and motility, volume normal	18%	159	0.34
Low total sperm, motility and volume	11%	56	**0.049**
Pregnancy rate is compared with the groups with all 3 parameters normal for the calculation of the p value. P value is two sided The reference is the 2010 World Health Organization semen analysis normal parameter recommendations. Statistically significant differences are in bold.			

Table 6. Preprocessing semen characteristics on the day of intra uterine inseminations for the different groups based on total sperm count in the specimen

Parameters	Volume (mL)	Concentration (millions/mL)	Motility (%)	Total motile sperm count (million)
All 3 normal	3.2±1.4	65.2±43.1	59.2±15.1	123.5±110.0
Low total sperm others normal	2.2±0.8	14.0±6.0	43.2±10.3	13.3±5.1
Low total sperm and volume, motility normal	0.8±0.3	32.3±17.0	50.1±12.3	12.9±6.2
Low total sperm and motility, volume normal	2.6±1.0	10.9±4.9	16.8±8.1	4.8±3.3
Low total sperm, motility and volume	0.8±0.3	23.3±14.1	16.9±8.0	3.2±2.3
Mean ± standard deviation. The reference is the 2010 World Health Organization semen analysis normal parameter recommendations.				

rates increased from 17.3% as opposed to 25.5% with TMSC less than 1 million and greater than 1 million. Clearly, a 17% pregnancy rate with a TMSC under a million remains an acceptable percentage. Pasqualotto et al. (24) concluded that the live birth rate increased with increased TMSC. However, they commented on the fact that success from IUI was mainly related to the percentage of motile sperm (24).

Typically, moderate male factor infertility is considered present when more than a single factor is abnormal (13,25,26) and therefore, one would expect to see decreased pregnancy rates in this situation. However, our results show similar pregnancy rates when one, two, and in most cases three parameters were abnormal. The exception occurred if the total count was less than 39 million sperm, the volume was less than 1.5 mL, and the forward motility was less than 32%, in which case pregnancy rates decreased significantly, although remaining acceptable. Therefore, a couple with mild-to-moderate male factor infertility should be offered IUI as we would expect similar pregnancy rates as quoted in the literature of 13-20% (6,23,27). Pregnancy rates in this study ranged from 11-25%, excluding those that had a total sperm count less than 39 million, plus volume and forward motility also being abnormal. These pregnancy rates are evidently acceptable. Therefore, these rates play an important role in counseling couples when they present for assistive reproductive technology treatments.

There is significant debate as to whether sperm concentration affects pregnancy rates. The literature suggests a direct relationship with the number of spermatozoa in the specimen and pregnancy rates (20,28). However, the results of the present study demonstrate that when sperm concentration is the single abnormal parameter, pregnancy rates (17%) are excellent. Dorjpurev et al. (19) found slightly lower pregnancy rates per cycle when comparing sperm concentration of $<20 \times 10^6$/mL (4.1%) vs $\geq 20 \times 10^6$/mL (7.3%). In a prospective study, Haim et al. (29) showed that there was no significant difference in pregnancy rates with increasing sperm concentration. Pregnancy rates were 7.5% with concentration $<10 \times 10^6$/mL, whereas they were 10.9% when concentrations were $>40 \times 10^6$/mL (29). Therefore, sperm concentration does not impact pregnancy rates significantly and, rather, TMSC is more predictive of successful IUI cycle.

A parameter that was not considered and poses a limitation to this study was sperm morphology. The majority of studies have consistently shown that sperm morphology is one of the best predictors of IVF and IUI outcomes (6). Coetzee et al. (30) demonstrated through a literature review that overall fertilization rates were 59.3% when morphology was <4% and 77.6% when >4% and pregnancy rates were 15.2% and 26.0%, respectively. A literature review by Van Waart et al. (6) concluded that the tendency to become pregnant when sperm morphology was ≤4% was significantly decreased, and this was further supported by a review conducted by van der Merwe et al. (31) who concluded that morphology was the best predictor of sub-fertility and that a cut-off of <5% should be used. However, sperm morphology is not traditionally calculated on the day of IUI because to do so would require killing a significant part of the specimen. It should also be noted that this population had a strict morphology on a recent semen analysis ≥4%, which places them in the WHO normal range.

Another weakness of the study was the small number of subjects in particular groupings of semen parameters. Although these small numbers make it hard to conclude about the grouping individually, consistencies in the data as a whole are visible, notably the lack of differences. Nevertheless, confirmation of the results based on an even larger study would be helpful.

Data were purposefully not presented on female parameters or the stimulation protocol used. Slightly less than 2% used natural cycle IUI. The remaining patients used clomiphene, letrozole or gonadotropins. These data were not provided because it most closely resembles patient counseling on the day of IUI, based on the sperm. The physician cannot interpret the interplay of maternal age, body mass index, years of infertility and stimulation protocol, combined with semen analysis parameters. The physician instead states the sperm parameters and as such whether pregnancy rates are normal or diminished. This study permits an evidence-based interpretation of these parameters on the day of IUI, for the first time. It should be noted that one of the factors that affect pregnancy rates obtained with IUI cycles include stimulation medications. Pregnancy rates are often lower with oral drugs and higher with gonadotropins. In theory, the non-inclusion of these parameters represent a weakness of this study. However, by maintaining the premise that physicians counsel patients based only on semen parameters on the day of IUI, stimulation medications are not taken into consideration and as such were not included in the analysis.

Concurrently, clinical pregnancy rates are not presented because they are affected by factors that do not necessarily affect the pregnancy rate, i.e., sperm DNA fragmentation, history of recurrent pregnancy loss, uterine anomalies, and endometrial quality, among other factors (33-35). Lastly, this is not an examination of multiple pregnancies in IUI cycles, just the likelihood of pregnancy, based on semen parameters on IUI day. To evaluate the effect of semen parameters on multiple pregnancy rates with IUI is an interesting study; however, do to this study would require significant space and is worthy of its own paper.

One question that arises is whether biochemical pregnancy or clinical pregnancy should be used to measure semen

parameter-related success. In our study, pregnancy rates were determined using serum β-hCG results, rather than with evidence of clinical pregnancy or live birth. However, it can be countered that semen capability is best measured in fertilization and biochemical pregnancy, whereas clinical pregnancy or live birth depends more on uterine environment, maternal age, and embryo developmental capacity. All these factors are sperm independent.

In conclusion, IUI remains an effective treatment when faced with a couple with male factor infertility. In all situations, pregnancy rates were at least 11% per cycle and therefore, certain abnormal semen analysis parameters should not be used to discourage IUI. Total sperm in the specimen and not the concentration of sperm per milliliter was the essential factor for predicting pregnancy. Therefore, a reorganization of the semen analysis report should be made emphasizing the total amount of sperm present and de-emphasizing the concentration of sperm.

Ethics Committee Approval: *Stanford University ethics committee approval was obtained.*

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

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Concept - C.A., A.K., M.H.D.; Data Collection or Processing - C.A., M.H.D.; Analysis or Interpretation - A.K., M.H.D.; Writer - A.K., M.H.D.*

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

Financial Disclosure: *NIH grant 5K12HD01249 and the Stanford University Medical Scholars Program.*

References

1. de Melo-Martin I. On cloning human beings. Bioethics 2002; 16: 246-65.
2. Grunewald S, Paasch U. Basic diagnostics in andrology. J Dtsch Dermatol Ges 2013; 11: 799-814.
3. Babayev SN, Park CW, Bukulmez O. Intracytoplasmic sperm injection indications: how rigorous? Semin Reprod Med 2014; 32: 283-90.
4. Tournaye H. Male factor infertility and ART. Asian J Androl 2012; 14: 103-8.
5. Ombelet W, Wouters E, Boels L, Cox A, Janssen M, Spiessens C, et al. Sperm morphology assessment: diagnostic potential and comparative analysis of strict or WHO criteria in a fertile and a subfertile population. Int J Androl 1997; 20: 367-72.
6. Van Waart J, Kruger TF, Lombard CJ, Ombelet W. Predictive value of normal sperm morphology in intrauterine insemination (IUI): a structured literature review. Hum Reprod Update 2001; 7: 495-500.
7. Redmon JB, Thomas W, Ma W, Drobnis EZ, Sparks A, Wang C, et al. Semen parameters in fertile US men: the Study for Future Families. Andrology 2013; 1: 806-14.
8. Keegan BR, Barton S, Sanchez X, Berkeley AS, Krey LC, Grifo J. Isolated teratozoospermia does not affect in vitro fertilization outcome and is not an indication for intracytoplasmic sperm injection. Fertil Steril 2007; 88: 1583-8.
9. Catanzariti F, Cantoro U, Lacetera V, Muzzonigro G, Polito M. Comparison between WHO (World Health Organization) 2010 and WHO 1999 parameters for semen analysis - interpretation of 529 consecutive samples. Arch Ital Urol Androl 2013; 85: 125-9.
10. Ombelet W, Dhont N, Thijssen A, Bosmans E, Kruger T. Semen quality and prediction of IUI success in male subfertility: a systematic review. Reprod Biomed Online 2014; 28: 300-9.
11. Yavuz A, Demirci O, Sözen H, Uludoğan M. Predictive factors influencing pregnancy rates after intrauterine insemination. Iran J Reprod Med 2013; 11: 227-34.
12. Speyer BE, Abramov B, Saab W, Doshi A, Sarna U, Harper JC, et al. Factors influencing the outcome of intrauterine insemination (IUI): age, clinical variables and significant thresholds. J Obstet Gynaecol 2013; 33: 697-700.
13. Murray KS, James A, McGeady JB, Reed ML, Kuang WW, Nangia AK. The effect of the new 2010 World Health Organization criteria for semen analyses on male infertility. Fertil Steril 2012; 98: 1428-31.
14. Cooper TG, Noonan E, von Eckardstein S, Auger J, Baker HW, Behre HM, et al. World Health Organization reference values for human semen characteristics. Hum Reprod Update 2010; 16: 231-45.
15. van Weert JM, Repping S, Van Voorhis BJ, van der Veen F, Bossuyt PM, Mol BW. Performance of the postwash total motile sperm count as a predictor of pregnancy at the time of intrauterine insemination: a meta-analysis. Fertil Steril 2004; 82: 612-20.
16. Khalil MR, Rasmussen PE, Erb K, Laursen SB, Rex S, Westergaard LG. Homologous intrauterine insemination. An evaluation of prognostic factors based on a review of 2473 cycles. Acta Obstet Gynecol Scand 2001; 80: 74-81.
17. Berker B, Şükür YE, Kahraman K, Atabekoğlu CS, Sönmezer M, Özmen B, et al. Absence of rapid and linear progressive motile spermatozoa "grade A" in semen specimens: does it change intrauterine insemination outcomes? Urology 2012; 80: 1262-6.
18. Demir B, Dilbaz B, Cinar O, Karadag B, Tasci Y, Kocak M, et al. Factors affecting pregnancy outcome of intrauterine insemination cycles in couples with favourable female characteristics. J Obstet Gynaecol 2011; 31: 420-3.
19. Dorjpurev U, Kuwahara A, Yano Y, Taniguchi T, Yamamoto Y, Suto A, et al. Effect of semen characteristics on pregnancy rate following intrauterine insemination. J Med Invest 2011; 58: 127-33.
20. Merviel P, Heraud MH, Grenier N, Lourdel E, Sanguinet P, Copin H. Predictive factors for pregnancy after intrauterine insemination (IUI): an analysis of 1038 cycles and a review of the literature. Fertil Steril 2010; 93: 79-88.
21. Akanji Tijani H, Bhattacharya S. The role of intrauterine insemination in male infertility. Hum Fertil (Camb) 2010; 13: 226-32.
22. Tomlinson M, Lewis S, Morroll D; British Fertility Society. Sperm quality and its relationship to natural and assisted conception: British Fertility Society guidelines for practice. Hum Fertil (Camb) 2013; 16: 175-93.
23. Kleppe M, van Hooff MH, Rhemrev JP. Effect of total motile sperm count in intra-uterine insemination on ongoing pregnancy rate. Andrologia 2014; 46: 1183-8.
24. Pasqualotto EB, Daitch JA, Hendin BN, Falcone T, Thomas AJ Jr, Nelson DR, et al. Relationship of total motile sperm count and percentage motile sperm to successful pregnancy rates following intrauterine insemination. J Assist Reprod Genet 1999; 16: 476-82.

25. Leushuis E, van der Steeg JW, Steures P, Repping S, Bossuyt PM, Mol BW, et al. Semen analysis and prediction of natural conception. Hum Reprod 2014; 29: 1360-7
26. Ombelet W, Bosmans E, Janssen M, Cox A, Vlasselaer J, Gyselaers W, et al. Semen parameters in a fertile versus subfertile population: a need for change in the interpretation of semen testing. Hum Reprod 1997; 12: 987-93.
27. Kupka MS, Ferraretti AP, de Mouzon J, Erb K, D'Hooghe T, Castilla JA, et al. Assisted reproductive technology in Europe, 2010: results generated from European registers by ESHRE. Hum Reprod 2014; 29: 2099-113.
28. Aydin Y, Hassa H, Oge T, Tokgoz VY. Factors predictive of clinical pregnancy in the first intrauterine insemination cycle of 306 couples with favourable female patient characteristics. Hum Fertil (Camb) 2013; 16: 286-90.
29. Haim D, Leniaud L, Porcher R, Martin-Pont B, Wolf JP, Sifer C. [Prospective evaluation of the impact of sperm characteristics on the outcome of intra-uterine insemination]. Gynecol Obstet Fertil 2009; 37: 229-35.
30. Coetzee K, Kruge TF, Lombard CJ. Predictive value of normal sperm morphology: a structured literature review. Hum Reprod Update 1998; 4: 73-82.
31. van der Merwe FH, Kruger TF, Oehninger SC, Lombard CJ. The use of semen parameters to identify the subfertile male in the general population. Gynecol Obstet Invest 2005; 59: 86-91.
32. Papillon-Smith J, Baker SE, Agbo C, Dahan MH. Pregnancy rates with intrauterine insemination: comparing 1999 and 2010 World Health Organization semen analysis norms. Reprod Biomed Online 2015; 30: 392-400.
33. Luco SM, Agbo C, Behr B, Dahan MH. The evaluation of pre and post processing semen analysis parameters at the time of intrauterine insemination in couples diagnosed with male factor infertility and pregnancy rates based on stimulation agent. A retrospective cohort study. Eur J Obstet Gynecol Reprod Biol 2014; 179: 159-62.
34. Zini A. Are sperm chromatin and DNA defects relevant in the clinic? Syst Biol Reprod Med 2011; 57: 78-85.
35. Zeadna A, Son WY, Moon JH, Dahan MH. A comparison of biochemical pregnancy rates between women who underwent IVF and fertile controls who conceived spontaneously. Hum Reprod 2015; 30: 783-8.

Analyzing the etiology behind mortality associated with antepartum, intrapartum, and post-partum cases in a tertiary care teaching hospital of West Bengal

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Abstract

Objective: The study was undertaken to understand the causes and circumstances of maternal deaths in West Bengal.

Material and Methods: One hundred ten maternal deaths were reported during the period December 2010 through June 2012 in the Maternity Ward of Medical College and Hospitals, West Bengal. These deaths were reviewed using a facility-based Maternal Death Review protocol. The number and percentages were calculated and binary logistic regression analysis was performed.

Results: The majority of the deaths occurred in the 20-24 years' age group, those with Hindu religion, in the first and second gravida, and the postpartum period. One third of mothers had cesarean sections. The majority (78.2%) of deaths were among referred cases. Eclampsia was the leading cause of maternal death (29.1%). Approximately half of the deceased women sought care after 10 hours of developing complications. More than one-third of maternal deaths were registered with type 1 delays.

Conclusion: Our study demonstrates that maternal deaths occurred among young women, referred cases, with cesarean sections and type 1 delays. We recommend that imparting basic skills and improving awareness to the community about the danger signs of pregnancy could be an effective measure to detect maternal complications at an earlier stage. (J Turk Ger Gynecol Assoc 2018; 19: 65-71)

Keywords: Maternal death, facility-based, West Bengal, eclampsia

Received: 4 December, 2017 **Accepted:** 25 March, 2018

Introduction

Everyday 830 women die due to pregnancy- or childbirth-related complications around the globe (1). According to a World Health Organization report, approximately 303,000 women died during pregnancy or its related complications in 2015. Developing countries accounted for approximately 99 percent of the global burden of maternal deaths (2). Every year, India contributes around 45,000 maternal deaths, which is the second largest number of maternal deaths after Nigeria (2). Maternal mortality ratio (MMR) is defined as "the number of maternal deaths per 100,000 live births" (2). In 2015, the MMR in India was estimated as 174 (2).

According to the latest Registrar General India-Sample Registration System survey report in 2013, the MMR in West Bengal was 117 (3). West Bengal (19.86 percent) has the lowest percentage fall in MMR compared with the other states of India (4). Many deaths still occur in West Bengal due to eclampsia, hemorrhage, severe anemia, obstructed labor, and puerperal sepsis (5-7). Thus, pregnancy-related complications continue to have an enormous effect on the life of mothers and their infants. To achieve the development goal pertaining to maternal and child health requires an increase to access and the coverage of key interventions and improvements in the quality of care (QoC) (8). Maternal death reviews in health facilities, which

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Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.2017.0136

is also called maternal death audit, helps to understand the problem of the importance of QoC. This type of audit identifies obstetric causes of maternal mortality and provides detailed information on avoidable factors related with maternal deaths (9). Analysis of these deaths by using the facility-based maternal death review (FBMDR) approach also gives a clear picture of the different types of delay that lead to deaths among pregnant women at different stages (10,11). The maternal death review helps to understand the complex reasons of these women's death and to set actions to address problems for improving QoC, and ultimately, to save lives in the future.

This facility-based study was performed to understand the causes and circumstances of maternal deaths in a tertiary care hospital of West Bengal so that corrective measures to reduce preventable maternal deaths could be suggested in that health setup.

Material and Methods

Study settings

The selected teaching hospital is Asia's oldest medical college, situated in eastern part of India, which serves as a major tertiary care center in West Bengal. This medical college serves the facilities of antenatal care and inpatient medical care for pregnant women. The doctors and the other health workers are qualified and experienced in handling maternal cases. Patients mostly come to this medical college and hospital in critical condition and in a moribund state from other health care units. Therefore, the hospital can give a representative sample to understand the cause and determinants of maternal death in the community as a whole.

Materials

The present study sought to understand the etiology of maternal deaths in West Bengal using the FBMDR approach. All 110 deaths that occurred between December 2010 and June 2012 in the Maternity Ward of the Medical College and Hospital, West Bengal, India, were analyzed. Deaths among reproductive-aged women (15-49 years) due to pregnancy-related complications and childbirth and occurring within 42 days of delivery were considered as maternal deaths. The maternal death review form and bed head tickets were used to acquire the information about the deceased women. We do not routinely follow thromboprophylaxis in our hospital because most pregnant mothers present as underweight at the time of admission.

Statistical analysis

The number and percentages were calculated to understand the causes and characteristics of maternal deaths. Logistic regression was performed to calculate the odds ratios of being unstable at the time of admission, experiencing any delay, Delay 1 (seeking care) and Delay 2 (reaching first level health facility). We considered age, gravidity, religion and referral status of the patient as independent variables. The level of significance was taken as $p<0.1$, $p<0.05$, and $p<0.01$. Microsoft Excel 2007 and IBM SPSS version 20 were used to analyze the data.

Ethics committee approval

Permission and ethical clearance for using the data were obtained from the ethics review committee of the selected Medical College and Hospital. No personal information of the patients was used. The data were analyzed anonymously.

Informed consent

We used the secondary data from the hospital. We did not interview/communicate with any patient. The ethics review committee waived the need for informed consent.

Results

The study found that the eclampsia accounted 29.1%, which made it the leading cause of maternal mortality, followed by hemorrhage (22.7%) and infections/sepsis (10.9%) (Table 1). About 80% of women died of direct causes. Among the indirect causes (16.4%), jaundice (8.2%) and anemia (3.6%) were the

Table 1. Distribution of causes of maternal deaths (n=110)

Causes	Percentage	Number of women
Direct cause	**71.8**	**79**
Eclampsia	29.1	32
Severe bleeding (Hemorrhage)	22.7	25
Infections/Sepsis	10.9	12
Unsafe abortions	6.4	7
Obstructed labor/Rupture uterus	2.7	3
Other direct causes	**8.2**	**9**
Ectopic pregnancy	2.7	3
Embolism	2.7	3
IUFD with DIC	2.7	3
Indirect causes	**16.4**	**18**
Jaundice	8.2	9
Heart failure	2.7	3
Anemia	3.6	4
Diarrhea	0.9	1
TB	0.9	1
Not determined	**3.6**	**4**

TB: Tuberculosis; IUFD: Intra uterine fetal death; DIC: Disseminated intravascular coagulation

major conditions. There were four women out of 110 women whose causes of death had not been identified.

Out of 110 maternal deaths, 60% were from the Hindu religion and the remaining 40% from the Muslim religion (Table 2). The number (about 46%) of women in the 20-24 years' age group was higher compared with the other age groups. More than one-third of maternal deaths were second gravida. The majority of maternal deaths were reported in primiparas women (42.7%), followed by nulliparous women (34.5%). Out of 110 maternal deaths, twenty women had at least one abortion in the past and five women had two abortions. Nearly half of the women had no living children. The majority of deaths (78.4%) were among referral cases. Among the referrals, most came from subdivision hospitals/community health centers or rural hospitals. The study found that about half of the deceased mothers had received at least one antenatal examination.

Table 2. Sociodemographic characteristics and health-seeking behavior of the deceased women (n=110)

Characteristics		Percentage	Number of women
Religion	Hindu	60.0	66
	Muslim	40.0	44
Age	15-19	14.5	16
	20-24	45.5	50
	25-29	26.4	29
	30 and above	13.6	15
Gravidity*	Primi	30.0	33
	2nd Gravida	35.5	39
	3rd Gravida	20.9	23
	4 and above	13.6	15
Parity$	0	34.5	38
	1	42.7	47
	2	13.6	15
	3	6.4	7
	4 and above	2.7	3
Previous abortions	0	81.8	90
	1	13.6	15
	2	4.5	5
Number of living children	0	46.4	51
	1	30.0	33
	2	15.5	17
	3	6.4	7
	4 and above	1.8	2
Referral status	Yes	78.2	86
	No	21.8	24
Antenatal care	Yes	54.5	60
	No	19.1	21
	Not available	26.4	29

*Number of times a woman has been pregnant; $Number of live births that the woman has had previously

Nearly half of the deceased women came to the medical college at the intrapartum stage (Table 3). Seventy-seven women died during the post-partum period and 11 died during labor (intrapartum). Pre-eclamptic toxemia and eclampsia (29.1%) was the main reason for admission, whereas 19.1 women had to come due to medical conditions. Half of the women (n=55) were unconscious at the time of admission and 38 women (34.5%) had cesarean sections. However, one-third of patients delivered vaginally without any assistance; 18 women died before they had delivered.

About half of the women sought care after 10 hours of developing complications (Figure 1). The percentages of deceased women who sought care within the first five hours and after five to 10 hours were 24.6% and 26.2%, respectively. About 50 percent of the maternal deaths occurred between 12:00 am and 10:00 am (Figure 2).

Among all maternal deaths, 37, 28, and 13 had Delay 1 (delay in deciding to seek care), Delay 2 (delay in reaching first level

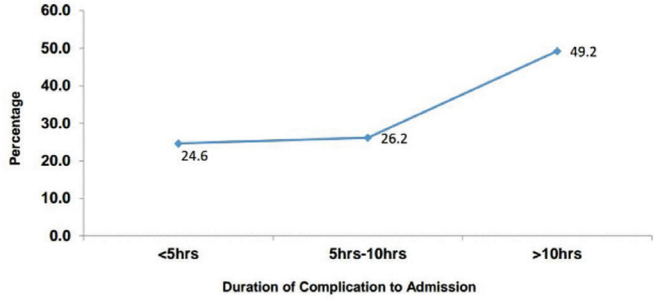

Figure 1. Percent distribution of women according to the duration of complication of admission (n=110)

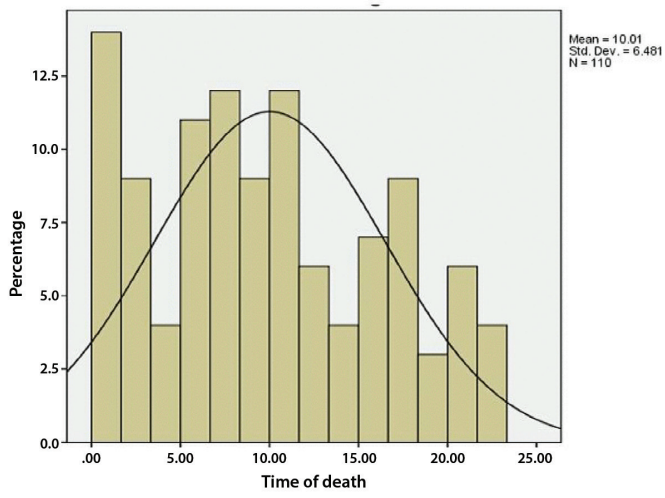

Figure 2. Percent distribution of women according to the timing of death (n=110)

health care facility) and Delay 3 (delay in receiving adequate care in facility), respectively (Table 4). In most of the cases of maternal deaths, multiple types of delay were co-existing. Delay in decision-making, illiteracy, and ignorance were the major contributors of first level delay. Both Delay 1 and Delay 2 were reported in 15 cases, and 5 cases had all types of delays.

The non-referred cases were less likely to be unstable at the time of admission compared with refereed cases (Table 5). In addition, any kind of delay increases the likelihood of being unstable at the time of admission by 2.6 times. It was observed that as the age of women increases the likelihood for any delay and the first delay decreases (Table 6). As compared to Hindu, Muslims were two times more likely to have the second delay.

Discussion

Currently, our understanding of maternal death and its associated factors is very poor, partly due to the scarcity of data related to maternal deaths and its determinants (12,13). Looking at the enormity of the issue, we tried to explore the relationship between maternal death and associated factors. This attempt was made using the facility-based maternal death review approach for determining the causes of maternal deaths and its circumstances in West Bengal.

The most common cause of maternal death was hypertensive disorders of pregnancy or eclampsia (29.1%), followed by hemorrhage (22.7%). Most of the studies conducted in West Bengal found that the eclampsia was the leading cause of maternal death in West Bengal (5-7,14-16). It is also known that a large number of maternal deaths at the time of pregnancy

Table 3. Obstetric complications, labor, and delivery status of the deceased women (n=110)

Characteristics		Percentage	Number of women
Period of admission	AN before 20 weeks ^	12.7	14
	Antenatal >20 weeks	11.8	13
	Intrapartum	48.2	53
	Postpartum/Natal up to 24 hours	10.0	11
	Post-natal 24 hours - 1 week	11.8	13
	Post-natal 1 week to 42 days	5.5	6
Period of death	Antenatal before 20 weeks	12.7	14
	Antenatal after 20 weeks	7.3	8
	Intrapartum*	10.0	11
	Postpartum/Postnatal	70.0	77
Reasons for admission	Normal delivery	5.5	6
	Multiple pregnancy	2.7	3
	Previous C section	8.2	9
	APH	1.8	2
	Abortion	7.3	8
	Ectopic pregnancy	2.7	3
	Vesicular mole	0.9	1
	Anemia	2.7	3
	PPH, PET & Eclampsia (all conditions)	10.9	12
	Medical conditions	19.1	21
	PET & Eclampsia	29.1	32
	Hydramnios & Medical conditions	0.9	1
	Others	7.3	8
	Not available	0.9	1
Condition at admission	Stable	30.9	34
	Semi-conscious responds to verbal commands	12.7	14
	Semi-conscious responds to painful stimuli	6.4	7
	Unconscious	50.0	55
Mode of delivery	Undelivered	16.4	18
	Spontaneous vaginal (with/without episiotomy)	32.7	36
	Vacuum/Forceps	1.8	2
	Cesarean section	34.5	38
	Not applicable/Not available	14.5	16

*During delivery; ^ Antenatal before 20 weeks; APH: Ante-partum hemorrhage; PET: Pre-eclamptic toxemia; PPH: Postpartum hemorrhage; AN: Antenatal

Table 4. Distribution of deceased women according to delay type

Delay	Percentage	Number of women (n=110)
Delay in seeking care (Delay 1)	**33.6**	**37**
Unawareness of danger signs	21.6	8
Illiteracy and ignorance	48.6	18
Delay in decision-making	59.5	22
No birth preparedness	18.9	7
Non-availability of health care professional	5.4	2
Delay in reaching first level health facility (Delay 2)	**25.5**	**28**
Delay in getting transport	50.0	14
Delay in mobilizing funds	42.9	12
Not reaching appropriate facility in time	35.7	10
Delay in receiving adequate care in facility (Delay 3)	**11.8**	**13**
Delay in initiating treatment	46.2	6
Lack of blood, equipment and drugs	53.8	7
Any other	23.1	3
Three Delay	**4.5**	**5**
Delay 1 and Delay 2	13.6	15
Delay 2 and Delay 3	6.4	7
Delay 1 and Delay 3	6.4	7

Table 5. Result of logistic regression showing odds ratio of being unstable at the time of admission

Background characteristics	Exp (β)
Age (C)	0.92
Religion	
Hindu (R)	0.578
Muslim	
Gravidity (C)#	1.058
Referral status	
Yes (R)	0.160***
No	
Any Delay	
No (R)	2.617*
Yes	
Pseudo r square	0.256
n	110
C: Continuous variable; R: Reference category; *p<0.1; ***p<0.01	

and childbirth occur due to hemorrhage in India and the world (17-24).

The present study revealed that about 46% of the maternal deaths were recorded among women between 20 and 24 years. Out of all deaths, 60% of mothers were from the Hindu community and the remaining 40% were Muslims. Several studies reported that higher numbers of maternal deaths were found in the 20-24 years' age group (6,17,24-26) among the Hindu community (17,26). The majority of maternal deaths (more than one-third) were second gravida and 13.6% women were fourth or higher gravida (27). More maternal deaths were reported in primiparous women (42.7%) compared with multiparous (about one-quarter) (27). This is comparable to the findings of other researchers who reported the highest proportion of maternal deaths occurred among multiparous and multigravida women (6,26,28).

An overwhelming majority of the deaths (78.2%) were among referral cases; most of such referrals were from subdivision hospitals/rural hospitals or community health centers and were in critical or irreversible condition at the time of admission. More than two-thirds of the women (70%) died following delivery and approximately half of the deceased women had sought care more than 10 hours after developing complications. Other studies also found high numbers of deaths among referred cases and within the first 24 hours of hospitalization (6,24,25,27-29). Similar to our findings, other studies have also shown that the majority of maternal deaths occur in the post-partum period (16,30).

Fifty-five percent of women had attended at least one antenatal care examination; 19% had not undergone any examinations. The majority of women had reported that lack of awareness was the major cause for not receiving antenatal care. In a study, it was found that the majority of women (70%) had not received

Table 6. Result of logistic regression showing odds ratio of experiencing any Delay, Delay 1 and Delay 2

Background characteristics	Any Delay	Delay 1	Delay 2
	Exp (β)	Exp (β)	Exp (β)
Age (C)	0.911*	0.865**	1.070
Religion			
Hindu (R)	0.688	1.259	2.638*
Muslim			
Gravidity (C)	1.241	1.253	0.712
Referral status			
Yes (R)	0.678	0.470	1.061
No			
Pseudo r square	0.056	0.102	0.067
n	110	110	110
C: Continuous variable; R: Reference category; *p<0.1; **p<0.05			

antenatal care during their pregnancy period (27). The study found more than one third of maternal deaths occurred with cesarean section (6,7,31).

This study also reveals that delays at various stages led to deaths. Type 1 delay was the major contributor in maternal deaths, about one-third of the women died due to this, followed by type 2 and type 3 delays. In a study, it was reported that type 1 and 2 delays had each influenced 58% of maternal deaths, and type 3 delays were registered in 46% of deaths (25). Comparable findings have been reported in a study where type 3 delays were the major contributor of maternal deaths (32). As compared with Hindus, Muslims were two times more likely to have type 2 delays, which was the delay in reaching the health facility. With the increasing age of the mother, the chance of delay decreases. Most of the deaths occurred at midnight and in the early morning, which is a matter of concern.

The most important question is why do women die even after reaching the hospital? The fact that women die in hospital raises important issues of delays in referral to the Medical College and Hospital. These issues also pose a question about the availability, competence, and skills of the medical staff, as well as their attitude towards people at the level of referral. It should be understood why Muslim women face more delays in reaching the health facility. Why is eclampsia the leading cause of death? Another question can be raised: why did most of the maternal deaths occur at midnight and in the early morning? This issue compels us to think about the availability of medical staff and doctors at the referral level.

There is a need to understand the reason behind higher second type of delay among Muslim women. Better understating of causes of maternal deaths remains incomplete without prior knowledge of non-medical factors. It is a well-established fact that facility-based maternal mortality statics fail to reflect the true extent of mortality because medical causes are mostly determined, correlated, and predefined by social, cultural, demographic and health-seeking behavior of the population.

Our study demonstrates that maternal deaths occurred among young women, referred cases, with cesarean sections and Type 1 delays. We recommend that imparting basic skills and improving awareness to the community about the danger signs of pregnancy could be an effective measure to detect maternal complications at an earlier stage. Further, health infrastructure improvement attention should be paid to Muslim areas to eliminate the second type of delay.

Ethics Committee Approval: *Permission and ethical clearance for using the data were obtained from the ethics review committee of the selected Medical College and Hospital.*

Informed Consent: *We used the secondary data from the hospital. We did not interview/communicate with any patient. The ethics review committee waived the need for informed consent.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Concept - M.I.K.S., A.C.; Design - M.I.K.S., A.C., A.A.; Supervision - A.C., T.K.N., S.C.; Data Collection and/or Processing - M.I.K.S., A.C.; Analysis and/or Interpretation - M.I.K.S., A.A.; Literature Review - M.I.K.S., A.A.; Writer - M.I.K.S., A.C., A.A.; Critical Review - A.C., A.A., T.K.N., S.C.*

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

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

References

1. World Health Organization. World health statistics 2016: monitoring health for the SDGs, sustainable development goals. Geneva, Switzerland: World Health Organization; 2016. Available at: http://apps.who.int/iris/bitstream/10665/206498/1/9789241565264_eng.pdf?ua=1 Last accessed 13 September 2017.
2. WHO, UNICEF, UNFPA, World Bank Group and the United Nations Population Division. Trends in maternal mortality: 1990 to 2015. Estimates by WHO, UNICEF, UNFPA, World Bank Group and the United Nations Population Division. Geneva, Switzerland: World Health Organization; 2015. Available at: http://apps.who.int/iris/bitstream/10665/194254/1/9789241565141_eng.pdf?ua=1 Last accessed 13 September 2017.
3. Office of the Registrar General of India, Ministry of Home Affairs, Govt. of India. Special Bulletin on Maternal Mortality in India 2010–12. New Delhi: Ministry of Home Affairs; 2016. Available at: http://www.censusindia.gov.in/vital_statistics/SRS_Bulletins/MMR_Bulletin-2010-12.pdf
4. National Institute of Public Cooperation and Child Development. An Analysis of Levels and Trends in Maternal Health and Maternal Mortality Ratio in India. New Delhi: National Institute of Public Cooperation and Child Development; 2015. Available at: http://nipccd.nic.in/reports/mhmm.pdf Last accessed 13 September 2017.
5. Khan A, Ghosh A, Banerjee PK, Mondal TK. Analysis of the causes of maternal death in eclampsia. IOSR Journal of Dental and Medical Sciences (IOSR-JDMS) 2014; 13: 7-10.
6. Shrivastava P, Nandy S, Saha I, Das KD, Lahiri KS. Deaths amongst Women of Reproductive Age Group in the Gynecology and Obstetrics Department of a Tertiary Care Hospital of Eastern India. Safety Science Monitor 2011; 15: 1-5.
7. Pahari K, Ghosh A. Study of pregnancy outcome over a period of five years in a postgraduate institute of west Bengal. J Indian Med Assoc 1997; 95: 172-4.
8. van den Broek NR, Graham WJ. Quality of care for maternal and newborn health: the neglected agenda. BJOG 2009; 116: 18-21.
9. Lewis G. Beyond the numbers: reviewing maternal deaths and complications to make pregnancy safer. Br Med Bull 2003; 67: 27-37.

10. Ministry of Health & Family Welfare, Government of India. Maternal death review Guidebook. New Delhi: Ministry of Health & Family Welfare; 2012. Available at: http://tripuranrhm.gov.in/Guidlines/MDRGuidelines/MDRFormats_Annex_Pg85_113.pdf Last accessed 13 September 2017.
11. WHO. Beyond the numbers: reviewing maternal deaths and complications tomake pregnancy safer. Geneva, Switzerland: World Health Organization; 2004. Available at: http://apps.who.int/iris/bitstream/10665/42984/1/9241591838.pdf
12. Colbourn T, Lewycka S, Nambiar B, Anwar I, Phoya A, Mhango C. Maternal mortality in Malawi, 1977–2012. BMJ Open 2013; 3: e004150.
13. WHO. International statistical classification of diseases and related health problems. 10th revision. Vol. 2. Instruction Manual. 2010 Edition. Geneva: World Health Organization, 2010: 134.
14. Bhattacharyya SK, Majhi AK, Seal SL, Mukhopadhyay S, Kamilya G. Mukherji J. Maternal mortality in India: a 20-year study from a large referral medical college hospital, West Bengal. J Obstet Gynaecol Res 2008; 34: 499-503.
15. Gun KM. Maternal mortality in a district hospital in West Bengal. Calcutta Med J 1970; 67: 186-91.
16. Das R, Biswas S, Mukherjee A. Maternal Mortality at a Teaching Hospital of Rural India: A Retrospective Study. International Journal of Biomedical And Advance Research 2014; 05: 114-7.
17. Radkar A, Parasuraman S. Maternal Deaths in India: An Exploration. Economic and Political Weekly 2007; 42: 3259-63.
18. World Health Organization. The World health report: make every mother and child count. Geneva, Switzerland: World Health Organization; 2005. Available at: http://www.who.int/whr/2005/whr2005_en.pdf
19. Montgomery AL, Ram U, Kumar R, Jha P, The Million Death Study Collaborators. Maternal mortality in India: causes and healthcare service use based on a nationally representative survey. PLoS One 2014; 9: e83331.
20. Government of India. Sample Registration System: Maternal Mortality in India 1997-2003, Trends, Causes and Risk Factors. New Delhi, India: Registrar General of India, in collaboration with Centre for Global Health Research, University of Toronto, Canada; 2006. Available at: http://www.cghr.org/wordpress/wp-content/uploads/RGI-CGHR-Maternal-Mortality-in-India-1997%E2%80%932003.pdf
21. Kausar R. Maternal Mortality in India - Magnitude, Causes and Concerns. Int J Prev Med 2006; 2: 1-5.
22. Arora P. Maternal Mortality- Indian Scenario. Med J Armed Forces India 2005; 61: 214-5.
23. WHO, UNICEF, UNFPA. Maternal Mortality in 2005: Estimates developed by WHO, UNICEF, UNFPA, and The World Bank. Geneva, Switzerland: World Health Organization; 2007. Available at: http://www.who.int/whosis/mme_2005.pdf
24. Bhat PN. Maternal mortality in India: an update. Stud Fam Plann. 2002; 33: 227-36.
25. Paul B, Mohapatra B, Kar K. Maternal Deaths in a Tertiary Health Care Centre of Odisha: An In-depth Study Supplemented by Verbal Autopsy. Indian J Community Med 2011; 36: 213-6.
26. Murthy KB, Murthy MB, Prabhu MP. Maternal Mortality in a Tertiary Care Hospital: A 10-year Review. Int J Prev Med 2007; 17: 121-130.
27. Tayade S, Bagde M, Shivkumar VP, Tayade A, Bagde N. Maternal death review to know the determinants of maternal mortality ın a District Hospital Of Central India. Int J Biomed Res 2012; 3: 157-63.
28. Shah JR, Ali I, Banday A, Fazili A, Khan I. Analysis of Maternal Mortality in a Small Teaching Hospital Attached to Tertiary Care Hospital (A 10 yr review). Indian J Community Med 2008; 33: 260-2.
29. Paul B, Sen M, Kar K, Mohapatra B. Facility Based Maternal Death Review: Learning from Maternal Deaths in a Teaching Hospital of Eastern India. Int J Biomed Res 2013; 4: 12-20.
30. Li XF, Fortney JA, Kotelchuck M, Glover LH. The postpartum period: the key to maternal mortality. Int J Gynaecol Obstet 1996; 54: 1-10.
31. Singh A, Shrivastava C. Changing trends in eclampsia and increasing cesarean delivery – an interesting retrospective study from a tertiary care hospital of Raipur, Chhattisgarh, India. Int J Reprod Contracept Obstet Gynecol 2016; 5: 1031-5.
32. Cham M, Sundby J, Vangen S. Maternal mortality in the rural Gambia, a qualitative study on access to emergency obstetric care. Reprod Health 2005; 2: 3.

Outcomes of robotic, laparoscopic, and open hysterectomy for benign conditions in obese patients

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Abstract

Objective: To compare outcomes of robotic-assisted (RAH), total laparoscopic hysterectomy (LH), and total abdominal hysterectomy (TAH) for benign conditions in obese patients.

Material and Methods: Retrospective cohort (Class II-2) analysis. All obese patients who underwent RAH, LH or TAH for benign conditions by a single surgeon at the University of Texas Medical Branch between January 2009 and December 2011 were identified and their charts reviewed. The patients' characteristics, operative data, and post-operative outcomes were collected and statistically analyzed.

Results: A total of 208 patients who underwent RAH (n=51), LH (n=24) or TAH (n=133) were analyzed. There were no significant differences among the groups in demographic characteristics, indications for surgery or pathologic findings. RAH and LH were associated with lower estimated blood loss (EBL) ($p<0.001$) and shorter length of hospital stay (LOS) ($p<0.001$) compared with TAH. In addition, RAH and LH had lower intraoperative and early postoperative (≤6 weeks) complications compared with TAH ($p=0.002$). However, the procedure time was longer in RAH and LH ($p<0.001$). No significant differences were noted among the groups for late post-operative complications (after 6 weeks) or unscheduled post-operative visits.

Conclusion: Minimally invasive hysterectomy appears to be safe in obese patients with the advantages of less EBL, fewer intraoperative complications, and shorter LOS. (J Turk Ger Gynecol Assoc 2018; 19: 72-7)

Keywords: Hysterectomy, robotic, laparoscopic, open, obese

Received: 22 February, 2018 **Accepted:** 23 April, 2018

Introduction

Obesity is defined by the World Health Organization as having a body mass index (BMI) ≥30 kg/m^2 (1). The prevalence of obesity among adults in the United States of America stayed around 15% from 1960 to 1980 before rapidly accelerating from 13.4% in 1980 to 35.7% in 2010 (2) and is projected to reach 42% by 2030 (3). Obesity is a well-known risk factor for medical problems (4) and surgical outcomes including hysterectomy (5-8).

Laparoscopic hysterectomy (LH) was first described in 1989 (9) and has been demonstrated to be safe and feasible (10). Its advantages include less blood loss, less post-operative pain, shorter hospital stay, faster recovery and better cosmetic outcome. More recently, the United States Food and Drug Administration approved the da Vinci® Surgical System (Intuitive Surgical Inc., Sunnyvale, CA) for hysterectomy in 2005. Thereafter, robotic hysterectomy has been reported to have several enhancements including improved dexterity with EndoWrist movements and 3D visualization (11-13). These enhancements are critical, especially in complex cases where extensive dissection is required (14). For these advantages,

This study was presented in part at the 41st Global Congress of Minimally Invasive Gynecology (AAGL 2012), November 2012, in Las Vegas, Nevada.

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Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.2018.0018

laparoscopic and robotic hysterectomy have been gaining momentum (13,15,16).

With the current epidemic-like status of obesity (17), and the medical risks it poses (4), it has also been demonstrated to pose a substantial surgical risk (5). In fact, it has been reported that obesity is associated with increased intra- and post-operative complications including bleeding and infections in patients undergoing hysterectomy (18). Whether obesity-related complications depend on the approach of hysterectomy for benign conditions is not clearly determined at the present time. With the growing adoption of robotic and LH, there is a growing need for more evidence about the safety and outcomes of laparoscopic and robotic hysterectomy in the obese. Although current evidence suggests that LH is associated with fewer complications than abdominal hysterectomy in obese patients (5), most of these studies include patients with cancer (19-22). There is a need for data exclusively from benign cases because patients with malignancy have a different outcome. The objective of this study was to analyze the outcomes of robotic and LH for benign conditions in obese patients in comparison to open approaches.

Material and Methods

This retrospective cohort study (Class II-2) was approved by the Institutional Review Board. Informed consents from patients were not required because it is retrospective chart review study. All obese patients who underwent robotic assisted hysterectomy (RAH), total LH or total abdominal hysterectomy (TAH) by a single surgeon from January 1st, 2009, to December 31st, 2011, were identified. Obesity was defined as having a BMI ≥30 kg/m^2 (1). All patients were thoroughly counseled about the risks and benefits and they chose the route of surgery. Patients with pre-operative diagnosis of gynecologic cancer were excluded.

All patients received standard antibiotics and thromboembolic prophylaxis according to the American College of Obstetricians and Gynecologists guidelines (23,24). The RAHs and LHs performed in this study were American Association of Gynecologic Laparoscopists type IVE, defined as total laparoscopic removal of the uterus and cervix including vaginal cuff closure (25). Patients undergoing RAH and LH were placed in the dorsal lithotomy position with Allen stirrups (Allen Medical System, Acton, MA). In this study, we followed the "Strengthening the Reporting of Observational Studies in Epidemiology guidelines (26).

Electronic medical records were reviewed and de-identified data were extracted and double-checked for missing values. The following pre-operative characteristics were obtained: age, race, gravidity, parity, BMI, prior pelvic/abdominal surgery including peritoneal entry, smoking status, medical problems, and indications for surgery. In addition, we collected the following operative data: procedure time (skin-to-skin), estimated blood loss (EBL), concomitant procedures, conversion to open route, specimen morcellation, intraoperative complications (defined as bleeding ≥500 mL; injury to bladder, ureter or bowel and significant ventilation problems), and transfusion (intra-operative and post-operative within 6 weeks). Finally, we included the following peri-operative characteristics: length of hospital stay (LOS), uterine weight, final pathologic diagnosis, and hospital readmission (within 6 weeks).

All patients were followed for one year. Post-operative complications were defined as: fever (body temperature ≥38 °C on 2 consecutive occasions at least 6 hours apart, excluding the first 24 hours); urinary tract infection; urinary retention (without a concomitant urinary incontinence procedure); pelvic hematoma or abscess; genitourinary fistulas; cuff dehiscence; positional nerve injuries; and port-site, cardiopulmonary, gastrointestinal (ileus or bowel obstruction) and ophthalmologic complications were retrieved and subdivided into early (within 6 weeks) or late (from 6 weeks to 1 year). Patients were asked if they had presented to other hospitals and data were obtained whenever applicable.

Statistical analysis

The first step in the data analysis was to double-check data for missing values. Means and standard deviations were calculated for continuous variables. Then, bivariate relationships were assessed using frequency cross-tabulation for categorical variables. One-way analysis of variance with Bonferroni post hoc analysis whenever applicable, was used for continuous variables, and the chi-square test and Fisher's exact test were used for categorical variables when appropriate. Data were analyzed using Statistical Analysis Software (SAS), v. 9.2 (SAS Institute, Cary, NC). In all instances, a p value <0.05 was considered statistically significant.

Results

A total of 208 consecutive hysterectomy cases were analyzed including RAH (n=51), LH (n=24), and TAH (n=133). Characteristics of the study population are summarized in Table 1. As shown, differences among groups in BMI and other characteristics including age, race, parity, history of medical problems, smoking status and indications for surgery were not significant. However, the TAH group had more prior abdominal/pelvic surgeries ($p<0.001$).

Next, we analyzed operative data and post-operative outcomes (Table 2). As shown, there were no significant differences among the groups in oophorectomy, concomitant procedures, conversion rate (only RAH and LH), or morcellation (only RAH and LH). There were three conversions in the RAH group for

bleeding, PK malfunction (converted to laparoscopy), and a minilaparotomy for specimen retrieval. In comparison, there were 2 conversions in the LH group for a patient who could not tolerate the Trendelenburg position and another for instrument malfunction. Intra-operative complications were higher in the TAH and LH groups compared with the RAH group (p=0.002). The vast majority of these complications were excessive intra-operative blood loss (n=2, n=3, and n=32 in the RAH, LH, and TAH groups, respectively).

In addition, we found that RAH and LH were associated with less EBL compared with TAH (p<0.001) with post hoc analysis showing significantly less EBL in RAH compared with LH (p=0.019). Furthermore, we found that TAH was associated with more blood transfusions compared with RAH and LH; however, the difference was not statistically different (p=0.052). On further analysis, we found that RAH and LH had significantly longer procedure times compared with TAH (p<0.001) with Bonferroni post hoc analysis showing no significant difference between RAH and LH (p=0.056). The LOS was significantly shorter in the RAH and LH groups (p<0.001). In addition, early post-operative complications (≤6 weeks) were lower in the LH group compared with RAH and TAH groups (p=0.002). However, late post-operative complications (between 6 weeks and up to 1 year after surgery) were not significantly different among the groups (p=0.113). Finally, there was no significant difference between groups in terms of final pathologic diagnosis (p=0.085). However, the uterine weight was highest in the TAH group (p<0.001), with Bonferroni post-hoc analysis showing significant differences between the RAH and LH groups (p=0.015).

Discussion

The results of this study demonstrate that RAH and LH in obese patients are associated with less EBL, fewer intraoperative and

Table 1. Characteristics of study population

Characteristic	RAH n=51	LH n=24	TAH n=133	p values
Age (years)	46.94±10.34	44.17±8.65	44.54±8.35	0.229
Gravidity (n)	2.33±1.41	2.92±1.47	2.99±2.04	0.094
Parity (n)	1.94±1.22	1.92±1.10	2.41±1.79	0.126
BMI (kg/m^2)	37.50±7.56	35.70±5.92	36.12±4.63	0.267
Prior abdominal/pelvic surgery including peritoneal entry (n)	0.49±0.92	1.08±0.88	1.17±1.34	<0.001*
Race				
White (n=69)	22 (43.1)	9 (37.5)	38 (28.6)	0.358
African American (n=103)	20 (39.2)	12 (50.0)	71 (53.4)	
Hispanic/American Indian (n=36)	9 (17.7)	3 (12.5)	24 (18.1)	
Smoking status				
No (n=159)	42 (82.4)	18 (75.0)	99 (74.4)	0.552
Yes (n=49)	9 (17.7)	6 (25.0)	34 (25.6)	
Medical problems				
None	20 (39.2)	7 (29.2)	42 (31.6)	0.676
Diabetes mellitus (DM)	2 (3.9)	2 (8.3)	4 (3.0)	
Hypertension (HTN)	13 (25.5)	3 (12.5)	43 (32.3)	
DM+HTN	4 (7.8)	2 (8.3)	10 (7.5)	
Thyroid disease	3 (5.9)	2 (8.3)	5 (3.8)	
Lung disease	2 (3.9)	2 (8.3)	7 (5.3)	
Renal disease	0	0	2 (1.5)	
Cardiac disease	0	2 (8.3)	8 (6.0)	
Liver disease	1 (2.0)	0	3 (2.3)	
Others	6 (11.8)	4 (16.7)	9 (6.8)	
Indications				
Abnormal uterine bleeding	35 (68.6)	18 (75.0)	90 (67.7)	0.555
Adnexal mass	4 (7.8)	2 (8.3)	22 (16.54	
Pelvic pain	5 (9.80)	1 (4.2)	6 (4.5)	
Cervical dysplasia	3 (5.9)	3 (12.5)	9 (6.8)	
Pelvic organ prolapse	3 (5.9)	0	3 (2.3)	
Others	1 (2.0)	0	3 (2.3)	

Data presented as mean (±SD) or number (percentage); *Statistically significant; LH: Laparoscopic hysterectomy; RAH: Robotic assisted hysterectomy; TAH: Total abdominal hysterectomy; BMI: Body mass index

early postoperative complications, less perioperative blood transfusion, and shorter LOS, although they require longer operating times compared with TAH. Moreover, EBL, LOS, and perioperative blood transfusion were noted to be less in the RAH group when compared with LH.

The findings in this study are in line with other studies. Gali et al. (27) found that RAH was associated with shorter hospital stays, and fewer infectious complications compared with TAH. Geppert et al. (19) also compared RAH with TAH in obese patients. The authors reported similar results and concluded that RAH was feasible but required training and special expertise. Another study by Eddib et al. (28) examined the impact of BMI on surgical outcomes of RAH. They concluded that procedure time was longer in morbidly obese patients; however, obesity had no impact on other outcomes. In contrast to this study, Nawfal et al. (29) reported no association between BMI and

Table 2. Operative data and post-operative outcomes

Outcome	RAH n=51	LH n=24	TAH n=133	p value
Oophorectomy No (n=92) Bilateral (n=102) Unilateral (n=14l)	 28 (54.9) 19 (37.3) 4 (7.8)	 14 (58.3) 9 (37.5) 1 (4.2)	 50 (37.6) 74 (55.6) 9 (6.8)	0.111
Concomitant procedures No (n=157) Yes (n=51)	 39 (76.5) 12 (23.5)	 19 (79.2) 5 (20.8)	 99 (74.4) 34 (25.6)	0.913
Conversion‡ No (n=48) Yes (n=5)	 48 (94.1) 3 (5.9)	 22 (91.7) 2 (8.3)	 n/a	0.653
Morcellation No (n=61) Yes (n=14)	 40 (78.4) 11 (21.6)	 21 (87.5) 3 (12.5)	 n/a	0.527
Intra-operative comp No (n=169) Yes (n=39)	 49 (96.1) 2 (3.9)	 21 (87.5) 3 (12.5)	 99 (74.4) 34 (25.6)	0.002*
Estimated blood loss (mL)	144.80±148.32	221.88±254.89	391.54±418	<0.001*
Transfusion No (n=194) Yes (n=14)	 51 (100) 0	 23 (95.8) 1 (4.2)	 120 (90.2) 13 (9.8)	0.052
Procedure time (minute)	276.96±79.32	214.46±68.65	184.83±65.50	<0.001*
LOS (day)	1.43±0.73	2.04±1.33	3.56±2.81	<0.001*
Postop. comp ≤6 weeks No (n=141) Yes (n=67)	 41 (80.4) 10 (19.6)	 21 (87.5) 3 (12.5)	 79 (59.4) 54 (40.6)	0.002*
Postop. comp >6 weeks No (n=196) Yes (n=12)	 50 (98) 1 (2)	 24 (100) 0	 122 (91.7) 11 (8.3)	0.113
Unscheduled post-op visits No (n=169) Yes (n=39)	 42 (82.4) 9 (17.7)	 20 (83.3) 4 (16.7)	 107 (80.5) 26 (19.6)	0.965
Final pathologic results Fibroids Adenomyosis Benign adnexal mass Malignancy Cervical dysplasia Others	 24 (47.1) 13 (25.5) 4 (7.8) 2 (3.9) 1 (2.0) 7 (13.7)	 14 (58.3) 2 (8.3) 2 (8.3) 0 2 (8.3) 4 (16.7)	 84 (63.2) 14 (10.5) 18 (13.5) 5 (3.8) 4 (3.0) 8 (6.02)	0.085
Uterine weight (g)	237.04±182.64	195.75±154.67	547.77±796.29	<0.001*

Data presented as mean ± standard deviation or number (percentage); *Statistically significant; n/a: Not applicable, LH: Laparoscopic hysterectomy; RAH: Robotic assisted hysterectomy; TAH: Total abdominal hysterectomy; LOS: Length of hospital stay

duration of surgery and similarly concluded that RAH might be a better approach to hysterectomy in obese and morbidly obese patients. Boggess et al. (30) compared outcomes in RAH, LH, and TAH in patients with endometrial cancer. The mean BMIs were 32.9, 29.0, and 34.7, respectively, and the results favored a robotic approach in terms of blood loss, hospital stay, and post-operative complications. In another study that compared RAH and TAH in obese women who underwent surgical staging for endometrial cancer, similar results and conclusions were reported (20).

This study has certain strengths. First, all procedures were performed by a single surgeon, eliminating potential confounding factors when analyzing cases performed by multiple surgeons. In addition, this study exclusively includes procedures performed for benign indications. This is in contrast to other studies in which patients with cancer were included in the analysis along with benign cases, which affects the validity of the outcomes. However, the study also has some limitations. First, the study design is a retrospective cohort analysis. We believe that this may have affected the results, potentially due to selection bias. Therefore, prospective randomized trials are needed to overcome this limitation. In addition, the sample size, especially of the LH group, was relative small and the study groups were not equal in size. Consequently, larger studies are needed to confirm the findings in this study. Finally, this study was performed in a teaching institution where residents participated in most cases. This needs to be considered when analyzing the study results, especially procedure time. However, as residents participated equally in the study groups, we do not think that this factor had an impact on the study conclusions.

There is a clear need to further investigate different clinical and financial aspects of minimally invasive hysterectomy in obese patients because we currently counsel obese patients based primarily on data from the general population. The initial evidence suggests that minimally invasive hysterectomy is safe and feasible in obese patients. For example, Gali et al. (27) examined the effects of the steep Trendelenburg position on cardiopulmonary function in obese patients. The authors found that although higher inspiratory pressures were needed in RAH compared with TAH, cardiopulmonary complications were not significantly different. However, several other variables and outcomes were not examined. For example, despite evidence that intraocular pressure goes up with the steep Trendelenburg position during minimally invasive gynecologic surgery (31), the magnitude of this effect has not been evaluated in obese patients. Also, although outpatient robotic hysterectomy was demonstrated to be safe and associated with financial savings (32-34), its safety and feasibility has not yet been evaluated in the obese patient subset. Similarly, costs of robotic gynecologic surgery in benign cases were analyzed with strategies for efficiency (35,36), but there is paucity of the effect of BMI on cost in benign robotic hysterectomy. In addition, because the incidence of occult cancer discovered after minimally invasive gynecologic surgery has been examined (37), there is a need to examine it in the obese patient population. All these clinical characteristics are important for the accurate counseling of obese patients. Also, with the current evidence of disparities in the use of LH (38), it is important to determine if it is adequately used for the obese patient population. Finally, there is a clear need to take important clinical variables such as BMI into account when designing and using simulators, which appear helpful in minimally invasive gynecologic surgical training (39,40).

In conclusion, our study demonstrates that in spite of a longer procedure time, robotic and laparoscopic hysterectomies are feasible, safe, and provide shorter hospital stays and less blood loss in the obese patient population. Finally, larger, prospective, randomized studies that also evaluate other clinical and financial outcomes are recommended.

Ethics Committee Approval: *Study was approved by Ethics Committee (Institutional Review Board IRB # 13-084).*

Informed Consent: *Informed consent was not required per IRB approval as study was retrospective and subjects were de-identified.*

Peer-review: *Externally and Internally peer-reviewed.*

Author Contributions: *Concept - G.S.K., Ö.L.T., İ.A., M.A.B.; Design - G.S.K., Ö.L.T., İ.A., M.A.B.; Supervision - M.A.B., G.S.K.; Materials - Ö.L.T., M.A.B., G.S.K.; Writer - M.A.B., Ö.L.T.*

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

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

References

1. WHO. Obesity 2018 [Feb 16,2018]. Available from: http://www.who.int/topics/obesity/en/
2. Fryar CD CM, Ogden CL. Prevalence of Overweight, Obesity, and Extreme Obesity Among Adults: United States, Trends 1960–1962 Through 2009–2010. 2012 [Feb 16, 2018]. Available from: http://www.cdc.gov/nchs/data/hestat/obesity_adult_09_10/obesity_adult_09_10.pdf
3. CDC. Weight of the nation [Feb 16, 2018]. Available from: http://www.cdc.gov/media/releases/2012/t0507_weight_nation.html
4. Kopelman PG. Obesity as a medical problem. Nature 2000; 404: 635-43.

5. Osler M, Daugbjerg S, Frederiksen BL, Ottesen B. Body mass and risk of complications after hysterectomy on benign indications. Hum Reprod 2011; 26: 1512-8.
6. Isik-Akbay EF, Harmanli OH, Panganamamula UR, Akbay M, Gaughan J, Chatwani AJ. Hysterectomy in obese women: a comparison of abdominal and vaginal routes. Obstet Gynecol 2004; 104: 710-4.
7. Khavanin N, Lovecchio FC, Hanwright PJ, Brill E, Milad M, Bilimoria KY, et al. The influence of BMI on perioperative morbidity following abdominal hysterectomy. Am J Obstet Gynecol 2013; 208: 449. e1-6.
8. Siedhoff MT, Carey ET, Findley AD, Riggins LE, Garrett JM, Steege JF. Effect of extreme obesity on outcomes in laparoscopic hysterectomy. J Minim Invasive Gynecol 2012; 19: 701-7.
9. Reich H, DeCaprio J, McGlynn F. Laparoscopic hysterectomy. J Gynecol Surg 1989; 5: 213-6.
10. Reich H. Total laparoscopic hysterectomy: indications, techniques and outcomes. Curr Opin Obstet Gynecol 2007; 19: 337-44.
11. Orady M, Hrynewych A, Nawfal AK, Wegienka G. Comparison of robotic-assisted hysterectomy to other minimally invasive approaches. JSLS 2012; 16: 542-8.
12. Advincula AP, Wang K. Evolving role and current state of robotics in minimally invasive gynecologic surgery. J Minim Invasive Gynecol 2009; 16: 291-301.
13. Kilic GS, Moore G, Elbatanony A, Radecki C, Phelps JY, Borahay MA. Comparison of perioperative outcomes of total laparoscopic and robotically assisted hysterectomy for benign pathology during introduction of a robotic program. Obstet Gynecol Int 2011; 2011: 683703.
14. Boggess JF, Gehrig PA, Cantrell L, Shafer A, Mendivil A, Rossi E, et al. Perioperative outcomes of robotically assisted hysterectomy for benign cases with complex pathology. Obstet Gynecol 2009; 114: 585-93.
15. Lee J, Jennings K, Borahay MA, Rodriguez AM, Kilic GS, Snyder RR, et al. Trends in the national distribution of laparoscopic hysterectomies from 2003 to 2010. J Minim Invasive Gynecol 2014; 21: 656-61.
16. Turner LC, Shepherd JP, Wang L, Bunker CH, Lowder JL. Hysterectomy surgery trends: a more accurate depiction of the last decade? Am J Obstet Gynecol 2013; 208: 277. e1-7.
17. CDC. Obesity trends 2018 [Feb 16, 2018]. Available from: http://www.cdc.gov/obesity/data/adult.html
18. David-Montefiore E, Rouzier R, Chapron C, Darai E, Collegiale d'Obstetrique et Gynecologie de Paris-Ile de F. Surgical routes and complications of hysterectomy for benign disorders: a prospective observational study in French university hospitals. Hum Reprod 2007; 22: 260-5.
19. Geppert B, Lönnerfors C, Persson J. Robot-assisted laparoscopic hysterectomy in obese and morbidly obese women: surgical technique and comparison with open surgery. Acta Obstet Gynecol Scand 2011; 90: 1210-7.
20. Seamon LG, Bryant SA, Rheaume PS, Kimball KJ, Huh WK, Fowler JM, et al. Comprehensive surgical staging for endometrial cancer in obese patients: comparing robotics and laparotomy. Obstet Gynecol 2009; 114: 16-21.
21. Gallo T, Kashani S, Patel DA, Elsahwi K, Silasi DA, Azodi M. Robotic-assisted laparoscopic hysterectomy: outcomes in obese and morbidly obese patients. JSLS 2012; 16: 421-7.
22. Rebeles SA, Muntz HG, Wieneke-Broghammer C, Vason ES, McGonigle KF. Robot-assisted total laparoscopic hysterectomy in obese and morbidly obese women. J Robotic Surg 2009; 3: 141.
23. ACOG Committee on Practice Bulletins Gynecology. ACOG practice bulletin No. 104: antibiotic prophylaxis for gynecologic procedures. Obstet Gynecol 2009; 113: 1180-9.
24. Committee on Practice Bulletins Gynecology, American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 84: Prevention of deep vein thrombosis and pulmonary embolism. Obstet Gynecol 2007; 110: 429-40.
25. Olive DL, Parker WH, Cooper JM, Levine RL. The AAGL classification system for laparoscopic hysterectomy. Classification committee of the American Association of Gynecologic Laparoscopists. J Am Assoc Gynecol Laparosc 2000; 7: 9-15.
26. Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Int J Surg 2014; 12: 1500-24.
27. Gali B, Bakkum-Gamez JN, Plevak DJ, Schroeder D, Wilson TO, Jankowski CJ. Perioperative Outcomes of Robotic-Assisted Hysterectomy Compared with Open Hysterectomy. Anesth Analg 2018; 126: 127-33.
28. Eddib A, Danakas A, Hughes S, Erk M, Michalik C, Narayanan MS, et al. Influence of Morbid Obesity on Surgical Outcomes in Robotic-Assisted Gynecologic Surgery. J Gynecol Surg 2014; 30: 81-6.
29. Nawfal AK, Orady M, Eisenstein D, Wegienka G. Effect of body mass index on robotic-assisted total laparoscopic hysterectomy. J Minim Invasive Gynecol 2011; 18: 328-32.
30. Boggess JF, Gehrig PA, Cantrell L, Shafer A, Ridgway M, Skinner EN, et al. A comparative study of 3 surgical methods for hysterectomy with staging for endometrial cancer: robotic assistance, laparoscopy, laparotomy. Am J Obstet Gynecol 2008; 199: 360. e1-9.
31. Borahay MA, Patel PR, Walsh TM, Tarnal V, Koutrouvelis A, Vizzeri G, et al. Intraocular pressure and steep Trendelenburg during minimally invasive gynecologic surgery: is there a risk? J Minim Invasive Gynecol 2013; 20: 819-24.
32. Moawad G, Liu E, Song C, Fu AZ. Movement to outpatient hysterectomy for benign indications in the United States, 2008-2014. PLoS One 2017; 12: e0188812.
33. Korsholm M, Mogensen O, Jeppesen MM, Lysdal VK, Traen K, Jensen PT. Systematic review of same-day discharge after minimally invasive hysterectomy. Int J Gynaecol Obstet 2017; 136: 128-37.
34. Borahay MA, Patel PR, Kilic CH, Kilic GS. Outpatient robotic hysterectomy: clinical outcomes and financial analysis of initial experience. Int J Med Robot 2014; 10: 244-50.
35. Zeybek B, Oge T, Kılıç CH, Borahay MA, Kılıç GS. A financial analysis of operating room charges for robot-assisted gynaecologic surgery: Efficiency strategies in the operating room for reducing the costs. J Turk Ger Gynecol Assoc 2014; 15: 25-9.
36. Moawad GN, Abi Khalil ED, Tyan P, Shu MK, Samuel D, Amdur R, et al. Comparison of cost and operative outcomes of robotic hysterectomy compared to laparoscopic hysterectomy across different uterine weights. J Robot Surg 2017; 11: 433-9.
37. Rodriguez AM, Asoglu MR, Sak ME, Tan A, Borahay MA, Kilic GS. Incidence of occult leiomyosarcoma in presumed morcellation cases: a database study. Eur J Obstet Gynecol Reprod Biol 2016; 197: 31-5.
38. Patel PR, Lee J, Rodriguez AM, Borahay MA, Snyder RR, Hankins GD, et al. Disparities in use of laparoscopic hysterectomies: a nationwide analysis. J Minim Invasive Gynecol 2014; 21: 223-7.
39. Asoğlu MR, Achjian T, Akbilgiç O, Borahay MA, Kılıç GS. The impact of a simulation-based training lab on outcomes of hysterectomy. J Turk Ger Gynecol Assoc 2016; 17: 60-4.
40. Borahay MA, Haver MC, Eastham B, Patel PR, Kilic GS. Modular comparison of laparoscopic and robotic simulation platforms in residency training: a randomized trial. J Minim Invasive Gynecol 2013; 20: 871-9.

Independent predictors of survival in endometrium cancer: platelet-to-lymphocyte ratio and platelet/neutrophil/monocyte-to-lymphocyte ratio

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Abstract

Objective: To evaluate the association between ratios of inflammatory markers and survival in endometrium cancer (EC).

Material and Methods: Four hundred ninety-seven patients with epithelial EC were included. The evaluated ratios were neutrophil (N)/lymphocyte (L), neutrophil count divided by the lymphocyte count; platelet (P)/lymphocyte, platelets divided by the lymphocyte count; lymphocyte/monocyte (M), lymphocytes divided by the monocyte count; NM/L, neutrophil plus monocyte divided by the lymphocyte count; PNM/L, the sum total counts of platelets, neutrophils and monocytes divided by the lymphocyte count.

Results: The median follow-up time was 24 months (1-129). Recurrence and exitus occurred in 34 (7%) and 18 (3.7%) patients, respectively. Metastasis in pelvic or para-aortic lymph nodes were significantly related only with low L/M. None of the inflammatory ratios were associated with disease-free survival. In multi-variant analysis, only high P/L (>168) and high PNM/L (>171) were related with a statistically significant hazard ratio for death of 2.91 (p=0.024) and 2.93 (p=0.023), respectively.

Conclusion: The P/L and PNM/L were in relation with worse overall survival and also independent prognostic factors for OS. (J Turk Ger Gynecol Assoc 2018; 19: 78-86)

Keywords: Endometrium cancer, platelet, monocyte, lymphocyte, neutrophil

Received: 22 September, 2017 **Accepted:** 7 January, 2018

Introduction

The inflammatory response plays an important role in carcinogenesis and progression of cancer (1). A cancer-related inflammatory microenvironment can be reflected in the blood as measurable parameters. The basic changes are reported as a neutrophilia, thrombocytosis, and lymphocytopenia (1). Owing to challenges related with clinical adaptations of separate counts of lymphocytes, neutrophils, thrombocytes and monocytes, ratios of these inflammatory markers such as platelet-to-lymphocyte, neutrophil-to-lymphocyte and lymphocyte-to-monocyte are evaluated and have been used as prognostic factors in both infectious diseases and non-infectious diseases (2-4). In recent years, these rates have been clarified as having prognostic significance and survival prediction in a variety of solid cancers (5-10). Although the utility of these inflammatory parameters is easy and inexpensive, there is a paucity of data about the value of these ratios in gynecologic cancers, especially for endometrial cancer.

Endometrium cancer (EC) is the most common gynecologic cancer of the genital tract (11), but there is no distinct marker to predict pathologic findings and survival in EC. Therefore, the present study aimed to determine the association between ratios of complete blood counts and survival in EC.

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Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.2017.0112

Material and Methods

Data of 497 patients with epithelial EC who underwent at least total abdominal hysterectomy and bilateral salpingo-oophorectomy between January 2005 and January 2016 in our clinic were reviewed whose results of complete blood counts were accessible. Data were obtained from the institution's electronic database. The presence of secondary malignancy, having uterine sarcoma, and receiving neo-adjuvant chemotherapy were exclusion criteria of the study. Patients with any infectious disease or thromboembolism during the preoperative evaluation do not undergo elective surgery in our clinic. Accordingly, infectious and thromboembolism conditions were also excluded. Institutional review board approval was obtained from Etlik Zübeyde Hanım Women's Diseases Training and Research Hospital before the study (2016; 206/16).

The surgical staging criteria of the International Federation of Gynecology and Obstetrics (2009) for EC (12) was used to determine the stage of disease. The largest tumor diameter in the uterus was accepted as the tumor size. Hematologic indices were calculated using an automated hematology analyzer system (ADVIA 2120, Siemens® Healthcare, Germany). Preoperative complete blood counts including absolute count of leucocytes, neutrophils (N), lymphocytes (L), platelets (P) and monocytes (M) were collected. Parameters for ratios were constructed as follows: (i) N/L, neutrophil count divided by the lymphocyte count; (ii) P/L, platelet count divided by the lymphocyte count; (iii) L/M, lymphocyte count divided by the monocyte count; (iv) NM/L, neutrophil count plus monocyte count divided by the lymphocyte count and, (v) PNM/L, the sum total counts of platelets, neutrophils, and monocytes divided by the lymphocyte count.

Patients who had complete clinical response to their initial treatment were followed up with pelvic examinations and abdomen-pelvic ultrasonography quarterly in the first two years, semi-annually for up to five years, and annually thereafter. Annual chest X-rays and thoracic and/or abdominal computed tomography if needed were performed during the follow-up. Disease-free survival (DFS) was defined as the time interval from initial surgery to recurrence of disease. The period from surgery to death because of the disease (except in the first month after surgery) or last visit was defined as overall survival (OS).

Descriptive statistics are expressed as number/percentage for categorical variables and median (minimum-maximum) or mean ± standard deviation for continuous variables. The statistical significance of the demographic and clinic-pathologic parameters was evaluated using the chi-square test, Student's t-test, and the Mann-Whitney U test. Survival on categorical variables was analyzed using the Kaplan–Meier method and the log-rank test was used to identify significant differences between groups. Multivariate analysis was performed using a Cox proportional hazards model that included variables (p-value <0.05) in the univariate analysis. The Statistical Package for the Social Sciences (SPSS version 11.5) was used in the analysis. P values less than 0.05 were considered to be statistically significant.

Results

The median age of the entire cohort at diagnosis was 58 years (range, 29-92 years). Clinical and histopathologic findings, and values of complete blood counts of the entire cohort are shown in detail in Table 1. Adjuvant therapy was administered to 123 (25.7%) patients as a radiotherapy and/or chemotherapy. The mean time between analysis of the complete blood count and operation was 8±6 days.

Non-endometrioid–type tumors and deep myometrial invasion were associated with significantly high P/L and high PNM/L. Advanced stage (≥ stage 2) and cervical stromal invasion were only related with low L/M. Although P/L, NM/L, N/L, and PNM/L were significantly high, L/M was significantly low in the presence of uterine serosal or ovarian involvement. P/L, NM/L, N/L and PNM/L were significantly high in the presence of lymphovascular space invasion (LVSI) and omental metastasis. The association between rates of complete blood counts and histopathologic findings are detailed in Table 2.

Only L/M was associated with the presence of pelvic or para-aortic lymph node metastasis. There were statistically significant relations between low L/M and pelvic lymph node metastasis, and para-aortic lymph node metastasis. According to this finding, when the median value of L/M (5.46) was accepted as a cut-off value, low L/M (≤5.46) was significantly related with the presence of pelvic lymph node metastasis ($p=0.031$), but not related with para-aortic lymph node metastasis ($p=0.087$).

The median follow-up time was 24 months (range, 1-129 months). Recurrence occurred in 34 (7%) patients during the follow-up period. The median recurrence time was 10 months (range, 1-56 months). Eighteen (3.7%) patients died of the disease. In all, 5-year DFS and 5-year OS were 86.5% and 94%, respectively. As shown in Table 3, non-endometrioid–type, advanced stage, high-grade, deep myometrial invasion, serosal involvement, cervical stromal invasion, LVSI, adnexal involvement, presence of lymph node metastasis, and omental metastasis were associated with worse DFS and OS.

The cut-off value was determined as 168 for P/L, 171 for PNM/L, 2.23 for NM/L, 5.46 for L/M, and 2.06 for N/L as the best value to differentiate between patients' survival in the entire cohort. Therefore, values were categorized as high and low levels according to their cut-off values. There were no statistically

Table 1. Findings of clinical, histopathologic, and complete blood count of the entire cohort

Clinical and histopathologic findings		**n (%)**
Histologic type	Endometrioid adenocarcinoma	435 (87.5)
	Clear cell adenocarcinoma	14 (2.8)
	Serous adenocarcinoma	20 (4.0)
	Mucinous adenocarcinoma	8 (1.6)
	Mixed type adenocarcinoma	17 (3.4)
	Undifferentiated adenocarcinoma	2 (0.4)
	Not reported	1 (0.2)
Stage	1	381 (76.7)
	2	35 (7.0)
	3A	18 (3.6)
	3B	1 (0.2)
	$3C_1$	16 (3.2)
	$3C_2$	27 (5.4)
	4	19 (3.8)
FIGO grade	Grade 1	296 (59.9)
	Grade 2	117 (23.7)
	Grade 3	81 (16.4)
	Not reported	3 (0.6)
Depth of myometrial invasion	<1/2	353 (71.0)
	≥1/2	144 (29.0)
Uterine serosal invasion	No	478 (96.2)
	Yes	19 (13.8)
Cervical stromal invasion	No	426 (85.7)
	Yes	71 (14.3)
Lympho-vascular space invasion	Negative	412 (82.9)
	Positive	85 (17.1)
Adnexal metastasis	Negative	469 (94.4)
	Positive	27 (5.4)
	Not reported	1 (0.2)
Omental metastasis	Negative	482 (97.0)
	Positive	15 (3.0)
Lymphadenectomy	No	199 (40.1)
	Yes	298 (59.9)
Lymphatic Metastasis[¥]	No	242 (81.2)
	Yes	56 (18.8)
Presence of recurrence	No	450 (93.0)
	Yes	34 (7.0)
Exitus	No	470 (96.3)
	Yes	18 (3.7)

Findings of complete blood count		
	Mean ± standard deviation	**Median (minimum-maximum)**
Platelet-to-lymphocyte ratio (P/L)	145.19±64.45	130.6 (39.5-615.8)
[Neutrophil + Monocyte]-to-lymphocyte ratio (NM/L)	2.67±2.21	2.2 (0.47-32)
[Platelet + Neutrophil + Monocyte]-to-lymphocyte ratio (PNM/L)	147.85±65.95	133 (41-647.8)
Lymphocyte-to-monocyte ratio (L/M)	5.67±2.24	5.46 (0.25-25.1)
Neutrophil-to-lymphocyte ratio (N/L)	2.45±2.12	2.05 (0.32-31)

[¥]Among the patients who underwent lymphadenectomy; FIGO: International Federation of Gynecology and Obstetrics

significant associations between preoperative ratios and DFS (Table 3). In the univariate analysis, both high preoperative P/L (>168) and PNM/L (>171) were significantly related with worse OS (Figure 1, 2). High P/L and PNM/L were related with a hazard ratio for death of 3.20 [95% CI: (1.27-8.07); p=0.014] and 3.25 [95% CI: (1.29-8.20); p=0.012], respectively (Table 3). According to these findings, because of the strong inter-relationship among the variables, two different models were created for multivariate analysis (Table 4). In the multivariate analysis, both high P/L (>168) and high PNM/L (>171) were related with a statistically significant hazard ratio for death of 2.91 [95% CI: (1.15-7.36); p=0.024] and 2.93 [95% CI: (1.16-7.40); p=0.023], respectively.

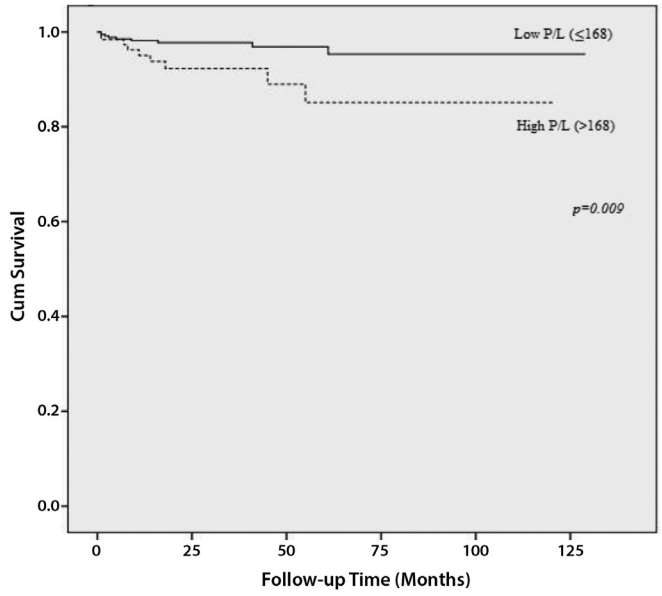

Figure 1. Association between overall survival and platelet-to-lymphocyte ratio
P/L: Platelet-to-lymphocyte ratio

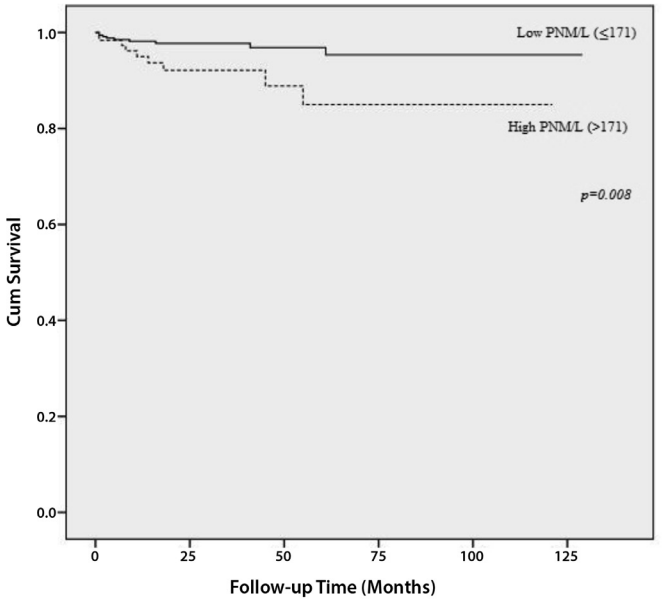

Figure 2. Association between overall survival and platelet/neutrophil/monocyte-to-lymphocyte ratio
PNM/L: Platelet/neutrophil/monocyte-to-lymphocyte ratio

Discussion

The key findings of our study are that both high P/L and high PNM/L were significantly related with worse OS and independent prognostic factors for OS. However, none of the inflammatory ratios could predict DFS.

Although EC is the most common gynecologic cancer, controversies continue with regard the extent of surgery, indications of lymphadenectomy, and criteria for the necessity of adjuvant therapy. Additionally, there are still no markers to give distinct prognostic information in EC. Intraoperative and postoperative pathology results are used to make decisions on those issues. Nevertheless, having a preoperative marker would provide more advantages such as increasing the accuracy of intraoperative decisions, avoiding overtreatment, preventing unnecessary adjuvant therapy, and providing more accurate information to patients about the management of their disease and prognosis.

Recent studies have focused on the prognostic role of the systemic manifestation of inflammatory cells in malignancies because one of the pathways of carcinogenesis is based on the inflammatory mechanism (1). The basic explanations for this argument are as follows; (1) neutrophilia and monocytosis are components of the proinflammatory process and are related with malignant cell proliferation, tumor-related angiogenesis and metastases, (2) thrombocytosis is explained by the paraneoplastic phenomenon that arises from tumor secretion of the proinflammatory cytokine interleukin-6, which increases thrombopoietin, but this mechanism is still not clear, (3) lymphocytes, which are an important component of host immunity, play a significant role in the anti-tumor immunologic reaction by inhibiting both proliferation and migration of tumor cells and inducing apoptosis (13,14).

Lymphocytopenia, neutrophilia, thrombocytosis or monocytosis are associated with poor prognosis in endometrial cancer (15). However, the togetherness of these inflammatory parameters rather than a single effect of each of these is the important point in carcinogenesis. Therefore, recent studies have focused on the ratios of complete blood counts for prognostic information, prediction of pathologic features, and survival. Although Wang et al. (16) found that cervical stromal invasion in EC was significantly related with high values of both P/L and N/L, Haruma et al. (17) reported this association for only P/L. In addition, Haruma et al. (17) determined that deep myometrial invasion, advanced stage, ovarian metastasis, non-

Table 2. Associations between clinical-histopathologic features and ratios of complete blood counts

Factors		P/L		NM/L		PNM/L		L/M		N/L	
	n (%)	Median (minimum-maximum)	p value	Median (minimum-maximum)	p value	Median (minimum-maximum)	p value	Median (minimum-maximum)	p value	Median (minimum-maximum)	p value
Histologic type											
Endometrioid	435 (87.7)	128.64 (48.78-615.82)	**0.001***	2.19 (0.47-32.00)	0.080	130.65 (50.18-647.82)	**0.001***	5.50 (0.82-25.10)	0.148	2.02 (0.32-31.0)	0.115
Non-endometrioid	61 (12.3)	154.76 (39.56-421.79)		2.52 (0.78-8.18)		157.43 (41.10-427.82)		5.23 (0.26-9.71)		2.29 (0.60-7.71)	
Stage											
Stage 1	381 (76.7)	129.70 (39.56-615.82)	0.053	2.19 (0.47-32.00)	0.065	131.48 (41.10-647.82)	0.051	5.61 (0.82-25.10)	**0.011***	2.02 (0.32-31.0)	0.092
Stage 2≤	116 (23.3)	142.80 (63.94-421.79)		2.33 (0.97-16.20)		145.35 (64.94-427.82)		5.07 (0.26-12.48)		2.12 (0.49-15.6)	
Grade											
1	296 (59.9)	129.30 (48.78-615.82)	0.127	2.17 (0.78-32.00)	0.092	131.39 (50.18-647.82)	0.121	5.48 (1.00-25.10)	0.059	1.9 (0.49-31)	0.124
2	117 (23.7)	128.64 (54.82-406.78)		2.27 (0.47-16.20)		130.30 (55.93-422.98)		5.70 (1.10-12.48)		2.07 (0.32-15.6)	
3	81 (16.4)	146.67 (39.56-421.79)		2.43 (0.82-11.08)		148.61 (41.10-427.82)		5.17 (0.26-9.26)		2.2 (0.63-10)	
Depth of myometrial invasion											
<1/2	353 (71.0)	127.35 (39.56-615.82)	**0.003***	2.23 (0.47-32.00)	0.684	129.71 (41.10-647.82)	**0.004***	5.55 (0.26-25.10)	0.073	2.06 (0.32-31)	0.728
≥1/2	144 (29.0)	149.65 (48.78-406.78)		2.19 (0.78-16.20)		151.90 (50.18-422.98)		5.29 (0.82-12.48)		2.00 (0.49-15.6)	
Uterine serosal invasion											
Negative	478 (96.2)	129.79 (39.56-615.82)	**<0.001***	2.21 (0.47-32.00)	**0.018***	131.94 (41.10-647.82)	**<0.001***	5.50 (0.26-25.10)	**0.003***	2.03 (0.32-31)	**0.022***
Positive	19 (3.8)	190.63 (96.79-406.78)		2.64 (1.56-16.20)		192.46 (99.43-422.98)		3.96 (1.97-9.26)		2.46 (1.45-15.6)	
Lymphovascular space invasion											
Negative	411 (82.9)	130.05 (39.56-615.82)	**0.045***	2.19 (0.47-32.00)	**0.010***	132.20 (41.10-647.82)	**0.044***	5.54 (1.00-25.10)	0.074	2.02 (0.32-31)	**0.015***
Positive	85 (17.1)	151.16 (64.09-421.79)		2.47 (1.12-16.20)		154.01 (65.50-427.82)		5.09 (0.26-11.56)		2.22 (1.00-15.6)	
Cervical stromal invasion											
Negative	426 (85.7)	130.33 (39.56-615.82)	0.239	2.19 (0.47-32.00)	0.102	132.96 (41.10-647.82)	0.235	5.55 (0.82-25.10)	**0.036***	2.02 (0.32-31)	0.153
Positive	71 (14.3)	136.11 (64.09-421.79)		2.38 (0.97-16.20)		137.53 (65.50-427.82)		4.88 (0.26-11.56)		2.13 (0.73-15.6)	
Ovarian metastasis											
Negative	472 (95.0)	129.79 (39.56-315.82)	**0.001***	2.20 (0.47-32.00)	**0.028***	131.94 (41.10-647.82)	**0.001***	5.52 (0.26-25.10)	**0.020***	2.03 (0.32-31)	**0.032***
Positive	25 (5.0)	175.26 (80.44-406.78)		2.60 (1.39-16.20)		178.68 (81.84-422.98)		4.84 (1.97-9.26)		2.29 (1.27-15.6)	
Tubal metastasis											
Negative	478 (96.2)	130.38 (39.56-615.82)	0.259	2.22 (0.47-32.00)	0.380	133.02 (41.10-647.82)	0.265	5.47 (0.26-25.10)	0.360	2.03 (0.32-31)	0.357
Positive	19 (3.8)	154.55 (71.26-283.48)		2.60 (0.97-6.30)		158.74 (72.67-289.78)		5.00 (2.25-11.92)		2.29 (0.69-5.8)	
Pelvic lymph node metastasis											
Negative	251 (84.2)	131.48 (48.78-406.78)	0.117	2.23 (0.47-16.20)	0.114	133.91 (50.18-422.98)	0.112	5.44 (0.82-11.92)	**0.018***	2.06 (0.32-15.6)	0.180
Positive	47 (15.8)	156.36 (63.94-421.79)		2.60 (1.00-8.18)		158.92 (64.94-427.82)		4.65 (0.26-12.48)		2.29 (0.49-7.7)	

Table 2. Continued

Factors		P/L		NM/L		PNM/L		L/M		N/L	
	n (%)	Median (minimum-maximum)	p value	Median (minimum-maximum)	p value	Median (minimum-maximum)	p value	Median (minimum-maximum)	p value	Median (minimum-maximum)	p value
Paraaortic lymph node metastasis											
Negative	247 (87.3)	132.54 (48.78-406.78)	0.455	2.19 (0.47-16.20)	0.238	134.05 (50.18-422.98)	0.460	5.41 (0.82-11.92)	**0.022***	2.01 (0.32-15.6)	0.403
Positive	36 (12.7)	150.01 (63.94-421.79)		2.58 (1.00-8.18)		152.73 (64.94-427.82)		4.66 (0.26-12.48)		2.28 (0.32-7.7)	
Omental metastasis											
Negative	482 (97.0)	129.96 (39.56-615.82)	**0.001***	2.20 (0.47-32.00)	**0.042***	132.09 (41.10-647.82)	**0.001***	5.50 (0.26-25.10)	0.054	2.03 (0.32-31)	**0.047***
Positive	15 (3.0)	178.36 111.24-283.48)		2.62 (1.85-6.30)		180.58 (113.86-289.78)		5.00 (2.25-7.12)		2.36 (1.6-5.8)	
Presence of recurrence											
Negative	450 (93.0)	130.38 (39.56-615.82)	0.529	2.23 (0.47-32.00)	0.645	133.02 (41.10-647.82)	0.517	5.47 (0.82-25.10)	0.850	2.06 (0.32-31)	0.854
Positive	34 (7.0)	134.03 (64.09-421.79)		2.27 (1.16-14.50)		136.41 (65.50-427.82)		5.22 (0.26-10.00)		2.04 (1.04-13.5)	

L/M: Lymphocyte-to-monocyte; ratio; N/L: Neutrophil-to-lymphocyte ratio; NM/L: [Neutrophil plus Monocyte]-to-lymphocyte ratio; P/L: Platelet-to- lymphocyte ratio; PNM/L: [Platelet plus Neutrophil plus Monocyte]-to-lymphocyte ratio; *p<0.05= statistical significance

endometrial–type tumors were related with both high P/L and N/L. Only one study to date also evaluated L/M in EC; Cummings et al. (18) showed that although both high P/L and N/L were associated with advanced stage and LVSI, low L/M was only related with advanced stage. In spite of that, Kurtoglu et al. (19) reported that neither N/L nor P/L predicted stage or LVSI in EC. In our study, the significant associations between pathologic findings of EC and ratios were as follows; non-endometrioid–type tumor and deep myometrial invasion were associated with high P/L and PNM/L; advanced stage and cervical stromal invasion were only related with low L/M; presence of LVSI was associated with P/L, NM/L, N/L, and PNM/L; all ratios were related with uterine serosal and ovarian involvement.

Clinically, counts of these cells in the blood can have a role in the prediction of metastatic lymph nodes in EC. Matsuo et al. (20) found that elevated monocyte counts were significantly related with the presence of metastasis in pelvic lymph nodes in EC. Both P/L and N/L were found significantly high in the presence of lymph node metastasis in EC (17,18,21). Cummings et al. (18) determined that both P/L and N/L but not L/M were related with metastatic lymph nodes. In our study, only L/M was associated with metastatic pelvic or para-aortic lymph nodes. L/M was significantly low in patients with either pelvic or paraaortic lymph node metastasis. This finding can be accounted for by the important role of T-lymphocytes in inhibiting the migration of tumor cells and with the responsibility of neutrophils and especially monocytes in angiogenesis, but the role of thrombocytes is still not clear for tumor angiogenesis or migration (13,20).

The ratios, including complete blood counts, can also provide survival and prognostic information for solid tumors. High P/L, high N/L, and low L/M were found to be related with worse OS, cancer-specific survival (CSS) or DFS in solid tumors (7,22,23). A limited number of studies have discussed this issue in EC. Takahashi et al. (24) determined that elevated N/L was significantly associated with shorter OS in a univariate analysis, but no statistically significant relationship was found in multivariate analysis. Haruma et al. (17) evaluated the relation of P/L and N/L with survival and found that only P/L was an independent factor for OS and none of these was independently associated with DFS. Cummings et al. (18) reported that P/L and N/L but not L/M were independent prognostic factors for OS and CSS. Cut-off values that predicted survival varied between 150 and 300 for P/L and ranged from 2 to 5 for N/L (7,17,18,23). In our study, only high P/L and high PNM/L were associated with worse survival and both were independent prognostic factors for OS. None of the ratios was associated with DFS. The cut-off values of PNM/L and P/L for prediction of survival were 171 and 168, respectively.

The major limitation of our study is the retrospective design, which can cause difficulties in controlling for potential

Table 3. Univariate analysis of histopathologic features and ratios of complete blood counts for disease-free survival and overall survival

		Disease-free survival				Overall survival			
		5-year (%)	p value	HR (95% CI)	p value	5-year (%)	p value	HR (95% CI)	p value
Histologic type	Endometrioid	87.8	0.004	Reference	0.006	96.7	<0.001	Reference	<0.001
	Non-endometrioid	74.9		3.07 (1.38-6.82)		69.9		9.12 (3.58-23.24)	
Stage	Stage 1	92.9	<0.001	Reference	<0.001	98.6	<0.001	Reference	<0.001
	Stage 2≤	62.5		5.95 (3.00-11.79)		77.2		9.82 (3.50-27.56)	
Grade	1	91.0	<0.001	Reference		96.9	<0.001	Reference	
	2	85.2		1.66 (0.69-4.00)	0.261	97.1		0.44 (0.05-3.64)	0.445
	3	69.2		4.43 (2.05-9.58)	<0.001	77.3		7.54 (2.78-20.43)	<0.001
Depth of myometrial invasion	<1/2	91.2	<0.001	Reference	<0.001	96.5	0.023	Reference	0.030
	≥1/2	73.5		3.75 (1.90-7.39)		87.0		2.79 (1.10-7.03)	
Serosal involvement	Negative	87.0	0.001	Reference	0.004	94.9	<0.001	Reference	<0.001
	Positive	None		5.87 (1.77-19.50)		None		14.48 (4.54-46.16)	
Lympho-vascular space invasion	Negative	88.7	<0.001	Reference	<0.001	95.9	0.001	Reference	0.002
	Positive	74.8		3.62 (1.81-7.23)		83.9		4.41 (1.74-11.19)	
Cervical invasion	Negative	89.1	0.013	Reference	0.016	95.7	<0.001	Reference	<0.001
	Positive	71.2		2.54 (1.19-5.45)		82.5		5.32 (2.10-13.50)	
Ovarian involvement	Negative	87.5	<0.001	Reference	<0.001	95.2	<0.001	Reference	<0.001
	Positive	69.5		4.94 (2.04-11.96)		69.4		7.74 (2.75-21.76)	
Tubal involvement	Negative	87.2	<0.001	Reference	0.002	94.8	<0.001	Reference	0.834
	Positive	72.5		5.39 (1.87-15.50)		68.9		7.04 (1.20-24.76)	
Omental metastasis	Negative	87.9	<0.001	Reference	<0.001	96.0	<0.001	Reference	0.002
	Positive	None		11.1 (4.23-29.39)		None		0.68 (0.23-2.05)	
Pelvic lymph node metastasis	Negative	86.7	<0.001	Reference	<0.001	93.1	0.001	Reference	0.003
	Positive	50.3		0.25 (0.11-0.56)		70.4		4.3 (1.63-11.3)	
Para-aortic lymph node metastasis	Negative	84.9	<0.001	Reference	<0.001	94.2	<0.001	Reference	<0.001
	Positive	48.9		6.04 (2.75-13.26)		46.2		8.28 (3.16-21.65)	
P/L	Low (≤168)	87.3	0.685	Reference	0.686	97.7	0.009*	Reference	0.014*
	High (>168)	83.8		1.17 (0.55-2.51)		85.1		3.20 (1.27-8.07)	
NM/L	Low (≤2.23)	85.6	0.789	Reference	0.790	96.4	0.266	Reference	0.272
	High (>2.23)	87.5		1.10 (0.56-2.15)		91.3		1.70 (0.66-4.39)	

Table 3. Continued

		Disease-free survival				Overall survival			
		5-year (%)	p value	HR (95% CI)	p value	5-year (%)	p value	HR (95% CI)	p value
PNM/L	Low (≤171)	87.3	0.656	Reference	0.657	96.9	0.008*	Reference	0.012*
	High (>171)	83.7		1.19 (0.56-2.55)		85.0		3.25 (1.29-8.20)	
L/M	Low (≤5.46)	84.6	0.570	1.22 (0.62-2.38)	0.571	95.1	0.287	1.66 (0.64-4.29)	0.293
	High (>5.46)	88.3		Reference		97.7		Reference	
N/L	Low (≤2.06)	85.6	0.788	Reference	0.788	96.4	0.265	Reference	0.271
	High (>2.06)	87.5		1.10 (0.56-2.15)		91.3		1.70 (0.66-4.40)	

L/M: Lymphocyte-to-monocyte; ratio; N/L: Neutrophil-to-lymphocyte ratio; NM/L: [Neutrophil plus Monocyte]-to- lymphocyte ratio; P/L: Platelet-to-lymphocyte ratio; PNM/L: [Platelet plus Neutrophil plus Monocyte]-to-lymphocyte ratio; HR: Hazard ratio; CI: Confidence interval; *p<0.05= statistical significance

Table 4. Multivariate analysis of P/L and PNM/L for overall survival

	Hazard ratio (95% CI)	p value
Model 1		
Stage	9.39 (3.34-26.40)	<0.001*
P/L	2.91 (1.15-7.36)	0.024*
Model 2		
Stage	9.34 (3.32-26.28)	<0.001*
PNM/L	2.93 (1.16-7.40)	0.023*

P/L: Platelet-to-lymphocyte ratio; PNM/L: [Platelet plus Neutrophil plus Monocyte]-to-lymphocyte ratio; *p<0.05= Statistical significance

confounding factors. To the best our knowledge, the present study is the first to evaluate the relationship between PNM/L and survival for EC. Furthermore, a considerable number of patients with only epithelial endometrial cancer in a single center was evaluated in our study.

In conclusion, the P/L and PNM/L ratios were associated with worse OS and also an independent prognostic factor for OS. However, there is a need for multi-center randomized controlled studies to make distinct conclusions. The togetherness of the inflammatory parameters has an important role in carcinogenesis. Therefore, future studies should focus on the role of combined ratios in EC and create a new risk model using ratios such as P/L and PNM/L.

Ethics Committee Approval: *Institutional review board approval was obtained from Etlik Zübeyde Hanım Women's Diseases Training and Research Hospital before the study (2016; 206/16).*

Informed Consent: *All patients signed an informed consent that allows the institution to use their clinical data.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Concept - G.K.C., O.T.; Design - G.K.C., A.K.; Supervision - D.B., T.T.; Materials - İ.K., S.S., S.Y.E.; Writer - G.K.C.*

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

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

References

1. Elinav E, Nowarski R, Thaiss CA, Hu B, Jin C, Flavell RA. Inflammation-induced cancer: crosstalk between tumours, immune cells and microorganisms. Nat Rev Cancer 2013; 13: 759-71.
2. Acet H, Ertas F, Akıl MA, Özyurtlu F, Polat N, Bilik MZ, et al. Relationship Between Hematologic Indices and Global Registry of Acute Coronary Events Risk Score in Patients With ST-Segment Elevation Myocardial Infarction. Clin Appl Thromb Hemost 2016; 22: 60-8.
3. Kara A, Guven M, Yilmaz MS, Demir D, Elden H. Are neutrophil, platelet and eosinophil-to-lymphocyte ratio and red blood cell distribution width can be used for nasal polyposis? Eur Arch Otorhinolaryngol 2018;275:409-13.
4. Guclu M, Faruq Agan A. Association of Severity of Helicobacter pylori Infection with Peripheral Blood Neutrophil to Lymphocyte Ratio and Mean Platelet Volume. Euroasian J Hepatogastroenterol 2017; 7: 11-6.
5. Njølstad TS, Engerud H, Werner HM, Salvesen HB, Trovik J. Preoperative anemia, leukocytosis and thrombocytosis identify aggressive endometrial carcinomas. Gynecol Oncol 2013; 131: 410-5.
6. Li MX, Liu XM, Zhang XF, Zhang JF, Wang WL, Zhu Y, et al. Prognostic role of neutrophil-to-lymphocyte ratio in colorectal cancer: a systematic review and meta-analysis. Int J Cancer 2014; 134: 2403-13.
7. Templeton AJ, McNamara MG, Šeruga B, Vera-Badillo FE, Aneja P, Ocaña A, et al. Prognostic Role of Neutrophil-to-Lymphocyte Ratio in Solid Tumors: A Systematic Review and Meta-Analysis. J Natl Cancer Inst 2014; 106: 124.

8. Kawata A, Une Y, Hosokawa M, Uchino J, Kobayashi H. Tumor infiltrating lymphocytes and prognosis of hepatocellular carcinoma. Jpn J Clin Oncol 1992; 22: 256-63.
9. Cho H, Hur HW, Kim SW, Kim SH, Kim JH, Kim YT, et al. Pre-treatment neutrophil to lymphocyte ratio is elevated in epithelial ovarian cancer and predicts survival after treatment. Cancer Immunol Immunother 2009; 58: 15-23.
10. Teng JJ, Zhang J, Zhang TY, Zhang S, Li BS. Prognostic value of peripheral blood lymphocyte-to-monocyte ratio in patients with solid tumors: a meta-analysis. Onco Targets Ther 2016; 9: 37-47.
11. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 2013; 49: 1374-403.
12. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynaecol Obstet 2009; 105: 103-4.
13. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature 2008; 454: 436-44.
14. Stone RL, Nick AM, McNeish IA, Balkwill F, Han HD, Bottsford-Miller J, et al. Paraneoplastic thrombocytosis in ovarian cancer. N Engl J Med 2012; 366: 610-8.
15. Matsuo K, Hom MS, Moeini A, Machida H, Takeshima N, Roman LD, et al. Significance of monocyte counts on tumor characteristics and survival outcome of women with endometrial cancer. Gynecol Oncol 2015; 138: 332-8.
16. Wang D, Yang JX, Cao DY, Wan XR, Feng FZ, Huang HF, et al. Preoperative neutrophil-lymphocyte and platelet-lymphocyte ratios as independent predictors of cervical stromal involvement in surgically treated endometrioid adenocarcinoma. Onco Targets Ther 2013; 6: 211-6.
17. Haruma T, Nakamura K, Nishida T, Ogawa C, Kusumoto T, Seki N, et al. Pre-treatment neutrophil to lymphocyte ratio is a predictor of prognosis in endometrial cancer. Anticancer Res 2015; 35: 337-43.
18. Cummings M, Merone L, Keeble C, Burland L, Grzelinski M, Sutton K, et al. Preoperative neutrophil:lymphocyte and platelet: lymphocyte ratios predict endometrial cancer survival. Br J Cancer 2015; 113: 311-20.
19. Kurtoglu E, Kokcu A, Celik H, Sari S, Tosun M. Platelet Indices May be Useful in Discrimination of Benign and Malign Endometrial Lesions, and Early and Advanced Stage Endometrial Cancer. Asian Pac J Cancer Prev 2015; 16: 5397-400.
20. Matsuo K, Yessaian AA, Lin YG, Pham HQ, Muderspach LI, Liebman HA, et al. Predictive model of venous thromboembolism in endometrial cancer. Gynecol Oncol 2013; 128: 544-51.
21. Suh DH, Kim HS, Chung HH, Kim JW, Park NH, Song Y, et al. Pre-operative systemic inflammatory response markers in predicting lymph node metastasis in endometrioid endometrial adenocarcinoma. Eur J Obstet Gynecol Reprod Biol 2012; 162: 206-10.
22. Nishijima TF, Muss HB, Shachar SS, Tamura K, Takamatsu Y. Prognostic value of lymphocyte-to-monocyte ratio in patients with solid tumors: A systematic review and meta-analysis. Cancer Treat Rev 2015; 41: 971-8.
23. Templeton AJ, Ace O, McNamara MG, Al-Mubarak M, Vera-Badillo FE, Hermanns T, et al. Prognostic role of platelet to lymphocyte ratio in solid tumors: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 2014; 23: 1204-12.
24. Takahashi R, Mabuchi S, Kawano M, Sasano T, Matsumoto Y, Kuroda H, et al. Prognostic significance of systemic neutrophil and leukocyte alterations in surgically treated endometrial cancer patients: a monoinstitutional study. Gynecol Oncol 2015; 137: 112-8.

Does progesterone have protective effects on ovarian ischemia-reperfusion injury?

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Abstract

Objective: The aim of the present study was to evaluate the effects of progesterone (PG) against ovarian ischemia-reperfusion (I/R) injury through the evaluation of biochemical and histopathologic parameters.

Material and Methods: Twenty-one female Wistar albino rats were divided into three groups. Group 1: Sham; group 2: I/R; group 3: I/R+PG (8 mg/kg). PG was administered intraperitoneally to the rats in group 3, 30 minutes before a detorsion operation. Ovarian I/R injury was evaluated in serum and tissue by using biochemical parameters including malondialdehyde (MDA), total antioxidant status (TAS), total oxidant status (TOS), oxidative stress index, neutrophil gelatinase-associated lipocalin (NGAL) and immunofluorescence staining by using a terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) assay.

Results: Serum and tissue TOS levels were significantly lower in group 3 than in group 2. Tissue TAS levels were higher in group 3 than in group 2 ($p<0.001$). NGAL and MDA levels were similar between the groups. Histologic score, including vascular congestion, hemorrhage, polymorphonuclear neutrophils, and interstitial edema, was higher in group 2. Pre-treatment with PG decreased the score, but this difference was not statistically significant. The number of apoptotic cells was higher in group 2 than in groups 1 and 3. The TUNEL-positive cell number decreased with PG in group 3.

Conclusion: Preoperative PG treatment might exert protective effects on ovarian I/R injury through its anti-apoptotic and antioxidative properties. (J Turk Ger Gynecol Assoc 2018; 19: 87-93)

Keywords: Ischemia-reperfusion, NGAL, progesterone

Received: 20 May, 2017 **Accepted:** 12 March, 2018

Introduction

Adnexal torsion is a serious cause of gynecologic emergency surgery, with a prevalence of 2.7%. Diagnosis and intervention are delayed because clinical findings in adnexal torsion are nonspecific. This can lead to a decrease in the patient's follicle reserve and infertility. Excision of the adnexa, detorsion of the pedicle, and evaluation of tissue perfusion are considered and conducted as the conservative approach today (1). After the detorsion procedure, there are increases in neutrophil infiltration and activation, production of nitric oxide and cytokines such as tumor necrosis factor, and superoxide radicals (SOR) in ovarian tissue. This condition, called ischemia-reperfusion (I/R) injury, causes more tissue damage than ischemia alone. Therefore, it has been suggested that the use of antioxidant pharmacologic agents during or prior to reperfusion may be beneficial in protecting against I/R injury (2).

Protective effects of progesterone on traumatized neurons, heart, and vascular tissues have been demonstrated. The focus of these studies is the suppressive effect of progesterone on the inflammatory process (3-6). It has been experimentally determined that progesterone reduces SOR formation

This study was presented as a poster presentation at the 2016 World Congress of the International Society of Gynecological Endocrinology (ISGE)

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Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.2017.0047

and prevents cellular damage through examining levels of malondialdehyde (MDA) and glutathione (GSH), which are lipid peroxidation products in the liver and kidney, after benzene-induced toxicity (7). Experimental studies have shown that PG suppresses SORs and their oxidative damage. It also has a protective effect against lipid peroxidation and cell membrane damage due to free radicals (8). It has been also shown in another study that progesterone reduces MDA and myeloperoxidase levels, significantly increases GSH and superoxide dismutase levels, and significantly suppresses apoptosis (9). All these studies suggest that progesterone may also have a protective effect on ovarian tissue.

This is the first experimental study to examine the effect of progesterone on ovarian I/R injury. For this purpose, we investigated whether progesterone caused changes in biochemical, histologic, and immunohistochemical markers in rat ovaries exposed to I/R.

Material and Methods

This study was conducted with the consent of the Animal Experiments Ethics Committee and "Principles of laboratory animal care" (NIH publication no: 86-23, revised 1985) were followed, as well as specific national laws where applicable. A total of 21 young adult female Wistar albino rats weighting 200-250 g were used in the study. The experimental animals were housed on a 12-hour light/dark schedule under a temperature of 21-22 °C with ad libitum feeding. Group 1: sham group (n=7); group 2: I/R, applied for 3 hours with torsion, and for 3 hours after detorsion, and saline intraperitoneally 30 minutes prior to detorsion (n=7); group 3: I/R+PG, administered for 3 hours with torsion, and for 3 hours after detorsion, and 8 mg/kg progesterone intraperitoneally 30 minutes prior to detorsion (n=7) (10). The rats were anesthetized using ketamine 75 mg/kg and xylazine 10 mg/kg intraperitoneally (11). They underwent laparotomy with a 2-cm midline incision and the right and left adnexa of all rats were torsioned for 3 hours, except for the control group. The torsion procedure was performed by rotating both adnexa 360 degrees clockwise. The torsioned adnexa was fixed to the abdominal wall muscles with 4/0 Vicryl, and the skin was also sutured with 3/0 Vicryl. Sham operations (placebo surgery) were performed on group 1, undergoing laparotomy only. Thirty minutes prior to detorsion, the rats in group 2 were injected with saline and the rats in group 3 were injected with progesterone intraperitoneally. At the end of the 3-hour torsion period, the rats were anesthetized again and underwent laparotomy via the same incision line. The detorsion procedure was then performed counterclockwise. At the end of the detorsion period, intracardiac blood samples were taken from all rats before they were sacrificed. After the rats were sacrificed, the right ovary was taken for biochemical analysis and the left ovary was taken for histopathologic analysis.

Biochemical analysis

Serum was separated by centrifuging whole blood at 825×g for 10 min and subsequently used for analyses of total protein, total antioxidant status (TAS), and total oxidant status (TOS) using commercially available kits in an autoanalyzer (Cobas Integra 800; Roche Diagnostics GmbH; Mannheim, Germany). Serum and ovarian TAS and TOS levels were measured spectrophometrically (PerkinElmer's Lambda 35 UV/Vis, USA) using a commercially available kit (Rel Assay Diagnostic, Turkey). The novel automated TAS method is based on antioxidants in the sample reducing dark blue-green colored 2, 2'-Azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) radical to the colorless reduced ABTS form. The TOS assay is based on oxidants present in the sample that oxidize the ferrous ion chelator complex to ferric ion (12). The assay was calibrated with hydrogen peroxide, and the results are expressed in terms of micromolar hydrogen peroxide equivalent per liter (μmol H_2O_2 Equiv./L) for serum and hydrogen peroxide equivalent per gram protein (μmol H_2O_2 Equiv./g protein) for ovarian extracts. The ratio of TOS to TAS was accepted as the OSI. In order to calculate this, the resulting unit of TAS was converted to μmol/L, and the OSI value was calculated using the following formula as previously published elsewhere (12):

OSI (arbitrary unit)=TOS (μmol H_2O_2 Equiv./L)/TAS (mmol Trolox equivalent/L)

Serum MDA levels were determined based on the spectrophotometric measurement of the product generated upon the reaction of MDA with thiobarbituric acid. The results are expressed as μmol/mL in serum and μmol/g protein in tissue. Serum neutrophil gelatinase-associated lipocalin (NGAL) measurement was conducted using SUNREDBIO-Human NGAL enzyme-linked immunosorbent assay kit 96 test according to guidelines in the kit guide.

Immunohistochemical analysis

After the rats were sacrificed, excised ovarian tissues were stored in 10% formaldehyde for fixation. The ovarian tissues were kept in fixation solution for 72 hours and then washed with running tap water. They were passed through graded alcohol series and cleared using xylol. Then they were embedded into paraffin and blocked. Sections of 5 μm were taken from the ovarian tissues and placed onto polylysine-coated laminas. Using a standard histologic follow-up method, the paraffin of the laminas were removed with xylol, and the laminas were passed through graded alcohol series (100%, 96%, 80%, 70%, 50%) and

washed with water. In order to determine the general histologic structure, the sections were stained using hematoxylin-eosin and Masson's trichrome, passed first through increasing alcohol series and then through xylol, and covered with a lamella using Entellan.

Follicular cell injury, hemorrhage, vascular congestion, and polymorphonuclear cell infiltration were evaluated in a histopathologic evaluation of ovarian injury. Semi-quantitative scoring was conducted using a value between 0-3 according to injury scoring of 0: no damage, 1: slightly damaged, 2: moderately damaged, and 3: severe (13).

A terminal deoxynucleotidyl transferase (TdT)-mediated dUTP nick end labeling (TUNEL) assay was used in order to determine apoptotic cells in all sections of tissues obtained at the end of the experiment. An ApopTag® Fluorescein *in situ* Apoptosis Detection Kit (EMD Millipore, Darmstadt, Germany) was used for staining. Ovarian tissues of 5-6 μm thickness were deparaffinized and rehydrated (absolute alcohol, 96%, 80%, 70%, 60%, and 50%), and then washed 3 times with PBS. Slides were incubated with proteinase K for 15 min, then washed with distilled water. The samples were treated with 3% hydrogen peroxide for 10 min to minimize endogenous peroxidase activity. The tissues were washed 3 times with PBS for 5 min each and then incubated with a TUNEL reaction mixture from the kit for 1 hour in humid and dark environment at 37 °C. The tissues were stained with contrast dye using 4',6-diamidino-2-phenylindole to observe the nuclei. All operations were performed in a humid chamber. The same procedures were conducted on the tissue used as a negative control but without adding TdT. The prepared samples were evaluated using a fluorescence microscope (Olympus BX51, Tokyo, Japan). To assess the number of TUNEL-positive apoptotic cells, at least five different areas were photographed on each tissue using a 40x lens. After the immunofluorescence staining procedure, positively-stained apoptotic cells were carefully counted using the Image J software program.

Statistical analysis

Statistical analyses were performed using SPSS v. 11.5. Data are shown as mean ± standard deviation, median (IQR) or median (minimum-maximum), as appropriate. For normally distributed data, the mean differences among groups were analyzed using one-way ANOVA and for the remaining data, the Kruskal-Wallis test was used for comparisons of the medians. A p-value less than 0.05 was considered statistically significant. When the p value from one-way ANOVA or Kruskal-Wallis test statistics were statistically significant, post hoc Tukey's honestly significant difference or Bonferroni-adjusted Mann-Whitney U test was used to specify which group significantly differed from the others.

Results

The serum TOS level was significantly higher in the I/R group compared with the sham group ($p<0.001$). The serum TOS level was found to be significantly lower in the I/R+PG group compared with the I/R group ($p<0.001$). The serum OSI level increased in the I/R group compared with the sham group, but decreased significantly in the group treated with progesterone ($p<0.001$) Serum MDA and NGAL levels decreased in the group treated with progesterone, although the differences were not statistically significant (Table 1).

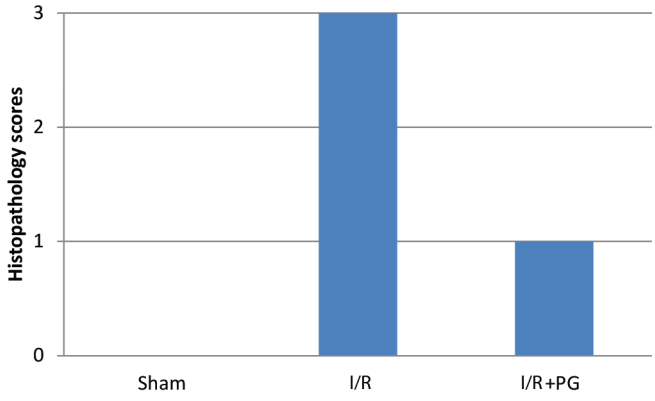
There was a statistically significant difference among groups in terms of tissue TOS levels; the tissue TOS level of I/R group was higher than in the sham group ($p<0.001$). Progesterone treatment was observed to result in a decrease in tissue TOS levels compared with the I/R group ($p<0.001$). The tissue TAS level was increased in the group treated with progesterone after I/R ($p<0.05$). The mean tissue OSI level was significantly higher in the I/R group compared with the sham and I/R+PG groups ($p<0.001$). The OSI level was decreased in the I/R+PG group compared with the I/R group ($p<0.001$) (Table 2).

There was a statistically significant difference between the groups in terms of histopathologic score. The median histopathology score of the I/R group was higher than that of the sham group ($p<0.001$). The histologic score was found to be lower in the I/R+PG group compared with the I/R group, although it was not statistically significant (Graphic 1). Considering apoptotic cell numbers, the number of ovarian TUNEL-positive cells in the I/R group was higher than in the sham group ($p<0.001$). In the group treated with progesterone,

Table 1. Biochemical (serum) measurements according to groups

	Sham (n=7)	I/R (n=7)	I/R+PG (n=7)	p value
MDA (mmol/L)	10.7±2.58	9.3±2.50	9.0±3.02	0.499†
NGAL (ng/mL)	7.8±0.74	8.1±1.01	7.2±1.63	0.379†
T-protein (g/L)	56.0 (9.00)	59.0 (10.00)	60.0 (3.00)	0.602‡
TAS (mmol Trolox equiv./L)	1.7±0.08	1.7±0.12	1.6±0.13	0.925†
TOS (mmol H_2O_2 Equiv./L)	6.8 (1.15)[a]	11.6 (2.71)[a,b]	6.7 (1.59)[b]	**<0.001**‡
OSI (arbitrary unit)	3.98 (1.09)[a]	7.16 (0.86)[a,b]	3.76 (0.78)[b]	**<0.001**‡

†: One-way ANOVA, ‡: Kruskal-Wallis test, [a]: Sham vs I/R ($p<0.001$), [b]: I/R vs I/R+PG ($p<0.001$), MDA: Malondialdehyde, NGAL: Neutrophil gelatinase-associated lipocalin, TAS: Total antioxidant status, TOS: Total oxidant status, OSI: Oxidative stress index, I/R: Ischemia-reperfusion, PG: Progesterone



Graphic 1. Histopathologic score in groups
I/R: Ischemia/reperfusion, PG: Progesterone

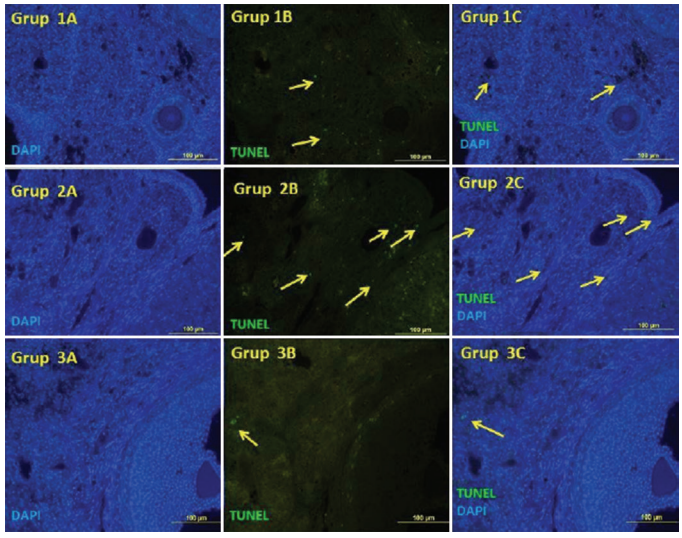


Figure 1. Apoptotic cells are stained with terminal deoxynucleotidyl TUNEL in groups. TUNEL-positive cells reflective green immunofluorescence. Positive apoptotic cells were counterstained with DAPI nuclear staining. There were many apoptotic cells in group 2. There were only a few TUNEL-positive cells in the ovaries of group 3 (Original magnification, 400x)
DAPI: 4',6-diamidino-2-phenylindole, TUNEL: Transferase-mediated dUTP nick end labeling

the number of TUNEL-positive cells decreased in the I/R group (Figure 1).

In the ovarian tissues of rats with I/R, normal histologic structure was deteriorated and there were pathologic findings such as interstitial edema and polymorphonuclear leukocyte infiltration. Congestion and diffuse hemorrhagic findings were also detected. The histologic structure was preserved in ovarian samples of rats in the I/R+PG group compared with those in the I/R group. In this group, less injury was noted in the follicles and the interstitial area.

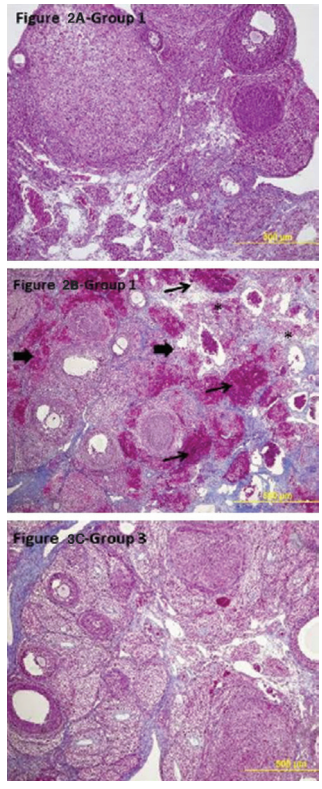


Figure 2. Light microscopic findings of the groups (100x, Original magnification, Masson trichrome). Ovarian sections in group 2 (I/R) showed severe damage, infiltration of polymorphonuclear leukocytes, vascular congestion, interstitial edema*, hemorrhage ➔ ➡
I/R: Ischemia/reperfusion

Table 2. Biochemical (tissue) measurements according to groups

	Sham (n=7)	I/R (n=7)	I/R+PG (n=7)	p value
MDA (mmol/g protein)	3.8 (0.83)	4.6 (2.94)	4.8 (1.30)	0.059†
NGAL (ng/mL)	6.0 (0.37)	6.2 (1.15)	5.1 (3.26)	**0.323**†
T-protein (g/L)	6.0 (3.00)[a]	7.0 (1.00)	11.0 (6.00)[a]	**0.025**†
TAS (mmol Trolox Equiv./g protein)	1.9 (0.32)	1.6 (0.42)[b]	2.0 (1.17)[b]	**0.026**†
TOS (mmol H_2O_2 Equiv./g protein)	12.2±1.36[c,d]	16.9±1.59[c,e]	8.7±0.69[d,e]	**<0.001**‡
OSI (arbitrary unit)	6.9±1.54[a,c]	10.3±1.87[c,e]	3.9±0.97[a,e]	**<0.001**‡

†: Kruskal Wallis test, ‡: One-way ANOVA, [a]: Sham vs I/R+PG (p=0.017), [b]: I/R vs I/R+PG (p=0.011), [c]: Sham vs I/R (p<0.001), [d]: Sham vs I/R+PG (p<0.001), [e]: I/R vs IR+PG (p<0.001), MDA: Malondialdehyde, NGAL: Neutrophil gelatinase-associated lipocalin, TAS: Total antioxidant status, TOS: Total oxidant status, OSI: Oxidative stress index, I/R: Ischemia-reperfusion, PG: Progesterone

Edema, vascular congestion, and polymorphonuclear leukocyte infiltration were found to be decreased in the interstitial area compared with the I/R group (Figure 2).

Discussion

Based on this experimental study, progesterone appears to play a protective role against I/R injury in ovarian torsion in rats. The mechanisms by which progesterone shows this effect are the suppression of apoptosis and decreased oxidative stress in both tissue and serum levels.

In this study, we demonstrated that progesterone shows a protective effect against ovarian I/R injury by reducing the number of apoptotic cells and this shows the anti-apoptotic effect of progesterone. Experimental studies have shown that oxidative damage mechanisms are suppressed with use of progesterone in cardiac tissue, brain tissue, and mitochondrial membrane (14). For instance, the protective effect of progesterone on neural tissue was demonstrated when progesterone was administered either 6, 24, and 48 hours after the onset of ischemia in rats with transient focal ischemia in the middle cerebral artery of the brain. The neuroprotective effect of progesterone was also investigated in rats with traumatic brain injury, and progesterone reduced edema even when it was administered 24 hours after trauma (3). Allen et al. (4) revealed the protective activity of progesterone on retinal ischemia and cerebral ischemia. Morrissy et al. (5) showed that progesterone provides a cardioprotective effect by increasing expression of the anti-apoptotic gene Bcl-xl. Sandhi et al. (6) indicated that progesterone treatment introduced renoprotective effects by reducing lipid peroxidation through increased GSH and catalase effect in rats.

We investigated the level of MDA, which is an important marker that has been efficiently used to assess ovarian reperfusion injury in previously published studies. Arikan et al. (15) showed that MDA levels significantly increased in the I/R group but then significantly decreased after tadalafil administration. Sayar et al. (16) found that MDA level increased in their I/R group but decreased in the I/R+ozone, I/R+ellegalic acid, and I/R+ozone+ellegalic acid groups. In another study, the MDA level was detected to increase in the I/R group compared with the I/R+ethyl pyruvate group (17). Taskin et al. (18) found no significant difference between tissue and serum MDA levels in sham, I/R, and I/R+2-amino ethoxy diphenyl borate (2-ABP) groups in their study with 2-APB. However, tissue MDA levels were lower in the group treated with 2-APB, although it was not statistically significant. This discrepancy might be attributed to several factors such as inadequate duration of I/R, variations in MDA measurement techniques or use of an inadequate progesterone dose.

In this study, using progesterone in I/R injury decreased serum and tissue TOS and OSI levels but increased tissue TAS level. The results can be attributed to the anti-oxidant effects of progesterone. It has been indicated in some studies that tissue produces antioxidants excessively in response to oxidative stress in order to control unwanted ROS. For this reason, we also included TAS, TOS, and OSI parameters besides MDA to detect I/R injury. The values obtained in the present study was similar to those in the literature. In an ovarian I/R injury model, curcumin treatment caused no change in TAS levels but caused a decrease in TOS level (19). Taskin et al. (18) showed that tissue and serum TOS and OSI levels increased in the I/R group but decreased after treatment with 2-APB.

The expression of NGAL after renal ischemia was shown to increase by Zhao et al. (20). Gong et al. (21) revealed that NGAL used the BCL2\BAX pathway in renal tubular epithelial cell apoptosis. Zang et al. (22) demonstrated that NGAL reduced apoptotic tubular cells and showed this renoprotective effect inhibiting caspase-3 activation. In the current study, the mean serum and tissue NGAL levels were statistically similar between the groups. However, tissue and serum NGAL levels increased in the I/R group compared with the sham group and decreased in the I/R+PG group, although they were not statistically significant. This finding could be due to an inadequate duration of I/R, variations in NGAL measurement techniques or the relatively small study cohort.

It was observed in a study using osajin in ovarian I/R injury that each dose of osajin reduced polymorphonuclear leukocyte infiltration at different levels (23). Borekçi et al. (24) found mononuclear cell infiltration, vascular dilatation, perivascular edema, and necrotic changes histopathologically in the I/R group in a study conducted using dehydroepiandrosterone. Haftacı et al. (25) evaluated edema, congestion, hemorrhage, and cohesion loss in their study conducted using vitamin C and selenium, and observed a reduction of cellular damage in the group administered vitamin C and selenium compared with the I/R group. Gungor et al. (26) showed in a study using omegaven that congestion, hemorrhage, and edema parameters were similar between the groups given high-dose omegaven and the sham group. In this study, we found a deterioration of normal histologic structure and pathologic findings such as interstitial edema and polymorphonuclear leukocyte infiltration in ovarian tissues of rats with I/R. Congestion and diffuse hemorrhagic findings were also found. The histologic structure was preserved in ovarian samples of rats with I/R+PG compared with the I/R group. In this group, less injury was noted in the follicles and the interstitial area. Histologic scores were found to be consistent with these findings.

In our study, the number of apoptotic cells observed as TUNEL-positive in the ovary was statistically higher in the I/R group compared with the sham group. On the other hand, the number of apoptotic cells decreased in the group given progesterone because it reflects the anti-apoptotic effects of progesterone. In an ovarian torsion experimental study using a TUNEL assay, Taskin et al. (18) showed that apoptosis in ovarian tissue was reduced by 2-APB treatment. Sahin Ersoy et al. (27) evaluated the effects of N-acetylcysteine and enoxaparin on ovarian I/R injury. Using a TUNEL assay, the authors demonstrated that both molecules reduced the number of apoptotic cells, and found that N-acetylcysteine provided greater reduction. Gencer et al. (11) observed in a study using quercetin that TUNEL-positive cell numbers and caspase-3 values decreased in a group treated with quercetin. Progesterone has been shown to inhibit apoptosis in many studies in the literature. Espinosa-García et al. (28) demonstrated with the TUNEL method that there was a decrease in DNA fragmentation and caspase-3 level, an indirect indicator of apoptosis, in hippocampal cerebral ischemia treated with progesterone. Ishrat et al. (29) showed that progesterone used in ischemic brain injury treatment reduced apoptosis in cerebral ischemia using phosphoinositol kinase/kinase B pathway.

There are some limitations to this study. For example, the duration of the ischemia is controversial. We used a similar duration to that used in experimental models in the literature. Another limitation is that we did not use different doses for progesterone. Also, the number of animals in each group was limited. There is another controversial point, not every experimental model identically reflects human physiology. Nevertheless, there are some strengths to this study. We evaluated both serum and tissue oxidation parameters and used the TUNEL method to determine the apoptotic cell number. The advantage of progesterone is that it is not toxic for human physiology and is generally used for gynecologic and obstetric conditions.

In our experiments, we found that progesterone inhibited the apoptosis process and decreased the oxidative burden in torsioned rat ovaries. The effect of progesterone needs to be tested in preclinical studies to better understand its role in protecting the ovary from ischemia and reperfusion injury in the management of ovarian torsion.

Acknowledgement

This article is a part of thesis of "Banu Güleç Başer accomplished under the supervision of Assoc. Prof. Dr. Mine İslimye Taşkın" and this study was supported by the research fund of Balıkesir University (grant number Tıp.BAP.2015.00137).

Ethics Committee Approval: *Çanakkale Onsekiz Mart University Faculty of Medicine Animal Experiments Ethics Committee (16/12/2014, 2015-0001).*

Informed Consent: *N/A.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Concept - M.İ.T., B.G.B.; Design - M.İ.T., B.G.B., E.A.; Supervision - M.İ.T., B.G.B., E.A.; Materials - M.İ.T., B.G.B., E.A.; Data Collection and/or Processing - M.İ.T., B.G.B., E.A., E.Ö.; Analysis and/or Interpretation - A.A.H., A.Y.; Literature Review - M.İ.T., B.G.B., E.Ö.; Writer - M.İ.T., B.G.B.; Critical Review - M.İ.T., B.G.B., A.Y., A.A.H.*

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

Financial Disclosure: *This study was supported by Balıkesir University Scientific Investigations Foundation (Project number: 2015/137).*

References

1. Ipek A, Tan S, Kurt A, Yesilkaya Y, Orhan D. Prenatal over kisti torsiyonu: US ve MR görüntüleme bulguları. Türkiye Klinikleri J Gynecol Obst 2010; 20: 262-5.
2. Maretta M, Toth SS, Bujdos M, Toth S Jr, Jonecova Z, Vesela J. Alterations of epithelial layer after ischemic preconditioning of small intestine in rats. J Mol Histol 2012; 43: 171-8.
3. Wang J, Jiang C, Liu C, Li X, Chen N, Hao Y. Neuroprotective effects of progesterone following stroke in aged rats. Behav Brain Res 2010; 209: 119-22.
4. Allen RS, Olsen TW, Sayeed I, Cale HA, Morrison KC, Oumarbaeva Y, et al. Progesterone treatment in two rat models of ocular ischemia. Invest Ophthalmol Vis Sci 2015; 56: 2880-91.
5. Morrissy S, Xu B, Aguilar D, Zhang J, Chen QM. Inhibition of apoptosis by progesterone in cardiomyocytes. Aging Cell 2010; 9: 799-809.
6. Sandhi J, Singh JP, Kaur T, Ghuman SS, Singh AP. Involvement of progesterone receptors in ascorbic acid-mediated protection against ischemia-reperfusion-induced acute kidney injury. J Surg Res 2014; 187: 278-88.
7. Verma Y, Rana SV. Effects of progesterone on benzenetoxicity in rats. Arh Hig Rada Toksikol 2008; 59: 1-9.
8. Lu N, Li C, Cheng Y, DU AL. Protective effects of progesterone against high intraocular pressure-induced retinal ischemia-reperfusion in rats. Nan Fang Yi Ke Da Xue Xue Bao 2008; 28: 2026-9.
9. Wright DW, Kellermann AL, Hertzberg VS, Clark PL, Frankel M, Goldstein FC, et al. Protect: a randomized clinical trial of progesterone for acute traumatic brain injury. Ann Emerg Med 2007; 49: 391-402.
10. Vandenberk N, Unluer EE, Gökmen N, Yurekli İ, Okmen E, Yılmaz O, et al. Neuroprotective effects of progesterone in spinal cord ischemia in rabbits. Am J Emerg Med 2013; 31: 581-4.
11. Gencer M, Karaca T, Güngör AN, Hacıvelioğlu SÖ, Demirtaş S, Turkon H, et al. The protective effect of quercetin on IMA levels and apoptosis in experimental ovarian ischemia-reperfusion injury. Eur J Obstet Gynecol Reprod Biol 2014; 177: 135-40.

12. Sak ME, Soydinc HE, Sak S, Evsen MS, Alabalik U, Akdemir F, et al. The protective effect of curcumin on ischemia-reperfusion injury in rat ovary. Int J Surg 2013; 11: 967-70.
13. Guven S, Muci E, Unsal MA, Yulug E, Alver A, Kadioglu Duman M, et al. The effects of carbon dioxide pneumoperitoneum on ovarian blood flow, oxidative stress markers, and morphology during laparoscopy: a rabbit model. Fertil Steril 2010; 93: 1327-32.
14. Booth EA, Lucchesi BR. Medroxyprogesterone acetate prevents the cardioprotective and anti-inflammatory effects of 17-estradiol in an in vivo model of myocardial ischemia and reperfusion. Am J Physiol Heart Circ Physiol 2007; 293: 1408-15.
15. Arikan DC, Bakan V, Kurutas EB, Sayar H, Coskun A. Protective effect of tadalafil on ischaemia-reperfusion injury of rat ovary. J Pediatr Surg 2010; 45: 2203-9.
16. Sayar I, Bicer S, Gursul C, Gürbüzel M, Peker K, Işik A. Protective effects of ellagic acid and ozone on rat ovaries with an ischemia/reperfusion injury. J Obstet Gynaecol Res 2016; 42: 52-8.
17. Caglayan EK, Caglayan K, Gocmen AY, Cinar H, Seckin L, Seckin S, et al. Protective effect of ethyl pyruvate on ischemia-reperfusion injury in rat ovary: biochemical and histopathological evaluation. Eur J Obstet Gynecol Reprod Biol 2014; 182: 154-9.
18. Taskin MI, Hismiogullari AA, Yay A, Adali E, Gungor AC, Korkmaz GO, et al. Effect of 2-aminoethoxydiphenyl borate on ischemia-reperfusion injury in a rat ovary model. Eur J Obstet Gynecol Reprod Biol 2014; 178: 74-9.
19. Eser A, Hizli D, Haltas H, Namuslu M, Kosus A, Kosus N, et al. Effects of curcumin on ovarian ischemia-re perfusion injury in a rat model. Biomed Rep 2015; 3: 807-13.
20. Zhao C, Ozaeta P, Fishpaugh J, Rupprecht K, Workman R, Grenier F, et al. Structural characterization of glycoprotein NGAL, an early predictive biomarker for acute kidney injury. Carbohydr Res 2010; 345: 2252-61.
21. Gong L, Yu H, ZhuGe Y, Yu Q. Neutrophil gelatinase-associated lipocalin protects renal tubular epithelial cell in ischemic/reperfusion injury rats via apoptosis-regulating proteins. Ren Fail 2012; 34: 777-83.
22. Zang XJ, An SX, Feng Z, Xia YP, Song Y, Yu Q. In vivo mechanism study of NGAL in rat renal ischemia-reperfusion injury. Genet Mol Res 2014; 13: 8740-8.
23. Çıgsar G, Keleş ON, Can S, Karaca M, Can I, Erol HS, et al. The Protective Effects of Osajin on Ischemia/Reperfusion Injury to Rat Ovaries: Biochemical and Histopathological Evaluation. Kafkas Univ Vet Fak Derg 2015; 21: 753-60.
24. Borekçi B, Gundogdu C, Altunkaynak BZ, Çalık M, Altunkaynak ME, Unal D, et al. The Protective Effect of Dehydroepiandrosterone on Ovarian Tissues After Torsion-Detorsion Injury: A Stereological and Histopathological Study. Eurasian J Med 2009; 41: 22-7.
25. Haftacı SM, Albayrak M, Demir Ş, Yıldırım Ü, Ankaralı H, Keskin F. Rat overinde oluşturulan adneksiyal torsiyon modelinde perioperatif selenyum ve C vitamini uygulamasının ovaryan nekroz üzerine etkilerinin değerlendirilmesi. Türk Jinekolojik Onkoloji Dergisi 2013; 4: 118-23.
26. Gungor AN, Turkon H, Albayrak A, Ovali M, Islimye M, Gencer M, et al. Does Omegaven have beneficial effects on a rat model of ovarian ischemia/reperfusion? Eur J Obstet Gynecol Reprod Biol 2014; 181: 240-5.
27. Sahin Ersoy G, Eken M, Tal R, Oztekin D, Devranoglu B, Isik Kaygusuz E, et al. N-acetylcysteine leads to greater ovarian protection than enoxaparin sodium in a rat ovarian torsion model. Reprod Biomed Online 2016; 33: 93-101.
28. Espinosa-García C, Vigueras-Villaseñor RM, Rojas-Castañeda JC, Aguilar-Hernández A, Monfil T, Cervantes M, et al. Post-ischemic administration of progesterone reduces caspase-3 activation and DNA fragmentation in the hippocampus following global cerebral ischemia. Neurosci Lett 2013; 550: 98-103.
29. Ishrat T, Sayeed I, Atif F, Stein DG. Progesterone is neuroprotective against ischemic brain Injury through its effects on the phosphoinositide 3-kinase/protein kinase b signaling pathway. Neuroscience 2012; 210: 442-50.

Pregnancy in papillary thyroid cancer survivors

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Abstract

Objective: To evaluate "papillary thyroid carcinoma-pregnancy" interaction among cancer survivors.

Material and Methods: The clinical records of 8 pregnant women who received treatment for papillary thyroid cancer before their pregnancy were evaluated. Clinical features, pregnancy/perinatal outcomes and high-risk factors were compared with 45 controls who were randomly assigned from the institutional perinatal medicine database.

Results: Patients in the cancer group were older than the control group (34.3 vs 29.8 years). The cesarean section rate was higher (62.5% vs 33.3%) and the APGAR scores at the 1st and 5th minutes were lower in the cancer group.

Conclusion: Management of pregnancies with papillary thyroid cancer treatment and follow-up requires a multidisciplinary approach with careful antenatal care and perinatal surveillance. Patients who have received papillary thyroid cancer treatment can safely undergo pregnancy. (J Turk Ger Gynecol Assoc 2018; 19: 94-7)

Keywords: Pregnancy, papillary thyroid cancer, thyroid cancer survivor, thyroid

Received: 20 October, 2017 **Accepted:** 16 February, 2018

Introduction

It has been reported that the incidence of papillary thyroid carcinoma (PTC) has been increasing over the last decades (1-3). It has also been reported that differentiated thyroid cancer is more common in women and is the second most common cancer diagnosed during pregnancy and the postpartum period with a prevalence of 14 per 100.000 live births (4-6). However, there are conflicting results and opinions in the literature related to PTC-pregnancy interaction and optimal timing of surgical and medical intervention (7-13).

Another critical issue of the "PTC-pregnancy interaction" is the management of pre- and post-operative thyroid gland problems (14-16). Treatment of hyperthyroidism is important in order to avoid fetal hypothyroidism (14,15). However, drug selection is also important because there is an increased risk of birth defects among methimazole users (14,16). Propylthiouracil, which is relatively hepatotoxic, is preferred in early pregnancy because of the possible teratogenicity of methimazole (14). On the other hand, management of hypothyroidism is critical in order to reduce the incidence rate of miscarriage and to maintain normal fetal brain development (14). The effects of radioactive iodine (RAI or I-131) therapy on gonads and pregnancy outcomes must also be carefully considered in patients with PTC (12,13).

Recently, it has been reported that high levels of pro- and anti-angiogenic factors may be a risk factor for adverse outcomes via their effect on maternal thyroid function (17). Ectopic production of β human chorionic gonadotrophin (hCG) by PTC cells must also be considered in clinical practice (18).

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Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.2017.0057

Thus, PTC and PTC-related changes may be critical both from the maternal and the perinatal morbidity/mortality rate point of view. In this clinical report, we analyzed medical/obstetric histories and the clinical features of 8 pregnancies with PTC.

Material and Methods

Our institution's pregnancy-associated cancer database, which consisted of 110 patients whose cancer was diagnosed between 2002 and 2015, was retrospectively evaluated (19). Eight PTC survivors were found to be eligible for the study. All of the patients received bilateral total thyroidectomy and were given RAI therapy after surgery as indicated (20).

Clinical features, treatment modalities and pregnancy/perinatal outcomes were evaluated and compared with 45 patients as a control group who were randomly assigned from the institutional perinatal medicine database, which included all pregnancies followed in the clinic. The evaluated parameters included patients' age, obstetric history, mode of delivery, gestational week (day) at delivery, birthweight, APGAR scores at the 1st, 5th, and 10th minute, and the Beksaç et al. (21,22) obstetrics index (BOI). The BOI is an index for the assessment of risk levels of high-risk pregnancy groups, which is (number of living children + π/10)/Gravida. BOIp is the calculation of the index during the course of the last pregnancy (the perinatal outcome of the last pregnancy is not considered during the calculation).

Statistical analysis

The Statistical Package for Social Sciences version 17 (IBM SPSS Statistics, USA) was used for data analysis. Pearson's chi-square and Fisher's exact tests were used for categorical variables, and the Mann-Whitney U and t-test was used for continuous variables. The last pregnancy of each patient was considered for evaluation. Sample size calculations were performed using G*Power v3.15 general power analysis program. We used 0.5 effect size, 0.8 power, and 5% level of significance (alpha) for calculations (23).

Results

Demographics and clinical features of each group are given in Table 1. Table 2 shows obstetric history, BOI, gestational day of delivery, pregnancy outcome, birthweight of the fetus, and obstetric complications of the last pregnancy of each patient. All patients received thyroid hormone replacement therapy after their respective surgery/management (gestational and teratologic risks of the drugs were considered in all cases with necessary precautions). All patients were alive and disease free at the time of retrospective evaluation. All patients became pregnant within the first year after RAI therapy.

The mean age in the thyroid cancer group was 34.3 years, which was statistically significantly higher than the control group, which was 29.8 years (p=0.013). We found that the cesarean section rate was higher in the thyroid cancer group (p=0.054,) which was 62.5% of the cases. We also found that the 1-minute and 5-minute APGAR scores were statistically significantly lower in the cancer group (p=0.022 and p=0.03, respectively). The mean interval between cancer treatment and pregnancy was 4.5±3.11 years (range, 1-11 years).

In this clinical series, 7 of 8 patients delivered (five by cesarean section and two by vaginal delivery), and one pregnancy ended with spontaneous abortion. One neonate had corpus callosum agenesis (the family refused to have induced abortion) and was delivered vaginally. Neonates of a twin pregnancy were delivered by cesarean section at the 37th gestational week (in

Table 1. Demographic and clinical features of patients

Characteristics of patients	Thyroid cancer group (n=8)	Control group (n=45)	p value
Age [mean (minimum-maximum)]	34.3 (29-39)	29.8 (20-44)	0.013**
Gravidity [median (minimum-maximum)]	2 (2-5)	2 (1-9)	0.128**
Parity [median (minimum-maximum)]	1 (1-2)	1 (0-6)	0.135**
Abortion [median (minimum-maximum)]	0 (0-3)	0 (0-3)	0.705**
Living child [median (minimum-maximum)]	1 (0-2)	1 (0-6)	0.321**
BOI [median (minimum-maximum)]	1.13 (0.26-1.16)	1.16 (0.46-1.31)	0.099**
BOIp [median (minimum-maximum)]	0.66 (0.16-0.77)	0.44 (0.16-0.77)	0.670**
Gestational day at birth [median (minimum-maximum)]	266 (252-268)	271 (200-286)	0.016**
Cesarean section, n (%)	5 (62.5%)	15 (33.3%)	0.054***
Birthweight (mean ± standard deviation)	3051±886	3195±566	0.599*
APGAR1 [median (minimum-maximum)]	7.5 (7-8)	9 (4-10)	0.022**
APGAR5 [median (minimum-maximum)]	8.5 (8-9)	10 (0-10)	0.030**
APGAR10 [median (minimum-maximum)]	10 (10-10)	10 (0-10)	0.936**

*: Independent samples t-test, **: Mann-Whitney U test, ***: Pearson's chi-square test, BOI: Beksaç obstetrics index, BOIp: Beksaç obstetrics index during the course of the last pregnancy

vitro fertilization twin; 2060 and 2060 g male neonates) with no complications. One patient was preeclamptic and delivered a 1900 g female neonate at the 36th gestational week (this neonate was discharged from the intensive neonatal care unit with no complications).

There was no statistically significant difference between the control and study groups in terms of birthweight (3195±566 g and 3051±886 g, respectively), and the gestational week at delivery was lower in patients with cancer (266 days vs 271 days; p=0.016). We believe that this finding is not critical in clinical practice. The obstetric history and perinatal outcomes of previous pregnancies of both groups were evaluated using BOIp and no statistical differences were observed.

Discussion

Thyroid cancer, with an incidence of 9 per 100.000 persons per year (24), has seriously increased over the last two decades, mainly due to the papillary type (1,2). It has also been reported that differentiated thyroid cancer is more common in women and is the second most common cancer diagnosed during pregnancy and the postpartum period with a prevalence of 14 per 100,000 live births (4-6). Several studies have suggested an association between PTC and reproductive variables such as estrogen and hCG (2,6).

The "Pregnancy-PTC" interaction is full of controversies. hCG, which is a weak thyroid-stimulating hormone agonist, may sometimes be secreted by PTC cells (18,25). On the other hand, various growth factors and pro- and anti-angiogenic factors may influence perinatal outcome via thyroid (dys) function (17). Some authors reported that pregnancy had no effect on PTC, whereas others suggested that PTC may progress during pregnancy (9,10). However, there is a consensus about the timing of surgery when PTC is diagnosed during pregnancy (7,8,26). Surgery can be delayed until after delivery in appropriate patients. It has been reported that I-131 therapy may result in transient ovarian dysfunction, but subsequent pregnancies are safe without any significant consequence to perinatal outcome (12,13). In our study, we have shown that pregnant women with thyroid cancer history are older than the general population. Actually, this finding is not surprising because most women should be in remission or disease free before getting pregnant for better maternal and fetal outcomes. The long treatment period and awareness the fetal teratogenic effect of medication seems to force women to delay their pregnancies. We believe that pregnancy planning should be postponed until after having proper PTC treatment due to these uncertainties.

Cancer-related worry is very important for patients with PTC who want to become pregnant (27). On the other hand, stress is an important determinant for patients whose PTC diagnosis was made during pregnancy (28). Waiting for surgery is another problem to be managed during pregnancy due to long wait times (29). Our findings demonstrate that PTC survivors might be encouraged to become pregnant if they are willing to do so even when considering the facts mentioned above.

The effect of PTC on pregnancy needs to be studied. There are no case-control prospective studies on the effect of PTC on obstetrics/perinatal complications. In our case series, we demonstrated that 1-minute and 5-minute APGAR scores were lower in PTC survivors and the cesarean section rate is higher in this group of patients compared with the control group. PTC-related immune and metabolic changes may be responsible for the inflammatory changes at the materno-fetal interface (injury of the cellular components of the intervillous space) and this might be the reason of impaired fetal perfusion going together with stress-intolerant

Table 2. Pregnancy outcome variables of patients with thyroid cancer

	Age	Obstetric history	BOI	BOIp	Gestational time at birth (day)	Pregnancy outcome	Birth weight (grams)	Obstetric complication	Interval between cancer treatment and pregnancy (year)
1	29	G2P1A0L1	1.157	0.657	259	Healthy neonate	3240	-	2
2	36	G2P1A0L1	1.157	0.657	266	Healthy neonate	4400	-	5
3	33	G2P1A0L1	1.157	0.157	259	IVF pregnancy; healthy neonates	2060/2060	-	6
4	38	G2P1A0L1	0.657	0.657	266	Congenital abnormality	3110	-	3
5	32	G2P1A0L1	1.157	0.657	252	Healthy neonate	1900	Preeclampsia	1
6	39	G5P1A3L1	0.263	0.263	42	Abortus	-	Repeated abortions	11
7	33	G3P2A0L2	1.104	0.771	268	Healthy neonate	3770	-	3
8	34	G3P1A1L1	0.771	0.438	266	Healthy neonate	2660	-	5

BOI: Beksaç obstetrics index, BOIp: Beksaç obstetrics index during the course of the last pregnancy, IVF: In vitro fertilization

babies, increased cesarean section rates, and low APGAR scores. All these factors and patient-specific surgical/medical treatment modalities necessitate a patient-specific antenatal care program and careful perinatal surveillance.

Ethics Committee Approval: *Ethic aproval number: GO16/217.*

Informed Consent: *It was taken.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Concept - K.B., F.A., G.Ö., H.T.Ç., A.S.Ö.E., M.S.B.; Design - K.B., F.A., G.Ö., H.T.Ç., A.S.Ö.E., M.S.B.; Supervision - M.S.B.; Materials - K.B., F.A., G.Ö., H.T.Ç., A.S.Ö.E., M.S.B.; Writer - K.B., M.S.B.*

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

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

References

1. Leenhardt L, Grosclaude P, Cherie-Challine L; Thyroid Cancer Committee. Increased incidence of thyroid carcinoma in france: a true epidemic or thyroid nodule management effects? Report from the French Thyroid Cancer Committee. Thyroid 2004; 14: 1056-60.
2. Sungwalee W, Vatanasapt P, Kamsa-Ard S, Suwanrungruang K, Promthet S. Reproductive risk factors for thyroid cancer: a prospective cohort study in Khon Kaen, Thailand. Asian Pac J Cancer Prev 2013; 14: 5153-5.
3. Xhaard C, Rubino C, Clero E, Maillard S, Ren Y, Borson-Chazot F, et al. Menstrual and reproductive factors in the risk of differentiated thyroid carcinoma in young women in France: a population-based case-control study. Am J Epidemiol 2014; 180: 1007-17.
4. Smith LH, Danielsen B, Allen ME, Cress R. Cancer associated with obstetric delivery: results of linkage with the California cancer registry. Am J Obstet Gynecol 2003; 189: 1128-35.
5. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015; 65: 5-29.
6. Imran SA, Rajaraman M. Management of differentiated thyroid cancer in pregnancy. J Thyroid Res 2011; 2011: 549609.
7. Uruno T, Shibuya H, Kitagawa W, Nagahama M, Sugino K, Ito K. Optimal timing of surgery for differentiated thyroid cancer in pregnant women. World J Surg 2014; 38: 704-8.
8. Cabezon CA, Carrizo LC, Costanzo PR. Evolution of differentiated thyroid cancer during pregnancy in a community University Hospital in Buenos Aires, Argentina. Arq Bras Endocrinol Metabol 2013; 57: 307-11.
9. Budak A, Gulhan I, Aldemir OS, Ileri A, Tekin E, Ozeren M. Lack of influence of pregnancy on the prognosis of survivors of thyroid cancer. Asian Pac J Cancer Prev 2013; 14: 6941-3.
10. Shindo H, Amino N, Ito Y, Kihara M, Kobayashi K, Miya A, et al. Papillary thyroid microcarcinoma might progress during pregnancy. Thyroid 2014; 24: 840-4.
11. Lee JC, Zhao JT, Clifton-Bligh RJ, Gill AJ, Gundara JS, Ip J, et al. Papillary thyroid carcinoma in pregnancy: a variant of the disease? Ann Surg Oncol 2012; 19: 4210-6.
12. Sioka C, Fotopoulos A. Effects of I-131 therapy on gonads and pregnancy outcome in patients with thyroid cancer. Fertil Steril 2011; 95: 1552-9.
13. Grammatikakis I, Trakakis E, Evangelinakis N, Hintipas E, Salamalekis G, Kassanos D. Successful pregnancy after radiotherapy with 131I for differentiated thyroid cancer. A case report and review of the literature. Clin Exp Obstet Gynecol 2010; 37: 328-30.
14. Momotani N, Iwama S. [Management of Graves' disease and hypothyroidism in pregnancy]. Nihon Rinsho 2012; 70: 1971-5.
15. Ma L, Qi H, Chai X, Jiang F, Mao S, Liu J, et al. The effects of screening and intervention of subclinical hypothyroidism on pregnancy outcomes: a prospective multicenter single-blind, randomized, controlled study of thyroid function screening test during pregnancy. J Matern Fetal Neonatal Med 2016; 29: 1391-4.
16. Li X, Liu GY, Ma JL, Zhou L. Risk of congenital anomalies associated with antithyroid treatment during pregnancy: a meta-analysis. Clinics (Sao Pulo) 2015; 70: 453-9.
17. Korevaar TI, Steegers EA, de Rijke YB, Visser WE, Jaddoe VW, Visser TJ, et al. Placental Angiogenic Factors Are Associated With Maternal Thyroid Function and Modify hCG-Mediated FT4 Stimulation. J Clin Endocrinol Metab 2015; 100: 1328-34.
18. Alikhan M, Koshy A, Hyjek E, Stenson K, Cohen RN, Yeo KT. Discrepant serum and urine beta-hCG results due to production of beta-hCG by a cribriform-morular variant of thyroid papillary carcinoma. Clin Chim Acta 2015; 438: 181-5.
19. Turgal M, Beksac K, Basaran D, Yazicioglu A, Ozyuncu O, Aran O, et al. Pregnancy after Cancer Treatment and Pregnancy Associated Cancer: A Single Center Experience with 96 Cases. Gynecology Obstetrics & Reproductive Medicine 2015; 21: 91-6.
20. Bohinc BN, Perkins JM. Appropriate dosing of adjuvant radioactive iodine for differentiated thyroid cancer. Curr Opin Oncol 2014; 26: 31-5.
21. Beksaç MS, Aydin E, Turgal M, Karaagaoglu E. An Obstetrics Index for the Assessment of Risk Levels of "High Risk Pregnancy" Groups. Gynecology Obstetrics & Reproductive Medicine 2015; 21: 10-3.
22. Beksaç K, Örgül G, Çağan M, Karaağaoğlu E, Arslan S, Beksaç MS . Retrospective evaluation of pregnant women with celiac disease. J Turk Ger Gynecol Assoc 2017; 18: 56-59.
23. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007; 39: 175-91.
24. Yasmeen S, Cress R, Romano PS, Xing G, Berger-Chen S, Danielsen B, et al. Thyroid cancer in pregnancy. Int J Gynaecol Obstet 2005; 91: 15-20.
25. Hershman JM. Human chorionic gonadotropin and the thyroid: hyperemesis gravidarum and trophoblastic tumors. Thyroid 1999; 9: 653-7.
26. Guerrero-Vazquez R, Moreno Reina E, Gros Herguido N, Martinez Brocca MA, Navarro Gonzalez E. Advanced thyroid carcinoma in pregnancy: case report of two pregnancies. Gynecol Endocrinol 2015; 31: 852-5.
27. Bresner L, Banach R, Rodin G, Thabane L, Ezzat S, Sawka AM. Cancer-related worry in Canadian thyroid cancer survivors. J Clin Endocrinol Metab 2015; 100: 977-85.
28. Buchmann L, Ashby S, Cannon RB, Hunt JP. Psychosocial distress in patients with thyroid cancer. Otolaryngology Head Neck Surg 2015; 152: 644-9.
29. Eskander A, Devins GM, Freeman J, Wei AC, Rotstein L, Chauhan N, et al. Waiting for thyroid surgery: a study of psychological morbidity and determinants of health associated with long wait times for thyroid surgery. Laryngoscope 2013; 123: 541-7.

Dual trigger with gonadotropin-releasing hormone and human chorionic gonadotropin for poor responders

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Abstract

Objective: To compare metaphase II (MII) rate, fertilization rate, and embryo quality with dual trigger gonadotropin-releasing hormone agonist (GnRH) and normal dose human chorionic gonadotropin (hCG) versus a normal dose hCG trigger in antagonist intracytoplasmic sperm injection (ICSI) cycles of poor ovarian responders.

Material and Methods: Patients defined as poor ovarian responders according to the Bologna criteria who underwent ICSI with GnRH antagonist protocol and triggered with dual trigger or hCG alone for oocyte maturation. Main outcome measures were MII rate, fertilization rate, and embryo quality.

Results: Total gonadotropin doses and E_2 levels on trigger day were higher in the hCG trigger group. There were no significant differences with regard to implantation rate (p=0.304), biochemical pregnancy rate (p=0.815), clinical pregnancy rate (p=0.378), and ongoing pregnancy rate (p=0.635) between the groups.

Conclusion: Dual trigger of oocyte maturation with GnRH agonist and normal dose hCG in poor responders does not demonstrate improved oocyte maturation, clinical pregnancy, and ongoing pregnancy rates. (J Turk Ger Gynecol Assoc 2018; 19: 98-103)

Keywords: Dual trigger, intracytoplasmic sperm injection, poor responders

Received: 13 April, 2017 **Accepted:** 7 March, 2018

Introduction

Poor ovarian response (POR) is known as the decrease of fecundity. The first systematic definition of POR was identified as the Bologna criteria in 2011 by The European Society of Human Reproduction and Embryology (1). Patients with POR have very poor outcomes despite improving treatment modalities such as the use of different stimulation protocols or adding adjuvant therapies (2).

Human chorionic gonadotropin (hCG) is almost always used to trigger final oocyte maturation and is required to pick-up mature oocytes from stimulated ovaries in in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) cycles. After the administration of gonadotropin-releasing hormone agonist (GnRH) antagonists in IVF/ICSI cycles, triggering with GnRH agonists and other methods (double trigger and dual trigger) has been introduced (3-6). These triggering methods provide the release of endogenous follicle-stimulating hormone (FSH) and luteinizing hormone (LH) surge like in the natural cycle for the maturation of follicles. "Dual trigger" was first introduced by Shapiro et al. (6) in co-treated patients with GnRH antagonist cycles for the purpose of Ovarian Hyperstimulation syndrome (OHSS) prevention. Besides prevention of OHSS, Lin et al. (7) demonstrated improved implantation, clinical pregnancy, and live-birth rates in normal responders using the dual trigger regimen.

Even though benefits were shown when using the dual triggering regimen in high-responder and normal-responder patients or having oocyte immaturity, few studies have been performed to show the effects when using this regimen in the poor-responder population (7-14).

The aim of the present study was to analyze whether the dual trigger in POR might improve ICSI cycle outcomes.

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Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.2017.0045

Material and Methods

This case-control study was approved by the institutional ethics committee. A total of 47 ICSI cycles in which a dual trigger was used for final oocyte maturation were performed from March 2015 until July 2015. Moreover, a review of medical records from May 2012 through April 2014 was performed for poor responders who were triggered with hCG. Controls included 62 ICSI cycles. Both cases and controls were recruited consecutively.

Participants and treatment protocol

All patients who fulfilled the criteria defined by the European Society of Human Reproduction and Embryology consensus in 2011 and underwent ICSI cycles with GnRH antagonist were considered eligible (1). The Bologna criteria for poor responders was defined as the presence of two of the following features: 1) Increased maternal age (40 years) or other risk factors for POR, 2) A previously demonstrated POR (≤3 oocytes with a conventional stimulation protocol), 3) An abnormal ovarian reserve test results (i.e., antral follicular count <5-7 follicles or anti-Müllerian hormone <0.5-1.1 ng/mL) (1). Patients with other infertility factors were excluded from the study.

Patients underwent controlled ovarian hyperstimulation with the multi-dose GnRH antagonist and with a starting gonadotropin (recombinant FSH or human menopausal gonadotropin) dose of ≥300 IU, which were administered from the second day of the cycle. GnRH antagonist (Ganirelix; Merck Sharp and Dohme) was started 0.25 mg subcutaneously from the day that the diameter of the leading follicle reached ≥14 mm or serum estradiol (E_2) reached >350 pg/mL, until the day of the trigger. Patients were excluded from the study whose cycles were cancelled because of unresponsiveness to the gonadotropins. Cases were triggered with a combination 250 mcg choriogonadotropin alpha (Ovitrelle; Merck) plus 0.2 mg triptoreline acetate (Gonapeptyl; Ferring) subcutaneously when follicles reached ≥17 mm in diameter. Controls were triggered only with 250 mcg choriogonadotropin alpha when follicles reached ≥17 mm in diameter. Serum E_2 levels were assessed on the day of the trigger. Transvaginal ultrasound-guided oocyte picks up was performed 35 hours after triggering.

Luteal phase supplementation was provided by daily administration of 90 mg vaginal progesterone gel (Crinone; Serono) from the day after oocyte pick up until either a negative pregnancy test or 10 weeks of gestation. If patients had embryos after oocyte retrieval, transfer day and the number of transferrable embryos were assessed according to embryo quality and number of embryos. One proficient physician transferred whole embryos that were at the cleavage stage. Embryo quality was based on cleavage and morphology scores assessing the size equality and percentage of the fragmentation rate of the cells, as described by Veeck (15).

Serum β-hCG level was measured 14 days after embryo transfer and positive pregnancy was defined above the level of >5 IU/L.

Outcome variables

The primary outcome was MII, fertilization and top-quality embryo rates. Secondary outcomes were clinical and ongoing pregnancy rate. Clinical pregnancy was defined as the presence of a positive heart beat after 4 weeks of positive pregnancy.

Statistical analysis

Statistical analyses were performed using the NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA). Data are presented as mean, standard deviation, median (range), ratio, minimum and maximum. Student's t-test was used to compare parametric data and the Mann-Whitney U test was used to compare non-parametric data. Qualitative clinical outcomes were examined using Fisher's exact test. $P<0.05$ was considered statistically significant.

Results

The baseline characteristics are shown in Table 1. In the hCG trigger group, day 3 FSH (9.6±5 vs 11±3.7, p=0.006) was significantly higher than the dual trigger group. Other characteristics did not significantly differ between the dual trigger group and the hCG trigger group.

In terms of the cycle characteristics of the two groups, total dose of gonadotropins (3165.4±1124.2 vs 3839.5±805.5 IU, p=0.001) and E_2 on trigger day (647.5±361.9 vs 923.9±603.1 pg/mL; p=0.017) were significantly higher in the hCG trigger group. Other parameters did not significantly differ between the dual trigger group and the hCG trigger group (Table 2).

Dual trigger group compared with hCG trigger group with regards to implantation rate, biochemical pregnancy rate, clinical pregnancy rate, and ongoing pregnancy rate. There was no statistically significant differences between ICSI outcomes (Table 3). We detected no OHSS in either group.

Discussion

This case-control study assessed the effect of dual triggering through an antagonist stimulation protocol in poor responder women undergoing ICSI cycles. Although total gonadotropin doses and E_2 levels on the trigger day were higher in hCG trigger group, the results of this study suggest there was no clinical difference when a dual trigger was used instead of an hCG trigger in poor responder women.

hCG triggers are used conventionally in IVF/ICSI cycles. Although this technique is thought to be successful, researchers

are investigating new tools to prevent OHSS and to improve the extent of mature oocytes obtained.

The GnRH agonist trigger was first introduced by Gonen et al. (3). Triggering with a GnRH agonist causes the release of both FSH and LH a natural cycle flares up, which is considered to be more physiologic. A Cochrane meta-analysis showed triggering with GnRH agonist instead of hCG was an acceptable method by transferring freeze/thaw embryos compared with conventional trigger in fresh cycles. The GnRH agonist trigger had similar live birth rates with a substantial reduction in OHSS rates (16). After an agonist trigger was defined, triggering with hCG and FSH concomitantly showed the improvement of oocyte maturation and fertilization in a previous study (17). GnRH receptors were identified in the endometrium, in preimplanted embryo, and in ovarian granulosa cells other than in the pituitary, and ovulation has been regulated by GnRH (18-20). Moreover, Raga et al. (21) showed that a GnRH agonist improved preimplantation embryonic developments in a murine model, independent of FSH.

The dual trigger was first introduced by Shapiro et al. (6). Despite there being a scarcity of studies that investigated the impact of a dual trigger in the literature; a dual trigger with standard dose hCG provided higher oocyte retrieval numbers (7,12), higher numbers of retrieved M2 oocytes (7,12), higher M2 oocyte rates (7,22), higher numbers of cryopreserved embryos (7,23); and improved implantation (7), clinical pregnancy (7,14) and live birth rates (7) in normal responder patients.

In our study, we hypothesized that a GnRH agonist and release of FSH due to a GnRH agonist flare up might have dual influence and may enhance oocyte quality, M2 oocyte rate, fertilized oocytes, and embryo quality, without affecting endometrial receptivity and implantation in poor responders. However, we found no differences in M2 oocyte retrieval, M2 oocyte rates, number of total oocytes retrieved, fertilized oocytes, fertilization rates, top and good quality embryos, and top-quality embryo rates between the dual trigger group and the hCG trigger group. Despite an enhancement of IVF/ICSI outcome when triggering with dual triggers in normal responder patients, the lack of difference between these parameters may depend on the reason of an underlying oocyte dysfunction. Aneuploidy and poor oocyte maturity is still the main problem needed to be solved in poor responder patients (24).

Although GnRH agonist triggers have been shown to induce oocyte maturation, low pregnancy and increasing miscarriage rates were associated with luteal phase insufficiency (25,26). Intensive luteal E_2 and progesterone were used to provide luteal phase support but results were conflicting. Babayof et al. (27) used this protocol first in patients at high risk for OHSS and this study showed poor reproductive outcomes. This result may be due to their low number of patients. In a previous prospective randomized study, Engmann et al. (28) found similar implantation and clinical pregnancy rates in patients at high risk for OHSS undergoing IVF. Despite using intensive luteal support, a retrospective study showed decreased implantation and pregnancy rates in OHSS patients with high risk (29). Other methods to support the luteal phase with GnRH agonist trigger include the use of hCG after the GnRH agonist trigger and dual trigger. Modified luteal phase support with hCG after a GnRH agonist trigger has shown similar results in implantation, and clinical and ongoing pregnancy rates compared with hCG (30). In the dual trigger method, hCG prevents the luteolytic effect of GnRH agonist and provides adequate luteal phase support (6). Although the implantation and pregnancy rates were not significantly different in normal responder patients undergoing

Table 1. Comparison of the dual trigger and human chorionic gonadotropin trigger: demographic characteristics

		Total (n=109)	Dual trigger (n=47)	hCG trigger (n=62)	p
Age (year)	Mean ± SD	35.6±3.9	35.3±4.1	35.8±3.8	0.495[a]
	Min-max (Median)	27-47 (36)	27-47 (36)	27-44 (36)	
BMI (kg/m^2)	Mean ± SD	25.4±2.5	25.9±2.3	25±2.7	0.080[a]
	Min-max (Median)	19.78-30.86 (26.1)	19.78-29.62 (26.3)	20.28-30.86 (25.1)	
Durationof infertility (years)	Mean ± SD	7.7±5.7	8.2±5.5	7.2±5.8	0.251[b]
	Min-max (Median)	1-25 (6)	1-20 (7)	1-25 (5)	
Number of antral follicle counts	Mean ± SD	4.8±1.7	5±1.8	4.7±1.7	0.203[b]
	Min-max (Median)	1-8 (5)	2-7 (6)	1-8 (5)	
Basal FSH (IU/L)	Mean ± SD	10.4±4.3	9.6±5	11±3.7	0.006**[b]
	Min-max (Median)	3.1-26.1 (9.57)	3.05-26.1 (8.7)	4.2-21 (10.3)	
Basal E_2 (IU/L)	Mean ± SD	64.1±64.8	51.4±32.4	73.7±80	0.132[b]
	Min-max (Median)	11.8-472 (45.3)	20-206 (44)	11.8-472 (48)	

[a]: Student's t-test; [b]: Mann-Whitney U test; *: p<0.05; **: p<0.01; SD: Standard deviation; hCG: Human chorionic gonadotropin; BMI: Body mass index; FSH: Follicle-stimulating hormone; E_2: Estradiol; Min: Minimum; Max: Maximum

Table 2. Comparison of the cycle characteristics between the dual trigger and human chorionic gonadotropin trigger

		Total (n=109)	Dual trigger (n=47)	hCG trigger (n=62)	p[b]
Duration of stimulation (day)	Mean ± SD	8.5±1.9	8.5±2.1	8.5±1.7	0.935
	Min-max (Median)	4-13 (8)	4-13 (9)	6-13 (8)	
Total dose of gonadotropins (IU)	Median ± SD	3548.9±1008.6	3165.4±1124.2	3839.5±805.5	0.001**
	Min-max (Median)	1200-5850 (3600)	1200-5550 (3000)	1800-5850 (3600)	
E_2 on trigger day (pg/mL)	Mean ± SD	804.7±529.3	647.5±361.9	923.9±603.1	0.017*
	Min-max (Median)	169-2812 (696)	169-1506 (547)	238-2812 (721.5)	
Number of M2 oocytes retrieved	Mean ± SD	2±1.5	1.7±1.4	1.9±1.5	0.423
	Min-max (Mediyan)	0-6 (1)	0-5 (1)	0-6 (2)	
MII rate	Mean ± SD	0.8±0.3	0.8±0.3	0.8±0.3	0.384
	Min-max (Median)	0-1 (1)	0-1 (1)	0-1 (0.7)	
Number of total oocytes retrieved	Mean ± SD	2.4±1.7	2.2±1.6	2.6±1.8	0.227
	Min-max (Median)	0-8 (2)	0-6 (2)	0-8 (3)	
Number of fertilized oocytes	Mean ± SD	1±1.2	1±1.01	1.1±1.3	0.778
	Min-max (Median)	0-5 (1)	0-4 (1)	0-5 (1)	
Number of top quality embryos obtained	Mean ± SD	0.3±0.5	0.3±0.5	0.4±0.5	0.607
	Min-max (Median)	0-1 (0)	0-1 (0)	0-1 (0)	
Number of good quality embryos obtained	Mean ± SD	0.9±0.7	0.9±0.7	0.8±0.7	0.643
	Min-max (Median)	0-2 (1)	0-2 (1)	0-2 (1)	
Top quality embryo rate	Mean ± SD	0.2±0.4	0.2±0.3	0.3±0.4	0.522
	Min-max (Median)	0-1 (0)	0-1 (0)	0-1 (0)	
Transfer day	Mean ± SD	2.5±0.7	2.6±0.8	2.4±0.6	0.206
	Min-max (Median)	1-5 (2)	2-5 (3)	1-3 (2)	
Number of embryos transferred	Mean ± SD	1.3±0.5	1.2±0.4	1.3±0.5	0.598
	Min-max (Median)	1-2 (1)	1-2 (1)	1-2 (1)	

[b]: Mann-Whitney U test; *: $p<0.05$; **: $p<0.01$; E_2: Estradiol; SD: Standard deviation; hCG: Human chorionic gonadotropin; MII: Metaphase II; Min: Minimum; Max: Maximum

Table 3. Comparison of the standard and dual trigger methods

	Dual trigger	hCG trigger	p
Fertilization rate (%)	41.6 (42/101)	43 (67/156)	0.829[c]
Implantation rate (%)	3.2 (1/31)	9.3 (4/43)	0.304[d]
Biochemical pregnancy rate (%) per transferred cycle	16 (4/25)	12.1(4/33)	0.815[c]
Clinical pregnancy rate (%) per transferred cycle	4 (1/25)	12.1(4/33)	0.378[c]
Ongoing pregnancy rate (%) per ET	3.2 (1/31)	7 (3/43)	0.635[c]

[c]: Pearson's chi-square; [d]: Fisher's exact test; ET: Essential thrombocythemia

ICSI in a previous randomized controlled study, other reports showed promising pregnancy results (7,8,14,23). In our study, implantation and clinical and ongoing pregnancy rates were not statistically significant. According to the previously mentioned studies, luteal phase deficiency was not a concern in dual trigger cycles. However, the lack of difference between implantation, clinical and ongoing pregnancy rates in our study might be due to our patient population who were all poor responders.

A limitation of this study is that it was underpowered regarding the implantation rate, biochemical pregnancy rate, clinical pregnancy rate, and ongoing pregnancy rate due to the low poor responder population in our clinic. Another limitation is that the hCG trigger group was recruited retrospectively.

In conclusion, no statistical significance was found between a dual trigger and conventional hCG trigger. However, larger prospective randomized controlled studies are needed to evaluate whether a dual trigger enhances oocyte maturation and improves ICSI outcome in poor responders.

Ethics Committee Approval: *The ethics committee approval of this study was obtained from İstanbul Zeynep Kamil Women and Child Diseases Training and Research Hospital (Ethics board number: 05/06/2015-84).*

Informed Consent: *Informed consent was taken to all participants.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Concept - A.E., B.D., E.B.E., Ç.Y.A.; Design - A.E.; Materials - B.D., E.B.E., Ç.Y.A.; Writer - A.E.*

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

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

References

1. Ferraretti AP, La Marca A, Fauser BC, Tarlatzis B, Nargund G, Gianaroli L, et al. ESHRE consensus on the definition of 'poor response' to ovarian stimulation for in vitro fertilization: the Bologna criteria. Human Reprod 2011; 26: 1616-24.
2. Patrizio P, Vaiarelli A, Levi Setti PE, Tobler KJ, Shoham G, Leong M, et al. How to define, diagnose and treat poor responders? Responses from a worldwide survey of IVF clinics. Reprod Biomed Online 2015; 30: 581-92.
3. Gonen Y, Balakier H, Powell W, Casper RF. Use of gonadotropin-releasing hormone agonist to trigger follicular maturation for in vitro fertilization. J Clin Endocrinol Metab 1990; 71: 918-22.
4. Beck-Fruchter R, Weiss A, Lavee M, Geslevich Y, Shalev E. Empty follicle syndrome: successful treatment in a recurrent case and review of the literature. Hum Reprod 2012; 27: 1357-67.
5. Hhas J, Zilberberg E, Dar S, Kedem A, Machtinger R, Orvieto R. Co-administration of GnRh-agonist and hCG for final oocyte maturation (double trigger) in patients with low number of oocytes retrieved per number of preovulatory follicles-a preliminary report. J Ovarian Res 2014; 7: 77.
6. Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Thomas S. Gonadotropin-releasing hormone agonist combined with a reduced dose of human chorionic gonadotropin for final oocyte maturation in fresh autologous cycles of in vitro fertilization. Fertil Steril 2008; 90: 231-3.
7. Lin MH, Wu FS, Lee RK, Li SH, Lin SY, Hwu YM. Dual trigger with combination of gonadotropin-releasing hormone agonist and human chorionic gonadotropin significantly improves the live-birth rate for normal responders in GnRH-antagonist cycles. Fertil Steril 2013; 100: 1296-302.
8. Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Hudson C. Comparison of "triggers" using leuprolide acetate alone or in combination with low-dose human chorionic gonadotropin. Fertil Steril 2011; 95: 2715-7.
9. O'Neill KE, Senapati S, Maina I, Gracia C, Dokras A. GnRH agonist with low-dose hCG (dualtrigger) is associated with higher risk of severe ovarian hyperstimulation syndrome compared to GnRH agonist alone. J Assist Reprod Genet 2016; 33: 1175-84.
10. Jung YH, Kim YY, Kim MH, Yoo YJ, Jo JD. Optimal usage of dual trigger to prevent HSS in a long protocol IVF cycle. Fertil Steril 2014; 102: 222.
11. Kim CH, Ahn JW, You RM, Kim SH, Chae HD, Kang BM. Combined administration of gonadotropin-releasing hormone agonist with human chorionic gonadotropin for final oocyte maturation in GnRH antagonist cycles for in vitro fertilization. J Reprod Med 2014; 59: 63-8.
12. Griffin D, Feinn R, Engmann L, Nulsen J, Budinetz T, Benadiva C. Dual trigger with gonadotropin-releasing hormone agonist and Standard dose human chorionic gonadotropin to improve oocyte maturity rates. Fertil Steril 2014; 102: 405-9.
13. Zilberberg E, Haas J, Dar S, Kedem A, Machtinger R, Orvieto R. Co-administration of GnRH-agonist and hCG, for final oocyte maturation (double trigger), in patients with low proportion of mature oocytes. Gynecol Endocrinol 2015; 31: 145-7.
14. Schachter M, Friedler S, Ron-El R, Zimmerman AL, Strassburger D, Bern O, et al. Can pregnancy rate be improved in gonadotropin-releasing hormone (GnRH) antagonist cycles by administering GnRH agonist before oocyte retrieval? A prospective, randomized study. Fertil Steril 2008; 90: 1087-93.
15. Veeck L. Preembryo grading. In: Veek LL, editor. Baltimore: Williams & Wilkins; 1991. p. 121-44.
16. Youssef MA, Van der Veen F, Al-Inany HG, Mochtar MH, Griesinger G, NagiMohesen M, et al. Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist-assisted reproductive technology. Cochrane Database Syst Rev 2014: CD008046.
17. Lamb JD, Shen S, McCulloch C, Jalalian L, Cedars MI, Rosen MP. Follicle-stimulating hormone administered at the time of human chorionic gonadotropin trigger improves oocyte developmental competence in in vitro fertilization cycles: a randomized, double-blind, placebo-controlled trial. Fertil Steril 2011; 95: 1655-60.
18. Kim YA, Kim MR, Lee JH, Kim JY, Hwang KJ, Kim HS, et al. Gonadotropin-releasing hormone agonist reduces aromatase cytochrome P450 and cyclooxygenase-2 in ovarian endometrioma and eutopic endometrium of patients with endometriosis. Gynecol Obstet Invest 2009; 68: 73-81.
19. Jelodar GA, Gholami S, Jafarpour F. Effect of GnRH on guinea pig endometrium at preimplantation stage. Indian J Exp Biol 2007; 45: 242-6.

20. Yu B, Ruman J, Christman G. The role of peripheral gonadotropin-releasing hormone receptors in female reproduction. Fertil Steril 2011; 95: 465-73.
21. Raga F, Casañ EM, Kruessel J, Wen Y, Bonilla-Musoles F, Polan ML. The role of gonadotropin-releasing hormone in murine preimplantation embryonic development. Endocrinology 1999; 140: 3705-12.
22. Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Thomas S. Gonadotropin-releasing hormone agonist combined with a reduced dose of human chorionic gonadotropin for final oocyte maturation in fresh autologous cycles of in vitro fertilization. Fertil Steril 2008; 90: 231-3.
23. Decleer W, Osmanagaoglu K, Seynhave B, Kolibianakis S, Tarlatzis B, Devroey P. Comparison of hCG triggering versus hCG in combination with a GnRH agonist: a prospective randomized controlled trial. Facts Views Vis Obgyn 2014; 6: 203-9.
24. Liu XJ. Targeting oocyte maturation to improve fertility in older women. Cell Tissue Res 2016; 363: 57-68.
25. Kolibianakis EM, Schultze-Mosgau A, Schroer A, Van Steirteghem A, Devroey P, Diedrich K, et al. A lower ongoing pregnancy rate can be expected when GnRH agonist is used for Triggering final oocyte maturation instead of hCG in patients undergoing IVF with GnRH antagonists. Hum Reprod 2005; 20: 2887-92.
26. Humaidan P, Bredkjaer HE, Bungum L, Bungum M, Grøndahl ML, Westergaard L, etal. GnRH agonist(buserelin) or hCG for ovulation induction in GnRH antagonist IVF/ICSI cycles: a prospective randomized study. Hum Reprod 2005; 20: 1213-20.
27. Babayof R, Margalioth EJ, Huleihel M, Amash A, Zylber-Haran E, Gal M, et al. Serum inhibin A, VEGF and TNF alpha levels after triggering oocyte maturation with GnRH agonist compared with HCG in women with polycystic ovaries undergoing IVF treatment: a prospective randomized trial. Hum Reprod 2006; 21: 1260-5.
28. Engmann L, DiLuigi A, Schmidt D, Nulsen J, Maier D, Benadiva C. The use of gonadotropin-releasing hormone (GnRH) agonist to induce oocyte maturation after cotreatment with GnRH antagonist in high-risk patients undergoing in vitro fertilization prevents the risk of ovarian hyperstimulation syndrome: a prospective randomized controlled study. Fertil Steril 2008; 89: 84-91.
29. Orvieto R, Rabinson J, Meltzer S, Zohav E, Anteby E, Homburg R. Substituting HCG with GnRH agonist to trigger final follicular maturation a retrospective comparison of three different ovarian stimulation protocols. Reprod Biomed Online 2006; 13: 198-201.
30. Kol S, Humaidan P, Itskovitz-Eldor J. GnRH agonist ovulation trigger and hCG-based, progesterone-free luteal support: a proof of concept study. Hum Reprod 2011; 26: 2874-7.

Current management of gynecologic cancer in pregnancy

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Abstract

Cancer during pregnancy is a particularly challenging complication. The incidence has increased in recent years due to childbearing at advanced maternal ages due to career choices and/or the development of reproductive technology. Approximately two thirds of cancer cases during pregnancy comprise invasive cervical cancers and breast cancer. Cancer during gestation is characterized by a need for specialized treatment due to major changes in the hormonal profile (estrogen-progesterone), metabolism (enhancement of anabolism), hemodynamic changes (hyperdynamic circulation), immunologic changes (cell-mediated and humoral immunity), and increased angiogenesis (increased blood flow towards the uterus). Moreover, the management of such patients is based on the trimester of pregnancy, type and stage of cancer, and informed consent of the mother based on her wishes. The optimal treatment of cancer during pregnancy remains elusive because there are limited data from retrospective studies with small samples. As a result, it is crucial that data regarding survival of the women and long-term follow-up of the children from different cancer centers and registries are shared. This need is dictated by the fact that the incidence of cancer during pregnancy will continue to rise as child-bearing age continues to increase. (J Turk Ger Gynecol Assoc 2018; 19: 104-10)

Keywords: Gynecologic cancer, pregnancy, breast cancer, endometrial cancer, vulvar cancer, cervical cancer

Received: 9 April, 2018 **Accepted:** 23 April, 2018

Introduction

The incidence of cancer during pregnancy is between 1/1000-1/1500 gestations (1). Importantly, the incidence has increased in recent years due to childbearing at advanced maternal age due to career choices and/or the development of reproductive technology. Approximately one third of cancer cases during pregnancy comprise invasive cervical cancers, another third of hematologic malignancies (lymphoma, leukemia), and the remaining third is mostly breast cancer (2). Cancer during gestation is characterized by a need for specialized treatment due to major changes in the hormonal profile (estrogen-progesterone), metabolism (enhancement of anabolism), hemodynamic changes (hyperdynamic circulation), immunologic changes (cell mediated and humoral immunity), and increased angiogenesis (increased blood flow towards the uterus) (3). Moreover, the management of such patients is based on the trimester of pregnancy, type and stage of cancer, and informed consent of the mother based on her wishes.

The aim of our narrative review was to discuss the current management of pregnant women who are diagnosed as having cancer based on the available current literature.

Methods

Data sources

An extensive electronic search was performed in PubMed (02/04/2018) and Scopus (02/04/2018). The adopted search strategy included the combination of the following keywords: cancer/carcinoma and/or pregnancy/gestation and management/treatment. In order to retrieve additional studies, the references of the included studies were also searched. Studies written in languages other than English were not included. The literature search had a limitation in the search range, only studies written after 1990 were considered eligible for this review. Eighteen studies were eligible to be included in our review. Studies reporting data on management of patients

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Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.2018.0044

with cancer during pregnancy were regarded as eligible for this review. Abstracts, conference papers, book chapters, animal studies, commentaries, editorials, as well as review articles were excluded from this review.

Breast cancer in pregnancy

Breast cancer is thought to be associated with gestation if it is diagnosed during or within one year of pregnancy. The incidence is 1/3000 gestations, and the average age at which it presents is 32-38 years (4). Importantly, it has been shown that the prognosis is worse if the diagnosis is made during lactation. The physiologic changes in the morphology of the mammary glands (engorgement of the breast) during pregnancy contribute to delayed diagnosis. Cancer during gestation can be diagnosed through mammogram; however, the false negative rate is high (around 25%) due to the increased density of the breast. For this reason, a biopsy of any palpable mass is essential to achieve early diagnosis. The level of radiation in diagnostic mammography is too low to harm the embryo. In addition, ultrasonography (USG)-guided biopsy is of paramount importance for diagnosis. Genetics play a major role, especially in BRCA1 and BRCA2 carriers.

Regarding treatment, the literature does not suggest a better prognosis if a pregnancy is terminated (5,6). Treatment is the same as in patients who are not pregnant. Small tumors are treated by lumpectomy, whereas larger tumors are managed by modified radical mastectomy and axillary lymph node dissection. In recent years, the role of the sentinel lymph node has also been under consideration in order to minimize the extent of dissection. According to Balaya et al. (7), the blue dye injection has a theoretical 2% anaphylactic shock rate. However, Tc-99m injection at a dose of 12.1-18.5 mBq is safe for the fetus and the obstetric outcome. Adjuvant chemotherapy can be initiated after 16 weeks' gestation, following the completion of organogenesis, while radiation is delayed until after delivery, despite evidence that radiation of the axilla or chest could be safe after the 1st trimester (8,9). External beam radiation can be used whenever the fetus can be exposed to secondary radiation due to head leakage, scatter from the machine, and scatter produced inside the patient (10). Appropriate selection of irradiation parameters and different shielding devises can minimize the risk. It seems that overall survival of patients with breast cancer diagnosed during pregnancy is worse compared with prior pregnancy controls as a principal result of a possible delayed diagnosis. The 5-year survival depends on cancer stage ranging from 85% in stage I down to 5% in stage IV (9).

Vulvar and vaginal pre-invasive and invasive lesions

Warts and intraepithelial lesions of the squamous epithelium (SIL) tend to increase in size during pregnancy. In most cases, no treatment is recommended unless the lesions are symptomatic (11). These lesions regress following delivery. Alternative forms of treatment are imiquimod (Aldara™), 5-FU, trichloroacetic acid, podophyllin, removal by laser ablation, surgical removal, loop electrosurgical excision procedure (LEEP) or cryotherapy (12).

Diagnosis of vulvar cancer during pregnancy is especially rare because it is more common in postmenopausal women, with the average age of diagnosis being 60-70 years. However, the literature describes 37 cases of vulvar cancer diagnosed during pregnancy (13,14). A systematic review of the literature shows that the mean age during diagnosis was 30.7 years old, three out of four women were diagnosed as having vulvar mass/swelling and more than 50% during the second trimester. Squamous histology was found in the majority of cases (13). Surgical removal is recommended (wide excision with unilateral or bilateral inguinal lymph node dissection) during the second or third trimester, more commonly before 36 weeks' gestation, in order for the wound to heal prior to delivery. Importantly, hemostasis is often challenging due to increased vascularity. The majority of cases result in excellent pregnancy outcomes; however, delayed diagnosis and management affect disease-free and overall survival (13).

The management of vulvar cancer in pregnancy does not differ from that in a non-pregnant patient and consists of radical vulvectomy and groin lymph node dissection when the depth of invasion is >1 mm. A systematic review concluded that in 72% of cases, the preferred procedure by gynecologic oncologists was radical vulvectomy, which was usually performed post-partum (59.3%). Less commonly, the procedure may also be performed during the second trimester, although only one patient underwent surgery in the first trimester (15). The majority of patients (95%) underwent bilateral inguinal femoral node dissection in the postpartum period. Regarding sentinel node biopsy with Tc-99m (no blue dye), only one such case has been reported in which there was no harm to the fetus (16).

Pre-invasive and invasive lesions of the cervix during pregnancy

The prevalence of human papilloma virus in women aged from 14 to 59 years is 42.5% (17). Regarding pre-invasive lesions of the cervix, 2-6.5% of cervical intraepithelial neoplasia (CIN)/ squamous intraepithelial lesion (SIL) cases present during gestation; 10-50 cases of cancer have been reported per 100,000 gestations (18). In addition, 1.9% of microinvasive cancer cases are diagnosed during pregnancy (19). Pap smears as well as colposcopy should be performed as a routine examination

for the diagnosis of pre-invasive lesions during pregnancy. During pregnancy, hypertrophy of the glandular epithelium is observed, resulting in the translocation of the transformation zone to the ectocervix. In addition, the increased vascularity, engorged cervix, and glandular hyperplasia make diagnosis through cytology and colposcopy challenging. There is a characteristic purplish hue due to the increased vascularity as well as a hypertrophy of the glandular epithelium and edema of the cervix. However, indications for colposcopy remain the same in pregnancy.

According to the literature, 0.4-10% of CIN II-III cases develop into invasive cancer (20). Conversely, 47-74% of cases regress (20-22). A conservative approach of pre-invasive lesions is necessary in order to avoid complications such as preterm labor. As a result, the patient should be monitored every 6-8 weeks, colposcopy should be performed every 12 weeks, and the patient should be reassessed 12 weeks after delivery (23,24). Treatment should be delayed until after delivery. During pregnancy, cone biopsy is recommended in patients who are suspected to have invasive cancer. However, an Israeli study suggested that LEEP during the first 15 weeks of gestation was safe and reconsideration of guidelines was proposed (25). More specifically, with a non-satisfactory colposcopy/Pap smear, adenocarcinoma in situ and microinvasive cancer are indications for a cone biopsy (24). Cone biopsy is performed during the 14-20th weeks of gestation. Postoperative complications include miscarriage (5%) and bleeding (9%) (24). Diagnostic examinations include magnetic resonance imaging (MRI) of the abdomen (use of computed tomography is limited during pregnancy), chest X-ray, carcinoembryonic antigen levels, cystoscopy, and rectal colonoscopy in order to achieve a complete staging. Counseling by a gynecologist oncologist is also recommended.

The appropriate treatment is often individualized and depends on whether the patient wishes to conserve her fertility, staging, and gestational age. More specifically, continuation of pregnancy until fetal lung maturity is achieved is suggested in stage I disease at 20 weeks' gestation and over. For stage IA1, cone biopsy is preferred with no additional treatment required (1.2% risk of lymph node metastases), with vaginal delivery being the preferred mode of delivery (23). For stage IA2, cone biopsy combined with pelvic lymph node dissection during pregnancy and excision of the cervix immediately following delivery is recommended (19). With regards to stage IA2 and IIA, a C-section followed by radical hysterectomy and lymph node dissection is recommended. Often, transposition of the ovaries out of the range of radiation, in order to conserve ovarian function is considered (26).

In a recent study by Vercellino et al. (27), laparoscopic pelvic lymphadenectomy was performed on 32 patients in their first and second trimester. The median number of excised lymph nodes was 14 (range, 8-57), and it was concluded that the optimal time for operation was prior to 22-24 weeks' gestation. In addition, no intraoperative complications were reported.

Radiation is the first choice in stage IIB or above (26). Prognosis of cervical cancer is not affected by gestation. Twenty percent of cases are diagnosed due to post-coital bleeding, and 63% do not present with an abnormal Pap smear (19). Mortality is low, and the survival rate is up to 95%.

In a recent cohort study by Bigelow et al. (28), a planned C-section was the preferred delivery method in cases of confirmed malignancy; vaginal deliveries performed on patients with microinvasive cancer or an unconfirmed diagnosis were not shown to affect disease progression and survival or cause perinatal complications. Despite these results, the authors concluded that elective C-section could be suggested as the optimal management, in view of potential local recurrence and distal metastasis (29-33).

The same study reported that survival was not affected in cases were surgical intervention was performed in the post-partum period, reporting 5-year survival rates comparable to those of large-population studies (34). Pregnant patients were not found to have any difference regarding oncologic outcome, despite the considerable delay between diagnosis and intervention. Thus, the authors suggested delaying delivery to a gestational age of 37-39 weeks, especially considering the significant morbidity and mortality associated with preterm delivery (35-38). Conversely, a number of recent publications regarding cervical cancer in pregnancy suggested preterm delivery in order to initialize treatment earlier (19,35,39). In addition, in a study by Xia et al. (33), delayed intervention was associated with decreased survival. However, this study group included a significant number of patients with malignant disease >4 cm and aggressive histopathology (33). Similar findings have not been reported by other studies (40-42).

Regarding chemotherapy, a platinum-based cisplatin is the preferred agent (50-100 mg/m^2) (19). This may be as a monotherapy or combined with paclitaxel (175 mg/m^2), bleomycin, vincristine, 5-fluorouracil or vincristine and bleomycin. Another combination that has been suggested is paclitaxel and carboplatin (43,44). It has been reported that chemotherapy should be administered every three weeks, and delivery should be scheduled at a minimum of three weeks following the final dose, in order to minimize risks of perinatal complications (45,46). Regarding intrauterine complications, it is suggested that chemotherapy should not be administered during the first trimester, due to risks of miscarriage and fetal malformation (47). More specifically, in the case of monotherapy, there is a 7.5-17% risk, and combination therapy is associated with a 25% risk (48).

The risks of chemotherapy are immediately correlated with gestational age. Exposure in weeks 1-2 (implantation phase) causes lethal mutations due to a direct effect on stem cells, and exposure between weeks 2 and 8 (organogenesis) affects the heart, limbs, and neural tube. Finally, exposure after week 8 endangers central nervous system (CNS) development as well (49). Conversely, a recent study by Köhler et al. (50) on 21 pregnant women undergoing chemotherapy with cisplatin reported no malformations or incidents of perinatal morbidity (50). Another study by Köhler et al. (50) found that levels of platinum in umbilical cord blood and amniotic fluid were lower than those in maternal blood. The authors formulated the hypothesis that the placenta provides a possible filtration mechanism.

Data on neonatal outcomes, following chemotherapy during the later stages of gestation are scarce, especially regarding long-term follow-up (51). One study by Amant et al. (52) on 70 patients followed up for a median of 22.3 months reported no adverse incidents regarding cognitive function. None of these cases included treatment in the first trimester after being exposed in utero to chemotherapy (52). Only 25 cases of neoadjuvant chemotherapy during stage IB1 have been documented. Again, there are few studies reporting long-term follow-up (51,53-56).

Endometrial cancer during pregnancy

The incidence of endometrial cancer in women aged below 40 years is very low. The majority of such patients are obese and diagnosed as having grade 1, stage I disease; however, women with low body mass index (BMI) (<25 kg/m^2) are more likely to have more aggressive tumors (clear cell or serous papillary) and/or more advanced stage (57). Gestation is a state of naturally increased progesterone, which acts protectively on the endometrium. It has been hypothesized that endometrial cancer during pregnancy might be due to an immature, progesterone-resistant endometrium. Malignancy may originate from immature basal cells, irresponsive to hormonal stimulation (58). The literature describes 31 cases of endometrial cancer stage I during pregnancy (59). Furthermore, fertility-sparing progestin therapy (oral medroxyprogesterone or/and levonorgestrel intrauterine system) is quite common nowadays in young nulliparous women. Park et al. (60) showed that pre- and post-treatment BMI <25 kg/m^2 could positively affect treatment response and recurrence rates.

Adnexal masses during pregnancy

The total incidence of adnexal masses during pregnancy is 1:500 gestations, and the incidence of ovarian cancer is 1:10,000-1:50,000 gestations (61,62). Adnexal masses are usually found incidentally during C-section (1/200-400 C-sections) (63). Of these, 33% are non-neoplastic (luteal cysts), 63% are benign (dermoid cyst 36%, serous cystadenoma 17%, mucinous cystadenoma 8%), 3% are malignant-low malignant potential and adenocarcinoma, and stromal or sex cord tumors comprise 1% (64). Germ cell tumors are more frequent in younger patients (65). However, the incidence of epithelial ovarian cancer is increasing as maternal age is also on the rise. The diagnostic tests for ovarian cancer during gestation include pelvic USG, MRI of the abdomen, chest X-ray, CA-125 (despite the fact that levels increase during pregnancy and normalize after 12 weeks gestation), alpha-fetoprotein (AFP), beta-human chorionic gonadotropin, lactase dehydrogenase, liver function tests, urea, creatinine, and intraoperative biopsy also plays a significant role.

Tumors of low malignant potential and non-epithelial tumors (e.g. sex cord tumors) are usually diagnosed at an early stage (stage I) (66), for which bilateral salpingo-oophorectomy, omentectomy and cytology at 16-18 weeks are recommended. Epithelial ovarian cancer at stage IA is treated with unilateral salpingo-oophorectomy, omentectomy, and cytology at 16-18 weeks. Further treatment is not needed and gestation can proceed safely. With regards to epithelial ovarian cancer stages IC-IV, chemotherapy should be delayed until after 12-16 weeks' gestation, and excision of the corpus luteum should be delayed until after 14 weeks' gestation (45,67). If diagnosis is made during the first trimester, pregnancy termination is recommended, followed by treatment. If the diagnosis is made during the second or third trimester, chemotherapy is administered (platine-paclitaxel) initially (63). After fetal lung maturity is achieved, C-section is performed followed by surgical tumor debulking.

In the event of suspected or confirmed cancer, surgical staging is recommended. Epithelial ovarian cancer standard treatment includes total hysterectomy, bilateral salpingo-oophorectomy, optimal debulking, followed by 6 cycles of combined carboplatin and paclitaxel (68). However, ovarian cancer during pregnancy may be treated more conservatively with ovarian cystectomy or unilateral salpingo-oophorectomy, including biopsies. Occasionally treatment will also include omentectomy, appendectomy, peritoneal biopsies, and pelvic and para-aortic lymphadenectomy (69). The aforementioned conservation of the contralateral ovary and uterus may be considered in stage IA, grade 1 to 2, following surgical staging, when histology is non-clear cell (70). Following the above, if the patient desires to continue the pregnancy, chemotherapy may be either delayed until after fetal lung maturity is achieved, and initiated after delivery, or administered neoadjuvantly (68,70). For stage III or IV, treatment varies by trimester of gestation. In the first trimester, if conservation of pregnancy prevents optimal

debulking, the pregnancy must be terminated due to the risks of chemotherapy treatment. During the second trimester, the optimal treatment is unilateral or bilateral oophorectomy, surgical excision of peritoneal tumors, omentectomy, and pelvic and para-aortic lymph node sampling and appendectomy. The above must be followed by initiation of chemotherapy and term C-section and hysterectomy. Finally, in the third trimester, chemotherapy after C-section, hysterectomy, and surgical staging are indicated (70). Several studies have reported on delaying completion of debulking until a few weeks following vaginal delivery and administering cycles of platinum-based chemotherapy. Conversely, other authors recommend a C-section after fetal lung maturity is achieved (69).

Regarding neonatal outcomes, a number of studies have shown favorable outcomes following treatment with carboplatin and paclitaxel combined during pregnancy. As mentioned above, chemotherapy is not administered during the first trimester due to the risk associated with the treatment. More specifically, teratogenesis may occur in up to 25% of cases of carboplatin treatment; the risk may be as low as 1.3% if treatment is in the second and third trimesters (71). The prognosis of ovarian cancer is not affected by gestation.

Cancer during pregnancy is a particularly challenging complication and the optimal treatment remains elusive because there are limited data from retrospective studies with small samples. As a result, it is crucial that data regarding survival of the women and long-term follow up of the children from different cancer centers and registries are shared. This need is dictated by the fact that the incidence of cancer during pregnancy will continue to rise as child-bearing age continues to increase.

Author Contributions: *Concept - C.I., E.E.M., I.D.G.; Design - C.I., E.E.M., I.D.G.; Supervision - C.I., E.E.M., I.D.G.; Materials - C.I., E.E.M., I.D.G.; Data Collection and/or Processing - C.I., E.E.M., I.D.G.; Analysis and/or Interpretation - C.I., I.D.G.; Literature Review - E.E.M., I.D.G.; Writer - C.I., E.E.M., I.D.G.; Critical Review - C.I., I.D.G.*

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

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

References

1. Esposito S, Tenconi R, Preti V, Groppali E, Principi N. Chemotherapy against cancer during pregnancy: A systematic review on neonatal outcomes. Medicine (Baltimore) 2016; 95: e4899.
2. Mahmoud HK, Samra MA, Fathy GM. Hematologic malignancies during pregnancy: A review. J Adv Res 2016; 7: 589-96.
3. Weisz B, Meirow D, Schiff E, Lishner M. Impact and treatment of cancer during pregnancy. Expert Rev Anticancer Ther 2004; 4: 889-902.
4. PDQ Adult Treatment Editorial Board. Breast Cancer Treatment During Pregnancy (PDQ®): Health Professional Version. PDQ Cancer Information Summaries [Internet]. Bethesda (MD): National Cancer Institute (US); 2002-2017 Dec 22.
5. Basta P, Bak A, Roszkowski K. Cancer treatment in pregnant women. Contemp Oncol (Pozn) 2015; 19: 354-60.
6. Keleher AJ, Theriault RL, Gwyn KM, Hunt KK, Stelling CB, Singletary SE, et al. Multidisciplinary management of breast cancer concurrent with pregnancy. J Am Coll Surg 2002; 194: 54-64.
7. Balaya V, Bonsang-Kitzis H, Ngo C, Delomenie M, Gosset M, Mimouni M, et al. What about sentinel lymph node biopsy for early breast cancer during pregnancy? J Gynecol Obstet Hum Reprod 2018; 47: 205-7.
8. Sasidharan R, Harvey V. Pregnancy and breast cancer. Obstet Med 2010; 3: 54-8.
9. Biglia N, Alessandro Peccatori F. Breast Cancer, Fertility Preservation and Reproduction. Springer International Publishing; 2015, p. 61-70.
10. Mazonakis M, Damilakis J. Estimation and reduction of the radiation dose to the fetus from external-beam radiotherapy. Phys Med 2017; 43: 148-52.
11. Tseng JY, Bastu E, Gungor-Ugurlucan F. Management of precancerous lesions prior to conception and during pregnancy: a narrative review of the literature. Eur J Cancer Care (Engl) 2012; 21: 703-11.
12. Yang LJ, Zhu DN, Dang YL, Zhao X. Treatment of condyloma acuminata in pregnant women with cryotherapy combined with proanthocyanidins: Outcome and safety. Exp Ther Med 2016; 11: 2391-4.
13. Matsuo K, Whitman SA, Blake EA, Conturie CL, Ciccone MA, Jung CE, et al. Feto-maternal outcome of pregnancy complicated by vulvar cancer: a systematic review of literature. Eur J Obstet Gynecol Reprod Biol 2014; 179: 216-23.
14. Hasanzadeh M, Zamiri-Akhlaghi A, Hassanpoor-Moghaddam M, Shahidsales S. Vulvar carcinoma in pregnant women aged less than 40 years: case report. Iran J Cancer Prev 2014; 7: 175-8.
15. Matsuo K, Whitman SA, Blake EA, Conturie CL, Ciccone MA, Jung CE et al. Feto-maternal outcome of pregnancy complicated by vulvar cancer: a systematic review of literature. Eur J Obstet Gynecol Reprod Biol 2014; 179: 216-23.
16. Nijman TA, Schutter EM, Amant F. Sentinel node procedure in vulvar carcinoma during pregnancy: A case report. Gynecol Oncol Case Rep 2012; 2: 63-4.
17. Hariri S, Unger ER, Sternberg M, Dunne EF, Swan D, Patel S, et al. Prevalence of genital human papillomavirus among females in the United States, the National Health and Nutrition Examination Survey, 2003-2006. J Infect Dis 2011; 204: 566-73.
18. Nguyen C, Montz FJ, Bristow RE. Management of stage I cervical cancer in pregnancy. Obstet Gynecol Surv 2000; 55: 633-43.
19. La Russa M, Jeyarajah AR. Invasive cervical cancer in pregnancy. Best Pract Res Clin Obstet Gynaecol 2016; 33: 44-57.
20. Mailath-Pokorny M, Schwameis R, Grimm C, Reinthaller A, Polterauer S. Natural history of cervical intraepithelial neoplasia in pregnancy: postpartum histo-pathologic outcome and review of the literature. BMC Pregnancy Childbirth 2016; 16: 74.
21. Paraskevaidis E, Koliopoulos G, Kalantaridou S, Pappa L, Navrozoglou I, Zikopoulos K, et al. Management and evolution of cervical intraepithelial neoplasia during pregnancy and postpartum. Eur J Obstet Gynecol Reprod Biol 2002; 104 : 67-9.
22. Yost NP, Santoso JT, McIntire DD, Iliya FA. Postpartum regression rates of antepartum cervical intraepithelial neoplasia II and III lesions. Obstet Gynecol 1999; 93: 359-62.

23. Han SN, Mhallem Gziri M, Van Calsteren K, Amant F. Cervical cancer in pregnant women: treat, wait or interrupt? Assessment of current clinical guidelines, innovations and controversies. Ther Adv Med Oncol 2013; 5: 211-9.
24. Gonçalves CV, Duarte G, Costa JS, Marcolin AC, Bianchi MS, Dias D, et al. Diagnosis and treatment of cervical cancer during pregnancy. Sao Paulo Med J 2009; 127: 359-65.
25. Siegler E, Lavie O, Amit A, Vaknin Z, Auslander R, Blumenfeld Z, et al. Should the Risk of Invasive Cancer in Pregnancy and the Safety of Loop Electrosurgical Excision Procedure During the First 15 Weeks Change Our Practice? J Low Genit Tract Dis 2017; 21: 299-303.
26. Eitan R, Abu-Rustum NR. Management of cervical carcinoma diagnosed during pregnancy. Primary care update for Ob/Gyns 2003; 10; 196-200.
27. Vercellino GF, Koehler C, Erdemoglu E, Mangler M, Lanowska M, Malak AH, et al. Laparoscopic pelvic lymphadenectomy in 32 pregnant patients with cervical cancer: rationale, description of the technique, and outcome. Int J Gynecol Cancer 2014; 24: 364-71.
28. Bigelow CA, Horowitz NS, Goodman A, Growdon WB, Del Carmen M, Kaimal AJ. Management and outcome of cervical cancer diagnosed in pregnancy. Am J Obstet Gynecol 2017; 216: 276.e1-276.e6.
29. Sood AK, Sorosky JI, Mayr N, Anderson B, Buller RE, Niebyl J. Cervical cancer diagnosed shortly after pregnancy: prognostic variables and delivery routes. Obstet Gynecol 2000; 95: 832-8.
30. Cliby WA, Dodson MK, Podratz KC. Cervical cancer complicated by pregnancy: episiotomy site recurrences following vaginal delivery. Obstet Gynecol 1994; 84: 179-82.
31. Goldman NA, Goldberg GL. Late recurrence of squamous cell cervical cancer in an episiotomy site after vaginal delivery. Obstet Gynecol 2003; 101: 1127-9.
32. Baloglu A, Uysal D, Aslan N, Yigit S. Advanced stage of cervical carcinoma undiagnosed during antenatal period in term pregnancy and concomitant metastasis on episiotomy scar during delivery: a case report and review of the literature. Int J Gynecol Cancer 2007; 17: 1155-9.
33. Xia T, Gao Y, Wu B, Yang Y. Clinical analysis of twenty cases of cervical cancer associated with pregnancy. J Cancer Res Clin Oncol 2015; 141: 1633-7.
34. SEER. Stat fact sheet: cervix uteri cancer. Available at: http://seer.cancer.gov/statfacts/html/cervix.html. Accessed March 28, 2017.
35. Greer BE, Easterling TR, McLennan DA, Benedetti TJ, Cain JM, Figge DC, et al. Fetal and maternal considerations in the management of stage I-B cervical cancer during pregnancy. Gynecol Oncol 1989; 34: 61-5.
36. Engle WA, Tomashek KM, Wallman C; Committee on Fetus and Newborn, American Academy of Pediatrics. "Late-preterm" infants: a population at risk. Pediatrics 2007; 120: 1390-401.
37. Leone A, Ersfeld P, Adams M, Schiffer PM, Bucher HU, Arlettaz R. Neonatal morbidity in singleton late preterm infants compared with full-term infants. Acta Paediatr 2012; 101: 6-10.
38. Sengupta S, Carrion V, Shelton J, Wynn RJ, Ryan RM, Singhal K, et al. Adverse neonatal outcomes associated with early-term birth. JAMA Pediatr 2013; 167: 1053-9.
39. Mogos MF, Salemi JL, Sultan DH, Shelton MM, Salihu HM. Trends in Cervical Cancer Among Delivery-Related Discharges and its Impact on Maternal-Infant Birth Outcomes (United States, 1998-2009). Open Nurs J 2015; 9: 42-50.
40. Zemlickis D, Lishner M, Degendorfer P, Panzarella T, Sutcliffe SB, Koren G. Maternal and fetal outcome after invasive cervical cancer in pregnancy. J Clin Oncol 1991; 9: 1956-61.
41. Germann N, Haie-Meder C, Morice P, Lhomme C, Duvillard P, Hacene K, et al. Management and clinical outcomes of pregnant patients with invasive cervical cancer. Ann Oncol 2005; 16: 397-402.
42. Kärrberg C, Rådberg T, Holmberg E, Norström A. Support for down-staging of pregnancy-associated cervical cancer. Acta Obstet Gynecol Scand 2015; 94: 654-9.
43. Zagouri F, Sergentanis TN, Chrysikos D, Bartsch R. Platinum derivatives during pregnancy in cervical cancer: a systematic review and meta-analysis. Obstet Gynecol 2013; 121: 337-43.
44. Robova H, Halaska MJ, Pluta M, Skapa P, Matecha J, Lisy J, et al. Oncological and pregnancy outcomes after high-dose density neoadjuvant chemotherapy and fertility-sparing surgery in cervical cancer. Gynecol Oncol 2014; 135: 213-6.
45. Amant F, Halaska MJ, Fumagalli M, Dahl Steffensen K, Lok C, Van Calsteren K, et al. Gynecologic cancers in pregnancy: guidelines of a second international consensus meeting. Int J Gynecol Cancer 2014; 24: 394-403.
46. Brewer M, Kueck A, Runowicz CD. Chemotherapy in pregnancy. Clin Obstet Gynecol 2011; 54: 602-18.
47. Cardonick E, Iacobucci A. Use of chemotherapy during human pregnancy. Lancet Oncol 2004; 5: 283-91.
48. Weisz B, Schiff E, Lishner M. Cancer in pregnancy: maternal and fetal implications. Hum Reprod Update 2001; 7: 384-93.
49. Schoenwolf GC, Bleyl SB, Brauer PhR, et al. Larsen's human embryology. 4th ed. Oxford, UK: Churchill Livingstone; 2008.
50. Köhler C, Oppelt P, Favero G, Morgenstern B, Runnebaum I, Tsunoda A, et al. How much platinum passes the placental barrier? Analysis of platinum applications in 21 patients with cervical cancer during pregnancy. Am J Obstet Gynecol 2015; 213: 206.e1-5.
51. Amant F, Vandenbroucke T, Verheecke M, Fumagalli M, Halaska MJ, Boere I, et al. Pediatric Outcome after Maternal Cancer Diagnosed during Pregnancy. N Engl J Med 2015; 373: 1824-34.
52. Amant F, Van Calsteren K, Halaska MJ, Gziri MM, Hui W, Lagae L, et al. Long-term cognitive and cardiac outcomes after prenatal exposure to chemotherapy in children aged 18 months or older: an observational study. Lancet Oncol 2012; 13: 256-64.
53. Marnitz S, Köhler C, Oppelt P, Schmittel A, Favero G, Hasenbein K, et al. Cisplatin application in pregnancy: first in vivo analysis of 7 patients. Oncology 2010; 79: 72-7.
54. Fruscio R, Villa A, Chiari S, Vergani P, Ceppi L, Dell'Orto F, et al. Delivery delay with neoadjuvant chemotherapy for cervical cancer patients during pregnancy: a series of nine cases and literature review. Gynecol Oncol 2012; 126: 192-7.
55. Ayhan A, Dursun P, Karakaya BK, Ozen O, Tarhan C. Neoadjuvant chemotherapy followed by cesarean radical hysterectomy in a triplet pregnancy complicated by clear cell carcinoma of the cervix: a case presentation and literature review. Int J Gynecol Cancer 2012; 22: 1198-202.
56. Gambino A, Gorio A, Carrara L, Agoni L, Franzini R, Lupi GP, et al. Cancer in pregnancy: maternal and fetal implications on decision-making. Eur J Gynaecol Oncol 2011; 32: 40-5.
57. Duska LR, Garrett A, Rueda BR, Haas J, Chang Y, Fuller AF. Endometrial cancer in women 40 years old or younger. Gynecol Oncol 2001; 83: 388-93.
58. Hoellen F, Reibke R, Hornemann K, Thill M, Luedders DW, Kelling K, et al. Cancer in pregnancy. Part I: basic diagnostic and therapeutic principles and treatment of gynecological malignancies. Arch Gynecol Obstet 2012; 285: 195-205.
59. Ilancheran A, Low J, Ng JS. Gynaecological cancer in pregnancy. Best Pract Res Clin Obstet Gynaecol 2012; 26: 371-7.
60. Park JY, Seong SJ, Kim TJ, Kim JW, Bae DS, Nam JH. Significance of body weight change during fertility-sparing progestin therapy in young women with early endometrial cancer. Gynecol Oncol 2017; 146: 39-43.
61. Cavaco-Gomes J, Jorge Moreira C, Rocha A, Mota R, Paiva V, Costa A. Investigation and Management of Adnexal Masses in Pregnancy. Scientifica (Cairo) 2016; 2016: 3012802.

62. Marret H, Lhommé C, Lecuru F, Canis M, Lévèque J, Golfier F, et al. Guidelines for the management of ovarian cancer during pregnancy. Eur J Obstet Gynecol Reprod Biol 2010; 149: 18-21.
63. Schwartz N, Timor-Tritsch IE, Wang E. Adnexal masses in pregnancy. Clin Obstet Gynecol 2009; 52: 570-85.
64. Owens GL, Kitchener HC. Premalignant disease in the genital tract in pregnancy. Best Pract Res Clin Obstet Gynaecol 2016; 33: 33-43.
65. Iavazzo C, Vorgias G, Iavazzo PE, Gkegkes ID. Fertility sparing approach as the standard of care in young patients with immature teratomas. J Turk Ger Gynecol Assoc 2017; 18: 43-7.
66. Iavazzo C, Gkegkes ID, Vrachnis N. Primary peritoneal cancer in BRCA carriers after prophylactic bilateral salpingo-oophorectomy. J Turk Ger Gynecol Assoc 2016; 17: 73-6.
67. Grimm D, Woelber L, Trillsch F, Keller-v Amsberg G, Mahner S. Clinical management of epithelial ovarian cancer during pregnancy. Eur J Cancer 2014; 50: 963-71.
68. Stuart GC, Kitchener H, Bacon M, duBois A, Friedlander M, Ledermann J, et al2010 Gynecologic Cancer InterGroup (GCIG) consensus statement on clinical trials in ovarian cancer: report from the Fourth Ovarian Cancer Consensus Conference. Int J Gynecol Cancer 2011; 21: 750-5.
69. Modares Gilani M, Karimi Zarchi M, Behtash N, Ghaemmaghami F, Mousavi AS, Behnamfar F. Preservation of pregnancy in a patient with advanced ovarian cancer at 20 weeks of gestation: case report and literature review. Int J Gynecol Cancer 2007; 17: 1140-3.
70. Minig L, Otaño L, Diaz-Padilla I, Alvarez Gallego R, Patrono MG, Valero de Bernabé J. Therapeutic management of epithelial ovarian cancer during pregnancy. Clin Transl Oncol 2013; 15: 259-64.
71. Doll DC, Ringenberg QS, Yarbro JW. Management of cancer during pregnancy. Arch Intern Med 1988; 148: 2058-64.

What is your diagnosis?

A 28-year-old pregnant patient in her 27th week of pregnancy with G2P0 was referred to our clinic due to the detection of a mass in the baby's heart. In an echocardiographic examination, a 13x6 mm hyperechogenic mass that was moving together with the pulmonary valve, and hypertrophy in the right ventricle were observed (Figure 1). No chromosome anomalies were detected in the genetic analysis performed via cordocentesis. The pregnant patient was sent to another hospital where she delivered the baby. The baby underwent surgery on the 20th day and died on the 10th postoperative day.

Received: 2 May, 2018 **Accepted:** 10 May, 2018

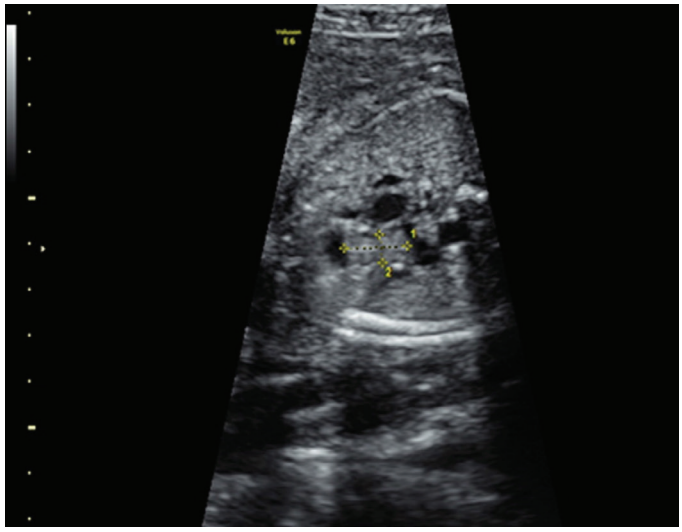

Figure 1. Ultrasonographic image of the mass

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Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.2018.0061

Answer

Primary cardiac tumors are mesenchymal or hamartomatous nodules originating from the heart layers located in the heart or pericardium. These tumors are rarely seen, but the diagnostic rates are increasing with the recent use of echocardiography. Metastatic cardiac tumors have also been described, but they are even rarer. Rhabdomyosarcomas are usually encapsulated and numerous. These are the most common, accounting for three-quarters of the cardiac masses detected in fetuses and newborns. Ninety percent of them are multiple and they tend to grow into cavities. The most common complications are hydrops fetalis, ventricular outflow obstruction, arrhythmia, and cardiac shock. Surgical treatment should be undertaken if it leads to mechanical stenosis in the heart or causes life-threatening arrhythmia (1). Intrauterine diagnosis is quite difficult. Most diagnoses are postpartum, ranging from 4.3 months to 18 years on average (2). The second most common type is teratomas, which form 15% of cardiac tumors, are single and encapsulated, and tend to grow in the pericardial cavities. Fibroma, hemangiomas, and myomas (less than 5%) are even less common. The rarest are lipomas. Myxomas are the most common benign tumors in adults and constitute approximately 50% of masses in the heart. However, very few cases have been reported during the neonatal period. Diagnosis is usually postpartum, but intrauterine diagnosis can be made in very few cases (3). These appear as echogenic, long pedunculated lesions in the 23rd gestational week with echocardiography. More than 90% are benign.

We present the following case because it is still difficult to diagnose intrauterine primary cardiac tumors.

The baby was diagnosed as having myxoma. A total of 32 fetal cardiac myxoma cases have been reported in the literature. Our case is the 33rd. It is usually seen in the left ventricle and the rarest site is the left atrium. In our case, the mass was located in the right ventricle. The localization and size of the mass may be predictive for prognosis. Echocardiography is the most reliable method for diagnosing myxoma as it is in diagnosing other cardiac tumors. It was reported that in the echocardiography performed in the 23rd gestational week, the myxoma was seen as a soft and echogenic mass with a long pedunculated lesion (4). Although standard therapy is surgical resection, an appropriate approach to embolism risk should be identified. Small and unobstructed immobile masses may be left and monitored, but large tumors bearing embolism risk and obstruction should be treated surgically. In utero open surgery in immature fetuses with hydrops can be an option. Small tumors, especially those on the heart wall and not protruding into the cavity, may not be easy to recognize. In particular, masses in the papillary muscle, seen as echogenic foci, may mimic rhabdomyomas. Rhabdomyomas are usually multiple nodular and echogenic masses seen in the atrium or ventricles. Myxomas are usually located in the atrium and move with cardiac contractions.

Growing tumors can cause cardiac tamponade, heart dysfunction, hydrops fetalis, and death. A different feature of cardiac rhabdomyomas from other primary cardiac tumors is tuberous sclerosis and its genetic background. Tuberous sclerosis was detected in approximately 76% of cases in which rhabdomyomas were detected. Most cases of tuberous sclerosis can be recognized by deletion mutations in the TSC2 and PKD1 genes (5). Fetal cardiac tumors may generally be recognized during the 20th-30th weeks of gestation. The earliest reported case week is 17. The most important method of diagnosis is echocardiography. Findings such as cardiomegaly, pericardial effusion, arrhythmia, and ventricular outflow obstructions suggest a tumor.

In conclusion we do not think it is appropriate to present termination as an option for pregnancies with primary fetal cardiac tumors because of the difficulty of intrauterine diagnosis.

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References

1. Padalino MA, Basso C, Milanesi O, Vida VL, Moreolo GS, Thiene G, et al. Surgically treated primary cardiac tumors in early infancy and childhood. J Thorac Cardiovasc Surg 2005; 129: 1358-63.
2. Padalino MA, Vida VL, Boccuzzo G, Tonello M, Sarris GE, Berggren H, et al. Surgery for primary cardiac tumors in children: early and late results in a multicenter European Congenital Heart Surgeons Association study. Circulation 2012; 126: 22-30.
3. Rios JC, Chávarri F, Morales G, Vera L, Adrianzén M, Abarca A, et al. Cardiac Myxoma With Prenatal Diagnosis. World J Pediatr Congenit Heart Surg 2012; 4: pp. 210-212
4. Paladini D, Tartaglione A, Vassallo M, Martinelli P. Prenatal ultrasonographic findings of a cardiac myxoma. Obstet Gynecol 2003; 102: 1174-6.
5. Zhang YX, Meng H, Zhong DR, Jiang YX, Dai Q, Zhang H. Cardiac rhabdomyoma and renal cyst in a fetus: early onset of tuberous sclerosis with renal cystic disease. J Ultrasound Med 2008; 27: 979-82.

Letter from a young female physician, *Candidate*

To the Editor,

In 2017, Suzanne Koven, M.D. wrote an outstanding letter to young female physicians (1). In her article, she drew attention to the struggles of the female physicians from different perspectives, as a medical student, a resident, a pregnant woman, an internal medicine specialist, as an academic, but most importantly as a woman! Maybe, she wrote what is already known! Her examples included additional challenges for women, their "pointless" presence at the urology clerkship, being paid less than their male counterparts, "bro humor" in the Department of Obstetrics and Gynecology despite the fact that they were the majority, and higher rates of imposter syndrome being seen in them (1). Nevertheless, a study published by JAMA in 2017 revealed that female internists had better patient outcomes than their male counterparts (2). Another study published by the BMJ in 2017 concluded that female surgeons had lower mortality rates than their male counterparts (3). On the other hand, the percentages of female physicians in the United States of America, Iceland, the European Union, Germany, and Turkey are approximately 34%, 37%, 48%, 46%, and 40% respectively (4,5). Although Turkey is a developing country, it demonstrates less unequal sex distribution among physicians than some of the developed countries (4,5). Hence, I am proud to observe this as a Turkish female medical student.

As a young female physician, and a very passionate candidate to be a gynecologist, I would like to emphasize that the key message from those two studies is not "women are better internists and surgeons than men" (4,5). As a matter of fact, it is that as physicians, our primary purpose is to exhibit our knowledge and skills for the best interest of our patients for whom we should be ready to accept our limitations and acknowledge our colleagues! Furthermore, above all, we must not discriminate against them based on their sexes but their profession. Hence, we are better together for our patients!

I read her article on the day that it was published with both delight and sadness. With the above ideas in my mind and my own experience, I wrote a message to her without the hope of that I would receive her reply. Two days later, I was honored to receive her comments regarding my "hopeless" message. First of all, I could not convince myself that as a medical student, I had received an answer from a future colleague from Harvard Medical School and an author of an NEJM article. However, it was real and I started writing a reply with my shaking hands… Since then, Dr. Koven and I have become friends, and I am honored to have her moral support.

As a medical student, I felt deep sorrow and empathy for Dr. Koven's experiences. The main reason for it is that in 2017 "we," the female physicians, are still exposed to a considerable amount of discrimination by our male counterparts and our female counterparts who were trained and worked under harsh conditions. Nevertheless, I must say that I had both the opportunity and the courage to write this letter only thanks to my extraordinary female colleagues namely Dr. Suzanne Koven and Dr. Emine Elif Vatanoğlu-Lutz.

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References

1. Koven S. Letter to a young female physician. N Engl J Med 2017; 376: 1907-9.
2. Tsugawa Y, Jena AB, Figueroa JF, Orav EJ, Blumenthal DM, Jha AK. Comparison of Hospital Mortality and Readmission Rates for Medicare Patients Treated by Male vs Female Physicians. JAMA Intern Med 2017; 177: 206-13.
3. Wallis CJ, Ravi B, Coburn N, Nam RK, Detsky AS, Satkunasivam R. Comparison of postoperative outcomes among patients treated by male and female surgeons: a population based matched cohort study. BMJ 2017; 359: j4366.
4. European Commission, Eurostat Health Care Database. Physicians by sex and age. 2017; Retrieved from ec.europa.eu/eurostat/web/health/health-care/data/database Accessed 6 Jan. 2018.
5. Association of American Medical Colleges. Active Physicians by Sex and Specialty, 2015; Retrieved from https://www.aamc.org/data/workforce/reports/458712/1-3-chart.html Accessed 6 Jan. 2018.

Received: 8 January, 2018 **Accepted:** 2 February, 2018

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Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.2018.0006

Highlights and future directions from the European Gynecological Oncology Congress 2017

To the Editor;

The European Gynecological Oncology Congress, 2017, was held in Vienna between November 4th-7th with more than 3200 participants and over 1300 abstracts. Some studies will draw perspectives for the future and innovate many researchers in new eras.

Nowadays, less radical cancer surgery is a topic of discussion to prevent morbidities. On the other hand, molecular and genomic research is increasing tremendously to solve the problem completely.

The Lymphadenectomy in Ovarian Neoplasms study by Lorusso et al. (1) evaluated the role of systematic pelvic and paraaortic lymphadenectomy in patients with advanced ovarian cancer. Six hundred forty-seven FIGO IIB-IV patients with epithelial ovarian, fallopian tube or primary peritoneal cancer were randomized in a ratio of 1:1 as those with and without excision of pelvic and paraaortic lymph nodes after macroscopic complete resection of intraperitoneal tumor sites in the absence of bulky lymph nodes pre and intraoperatively. Total operation time, blood loss, number of blood transfusions, re-laparotomy and re-admission rates, and intensive care unit administration were decreased significantly with no lymph node excision (LNE). The median progression-free survival was 26 months after platinum-based chemotherapy in both arms, and the overall survival was 66 and 69 months in the LNE and no-LNE arms, respectively. It is worth reminding that omitting lymphadenectomy in clinically negative lymph nodes improves morbidity and mortality rates in terms of advanced ovarian cancer surgery, without any harm to survival periods.

Cervical cancer is generated by human papilloma virus (HPV) infection and the efficacy of HPV vaccines for the prevention of cervical cancer has previously been documented with bivalent and quadrivalent HPV vaccines. The 9-valent HPV vaccine targets HPV type 6, 11, 16, 18 and 31, 33, 45, 52, 58. Joura (2) randomized 14215 participants to 3 doses of 9-valent HPV vaccine and 3 doses of quadrivalent HPV vaccine. After 6 years of follow-up, incidence of HPV types 6, 11, 16, and 18-related infection, cytologic abnormalities, and treatment rates were similar in both groups; however, HPV types 31, 33, 45, 52, and 58-related infections and cytologic abnormalities were less common in the 9-valent group with an antibody efficacy of 5 years.

Despite efforts to prevent HPV infection before serious high-grade cervical preinvasive lesions, whether high-grade lesions or cervical carcinoma can be treated with vaccines is a matter of research. Park et al. (3) reported the latest study on GX-188E, a DNA therapeutic vaccine encoding for HPV types 16/18 - E6/E7. GX-188E had a successful phase I trial on nine patients, seven of whom had complete regression of cervical intraepithelial neoplasia 3 (CIN3). Sixty-eight patients with confirmed CIN3 and HPV 16 or 18 were randomized to 1 mg or 4 mg GX-188E at weeks 0, 4, and 12 (1:1). At week 20 and 36, 51.5% and 59.4% of patients regressed to CIN1, respectively. Small lesions (<50% of cervix by gross colposcopic evaluation) had better regression rates (78.8% vs 38.7%) and 1 mg of GX-188E had higher rates, albeit not significant, of regression at week 36 when compared with 4 mg of GX-188E (66.7% vs 52.9%).

New HPV vaccines, with regard to prevention and treatment, will have a role in the limitation and possibly the eradication of cervical cancer.

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Received: 10 January, 2018 **Accepted:** 23 January, 2018

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Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.2018.0007

References

1. Lorusso D, Sehouli J, Reuss A, Vergote I , Marth C, Kim JW, et al. LION – lymphadenectomy in ovarian neoplasms. a prospective randomized AGO study group led gynecologic cancer intergroup trial. European Gynaecological Oncology Congress; 2017.
2. Joura E. Long-term efficacy and immunogenicity of the 9-valent human papillomavirus vaccine: final analyses of a double-blind, randomized clinical study. European Gynaecological Oncology Congress; 2017.
3. Park SH, Lee K, Kim J, Choi Y, Lee S. Therapeutic HPV vaccine-is it clinically useful? European Gynaecological Oncology Congress 2017 (ESGO) 2017; ESGO7-1296.

CONGRESS CALENDER

INTERNATIONAL MEETINGS

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

June 7-9, 2018	**42nd National Congress of the Italian Society of Urodynamics 2018, Napoli, Italy**
June 10-13, 2018	**41st Nordic Congress of Obstetrıcs and Gynecology 2018, Odense, Denmark**
June 14, 2018	**Begin Before Birth 2018, London, United Kingdom**
June 24-28, 2018	**17th World Congress in Fetal Medicine 2018, Athens, Greece**
June 26-29, 2018	**Society of Obstetricians and Gynecologists of Canada 74th Annual Clinical Meeting 2018, Victoria, BC, Canada**
June 27-30, 2018	**International Urogynecological Association 43rd Annual Meeting 2018, Vienna, Austria**
June 28-July 3, 2018	**38th Annual Meeting of the American Society for Reproductive Immunology and 6th Annual Meeting of the Chinese Society for Reproductive Immunology 2018, Shanghai, China**
July 1-4, 2018	**European Society of Human Reproduction and Embryology 34th Annual Meeting 2018, Barcelona, Spain**
July 8-11, 2018	**22nd International Conference on Prenatal Diagnosis and Therapy 2018, Antwerp, Belgium**
August 1-4, 2018	**25th Annual Summer Conference on Obstetrics and Gynecology 2018, Naples, United States**
August 28-31, 2018	**International Continence Society 48th Annual Meeting 2018, Philadelphia, Pennsylvania, United States**
September 5-8, 2018	**26th European Congress of Perinatal Medicine 2018, Saint Petersburg, Russia**
September 7-9, 2018	**International Society for the Study of Vulvovagınal Disease 24th Congress 2018, Chicago, United States**
September 20-22, 2018	**32nd Annual Fall Conference on High Risk Obstetrics 2018, San Francisco, United States**
September 27-29, 2018	**Society of European Robotic Gynecological Surgery 10th Annual Meeting 10 Years of Robotic Surgery 2018, Milano, Italy**
October 3-6, 2018	**North American Menopause Society 29th Annual Meeting 2018, San Diego, United States**
October 6-10, 2018	**American Society for Reproductive Medicine Annual Meeting 2018, Denver, United States**
October 7-10, 2018	**European Society for Gynecological Endoscopy 27th Annual Congress 2018, Vienna, Austria**
October 9-13, 2018	**American Urogynecologic Society Pelvic Floor Disorders Week 2018, Chicago, United States**
October 14-19, 2018	**22nd FIGO World Congress of Gynecology and Obstetrics 2018, Rio De Janeiro, Brazil**
October 18-21, 2018	**International Pelvic Pain Society Annual Meeting 2018, Chicago, United States**
October 20-24, 2018	**28th World Congress on Ultrasound in Obstetrics and Gynecology 2018, Singapore**
October 25-27, 2018	**11th Annual Congress of the European Urogynecological Association | Leading Lights in Urogynecology 2018, Milano, Italy**
October 26-27, 2018	**Comprehensive Laparoscopic Gynecology Course 2018, Hamilton, Ontario, Canada**
November 11-15, 2018	**47th AAGL Global Congress on Minimally Invasive Gynecology 2018, Las Vegas, United States**

CONGRESS CALENDER

NATIONAL MEETINGS

(for detailed International Meeting please go website:
http://www.kongre2017.com)

May 31-June 2, 2018	**Türkiye Maternal Fetal Tıp ve Perinatoloji Derneği Kongresi, Ankara, Turkey**
June 21-23, 2018	**Ege Jinekolojik Endoskopi Sempozyumu ve Laparoskopik Sütür Kursu, İzmir, Turkey**
June 10, 2018	**IVF'de Güncel Yaklaşımlar Sempozyumu, İstanbul, Turkey**
September 6-9, 2018	**6. Uluslararası Ürojinekoloji Kongresi, İstanbul, Turkey**
September 20-21, 2018	**36. Zeynep Kamil Jineko-Patoloji Kongresi, İstanbul, Turkey**
September 27-30, 2018	**10. Ulusal Obstetrik ve Jinekolojik Ultrasonografi Kongresi, Muğla, Turkey**
September 27-30, 2018	**1. Uluslararası Rekonstruktif - Estetik Genital Cerrahi & Seksoloji Kongresi, İstanbul, Turkey**
October 3-5, 2018	**Anne Sütü ve Emzirme Kongresi, İzmir, Turkey**
October 4-7, 2018	**Ovülasyon İndüksiyonu ve İnfertilitede Güncel Yaklaşımlar, Muğla, Turkey**
October 5-7, 2018	**2. Uluslararası Katılımlı Health 4.0 Sağlıkta Yenilikler Kongresi, İstanbul, Turkey**
October 25-28, 2018	**Kozmetoloji ve Kozmetik Jinekoloji Kongresi, İstanbul, Turkey**
November 8-11, 2018	**TSRM Kongresi, Antalya, Turkey**
November 17-18, 2018	**2. Türk-Rus Ürojinekoloji Sempozyumu, İstanbul, Turkey**
November 21-25, 2018	**Ulusal Jinekolojik Onkoloji Kongresi, Antalya, Turkey**

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*Jeannerot F ve ark. Exp Opin Drug Deliv 2016; 13(9): 1221-9.

Ürün bilgisi için lütfen standımıza başvurunuz.

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NOTES

NOTES

2. jenerasyon DMAH[1]

HIBOR®

Bemiparin Sodyum

Antitrombotik tedavide ve profilakside doğru yerdesiniz!

Düşük kanama riski[1]

En düşük molekül ağırlıklı DMAH[1]

Günde tek doz[2]

Yüksek Anti-FXa aktivitesi[1]

Yüksek antitrombotik etki[1]

VTE profilaksisi için doz şeması[2]

Medikal/cerrahi profilakside:
HIBOR® 3.500 IU / 0,2 ml - (Günde tek doz)

VTE Riski
Orta ve yüksek

VTE tedavisi için doz şeması[2]

	Ağırlık
HIBOR® 5.000 IU / 0,2 ml - (Günde tek doz)	<50 kg
HIBOR® 7.500 IU / 0,3 ml - (Günde tek doz)	50 kg - 70 kg
HIBOR® 10.000 IU / 0,4 ml - (Günde tek doz)	70 kg - 100 kg

100 kg üzerindeki hastalar için 115 IU/kg/gün şeklinde hesaplama yapılmalıdır.

VTE : Venöz tromboembolizm

Günde tek doz ile[2] 24 saat boyunca etkinlik[1]

Referanslar: 1. Planès A. Review of bemiparin sodium - a new second-generation low molecular weight heparin and its applications in venous thromboembolism. Expert Opin Pharmacother. 2003; 4(6): 1551-1561. 2. HIBOR® KÜB.

HIBOR® Kullanıma Hazır Enjektör Steril - Apirojen
HIBOR® 3.500 IU/0.2 mL kullanıma hazır enjektör. **Etkin madde:** Bemiparin sodium. Anti-Xa/anti-IIa oranı yaklaşık 8'dir. **Terapötik endikasyonlar:** Genel cerrahi ve ortopedik cerrahi girişim yapılacak hastalarda tromboembolinin önlenmesi, yüksek ya da orta dereceli risk taşıyan cerrahi dışı hastalarda tromboembolinin önlenmesi, derin ven trombozu ve geçici olarak yüksek risk faktörleri olan hastalarda venöz tromboembolizm nükslerinin ikincil önlenmesi, pulmoner embolinin eşlik ettiği veya tek başına seyreden derin ven trombozu tedavisi, hemodiyaliz sırasında ekstrakorporeal devrede pıhtılaşmanın önlenmesi. **Uygulama şekli:** Subkutan enjeksiyonla uygulanır. Böbrek ve karaciğer yetmezliği olan hastalarda dikkatli kullanılmalıdır. **Pediyatrik popülasyon:** Çocuklarda bemiparin kullanımının güvenliği ve etkinliği henüz kanıtlanmadığından, çocuklarda kullanılması önerilmez. **Kontrendikasyonlar:** Bemiparin sodyum ve heparin ve diğer düşük molekül ağırlıklı heparine (DMAH) karşı aşırı duyarlılık durumlarında, doğrulanmış ya da şüphenilen, immün kaynaklı, heparin ile indüklenen trombositopeni öyküsü varlığında, hemostazın bozulmasına bağlı kanama riskinde artış ya da aktif hemoraji varlığında, karaciğer ve/veya pankreasın ciddi rahatsızlıklarında, son iki ay içinde geçirilmiş santral sinir sistemi, göz ve kulak yaralanmaları ya da ameliyatlarında, heparin ile indüklenen trombositopeniye bağlı Yaygın Damariçi Koagülasyon Bozukluğu (DİC) varlığında, akut bakteriyel endokarditli olanlarda ve kanama riski yüksek organik lezyon (örn. Aktif peptik ülser, hemorajik inme, serebral anevrizma ya da serebral neoplazm) bulunması durumlarında kontrendikedir. **Gebelik ve laktasyon:** Gebelik kategorisi: B **Gebelik dönemi:** Gebelerde bemiparin kullanımı değerlendirmek yeterli veri mevcut değildir. Bu nedenle gebelerde bemiparin kullanımında dikkatli olunmalıdır. **Doz aşımı ve tedavisi:** Aşırı doz durumunda ana semptom olarak kanama görülür. Hafif hemorajiler nadiren özel tedavi gerektirir. Şiddetli hemoraji durumunda protamin sülfat kullanılması gerekebilir. Protamin sülfat, uygulanan her 100 IU anti-Xa'da 1.4 mg protamin sülfat dozunda, i.v. uygulamadan 2 saat sonra anti-Xa aktivitesi üzerinde kısmi bir azalma yaratır. Hemorajinin şiddetine ve trombor riskine bağlı olarak bemiparin uygulamasına son verilmesi gerekebilir. **Raf ömrü:** 24 ay **Saklamaya yönelik özel tedbirler:** 25°C'nin altındaki oda sıcaklığında saklanmalıdır. **Ticari Takdim Şekli ve 19.02.2018 tarihli PSF'leri:** HIBOR® 3.500 IU/0,2 ml 10 enj 124,70 TL; HIBOR® 5.000 IU/0,2 ml 2 enj 72,26 TL; HIBOR® 7.500 IU/0,3 ml 2 enj 81,41 TL; HIBOR® 10.000 IU/0,4 ml 2 enj 102,73 TL. Preparat dondurulmamalıdır. **RUHSAT NUMARASI:** 123/63 **İLK RUHSAT TARİHİ:** 28.12.2007 **RUHSAT SAHİBİ:** Dem İlaç San. ve Tic. A.Ş. Dem Plaza İnönü Mah. Kayışdağı Cad. No: 172 34755 Ataşehir - İSTANBUL Tel: 0216 428 40 29

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BAYER

Tecrübesiyle Güven Verir[1,2]

- Akne tedavisi ve tüylenmede azalma[1]
- Antimineralokortikoid etkiyle kilo aldırmama[1]
- İyi siklus kontrolü[2]

Kesintisiz Konfor Sağlar[3,4]

- Düşük dozla daha iyi tolerabilite[3,4]
- 24+4 rejim ile kullanım kolaylığı ve yan etkilerde azalma[3,4]
- Akne tedavisi ve tüylenmede azalma[3,4]
- Antimineralokortikoid etkiyle kilo aldırmama[3,4]
- Adet öncesi gerginlik endikasyonu[4]

Doğal Ritmi Korur[5-8]

- E_2V - doğala özdeş östrojen ile yan etkilerde azalma[5]
- Kesintisiz ve dinamik doz rejimi ile doğal hormon seviyelerine uyum[5]
- Şiddetli adet kanaması endikasyonu[6,7]
- Yüksek kullanıcı memnuniyeti[8]

LTR.MKT.WH.01.2018.0659

Referanslar: 1. Yasmin® Kısa Ürün Bilgisi. **2.** Kelly S, et al. Clin Drug Investig 2010;30 (5):325-36. **3.** Bachmann G, et al. Contraception 2004;70:191-8. **4.** Yazz® Kısa Ürün Bilgisi. **5.** Fruzetti F, et al. Gynecological Endocrinology 2012; 28(5): 400-8 **6.** Qlairista® Kısa Ürün Bilgisi. **7.** Fraser Iset al. Eur J Contracept Reprod Health Care. 2011;16(4):258-69 **8.** S. Palacios et al. European Journal of Obstetrics & Gynecology and Reproductive Biology 149 (2010) 57–62