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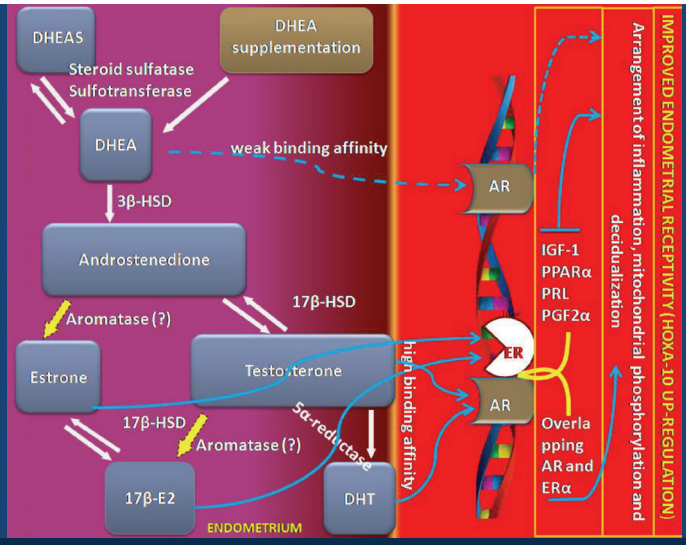

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Cover Picture: DHEA and Endometrium Receptivity. Celik et al. *(Page 165)*

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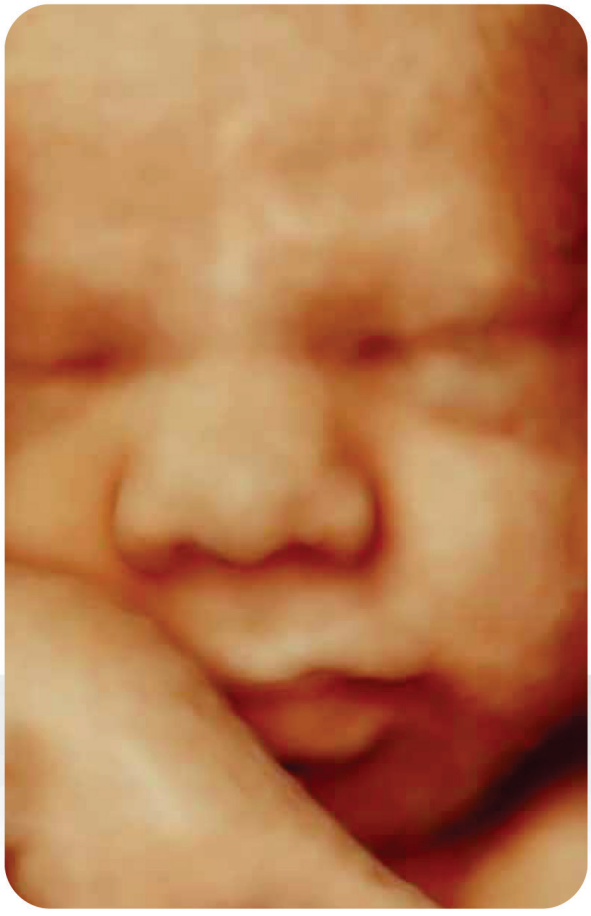

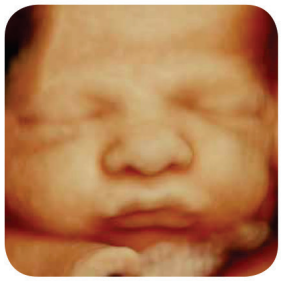

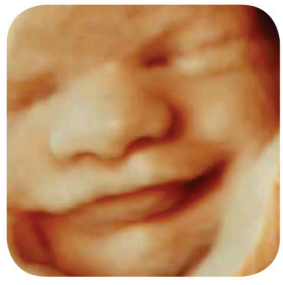

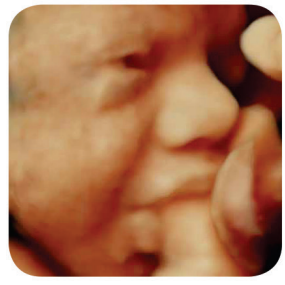

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Editorial

Dear Colleagues,

I am delighted to introduce the final issue of the *J Turk Ger Gynecol Assoc* in the publishing year of 2017.

Our *J Turk Ger Gynecol Assoc* since 2000 is publishing original studies on all aspects of Gynecology and consists of research studies on scientific advances, new medical and surgical techniques, obstetric management, and clinical evaluation of drugs and instruments. I would also like to remind you that the archive of our journal starting with September 2009 issue has been indexed in PubMed Central and available for access. It is important toremember the journal is an Open Access publication and the full text content of its archive is available free of charge.

At this year's final issue we have once again gathered some of the most interesting researches which were submitted to our journal. As you know, DHEA is a critical substrate for sex steroid production in aging women. DHEA supplementation in poor responders may improve reproductive performance. One of our articles investigates whether DHEA supplementation had an impact on endometrial receptivity in women who were poor responders. There is no controlled study investigating the possible effect of DHEA supplementation on homeobox genes (HOXA-10 and HOXA-11) and leukemia-inhibitory factor (LIF). The manuscript on the effect of vascular endothelial growth factor (VEGF) on the survival rate of preantral follicles following ovarian transplantation is also very interesting. You will read a very informative review from Germany on the role of hormones in hypoactive sexual desire disorder and current treatment. Besides all of these manuscripts, you will also find other interesting articles and a quiz in this issue. Enjoy reading!

We would also like to remind you that time is rapidly approaching to our prestigious 12th Turkish-German Gynecology Congress which will be held in Cyprus between April 27 and May 1 of 2018. As of before, our congress will be held to the highest scientific standards and we are working round the clock to optimize our traditionalized congress. At this year's congress every morning we will be having keynote lectures with the world's most reputable speakers; Prof. Jan Deprest (Fetal Medicine: In utero spina bifida repair), Prof. Thomas Ebner (The importance of mitochondria on early embryonic development and possible therapeutic interventions for the future in ART), Prof. Camran Nezhat (Management of genitourinary endometriosis to prevent silent loss of kidney), Prof. Farr Nezhat (Hereditary cancer risk assessment). In addition we will hold live surgery from Germany and Turkey.

Dear Researchers,

The best 3 abstracts submitted to the Congress Scientific Committee within the scope of the XI. Turkish-German Gynaecology Congress will be rewarded with the Bayer Abstract Award. The best abstract will be rewarded with 5000 TL. As traditional, the best video presentation submitted in the field of Endoscopic Surgery will receive a 4000 TL Aysun - Cihat ÜNLÜ reward. The aim of these awards is to appreciate the prolificacy of our colleagues in research projects and to encourage especially our young colleagues for the forthcoming years.

Journal of the
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Editorial

We are confident that the congress will give you not only the pleasure of keeping you updated with its rich scientific agenda but also the joy of a well-organized social program and beautiful environment.

Please do not forget to mark April 27- May 1 2018 on your calendars in order to not to miss this scientific festival.

I would like to wish you all a very happy and prosperous new year with your loved ones.

Sincerely,

Prof. Cihat Ünlü, M.D.

Editor in Chief of *J Turk Ger Gynecol Assoc*

President of TGGF

DHEA supplementation improves endometrial HOXA-10 mRNA expression in poor responders

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Abstract

Objective: The study was planned to investigate whether DHEA supplementation had an impact on endometrial receptivity in women who were poor responders (POR).

Material and Methods: Twenty-eight POR women who were undergoing hysteroscopy and five fertile control subjects were included. The POR women were equally subdivided into two separate groups as patients who were currently using DHEA and those who were not. Endometrial samples of the subjects were obtained during hysteroscopy at the late follicular phase. Expression levels of endometrial HOXA-10, HOXA-11, and LIF mRNA were measured with the using real-time polymerase chain reaction. Spontaneous clinical pregnancy rates were also noted.

Results: Compared with POR women who were not given DHEA, upregulated endometrial HOXA-10 (7.33-fold) and HOXA-11 (2.39-fold) mRNA expression were detected in POR women on DHEA. The increase in HOXA-10 mRNA was significant ($p<0.03$). The fold increase in HOXA-11 mRNA was found as 2.39, which indicated a positive upregulation. However, this fold increment was insignificant ($p<0.45$). An insignificant increase in spontaneous clinical pregnancy rates in POR women on DHEA (53.3%) was observed compared with POR women who were not given DHEA (43.8%).

Conclusion: Oral DHEA supplementation in POR upregulates endometrial HOXA-10 mRNA expression, which is known to positively modulate endometrial receptivity. (J Turk Ger Gynecol Assoc 2017; 18: 160-6)

Keywords: Endometrium, DHEA, homeobox genes, poor responder

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Introduction

A fall in androgens, their metabolites, and DHEA decrease progressively during reproductive period (1-3). DHEA is a critical substrate for sex steroid production in aging women (4). A recent review reported that ovarian synthesis of DHEA decreases with age (5). A little more than half of DHEA is of adrenal origin, the remaining amount is released from the ovary (6). Similarly, the pool of androgens including DHEA decreases gradually with age (7,8). Local endometrial androgen levels also decrease due to a remarkable decline in the synthesis of adrenal androgens. All these could be responsible for the decline in reproductive performance in aging women (7).

The decrease in ovarian reserve is not only a reality in older women, it also might occur in young women with infertility

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(1,2). DHEA looks like a breakthrough therapeutic medication in improving ovarian responses in poor-responder (POR) patients. Despite the common use of DHEA as a supplement in POR, the exact mechanism of DHEA action on reproductive events remains speculative. To date, information related to the impact of DHEA on reproductive outcome has largely focused on the potential for the count of retrieved oocytes. Concordantly, androgens have an important role in the early phase of follicular growth, before follicles become follicle-stimulating hormone (FSH) sensitive. They inhibit apoptosis in follicles and improve the action of FSH. In line with these findings, it has been reported that the use of androgen patches increased both pregnancy and take home baby rates in POR women (9,10).

As apart from the decreased retrieval of mature oocytes, the decline in endometrial receptivity might adversely affect reproductive performance in aging women. Accordingly, the reality of endometrial aging and the critical role of androgens have been noted (11). Such as with ovarian aging, it is reasonable to assume a decline in efficiency of endometrium receptivity during the advancing reproductive period. It is most likely that androgenic endometrial milieu changes as women age because DHEA levels significantly decrease with advancing age (1,2).

Some extragonadal tissues consist of steroidogenic enzymes that may convert DHEA to active androgens and estrogens. This cell-specific intracrinology may cause the local production of potent metabolites in accordance with cell-specific requisitions. In support, a regulatory effect of androgens on endometrial cell survival has been reported (12). In view of the above mentioned facts, we hypothesized that DHEA supplementation in POR women may improve reproductive performance through other mechanisms than the number of retrieved oocytes. The endometrium, therefore, may be the most likely area where potential positive effects of DHEA are seen. Although expression of androgen receptor (AR) has been reported in the human endometrium (13), the effect of DHEA on endometrium receptivity genes remained elusive. There is no controlled study investigating the possible effect of DHEA supplementation on homeobox genes (HOXA-10 and HOXA-11) and leukemia-inhibitory factor (LIF). These are the key receptivity genes that regulate decidualization and implantation rates (14,15). To detect the possible influence of DHEA on receptivity we compared the expression intensities of endometrial HOXA-10, HOXA-11, and LIF mRNA in POR women who were given DHEA and others that were not.

Material and Methods

The primary outcome of this work was to investigate the hypothesis that DHEA improves endometrium receptivity in POR. The secondary outcome was to determine spontaneous clinical pregnancy rates. The presence of at least two of the following three features were accepted as a POR (16): (i) Maternal age ≥40 years; (ii) Previous history of retrieving fewer than 3 oocytes; (iii) Previous history of decreased ovarian reserve [antral follicle count (AFC), 5-7 follicles or anti-müllerian hormone (AMH), 0.5-1.1 ng/mL]. Some women in our study had lower levels of AMH than 0.5 ng/mL. Most of the POR patients in the study group were aged less than 40 years and met the criteria in sections (ii) and (iii).

Twenty-eight women with POR fulfilled the eligibility criteria and participated in the study. At the initial visit, although the participants had a diagnosis of POR, they underwent confirmatory ultrasound examination for their AFC. Blood was also obtained from all participants for AMH measurement. Following verbal informed consent and local Institutional Review Board approval, the POR women were equally divided in to two groups as subjects who were currently using DHEA (n=14) and those were not (n=14). POR women with a history of taking DHEA for at least 6 weeks were included in the DHEA treatment group. This time interval was chosen because of the early follicular growth induced by DHEA that occurs within 2 months of treatment. The POR women who were not using DHEA were accepted as the control group. Five fertile subjects were accepted as the second control group. POR women in the treatment group received oral DHEA with 25 mg/TID. Women with untreated hydrosalpinges, submucous or intramural leiomyomas, endometrial polyps, male factor infertility, and tubal factor infertility were excluded. Women with endocrine disorders such as insulin-dependent diabetes mellitus, congenital adrenal hyperplasia, thyroid diseases, and hyperprolactinemia were also excluded. Women with a history of allergy to DHEA were not included. Endometrial thickness was measured at the late follicular phase following hysteroscopy and serum samples were obtained for hormonal evaluation.

In order to establish endometrial causes of former failed *in vitro* fertilization (IVF) cycles and local endometrial damage, the decision for hysteroscopy was taken for both groups of POR participants. All subjects underwent hysteroscopy at the late follicular phases and endometrial samples were obtained. Following repetitive washing of samples with a saline solution, they were transferred into an RNA stabilization buffer and stored at -80 °C. POR subjects were left for a 4-5 month waiting period after hysteroscopy; if the women did not achieve pregnancy during this time period they underwent *in vitro* fertilization/ intracytoplasmic sperm injection (IVF/ICSI).

Real-time polymerase chain reaction (RT-PCR)

Sample preparation and RNA isolation

Both the RT-PCR method used for measuring expression levels of endometrial mRNA and comparative RNA

expression analysis methods were the same as used in the recent study conducted by our team; more information can be found elsewhere (17). Unless otherwise specified, the kits used in this study were obtained from Qiagen, Hilden, Germany.

Reverse transcription cDNA synthesis

Complementary DNA was prepared by using a QuantiTect Reverse Transcription kit (17).

RT-PCR analysis of homeobox and LIF genes

Both positive controls and other genes were prepared using PrimerDesign to analyze the efficacy of the PCR reaction. The mRNA levels of sampling tissues were normalized to that of the house-keeping gene (β-actin) mRNA level. RT-PCR results are expressed as cycle threshold (Ct), delta Ct (ΔCt) and ddCt (ΔΔCt). For the calculation of average Ct values, each endometrial sample was studied three times. The sequence and accession numbers of all primers designed to be used as forward and reverse primers for RT-PCR were: *HOXA*-10(NM_018951),F-5'-GGTTTGTTCTGACTTTTTGTTTCT-3', R-5'TGACACTTAGGACAATATCTATCTCTA-3';*HOXA*-11(NM_005523),F-5'-AGTTCTTTCTTCAGCGTCTACATT-3', R-5'TTTTTCCTTCATTCTCCTGTTCTG-3'; *LIF*(NM_002309),F-5'GGAGGTCACTTGGCATTCAG-3', R-5'GGAAGAGAACGAAGAACCTACC-3';andACTB(NM_001101), F-5'GCAAGCAGGAGTATGACGAGT-3', R-5'CAAGAAAGGGTGTA ACGCAACTAA-3'.

Statistical analysis

The expression of the studied genes was determined using the $2^{-\Delta\Delta CT}$ method. All data were normalized according to the ACTB gene (β-actin) mRNA content. The normalized gene expression of POR women was divided by the normalized gene expression of the control subjects. The fold increase were considered positive or an up-regulation for transcript overexpression when the corresponding mRNA level was at least 2-fold higher than that of the initial transcript expression, negative or down-regulation, if lower than 2-fold. The Kolmogorov-Smirnov test showed normal distributions of data. The ANOVA test with post hoc Tukey's procedure and Mann-Whitney U test were used for analyzing continuous variables. Pearson's Chi-square test was used for analyzing other data. $P<0.05$ was accepted as statistically significant. The results are given as mean and standard deviation (SD).

Results

POR women on DHEA and without DHEA had similar age, AFC, FSH, and endometrial thickness (Table 1). Significantly lower AMH levels were detected in women on DHEA compared with women who were not taking DHEA (0.33±0.23 vs. 0.64±0.12 μg/mL). The mean age of the fertile controls was 33.1+2.3 years. The mean age of the POR women on DHEA (33.0±4.57 years), those without DHEA (33.2±6.18 years), and controls were similar. The mean baseline FSH (5.6±0.5 mIU/mL) levels of the fertile group were lower than in POR women on DHEA (10.8±1.12 mIU/mL). The mean baseline endometrial thickness of the fertile group (7.4±0.5) and women on DHEA (7.73±0.79) were similar. The mean baseline AFCs of the fertile group (4.67±1.87) was higher than in POR women on DHEA (1.80±0.67). Trends toward an increase in clinical spontaneous pregnancy rates in POR women on DHEA were detected compared with the POR women who were not given DHEA (53.3% vs. 43.8%). However, the difference was found insignificant ($p<0.59$). One subject had early pregnancy loss among the POR women on DHEA, and 3 of the 14 women who were not given DHEA had pregnancy loss (Table 1).

The expression levels of endometrial HOXA-10 and HOXA-11 mRNA of subjects who were not given DHEA and fertile women were the same ($p<0.44$ and $p<0.25$ respectively).

Table 1. Clinical characteristics of POR women on DHEA and without DHEA

	POR on DHEA	POR without DHEA	p* value
Age (years)	33.0±4.57	33.2±6.18	0.79
AMH (ng/mL)	0.33±0.23	0.64±0.12	<0.0001
AFC	1.80±0.67	2.00±0.63	0.38
FSH (mIU/mL)	10.8±1.12	10.3±1.20	0.29
Endometrial thickness (mm)	7.73±0.79	7.25±0.68	0.07
Infertility duration (year)	7.53±3.22	6.10±3.76	0.25
Previous IVF attempt	1.00±1.30	1.21±1.80	0.93
Clinical pregnancy rates (%)	53.3	43.8	0.59
Early pregnancy loss	1	3	-

AMH: anti-müllerian hormone; AFC: antral follicle count; FSH: follicle-stimulating hormone; IVF: *in vitro* fertilization; POR: poor responders; Data are presented as mean ± standard deviation; *p<0.05 is accepted statistically significant

Expression levels of LIF mRNA were found to be lower in the endometrium of POR subjects who were not given DHEA as compared with the fertile controls. However, the difference was noted as insignificant ($p<0.48$). Upregulated HOXA-10 and 11 mRNA expressions were found in women taking DHEA. POR women on DHEA showed a 7.33-fold increment in HOXA-10 mRNA expression, and a 2.39-fold increment was detected in HOXA-11 mRNA expression. Only the increment in HOXA-10 mRNA expression was significant ($p<0.03$). The fold increment in HOXA-11 mRNA after DHEA supplementation was found as 2.39, which was greater than two, thus indicating an upregulation. However, this increment was not significant ($p<0.45$). Likewise, an insignificant increase in LIF mRNA expression (1.76-fold, $p<0.36$) was detected after DHEA supplementation. Due to the fold rise in LIF mRNA following DHEA being smaller than 2-fold, it was considered to be down-regulation (Table 2, Figure 1).

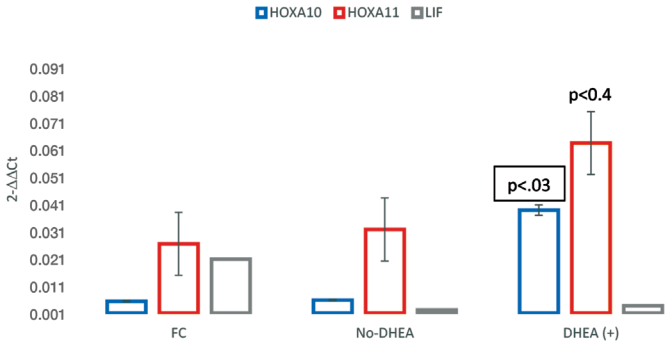

Figure 1. The relative gene expression was determined using the $2^{-\Delta\Delta CT}$ method. All data were compared with the fertile control group and normalized to ACTB gene (actin, beta) mRNA content. No-DHEA; POR women who were not given DHEA, DHEA (+); POR women on DHEA
FC; fertile control; POR: poor responders

Discussion

The two main results arising from this study are the increased endometrial HOXA-10 mRNA expression and the spontaneous pregnancy rates being higher than those reported in the literature. Although DHEA supplementation increases follicle recruitment, potentializes gonadotrophin effect, reduces follicle apoptosis, and enhances IGF-1 levels, how DHEA improves fertility outcomes is still not accurately known (18-20). Barad et al. (21) reported the clinical pregnancy rates in DOR women on DHEA as 10.9-28.1%, and half of the pregnancies occurred spontaneously. In the current study, more than 50% of POR women on DHEA (53.3%) conceived within 4-5 months after the hysteroscopy. In line with our results, a study conducted by Fusi et al. (22) showed that DHEA improved the chance of spontaneous pregnancies in POR women. High spontaneous pregnancy rates in POR patients on DHEA might be due to the positive impact of DHEA on the endometrial microenvironment, as well as the positive impact on oocyte development.

In order to clarify enhanced endometrial receptivity following DHEA administration, both average $2^{-\Delta Ct}$ and fold change values for each gene were measured. The main result from the current study is the 7.3-fold rise in HOXA-10 and 2.3-fold rise in HOXA-11 mRNA expression after DHEA. Based on upregulated expressions of both genes, we can strongly suggest that exogenous DHEA improves endometrial receptivity. However, it is not evident whether DHEA has a direct effect on endometrial receptivity or its function only as a precursor to estrogens. Accordingly, androgens are not solely a substrate for estrogen production but may also modulate the effects of estrogen in the endometrium (23). If we accept the idea that DHEA increases endometrial receptivity by transforming into estrogen, it is logical to believe that administration of exogenous estrogens should improve endometrial receptivity. Confirmation of our hypothesis comes from an egg donation study of women with

Table 2. Comparison of expression levels of endometrial HOXA-10, HOXA-11, and LIF mRNA in the fertile control, POR women on DHEA, and without DHEA

Gene	Group	Average $2^{-\Delta Ct}$	Fold change	95% CI	p value	Regulation
HOXA-10	No-DHEA	0.005799	1.0852	0.00001-2.54	0.446	-*
	DHEA (+)	0.03918	7.3322[a]	0.00001-16.97	0.032[b]	UP (7.3- fold)
	Fertile control	0.001-0.011	NA	-	-	-
HOXA-11	No-DHEA	0.041521	1.5562	0.00001-4.02	0.254	*
	DHEA (+)	0.064035	2.3999[a]	0.00001-6.63	0.451	UP (2.3- fold)
	Fertile control	0.025	NA	-	-	-
LIF	No-DHEA	0.002173	1.038	0.00001-2.22	0.480	*
	DHEA (+)	0.003692	1.7639	0.00001-5.91	0.364	*
	Fertile control	0.021	NA	-	-	-

POR: poor responders; NA: Not applicable; No-DHEA; women were not given DHEA, DHEA (+); women on DHEA. [a]Fold change value >2 was accepted as positive regulation for the genes studied. [b]$p<0.05$; *No significant change was detected compared with controls

advanced reproductive age (24). Estrogen priming of these women improves both endometrial thickness and implantation. However, increased implantation is not only due to the positive impact of estrogen. It should be remembered that good quality oocytes from healthy donors may overcome any age-related receptivity defect.

Peripheral interconversion of DHEA to active androgens, estrogens, and progesterone may be the first reason of the increased endometrial HOXA10 mRNA expression. It is a well-known fact that expression of homeobox genes are modulated by sex steroids (25). Concordantly, endometrial HOXA10 mRNA was found to be associated with circulating 17-β estradiol (25). Likewise, androgens are also regulators of the HOXA10 gene (26). As DHEA turns estrogens in peripheral tissues (27,28), exogenous DHEA can exhibit a positive impact on endometrial HOXA10 mRNA expression in POR women on DHEA.

The second possibility of the positive effect of DHEA on HOXA10 mRNA might be the substitution of androgens or estrogens because circulating levels of androgen and estrogen decrease with advancing age (29). Nevertheless, local transformation of DHEA of other steroids in the endometrium is restricted by the altered levels of steroidogenic enzymes (11). Some authors believe in the local production of estradiol in the endometrium, whereas others do not support this notion (30,31). The lack of aromatase activity and the existence of endometrial atrophy in postmenopausal women support the idea that the endometrium does not have the ability to produce local estrogen (11,30). In contrast, Bukulmez et al. (32) reported that mRNA expression of aromatase enzyme in cultured endometrial cells were up-regulated by androstenedione (33). If a rise in HOXA10 mRNA following DHEA is secondary to conversion of DHEA to estrogens, why does endometrial thickness not alter significantly? In contrast to the stimulatory effect of estrogen on the endometrium, DHEA does not exert a stimulatory impact on endometrium (7). In good agreement with this, Labrie et al. (34) reported that the stimulatory impact of DHEA on the vagina was not detected in the endometrium of postmenopausal women and their endometrium remained atrophic after one year of DHEA supplementation. Likewise, endometrial thickness of women on DHEA and those that were not given DHEA were similar in our study. Together, upregulation of endometrial HOXA-10 mRNA after DHEA treatment could be attributed to either DHEA itself or a function of its active compounds. If absolute androgen deficiency has a negative impact on endometrial androgen levels, we may suggest that exogenous DHEA may lead to a rise in local androgens that induce endometrial HOXA-10 mRNA expression.

AR have been shown in both pre- and postmenopausal human endometrium (35,36). Estrogen increases AR, and progesterone inhibits it (37,38). Therefore, a third possibility of augmented HOXA-10 expression after DHEA might be related to an AR enhancer effect of DHEA. The greatest support for our hypothesis come from the study by Qin et al. (39) who investigated the impact of DHEA on decidual PRL-related protein (dPRP), AR, and HOXA-10 expressions in mouse endometrial cells. They reported that DHEA had an insignificant effect on endometrial dPRP expression. The authors also noted that when given the dose of 100 nM, DHEA caused a significant increase in HOXA-10 mRNA. Moreover, they showed that DHEA-mediated upregulation in HOXA-10 was diminished by treatment with an AR antagonist. Together, if physiologic androgen deficiency in aging women leads to a decline in AR, we can suggest that exogenous DHEA can increase endometrial AR, which might lead to a rise in HOXA-10 (39).

The fourth possibility of improved receptivity after DHEA may be related to decidualization. By stimulating decidual prolactin production, androgens regulate decidualization (40,41). Exogenous DHEA might upregulate HOXA-10 mRNA expression because homeobox genes induce decidualization and pinopode formation (14,42).

There are some limitations to the current study. The study population is small in the studied groups. Alterations in mRNA expression are not confirmed by protein analyses. As opposed to our findings, patients with hyperandrogenism secondary to Polycystic Ovarian syndrome (PCOS) demonstrated low HOXA-10 and β3-integrin expression (43,44), suggesting androgens may have a detrimental impact on the endometrium. For this reason, one may suggest that the use of exogenous DHEA could impair the endometrial micro-milieu and that there is no need for androgen supplementation in POR women. Actually, DHEA may cause a PCO-like appearance in ovaries of POR women (45,46). However, as exogenous DHEA does not exactly mimic clinical and biochemical features of genuine PCOS, results obtained from subjects with PCO-like ovaries cannot be applied to POR women on DHEA.

Finally, we demonstrated for the first time that oral DHEA supplementation augments endometrial HOXA-10 mRNA expression. As well as the known possible positive effect on the count of oocytes retrieved, DHEA may increase implantation and pregnancy rates by modulating receptivity genes (17) or signal molecules (47). The receptivity enhancing effects of DHEA might be realized via transformation of DHEA to active metabolites (Figure 2). If DHEA indeed has a positive impact on endometrial receptivity, it can be used to enhance implantation rates in women with POR. Whatever the mechanism, the present study showed that DHEA exerted a positive effect on endometrial receptivity. If our results are supported by extensive studies, augmentation of endometrial receptivity with DHEA

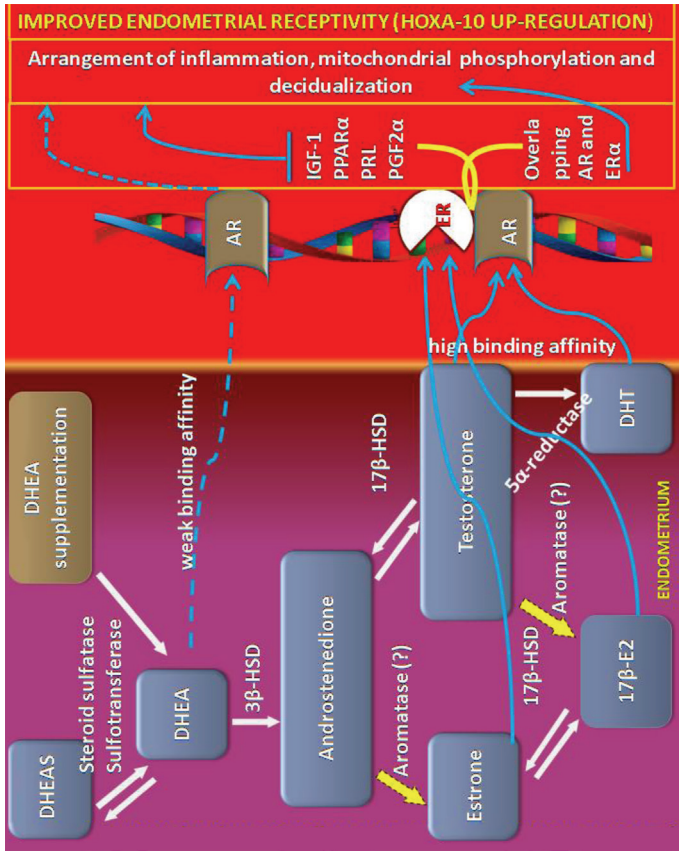

Figure 2. Abbreviated pathways to illustrate the possible mechanism of action of DHEA on endometrium receptivity.

might be a key factor for the management of women with implantation failure.

Acknowledgement: *Authors acknowledge the help of Turkish German Gynecologic Research and Education Foundation for providing of HOXA and LIF genes kits.*

Ethics Committee Approval: *Ethics committee approval was received for this study from the ethics committee of Medipol University School of Medicine (No: 10840098-604.01.01-E.13011).*

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

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Concept - Ö.Ç., M.A.; Design - Ö.Ç., M.A., B.O., C.Ü., E.Ç.; Supervision - C.Ü., Ö.Ç., B.O., E.Ç.; Materials - Ö.Ç., M.A., B.O., C.Ü., E.Ç.; Data Collection and/or Processing - A.İ., N.Ç., A.E., L.H.A.; Analysis and/or Interpretation - B.O., Ö.Ç., M.A., C.Ü., E.Ç.; Literature Review - Ö.Ç., M.A., S.Ç.; Writer - Ö.Ç., M.A., B.O., C.Ü., E.Ç.; Critical Review - Ö.Ç., M.A., A.İ., N.Ç., A.E., L.H.A., B.O., S.Ç., E.Ç., C.Ü.*

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An *in vitro* study on oocyte and follicles of transplanted ovaries treated with vascular endothelial growth factor

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Abstract

Objective: Retrieval of high quality follicles and oocytes from transplanted ovaries is essential for higher fertility preservation efficiency. The effect of vascular endothelial growth factor (VEGF) was evaluated on the survival rate of preantral follicles following ovarian transplantation.

Material and Methods: Prepubertal female mice were divided to 6 groups including: control (C), transplanted with no VEGF treatment (T) and transplanted with different dosages of VEGF [0.5 μg/mL (TV1), 1 μg/mL (TV2), 2 μg/mL (TV3), and 4 μg/mL (TV4)]. Twenty-one days later, the left ovaries were removed and transplanted on gluteal muscle. Each dose was injected directly into transplanted ovary. Twenty-one days after transplantation, the ovaries were taken, and follicles and cumulus-oocyte-complexes (COCs) were released using 26-gauge needles with a stereo microscope. The number of healthy COCs, matured oocytes, and *in vitro* developed embryos after fertilization *in vitro* were evaluated to determine the best dose of VEGF. Follicle number and follicular growth was evaluated relative to the dose of VEGF provided. Transplantation and VEGF treatment with the best dose was performed as mentioned above and *in vitro* follicle growth in transplanted ovaries was compared with opposite ovaries (OPP).

Results: COC retrieval was significantly lower in the transplanted groups compared with the control group ($p<0.05$). The percentage of metaphase II oocytes was significantly lower in the group treated with 4 μg/mL VEGF compared with the controls ($p<0.01$). In the TV2 (1 μg/mL) and TV3 (2 μg/mL) groups, the percentages of morula and blastocysts were significantly improved compared with the T group ($p<0.01$). In the OPP group, the number of follicles was significantly higher compared with the transplanted groups ($p<0.01$).

Conclusion: The improving effect of VEGF on *in vitro* maturation and *in vitro* development outcome indicates that VEGF administration may increase transplantation efficiency for fertility preservation. (J Turk Ger Gynecol Assoc 2017; 18: 167-73)

Keywords: Follicle, oocyte, ovary, transplantation, vascular endothelial growth factor

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Introduction

A long-term adverse effect of chemotherapy for patients with cancer is ovarian toxicity, reduced follicular number, which results in premature menopause and infertility (1,2). For these patients, collection and storage of oocytes, embryo, primordial follicles, and ovarian tissue is possible, but there are multiple technical problems (3).

Many patients with cancer now have the opportunity for fertility preservation using ovarian tissue transplantation after ovarian cryopreservation, which can be combined with other processes of assisted reproductive technology (4). Although live birth has been reported after ovarian cryopreservation and transplantation, the efficiency has been low (5-7). Ovarian tissue cryopreservation may be advantageous over other options because collection of ovarian tissue is easy, can be performed before cancer treatment, and it is appropriate for young patients (3). Other advantages of ovarian preservation are the possibility of immediate cancer therapy without the need for hormone

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therapy. Furthermore, ovarian transplantation is the only way for fertility preservation in pre pubertal females (8). The storage of a large number of primordial and primary follicles is possible with cryopreservation and it is also possible to perform this process rapidly at any time of the menstrual cycle (9,10). Successful ectopic transplantation of cryopreserved or fresh ovarian tissue pieces has been previously reported (11). Despite encouraging results of ovarian tissue transplantation, the most important disadvantage is accruing ischemia (12). Therefore, the graft needs to receive adequate blood supply, otherwise ischemia-reperfusion during the first 24-48 hours (13) damages transplanted ovarian tissue with adverse effects on follicular population (14). Ischemia can cause dramatic follicular depletion in the transplanted ovary (12). Ischemia results from inadequate vascularization during a proper time. To minimize ischemia, some growth factors, antioxidants, and hormones have been administered during ovarian tissue transplantation (12). Vascularization between host and transplanted ovary is necessary to prevent ischemia (12).

Vascular endothelial growth factor (VEGF), as a permeability factor, increases permeability of the endothelium through the formation of intercellular gaps, vacuoles, fenestrations, and vesicovascular organelles (15). VEGF induces endothelial nitric oxide synthase (eNOS) and the subsequent increase in nitric oxide production, which causes vasodilatation (16). Follicular development is dramatically dependent on the effect of VEGF because it has been reported that VEGF inhibitors caused suppression of follicular development from early stages to antral stage (17). It has been shown that theca cell layer proliferation of the micro vascular network within the ovary is stimulated by VEGF (18). Vascularization and angiogenesis increases with VEGF, which can cause increasing blood supply reduction of ischemia in ovarian tissue (19). It has been reported that VEGF mediates ovarian angiogenesis and affects follicle growth cycles in the ovaries. Follicular growth and corpus luteum formation are dependent on the proliferation of the new network of vessels (20). In a previous study, the histologic status of whole transplanted ovaries on gluteal muscle after vitrification revealed more angiogenesis in transplanted ovarian tissue (21). Furthermore, VEGF improved oocyte up take, *in vitro* maturation (IVM), and the possibility of subsequent *in vitro* embryo development (22).

The possibility of follicle culture from early stages is necessary to achieve full success in ovarian tissue transplantation (23). The majority of follicular population in the ovary after primordial follicles are preantral follicle (24), which are a large source of fertilizable oocytes (25). Therefore, retrieval and culture of preantral follicles is possible and increases successful fertility preservation with the process of ovarian transplantation. To retrieve higher quality preantral follicles and oocytes from transplanted ovaries, improved transplantation protocols are necessary.

The objective of this study was to examine the effect of VEGF administration on the ability of retrieved oocytes to develop and reach blastocyst stage.

Material and Methods

Chemicals and ingredients except those mentioned in the materials and methods were purchased from Sigma company (Germany).

Animals

Standards for animal use and care upheld in accordance with the Declaration of Helsinki and the Guiding Principles (DHEW publication, NIH, 80-23). Swiss Webster female mice were purchased, kept and bred at a proper temperature (20-25 °C) and humidity (50%) during experiments in a determined light period (12 h light: 12 h dark) with sterile food and water. For surgery, mice were given intraperitoneal injections of ketamine-xylazine (100 mg/kg ketamine and 10 mg/kg xylazine) for anesthesia. Cervical dislocation was performed to kill the animals at the end of the experiment.

Auto-transplantation

After anesthesia, the left ovaries were taken and the adipose tissue that surrounded the ovary was dissected in α MEM (GIBCO, USA) medium using 28-gauge needles under a stereomicroscope, and the incisions were sutured using 6-0 absorbable suture (Ethicon, Belgium). The experimental doses of VEGF was injected directly into transplanted tissue before closing the incision. Afterwards, the ovaries were auto-grafted on the gluteal muscle of the same mouse by making a 2-mm deep incision in the skin to access the gluteal muscle, placing the ovary on the muscle, and the skin incision was closed with a 5-0 absorbable suture. At the end of surgery, the mice recovered and were kept in the animal house for 21 days to evaluate the transplanted ovaries.

Determination of the best dose of VEGF

Experimental groups

VEGF was diluted in phosphate-buffered saline for the preparation of different doses including TV1 (0.5 μg/mL), TV2 (1 μg/mL), TV3 (2 μg/mL), and TV (4 μg/mL), which were justified empirically with consideration of the evaluated dose of VEGF on the biologic function of endothelial cells (26). The number of each transplanted ovary for each group was considered as one replication. Twenty-one days after auto-transplantation, all groups were given 7.5 IU pregnant mare serum gonadotropin

(Folligon, Intervet), and with 24-hour intervals, 7.5 IU human chorionic gonadotropin (hCG) (Pregnenlone, intervet) were injected peritoneally. Fourteen hours after hCG injection, the mice were killed and grafted ovaries were taken from the gluteal muscle. Subsequently, the rates of IVM, *in vitro* fertilization, and *in vitro* developmental competence of retrieved oocytes obtained after dissection of transplanted ovaries were evaluated to determine the most effective dose of VEGF.

Cumulus-oocyte-complex isolation *in vitro* embryo production

Transplanted and opposite ovaries (OPP) were removed and transferred to 100 μL droplets of α-minimal essential medium (α-MEM; Gibco, Invitrogen), which was supplemented with fetal bovine serum (FBS) (10%), penicillin, and streptomycin, each of which as 100 IU/mL. COCs were released from ovaries, which were dissected with 26-gauge needles under a stereomicroscope for *in vitro* studies. The number of oocytes from each ovary was recorded. Retrieved oocytes that were at germinal vesicle (GV) stage were washed three times in α-MEM medium supplemented with a combination of penicillin (100 IU), streptomycin (100 IU), FBS (5%), recombinant human follicle-stimulating hormone (rhFSH) (7.5 IU/mL) (Organon, Holland), and hCG (100 IU/mL) (Organon, Holland) and incubated at 37.5 °C in 5% CO_2. Sixteen hours after incubation, the nuclear maturation stage was evaluated under a stereomicroscope (Olympus).

***In vitro* embryo production**

Mice at 6-8 weeks' age were killed and their epididymis were removed, ruptured using scissors, and placed in T6 media containing 15 mg/mL BSA, which was equilibrated in the incubator adjusted at 37.5 °C in 5% CO_2 for at least for 15 minutes. Sperms were released from ruptured epididymis and for capacitation, they were incubated at for least 30 minutes. Oocytes obtained from each group were exposed to the IVF process as they were transferred into 100 μL IVF medium droplets and $2x10^6$ sperm/mL was added to the droplets. After 6 hours of incubation, each IVF droplet that contained oocytes and sperms was evaluated using an inverted microscope and the percentage of embryos with male and female nuclear (2PNs) was recorded as the fertilization rate. Afterwards, the newly produced 2PNs were washed and transferred to T6 medium containing 4 mg/mL BSA, which had been incubated (37.5 °C in 5% CO_2) for 96 hours. Embryos at the 2 cell, 4- to 8-cell, morula, and blastocyst stages were counted 24, 48, 72, and 96 hours after IVF (22).

Follicle isolation and *in vitro* culture

Autotransplantation was performed with an injection of the best dose of VEGF obtained through previous evaluations, which was the same as above mentioned methods for transplantation. Twenty-one days after autotransplantation, the mice were killed by cervical dislocation. Both transplanted and OPP were removed and transferred into dissection droplets of α-MEM medium with 5% FBS. For preantral follicle isolation, mechanical dissection was performed using 27-gauge needles. High quality preantral follicles that contained round and central oocytes surrounded by at least two theca layers were selected, and each follicle was individually cultured in 20 μL droplets of α-MEM medium containing FBS (5%), rhFSH 100 mIU/mL, 1% ITS (Gibco, Invitrogen), penicillin, and streptomycin, each of which as 100 IU/mL for 12 days. Droplets were under mineral oil and incubated in the humidified incubator, which was adjusted at 37 °C in 5% CO_2. After 11 days of follicle culture, 5 ng/mL rEGF and 1.5 IU/mL hCG were added to the media to induce *in vitro* ovulation. The follicle survival rate was recorded using an inverted microscope (Olympus).

Statistical analysis

One-way analysis of variance was performed followed by separating the means employing Duncan protected least-significant tests, (SAS version 1.9 Cary, NC, USA). If variances were found unequal, an arc sine transformation was performed before analysis. Data were normalized using arc sine transformation before analysis. Data are expressed as mean ± standard error of mean and p values <0.01 were considered as statistical significances.

Results

The number of retrieved COCs

The number of COCs retrieved from all transplanted ovaries was significantly lower when compared with the control group ($p<0.01$; Table 1). There was no significant difference in the number of retrieved COCs in the transplanted groups with or without VEGF treatment.

Oocyte maturation

The percentage of metaphase II (MII) oocytes was not significantly different between the groups including: C, T, TV1 (0.5 μg/mL), TV2 (1 μg/mL), and TV3 (2 μg/mL); however, the percentage of MII oocytes was significantly decreased in the TV4 (4 μg/mL) group compared with the control group ($p<0.01$; Table 1). No significant difference was observed in the percentage of oocytes that initiated meiosis [MII + germinal vesicle break down (GVBD)] and the percentage of GVBD oocytes between the experimental and control groups. The percentage of GV arrested oocytes was significantly higher in the T group compared with the TV3 (2 μg/mL) and C groups ($p<0.01$; Table 1).

Fertilization rate and developmental competence *in vitro*

The highest percentage of 2PN was in the TV2 (1 μg/mL) group, but no significant difference was observed between the groups (Table 2). The percentage of 2- and 4-cell stage embryos was not significantly different between the groups. However, 2- and 4-cell stage embryo percentages were similar in all evaluated groups. As shown in Table 3, the control group had a significantly higher percentage of 8-cell, morula, and blastocyst stage embryos compared with the transplanted groups ($p<0.01$). Transplantation caused significant depletion in the rate of morula and blastocyst formation when compared with the control group ($p<0.01$; Table 3). The lowest percentages of morula and blastocysts was observed in the T group compared with the other transplanted groups and the control group ($p<0.01$; Table 3). The highest percentage of morula and blastocysts were obtained in the TV2 (1 μg/mL) and TV3 (2 μg/mL) groups, and significantly increased compared with the T group ($p<0.01$).

Follicle number and survival rate *in vitro*

The number of retrieved follicles was the highest in the OPP group compared with T and TV ($p<0.01$; Table 4). The number of retrieved preantral follicles was not significantly different

Table 1. Maturation of oocytes retrieved from ovaries in different experimental groups

Experimental groups	Transplanted ovary (NO)	Retrieved COCs (%)	MII %	GVBD (%)	MII+GVBD (%)	GV (%)
C	4	41.25±4.13^{a}	59.36±1.25^{a}	21.73±1.17^{a}	69.63±1.33^{a}	20.37±1.33^{b}
T+H	3	7.00±0.57^{b}	54.89±1.58^{ab}	29.15±3.80^{a}	55.78±3.26^{b}	38.23±3.25^{a}
TV1+H	2	2.00±00^{b}	60.00±0.00^{a}	30.00±0.00^{a}	60.00±0.00^{ab}	30.00±0.00^{ab}
TV2+H	2	2.50±0.5^{b}	52.50±7.50^{ab}	25.35±4.65^{a}	56.35±7.06^{ab}	33.50±7.50^{ab}
TV3+H	3	1.33±0.33^{b}	55.00±5.00^{ab}	35.00±5.00^{a}	63.10±3.10^{ab}	26.90±3.09^{b}
TV4+H	3	4.33±0.23^{b}	41.76±3.25^{b}	33.66±7.06^{a}	52.50±7.50^{b}	33.23±3.25^{ab}

C: control; T+H: transplanted received hormone; TV1+H: transplanted ovary treated with 0.5 μg/mL vascular endothelial growth factor (VEGF) and receive hormone; TV2+H: transplanted ovary treated with 1 μg/mL VEGF and receive hormone; TV3+H: transplanted ovary treated with 2 μg/mL VEGF and receive hormone; TV4+H: transplanted ovary treated with 4 μg/mL VEGF and receive hormone; Data are expressed as mean ± standard error of mean and in each column values with different superscripts (a and b) are significantly different ($p<0.01$); The percentages of MII, GVBD, MII+GVBD and GV are based on the number of retrieved COCs in each experimental group
VEGF: vascular endothelial growth factor; MII: metaphase II; GVBD: germinal vesicle break down; GV: germinal vesicle; COCs: cumulus-oocyte-complexes

Table 2. The percentage of 2PN

Experimental groups	Transplanted ovary (NO)	MII (NO)	2PN (%)
C	5	109	53.99±1.25
T	4	14	53.99±5.35
TV1	3	2	50.00±10.00
TV2	2	3	60.00±5.03
TV3	4	3	53.82±6.18
TV4	4	3	48.75±7.18

MII: metaphase II, C: control, T: transplanted without vascular endothelial growth factor (VEGF) treatment, TV1, TV2, TV3, TV4 transplanted groups treated with dosages of VEGF including 0.5, 1, 2, 4 μg/mL. Data are expressed as mean ± standard error of mean, the percentage of 2PN is based on the total MII oocytes in each experimental group

Table 3. Embryo development during 96 hours in different experimental groups

Experimental groups	Transplanted ovary (NO)	2PN (NO)	2-cell	4-cell	8-cell	Morula (%)	Blastocyst (%)
C	5	72	64.56±1.59	66.70±2.08	59.78±1.94^{a}	56.25±2.48^{a}	42.05±1.69^{a}
T	4	9	71.78±3.24	71.78±3.24	34.06±5.00^{b}	15.39±2.32^{c}	15.40±2.32^{c}
TV1	2	3	52.50±7.50	52.50±7.50	25.35±4.65^{b}	25.35±4.64^{bc}	25.35±4.65^{bc}
TV2	3	1	60.00±0.00	60.00±0.00	30.00±0.00^{b}	30.00±0.00^{b}	30.00±0.00^{b}
TV3	2	1	63.10±3.10	63.10±3.10	30.00±0.00^{b}	30.00±0.00^{b}	30.00±0.00^{b}
TV4	4	4	56.35±7.06	56.35±7.06	26.70±3.31^{b}	26.69±3.30^{bc}	26.69±3.30^{bc}

C: control, T: transplanted without vascular endothelial growth factor (VEGF) treatment, TV1, TV2, TV3, TV4 transplanted groups treated with dosages of VEGF including 0.5, 1, 2, 4 μg/mL; Data are expressed as mean ± standard error of mean; in each column values with different superscripts (a, b and c) are significantly different ($p<0.01$). The percentage of each stage embryo is based on the total 2PN oocytes in each experimental group

between the T and TV groups. The follicle survival rate at day 4 and day 14 was the same in all three groups (OPP, T, and TV). Also the percentage of degenerated follicles after 14 days in culture was not significantly different in the three experimental groups.

Discussion

Ovaries and uterus transplantation are old methods that have recently gathered more interest in reproductive medicine because it provides an opportunity for women to maintain their fertility in the event of major illness. Induction of angiogenesis and prevention of ischemia reperfusion helps to save the follicular population. VEGF, as a growth factor, has been demonstrated to be able to induce angiogenesis in transplanted tissue (19). Previous histologic work indicated that, with a proper dose of VEGF, the percentage of follicles in transplanted ovaries reached the same level as intact ovaries (27). However, the current study shows that the number of healthy preantral follicle retrieved in transplanted ovaries with the effect of different doses of VEGF remained lower than OPP ovaries (Table 4). Furthermore, the number of COCs retrieved from treated transplanted ovaries was also lower than the number of oocytes retrieved from intact ovaries (Table 1).

Orthotopic transplantation circumvents the need for IVM, IVF, and subsequent *in vitro* development (IVD) (5). However, the process of transplantation may cause dysfunction in necessary systems for proper follicle survival and development *in vitro*. A malfunction induced by transplantation can cause reduction in retrieval of good quality oocytes for embryo *in vitro* production (28). Oocytes with the best quality were selected for the IVM process, which contributed to the percentage of produced MII oocytes after IVM in transplanted ovaries being the same as the non-transplanted group. The lowest percentage of arrested oocytes at GV stage was observed in the TV+H group, which was treated with 2 μg/mL VEGF. Furthermore, MII+GVBD, which indicates meiotic resumption, was increased in the TV+H group to the same level as the control group (Table 1).

The lower GV of arrested oocytes and the higher meiotic resumption in treated transplanted ovaries with a proper dose of VEGF indicates that administration of VEGF for transplanted ovaries improves quality of oocytes and increases their ability for meiotic resumption. Previously, higher angiogenesis and lower apoptosis was observed in transplanted ovaries treated with TV4 (4 μg/mL) VEGF compared with transplanted ovaries without VEGF treatment (27). The observation of the positive effects of 2 μg/mL VEGF on oocyte maturation with an increasing rate of meiotic resumption confirms previous histologic reports. However, the higher IVM rate of oocytes with the effect of TV3 (2 μg/mL) compared with 4 μg/mL indicates that a lower dose may exert a greater improving effect on oocyte quality and IVM rate.

The addition of VEGF to maturation medium improved IVF and IVD rates of bovine (29,30) and porcine (31) oocytes. *In vitro* matured oocytes retrieved from transplanted ovaries treated with different doses of VEGF were subjected to IVF and IVD processes. Table 2 shows that the IVF rate of oocytes retrieved from transplanted ovaries treated with VEGF was similar to the control group. Nevertheless, the effect of VEGF was more effective on the developmental competence of produced embryos after IVF until the blastocyst stage. The percentage of 2- and 4- cell embryos was similar in all groups and there was a subsequent decrease in the number of viable embryos at the 8-cell stage. Subsequently, it was demonstrated that VEGF improved survivability at the morula and blastocyst stages (Table 3). As shown in Table 3, the percentage of more developed embryos was significantly decreased in the transplanted group. However, treatment with TV2 (1 μg/mL) or TV3 (2 μg/mL) significantly improved the rate of blastocyst formation compared with the transplanted group with no treatment. There were no significances in the rate of follicle survival in the OPP, TC, and TV groups (Table 4).

VEGF has no effect on the number of oocytes and preantral follicle retrieval. However, previous histologic research on mouse (27), sheep (19), and human ovarian tissue (32) indicated preservation of follicular population in ovarian tissue. In spite of histologic data about higher follicle preservation with VEGF treatment, retrieval of high quality oocytes and follicles in the present study remained lower than intact ovaries. It has been reported that VEGF can support the transition of bovine primary follicles to secondary follicles during *in vitro* culture (33). The same rate of *in vitro* follicle survival in transplanted groups with or without VEGF treatment and OPP as the control group suggests that high quality follicles from transplanted or non-transplanted ovaries have the same ability to grow *in vitro*

Table 4. The rate of preantral follicle retrieval from each ovary and *in vitro* growth rate

Experimental groups	Ovary (NO)	Retrieved preantral follicles (NO)	4 days (%)	14 days (%)	Degenerated (%)
OPP	8	7.01±1.3[a]	63.7±1.6	52.6±2.9	37.4±2.9
Tc	5	4.40±1.5[b]	62.7±2.9	51.2±5.6	39.6±5.6
Tv	3	5.00±2.4[b]	66.7±3.38	50.4±7.0	38.9±7.0

OPP: opposite ovaries; Tc: transplanted ovaries without vascular endothelial growth factor (VEGF); Tv: transplanted ovaries with 2 μg/mL VEGF, Data are expressed as mean ± standard error of mean. In each column Values with different superscripts (a and b) are significantly different ($p<0.01$). The percentage of grown follicles and degenerated follicles are based on the total retrieved preantral follicles in each experimental group

for 14 days. Accordingly, obtaining higher numbers of good quality and healthy follicles seems to be a key factor for higher efficiency fertility preservation with the application of the ovarian transplantation process.

Previous results on studies of transplanted ovaries affected with different doses of VEGF indicated that the highest evaluated dose was the most effective preserving higher follicular population, higher angiogenesis, and lower apoptosis (18). *In vitro* evaluations showed that the *in vitro* process after ovarian transplantation had more improvement with 1 or 2 μg/mL VEGF treatment. Surprisingly, the lowest IVM and IVD rates were seen in the group treated with 4 μg/mL, which is possibly due to the possible toxic effects of higher doses of VEGF on transplanted ovaries. Therefore, doses between 2 to 4 μg/mL VEGF should be evaluated to obtain a more improved dose.

In conclusion, administration of an appropriate dose of VEGF for transplanted ovaries probably helps to preserve high quality oocytes with a greater ability to develop *in vitro* and produce a higher percentage of blastocyst embryos, which is possibly due to the prevention of ischemia in transplanted tissue by increasing angiogenesis. Furthermore, the physiologic effects of VEGF on the higher permeability of gonadotropin hormones, growth factors, and nutrients, which increases proper folliculogenesis, has been reported. Therefore, it is also suggested that higher vitro meiotic resumption of oocytes and subsequent IVD is related to more efficient folliculogenesis in transplanted ovarian tissue.

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Is there any difference between the distances created by towel clamp lifting and towel clamp plus manual lifting of the anterior abdominal wall for direct trocar entry in laparoscopic gynecologic surgery? A prospective interventional study

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Abstract

Objective: Most surgeons prefer to perform anterior abdominal wall lifting during abdominal entry to avoid damage to intestines or main vessels. Anterior abdominal wall lifting is assumed to prevent vital organ injuries by creating an adequate distance prior to entry into the peritoneal cavity. In this study, we compared the distance created for trocar entry into the peritoneal cavity with towel clamp lifting and towel clamp plus manual elevation of the anterior abdominal wall.

Material and Methods: Forty patients who underwent various laparoscopic procedures were enrolled. The study was performed in two steps: first the anterior abdominal wall was lifted using towel clamps (TC group), next the anterior abdominal wall was lifted via maximal manual elevation from the lower abdomen in addition to towel clamps (TCM group). The insertion distance of a plastic ruler into the abdomen was measured from the parietal peritoneum to the intra-abdominal structure in both groups.

Results: There was a statistically significant difference between the two groups (TC group 3.9±1.5 cm vs. TCM group 4.5±1.5 cm, $p<0.001$). Correlation analysis of the relationship of distance with BMI in the study groups revealed a strong negative linear correlation [TC group vs. body mass index (BMI); $r=-0.719$, $p<0.001$ and TCM group vs. BMI, $r=-0.749$, $p<0.001$]. Correlation analysis of the relationship between the study groups and parity number revealed a weak negative linear correlation (TC group vs. parity number, $r=-0.071$, $p=0.76$ and the TCM group vs. parity number, $p=0.61$), which did not reach statistical significance.

Conclusion: The recruitment of both towel clamps and manual elevation in anterior abdominal wall lifting provides significantly greater distance for trocar entry in laparoscopic surgery. (J Turk Ger Gynecol Assoc 2017; 18: 174-80)

Keywords: Abdominal wall lifting, laparoscopic entry, abdominal wall elevation

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Introduction

Complications that arise during abdominal cavity entry constitute about 50% of all complications encountered in laparoscopic surgery. Most surgeons prefer to perform anterior abdominal wall lifting during abdominal entry to avoid damage to the intestines or main vessels. Veress needles, direct trocar insertion, the Hasson technique, and visual trocar systems might be used for abdominal entry to create pneumoperitoneum. The conventional method of creating pneumoperitoneum in closed entry techniques entails blindly advancing the Veress needle or trocar from the umbilicus into the peritoneal cavity during abdominal wall lifting. Abdominal wall lifting might be performed manually and/or with the help of towel clamps (TC). The main goal of the procedure is to avoid intestinal and vascular injuries, and increase skin resistance to facilitate subcutaneous tissue perforation during abdominal entry (1,2). Anterior abdominal wall lifting is assumed to prevent vital

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organ injuries by creating an adequate distance prior to entry into the peritoneal cavity. The primary objective of our study was to compare the distances created in towel clamp lifting, and towel clamp plus manual lifting of the anterior abdominal wall. Hence, we aimed to determine whether the additional manual upwards lifting of the anterior abdominal wall prior to laparoscopic entry provided any significant increase in the distance compared with the use of towel clamps alone. Furthermore, we compared the relationship of both procedures with body mass index (BMI) and parity number.

Material and Methods

Study design

The study was designed as a prospective observational clinical study and performed at Bağcılar Training and Research Hospital. Forty patients, who underwent laparoscopic surgery for benign and premalignant-malignant gynecologic diseases at the Clinic of Obstetrics and Gynecology between November 2013 and December 2015, were included in the study. The study did not alter the type or form of the planned surgical procedure. The study group consisted of volunteer patients. Patients were informed in detail about the entire scope of surgical procedure as well as all potential intraoperative and postoperative complications. Age, obstetric and gynecologic history, and family history of the patients were recorded in the first preoperative visit. Height and weight were measured to calculate BMI (kg/m^2) preoperatively. All study procedures were performed in accordance with the Declaration of Helsinki. Institutional ethics committee approval was obtained, and written informed consent was obtained from each subject prior to the performance of any study procedures. The clinical trial registration number is NCT01726231 (ClinicalTrials.gov).

The required sample size was calculated, anticipating a goal of 25% increase in the abdominal wall to the nearest intra-abdominal structure distance, with a power value of 80% and an alpha-error value of 0.05. The number of subjects needed for the study was found as 36; 46 patients were enrolled in both groups. The 3 patients who refused to participate in the study at the last minute despite agreeing to undergo laparoscopy comprised 2 patients with severe adhesions (grade 4) (3) that precluded intra-abdominal imaging, and 1 patient with minimal umbilical herniation noted immediately before direct trocar entry; these patients were excluded from the study. In total, 40 patients were included in the study.

Antithrombotic prophylaxis was performed in line with the recommendations of the American College of Obstetrics and Gynecology and the American College of Chest Physicians to include early mobilization in patients at low risk, the use of gradual compression socks, and administration of 40 mg enoxaparin preoperatively 2 hours before the procedure and postoperatively until discharge in patients at moderate risk, and the use of gradual compression socks and administration of 40 mg enoxaparin preoperatively 2 hours before the procedure and postoperatively until week 4 in patients at high risk (4,5). Additionally, intermittent pneumatic compression devices were applied to both legs during the operation. All laparoscopic procedures were performed under general anesthesia. Gastric decompression was performed using oral-gastric tubes. Foley catheters were inserted preoperatively and removed 8 hours postoperatively. All study procedures were performed by 2 experienced surgeons.

Study setting

Intra-umbilical incisions were performed in the supine position in all patients. Subcutaneous tissue thickness beneath the umbilicus was measured in centimeters using a plastic ruler prior to creating pneumoperitoneum. Next, the anterior abdominal wall was lifted vertically upwards using towel clamps on both sides of the umbilicus and manual lifting from the lower abdomen. A 10-mm disposable trocar was advanced into the abdomen at steady pressure under the guidance of index finger. The abdominal viscera were observed by introducing the telescope via the first trocar. The abdomen was inflated with CO_2 gas to reach an intraperitoneal pressure of 20 mm Hg. A second 10-mm disposable trocar was inserted in the right lower quadrant in the Trendelenburg position. Examinations were performed via direct observation through the telescope in the second trocar.

The study was performed in two steps: first the anterior abdominal wall was lifted using towel clamps inserted on both sides of the umbilicus (TC group; Figure 1), next the anterior

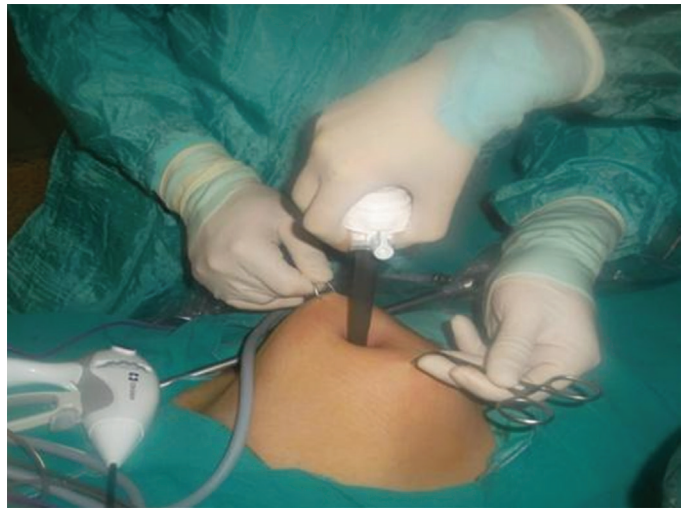

Figure 1. The skin was held and lifted using 2 towel clamps placed laterally at the level of the umbilicus, while the patient lay in the supine position

abdominal wall was lifted via maximal manual lifting from the lower abdomen in addition to towel clamps (TCM group; Figure 2). Distance obtained through anterior abdominal wall lifting was defined as the distance from the parietal peritoneum beneath the umbilicus to the closest intra-abdominal structure identified by direct observation.

Step 1 (TC group): The telescope was removed to carry out the study procedures and the intra-abdominal CO_2 gas was evacuated. The anterior abdominal wall was lifted using towel clamps on both sides of the umbilicus. Next, the telescope was re-inserted into the abdomen through a 10-mm assistant-trocar. A plastic ruler was advanced into the abdomen through the trocar at the umbilicus. The tip of the plastic ruler was held touching the closest visceral organ at a 90-degree angle under direct observation. The insertion distance of the plastic ruler into the abdomen was measured from the parietal peritoneum to the intra-abdominal structure in centimeters and recorded (Figure 3).

Step 2 (TCM group): In the second stage of the study, the lower abdomen was grasped manually midway between the umbilicus and the pubic symphysis and lifted, in addition to the towel clamps inserted on both sides of umbilicus (Figure 3). Next, the same measurement technique was used to determine how much the abdomen was lifted in centimeters.

All study data were analyzed using SPSS® version 19.0 (SPSS Inc., demo, Chicago, IL, USA). Descriptive statistics including numbers, percentages, means and standard deviation were used to interpret the data. The distribution of continuous variables was assessed using the Shapiro-Wilk test. Wilcoxon's signed-rank test was used to compare data with non-uniform distribution. The relationship between continuous variables was analyzed using Spearman's correlation analysis. The results were interpreted at 95% confidence intervals, and $p<0.05$ was interpreted as significant.

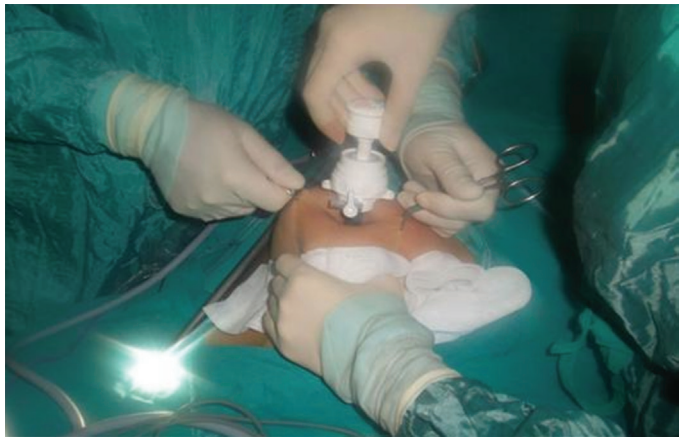

Figure 2. Manual lifting of the anterior abdominal wall from lower abdomen in addition to the use of 2 towel clamps at the level of the umbilicus, while the patient lay in supine position

Results

A total of 40 females were included in the study. Demographics and baseline characteristics of the study patients are summarized in Table 1. The mean baseline subcutaneous tissue thickness at the umbilicus level was 3.3±1.0 cm (range, 1.2-6 cm) in the study population. There was a weak positive correlation between subcutaneous tissue thickness beneath the umbilicus and BMI (r=0.286); however, this relation did not reach statistical significance (p=0.08).

The mean distance achieved during anterior abdominal wall lifting was 3.9±1.5 cm (range, 1.5-7 cm) in the TC group, and 4.5±1.5 cm (range, 2-7.5 cm) in the TCM group. There was a statistically significant difference between the two groups ($p<0.05$) (Figure 4).

Entry into the peritoneal cavity was achieved in the first trial in all patients. A minimal omental injury occurred in one patient during direct trocar entrance, whereby bleeding stopped spontaneously and did not preclude inclusion in the study.

Correlation analysis of the relationship of distance with BMI in the study groups revealed a strong negative linear correlation (TC group vs. BMI, r=-0.719, $p<0.001$; and TCM group vs. BMI, r=-0.749, $p<0.001$, Figure 5). The relationship with BMI had statistical significance in both groups.

Correlation analysis of the relationship between the study groups and parity number revealed a weak negative correlation (TC group vs. parity number, r=-0.071, p=0.76; and TCM group

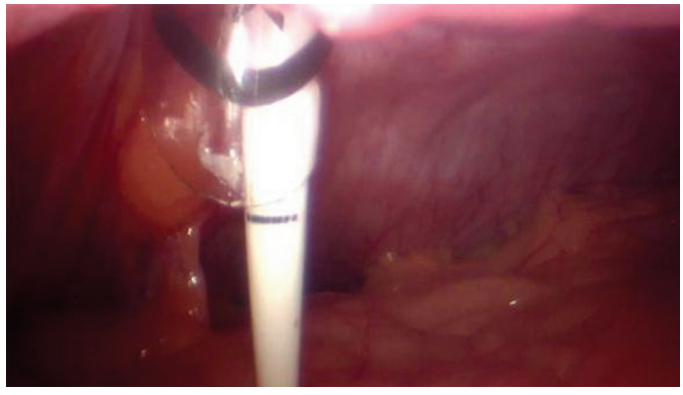

Figure 3. Image of the plastic ruler and demonstration of how to measure the distance from the anterior abdominal wall to intraperitoneal structures during anterior abdominal wall elevation while patient lies in the supine position. The plastic ruler is advanced through the umbilicus into the abdominal cavity and held at a 90-degree angle with its tip touching the closest visceral organ, under camera observation through the assistant trocar. The distance between the parietal peritoneum on the anterior abdominal wall and visceral organs are measured in centimeters

vs. number of parity, r=-0.12, p=0.61, Figure 5), which did not reach statistical significance.

Discussion

Creating pneumoperitoneum constitutes the primary and most important step of laparoscopic surgery. Four basic abdominal entry techniques have been described for this purpose: the classical Veress needle introduction, open (Hasson) entry technique, direct trocar insertion, and the visual trocar system. However, there is no consensus on the most effective and safest abdominal entry technique (2,6). The incidence of major vascular injuries and intestinal injuries has been reported as 0.02-0.5% and 0.06-0.1%, respectively (7,8). Among the vascular structures, the abdominal aorta, inferior vena cava, and iliac vessels are injured most commonly. The majority of major vessel injuries have been reported in patients with previous history of abdominal surgery and associated intra-abdominal adhesions. However, timely diagnosis of intestinal injury deserves special attention because laparoscopy-related mortality is more common in cases of missed intestinal perforations than major retroperitoneal vessel injuries (9,10).

Six principles should be followed to prevent injury to vital structures during entry into the peritoneal cavity: visualization, stabilization, adequate incision, controlled penetration, proper direction, and minimization of insertion (11). In clinical practice, the anterior abdominal wall is lifted upwards using towel clamps or manually from the lower abdomen. The objective of abdominal lifting is to distance the anterior abdominal wall from the intestines and vascular structures as much as possible before entry into the peritoneal cavity. Blind entry into the peritoneal cavity has been considered to be safer and more effective in this process (6,12).

No major complications other than a minimal omental injury were encountered in our study. In this technique, the trocar is inserted directly downwards at 90 degrees to the abdominal wall following upwards lifting of the anterior abdominal wall using towel clamps, as well as manual lifting from lower abdomen. Hence, a safe distance is established to prevent injury to the closest vital organ and risk of entry failure (e.g.

Table 1. Patient characteristics (all patients)

	n=40
Age#	39.9±13.1
Number of parity#	2.34±2.0
One§	4 (10)
Two§	15 (37.5)
Three§	5 (12.5)
More than three§	7 (17.5)
BMI (kg/m²)#	27.5±14.4
≤18.5§	3 (7.5)
18.5-24.9§	11 (27.5)
25-29.9§	12 (30)
30-34.9§	7 (17.5)
35-39.9§	6 (15)
≥40§	1 (2.5)
Thickness of the subcutaneous tissue (cm)#	3.34±1.0
Previous abdominal surgery§	32.5 (13)
Type of surgery§	
Total laparoscopic hysterectomy	14 (35)
Laparoscopic ovarian cystectomy	13 (32.5)
Laparoscopic tubal ligation	7 (17.5)
Diagnostic laparoscopy	5 (12.5)
Laparoscopic myomectomy	1 (2.5)
Indication of procedure§	
Diagnostic (e.g pain)	5 (12.5)
Adnexal pathology	13 (32.5)
Uterine myoma	5 (12.5)
Sterilization	7 (17.5)
Premalignant and malignant pathology	10 (25)
Intraabdominal adhesion score¶	
Grade 0	34 (85)
Grade 1	5 (12.5)
Grade 2	1 (2.5)
Grade 3	0 (0)
Overall complications	1 (2.5)

#SD: Standard deviation, BMI: Body mass index. Values are given as means ± standard deviation; §n (%); ¶Grading by the Nair classification of intra-abdominal adhesions retrospectively reviewed through video recordings

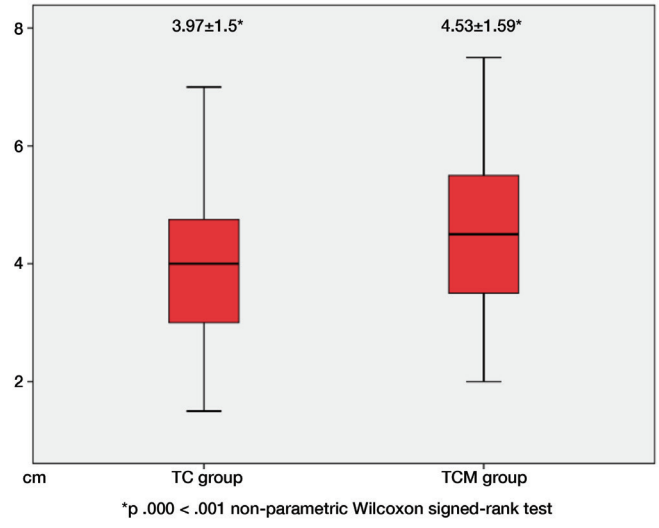

Figure 4. There was a statistically significant difference between the two groups
TC: Towel clamps

extraperitoneal insufflation) is minimized. It appears that manual lifting of the anterior abdominal wall in addition to the use of towel clamps increases the success rate of direct trocar entry and facilitates entry.

The umbilicus is the most common site of entry into the abdominal cavity in laparoscopic surgery due to its unique characteristic features including being the thinnest and least vascular site of the anterior abdominal wall. The abdominal wall layers are at their thinnest at this level. This site is minimally influenced by body type and BMI (6). The presence of a thick abdominal wall might decrease tactile sensation and therefore complicate closed entry into the peritoneal cavity (via direct trocar or Veress needle) in obese patients. On the other hand, the abdominal wall lies too close to the retroperitoneal structures in thin patients (13). The main goal of the first entry in laparoscopic surgery is to prevent injury to vital structures in thin patients and reduce failed entry rates in obese patients (12).

Approaching the abdominal wall at a 90-degree angle is of primary importance for the success of entry into the peritoneal cavity in obese patients. Otherwise, the trocar or Veress needle might proceed in subcutaneous tissue and extraperitoneal insufflation risk might emerge. Classic texts recommended horizontal entry with the recruitment of 45-degree angle to prevent vascular injuries in thin patients; however, this has also been reported to potentially increase the risk of extraperitoneal insufflation (12,13). In our study, we found that vertical entry into the peritoneal cavity was feasible in thin patients (within the TCM group). The risk of injury to vital structures might be minimized with the recruitment of maximum abdominal wall lifting and controlled trocar entry at stable strength. Naturally, controlling entry axial force is easier for operators with stronger upper bodies and might pose a problem for female surgeons (10).

Lifting the fascia is technically easier in patients with low BMI. In our study, we noted that the distance between anterior abdominal wall parietal peritoneum and visceral organs decreased statistically significantly with increased BMI in both groups. However, this reduction was more prominent in the TC group. Our results also demonstrated that additional manual

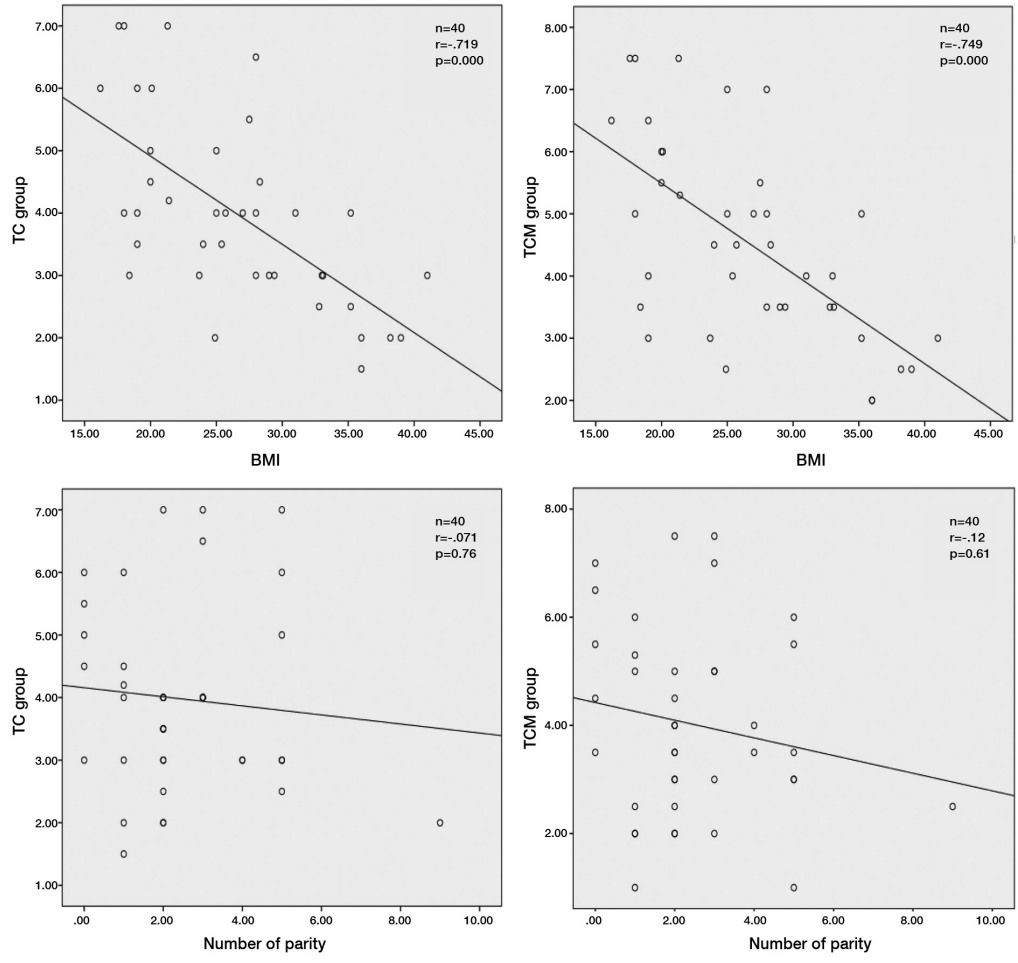

Figure 5. Correlation analysis of the relationship of distance with body mass index and parity number in the study groups
BMI: Body mass index, TC: Towel clamps

lifting performed in the TCM group provided greater lifting of the parietal peritoneum in patients with higher BMI. Previous studies have reported that the distance between the parietal peritoneum and closest intestinal organs increased only at the lifted parts of the abdominal wall, and blind abdominal entry had to be performed at a 90-degree angle (2).

Observation through the assistant trocar showed that maximal lifting of the anterior abdominal wall occurred only at the exact site of lifting in the TC group. Intestinal structures at the site of lifting might potentially get stuck in the anterior parietal peritoneum during abdominal lifting due to the cone-shaped configuration of the peritoneum at the base of the umbilicus (10,14). However, we saw that peritoneal tenting was removed with additional manual lifting of the anterior abdominal wall in the TCM group, providing the laparoscopist adequate distance in the direction of trocar in thin patients.

To the best of our knowledge, our study is the first to investigate the relationship between anterior abdominal wall lifting and parity number. Multiparity is currently the best known etiologic cause of rectus diastasis (15). The results of our study demonstrated a weak negative, though statistically not significant, correlation between parity number and the intra-abdominal distance created by anterior abdominal wall lifting. A possible explanation is the disruption of the integrity of thin, single-layer stratum consisting of skin, fascia, and peritoneum beneath the umbilicus due to multiparity (14).

With this study, we found that upwards lifting of the anterior abdominal wall during abdominal entry provided a mean safe working distance of 3.97±1.5 cm with the use of towel clamps alone, and 4.53±1.59 cm with the use of towel clamps plus manual lifting from the lower abdomen. These results suggest that the recruitment of both towel clamps and manual lifting for anterior abdominal wall lifting to create pneumoperitoneum, the most important component of laparoscopic surgery, provided a significantly greater distance. This distance resulting from maximal lifting might provide a safe working space to laparoscopists to prevent intestinal and vascular injuries.

Study limitations

The main limitation of our study is the lack of measurement of the traction force of anterior abdominal wall with a standardized device. Although study procedures were performed by the same two surgeons and the same surgeon performed the anterior abdominal wall lifting throughout the study, the possibility of exertion of different traction forces in each case cannot be ruled out.

Our results explicitly demonstrated that manual lifting of the anterior abdominal wall provided significantly greater intra-abdominal distance prior to first entry with a promising protective effect for the closest vital structure. Accordingly, the distance was greatest beneath the exact site of lifting. Consequently, despite the achievement of an adequate entry distance with the use of anterior abdominal wall lifting with towel clamps alone prior to direct trocar entry, the recruitment of manual lifting from the lower abdomen as well as towel clamps provide the surgeon with both a statistically significantly greater entry space and a rigid parietal peritoneum that facilitates entry.

Ethics Committee Approval: *Ethics committee approval was received for this study from the ethics committee of Istanbul Health Sciences Bağcılar Training and Research Hospital (No: 2012/77).*

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

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

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Prevalence of group B Streptococcal colonization among pregnant women and neonates in a tertiary hospital in India

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Abstract

Objective: To estimate the prevalence of group B *Streptococcus* (GBS) carriage among pregnant women attending the antenatal clinic, and the colonization rates among newborn born to colonized mothers.

Material and Methods: Women attending the antenatal clinic between 35-37 weeks were screened using rectal and lower vaginal swab. Swabs were initially plated on sheep blood agar and LIM broth. The LIM broth was subcultured after 24 hours onto blood agar and CHROMagar StrepB plates with all plates checked for growth at 24 and 48 hours. All babies born to mothers in the study had surface swabs taken to estimate the vertical transmission rate.

Results: Between September 2012 and March 2013, 305 consecutive mothers were screened. Of these, eight mothers were GBS positive in 5% blood agar (2.6%) and 23 mothers showed GBS positivity in enriched media (7.6%). Sixteen of 238 babies (6.7%) were colonized.

Conclusion: Though lower than rates from most countries, 7.6% of mothers attending an antenatal clinic in south India were colonized with GBS. Use of enrichment media markedly increased the detection rate. Approximately two-thirds of newborn born to colonized mothers were also colonized. There were no instances of invasive GBS disease, indirectly proving the efficacy of intrapartum prophylaxis in preventing neonatal GBS disease. (J Turk Ger Gynecol Assoc 2017; 18: 181-4)

Keywords: Pregnancy, newborn, India, group B *Streptococcus*, infection

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Introduction

Group B *Streptococcus* (GBS) is one of the major causes of perinatal infections. It causes sepsis, meningitis, and pneumonia in the newborn and young infants. In the mother, it is one of the important causes of chorioamnionitis, post-partum endometritis, urinary tract infections, post cesarean febrile illness, and rarely, endocarditis.

GBS colonizes the lower genito-urinary and gastro intestinal tracts in adults, with the colonization being chronic or intermittent. In the United States of America (USA), it is estimated that 15-40% of pregnant women are carriers of GBS (1). In a colonized woman, the bacteria can be transmitted to the fetus in the intra-uterine or perinatal period. This transmission from the mother to the newborn occurs variably and the transmission rate is estimated to be between 40-73%. Of the babies born to colonized mothers, 1-2% develop infection in the immediate neonatal period (early onset sepsis). Reduction of this vertical transmission of GBS to the newborn has been a priority over the past three decades. The method that has proved most successful has been screening of all pregnant women during pregnancy, with intrapartum antibiotics given to colonized women in labor. Using this strategy, GBS infection among newborn in the USA has been reduced from 1.7-1.9 per 1000 live births in the early 1990s, to 0.34-0.37 per 1000 newborn in 2008 (2). Cost-benefit analysis shows that this strategy would be most helpful in regions where neonatal GBS sepsis prevalence is high (more than 1.2

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per 1000 live births). In regions where the prevalence of GBS infection in newborn is low, intra partum antibiotics given in the presence of specific maternal risk factors deemed to be high risk for transmission to the fetus/newborn might be more useful.

GBS carriage in mothers varies between geographic regions and races. Studies in various developed nations have shown GBS carriage rates of between 20-40%. The few studies published from developing countries have shown comparatively lower prevalence rates. There have been only two studies from the Indian subcontinent on GBS carriage among pregnant women. One study from our institution in the early 1980s showed a prevalence of 5.8% (3). The other study from Pondicherry in south India showed a prevalence of 2.3% (4).

The prevalence of neonatal early onset sepsis with GBS in our hospital was 0.17/1000 live births in the period 1988-1997 (5). This has increased subsequently to 0.68/1000 live births between 1998 and 2010 (6). We hypothesized that maternal carriage rates must have increased in these two decades to cause the increase in newborn early-onset infections; hence the need to document maternal carriage rates among pregnant women. This would help to decide whether universal screening should be offered during pregnancy to prevent maternal and neonatal morbidity.

Material and Methods

The study was conducted in the Obstetric and Neonatology departments of a tertiary level perinatal hospital in south India that has around 13.000 deliveries/year. All pregnant women booked with Obstetric Unit IV were approached for screening and those who consented to take part and were likely to deliver in this hospital were recruited.

Swabs were taken from the lower vagina and rectum as per the Centers for Disease Control and Prevention guidelines (2).The swabs were transported immediately to the Clinical Microbiology Department where they were plated directly on quality passed 5% sheep blood agar plates prepared in-house, CHROMagar StrepB (CHROMagar, France) and inoculated in Lim broth (Becton, Dickinson and Co., NJ). Following incubation for 24 hours at 37 °C under 5% CO_2 atmospheric air, the Lim broth was then subcultured onto both blood agar and CHROMagar StrepB plates. The primary plates were checked for growth at 24 and 48 hours. The plates subcultured from Lim broth were also checked for growth at 24 and 48 hours. Plates were then classified as showing no growth or growth of GBS. When growth occurred in the primary culture itself, it was deemed to be heavy colonization, and if it occurred only in Lim broth, it was light colonization (7).

GBS was identified by either beta or gamma hemolysis on blood agar, mauve colonies on chromogenic media, and a positive latex agglutination with group B antisera (Plasmatec laboratories Ltd, UK). Organism identification was confirmed using the Christie, Atkins, and Munch-Petersen test. Beta-hemolytic ATCC 12386 *Streptococcus agalactiae* and non-hemolytic ATCC 13813 *S. agalactiae* were used as quality control strains. Mothers who showed positive growth for GBS received intra partum antibiotic prophylaxis with ampicillin.

All babies born to mothers who participated in the study had surface swabs (umbilical and external ear) taken within 30 minutes of delivery to estimate the newborn colonization rates. Babies born to mothers who were colonized as well as those with traditional risk factors for early-onset sepsis had a peripheral blood cultures taken (irrespective of maternal intrapartum antibiotic status) and were started on antibiotics (crystalline penicillin and gentamicin) until the culture showed no growth.

Details of the mother's medical and obstetric history, along with delivery details were recorded. The baby's birth demographics and neonatal course was also documented.

Sample size: The study conducted in our hospital in 1982 showed a prevalence of 5.8%. Hence, the estimated sample size for a prevalence of 6% with a precision of 3% needed a minimum of 241 patients to be screened. Allowing for 20% dropout, we planned to screen 290 mothers.

Analyses were performed using SPSS 13.5. Prevalence rates were calculated as percentages.

The study was approved by the institutional review board. The study complied with the ethical conduct of research using human subjects.

Results

A total of 305 pregnant women were screened between September 2012 and March 2013. The mean age of the women in the cohort was 26±4.2 years. Most women were in the 26-30-years' age range (33.4%) and a large proportion of them (62%) were primiparous.

The primary cultures were positive for GBS in eight mothers (2.6%) (heavy colonization), and 23 swabs were positive in the Lim broth subcultures (7.64%) (light colonization). Two hundred thirty-six of the 305 mothers delivered 238 babies in this hospital and the babies were evaluated with surface swabs and sepsis screen. This included 20 of the women who were GBS-positive. The other women delivered elsewhere and hence the babies could not be screened. Of the women who were GBS-positive, 6 did not receive intrapartum antibiotics. The surface swabs from 3 newborn babies were positive for GBS on primary cultures (1.3%), and 16 after inoculation in enriched media (6.7%). The latter included three babies whose mothers were not found to be colonized. None of the

babies were symptomatic or had positive blood culture for GBS.

Discussion

GBS has been identified as an important cause of infection in the perinatal period in both the mother and her newborn. This bacterium is of particular interest because of the fact that intrapartum antibiotics given to colonized mothers can reduce the burden of early-onset disease in the newborn. This requires screening of pregnant women late in pregnancy or in labor and administration of antibiotics to those colonized. The prevalence of colonization varies with geographic region, sociodemographic status, ethnicity, and sexual activity. In low prevalence areas, it might be more cost effective to give intrapartum antibiotics to mothers in labor with certain identified risk factors that place their newborn at higher risk of early-onset infection.

Studies in various developed nations have shown different GBS carriage rates: Canada 19.5% (8), the United Kingdom (Oxford) 21.3% (9), the USA 15-40% (1), and Sweden 25.3% (10). The few studies published from developing countries have shown comparatively lower prevalence rates: Lebanon 17.7% (11), Brazil 17.9% (12), India (Vellore) 5.8% (3), and Pondicherry 2.3% (4). The exception is Zimbabwe, where colonization rates of 60.3% were noted (13).

The incidence of early-onset infection in the newborn has increased four-fold in the last two decades in our hospital compared with the 1990s, inspite of risk-based intrapartum antibiotics being given to mothers in labor since 2004. In the present study, we found that the colonization rate was 7.6%, which is an increase from the previous study, and also much higher than the study from Pondicherry. It is, however, much less than the prevalence rates quoted in studies from other low- and middle-income countries. Thus, it might be argued that GBS colonization rates are lower in India compared with most high- or middle-income countries.

Our study showed that nearly 65% of newborn born to GBS-positive women were colonized with GBS, though none developed invasive infection. This might point to the effectiveness of intrapartum antibiotics in preventing invasive disease. Thus, it was seen that the GBS colonization rate had increased in pregnant women since the 1980s, but was still far below the prevalence rates seen in developed countries and other middle-to-low income countries. It is also not commensurate with the multi-fold increase in early-onset neonatal sepsis. Whether screening in labor is therefore the next logical solution is to be determined.

The transmission rate to the fetus was high, though there were no cases of invasive disease in the newborn. Therefore, it appears that universal maternal screening for GBS may, at present, be cost-ineffective in India. Selective screening is not possible because there are no significant risk factors identifiable for maternal colonization. Risk-based antibiotic prophylaxis to mothers and selective sepsis examinations in newborn would be the best choice in this scenario to prevent early-onset GBS disease in newborn.

Ethics Committee Approval: *This study was approved by the Institutional Review Board, Christian Medical College, Vellore. All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.*

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

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

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Excisions of severe cervical dysplasia: Are there mandatory diameters of the cone that need to be considered?

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Abstract

Objective: To achieve optimal depth for negative margin cones after loop electrosurgical excision procedures (LEEP) for cervical dysplasia.

Material and Methods: Retrospective cohort analysis of LEEP cones of 201 patients with cervical dysplasia during a four-year period. Analysed cones were divided into two different groups: cones with negative margins without dysplasia, and cones with margins positive for dysplasia. In order to determine the cut-off value of the depth of the resected cones, receiver operating characteristic (ROC) analysis was performed.

Results: Negative margins were found in 71.0% (n=49) of all cones, whereas positive margins were reported in 29.0% (n=20). Negative margin cones were achieved in 100% with a cone depth of ≥20 mm. A resection depth between 10-19.9 mm led to 73.0% negative margin cones. Calculation of cone volume shows for 2.0 cm^3, a sensitivity of 79% and a specificity of 64%. Statistical analysis using an ROC model showed p=0.002.

Conclusion: Forth greatest safety of patients, cone depths from LEEPs for cervical dysplasia should be ≥20 mm to achieve negative margins. (J Turk Ger Gynecol Assoc 2017; 18: 185-9)

Keywords: Dysplasia, high-grade squamous intraepithelial lesion, loop electrosurgical excision procedures, preterm delivery, depth

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Introduction

More than 270.000 women die per year from cervical cancer according to the World Health Organization (1). Thus, prevention and early detection of cervical carcinoma and its dysplastic precursor lesions are of essential importance. Precursor lesions of cervical carcinoma can be classified as low- or high-grade squamous intraepithelial lesions (LSIL or HSIL). These lesions are located around the transformation zone of the cervix uteri. Before acquiring the ability for malignant invasion, precursor lesions may rest for up to ten years (2). Grade of dysplasia and time of its detection determine the chance of invasive growth (3).

Preinvasive lesions of the cervix uteri and cervical cancer are still a major health issue in Germany.

The treatment of dysplastic lesions of the cervix uteri is challenging; in Germany the majority of patients is older than 30 years according to public health statistics (4); therefore, the question of family planning arises when discussing excisions of the cervix uteri. On the one hand, excisions of dysplastic lesions of the cervix uteri have to demonstrate negative margins (i.e., without dysplasia) to maximize safety for patients. On the other hand, Noehr et al. (5) described an increasing risk for preterm delivery depending on the depths of the resected cone. Due of this dilemma, there are no clear recommendations for depth of excisions of dysplastic lesions of the cervix uteri (6-8). Thus, the aim of this study was to find the optimal size of resected cone in order to achieve negative margin samples.

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Material and Methods

This study was approved by the ethics board of the University of Luebeck, Germany (registration number 12-234). The Department of Obstetrics and Gynecology at University Hospital of Luebeck is certified and registered for treating patients with dysplasia according to national guidelines by the *"Arbeitsgemeinschaft Zervixpathologie und Kolposkopie e.V."*. Data of all patients (n=517) who were referred to the Department of Obstetrics and Gynecology because of cervical dysplasia during a period of four years were screened retrospectively, as depicted in Figure 1.

Inclusion criteria were defined as: recommendation for operative therapy, current Papanicolaou smear test, histologic confirmed cervical dysplasia, and available standardized histologic analysis report.

Exclusion criteria were defined as: pregnancy ≥16 weeks of gestation, negative informed consent. LEEPs were performed under colposcopic surveillance using a Leisegang 3MVS LED colposcope (45.000-52.000 Lux; 300 mm free working distance) with integrated camera. Portio-examinations: natively, aceto acid 5% and iodine stained.

All LEEPs were performed in a sterile operation room using tungsten snare electrodes (ERBE) of different sizes under regional or general anaesthesia. Endocervical curettage was routinely performed prior to LEEP. Hemorrhage was stopped using high-voltage spray for cauterization. No sutures were used. The resected cone was marked with a suture at twelve o´clock for orientation and transported to the pathology department in a formalin container. The examination of the cone was perfomed according to Westra et al. (9).

The cone volume was calculated using the formula $(\frac{\pi \times r^2 \times H}{3})$ based on the data of the acquired pathologic report.

Surgical margins were considered *positive* when the dysplastic lesion was closer than 1 mm to the margin, otherwise for >1 mm distance to the lesion it was considered *negative*.

For better analysis, resected cones were differentiated into three different categories according their resection depth: plane: 0-9.9 mm, medium: 10-19.9 mm, deep: 20-100 mm.

Power calculation

A statistical a priori-power analysis was performed for sample size estimation, based on the assumption that the effect size in this study was medium using Cohen's (1988) criteria. Thus, sample size of 109 observations would achieve 80% power.

Statistical analysis

Data were collected in Microsoft® Access 2003 from MS Office® Package. Statistical analysis was performed using IBM SPSS Statistics® version 22.0 for windows. Analysis included the Mann-Whitney U test for continuous data, the chi-square test for categorical data, and Fisher's exact T-test. The level of significance was defined $\alpha=0.05\%$. For statistical evaluation of the negative margin samples according to the volume of the cone, the area under the curve of a receiver operating characteristic analysis (ROC) was calculated.

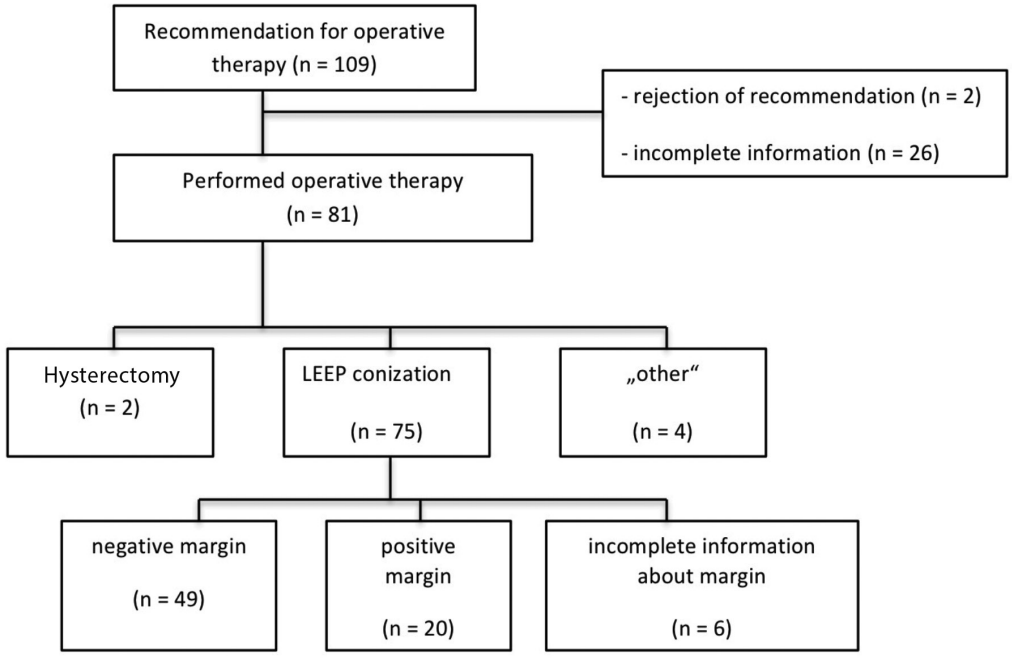

Figure 1. Flowchart of patients

Results

In total, 109 patient received recommendations for operative therapy and were included in this study, as shown in Figure 1. The mean age of the patients was 31.2 years with a standard deviation of 7.3 years. The basic demography of the study population is shown in Table 1.

Margins of cones from LEEPS

Sixty-nine excisions from LEEPs could be analyzed: Negative margins were found in 71.0% (n=49) of all LEEPs. A positive margin was reported by the pathologist in 29.0% (n=20) of the cases. Negative margin cones were achieved in 100% of cases for a depth equal or larger than 20 mm (n=3). A resection depth of 10-19.9 mm led to a negative margin rate of 73.0% (n=37) (Figure 2). The histologic results of LEEPs are depicted in Table 2.

Receiver operating characteristic analysis

Initially, the volume of the cone was analyzed. A resected volume of 2.0 cm^3 displayed a sensitivity of 79% with a specificity of 64%. A ROC model displayed a statistical significance of p=0.002 for margin status. According to the depth of the resected cone, a statistical significance of 0.036 was found. A depth of ≥19 mm revealed a sensitivity of 79% with a specificity of 41%, which is reflected in Figure 3 (for legend for Figure 3, Table 3).

Table 1. Demography of study population

	Recommendation for operative therapy n=109	
Age (years) (MV ± SD)	31.2	7.3
Ethnicity (%/n)		
Caucasian	88	96
No information	1.8	2
Marital status (%/n)		
Unmarried	44	48
Married	17.4	19
Divorced	1.8	2
No information	26.6	29
Parity (%/n)		
0	25.6	28
1	29.3	32
2	12.8	14
>2	4.5	5
No information	16.5	18
Smoking (%/n)	55	60
Oral contraceptive (%/n)	34.8	38
HPV Infection (%/n)	55	60
HPV Vaccination (%/n)	1.8	2
MV: mean value; SD: standard deviation; HPV: human papillomavirus		

Discussion

In this study, the histologic status of the margins of resected cones correlated clearly with the depth of the resected

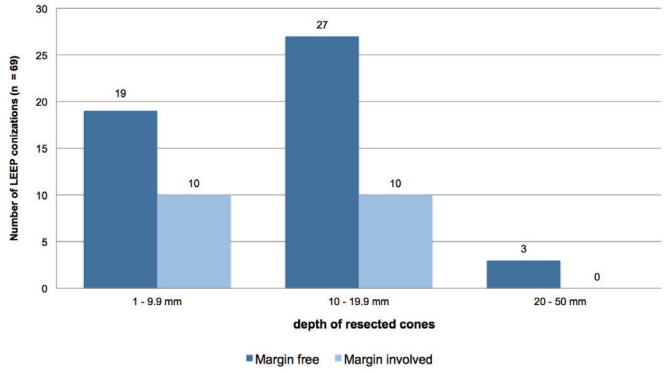

Figure 2. Depth of resected cones and margin status

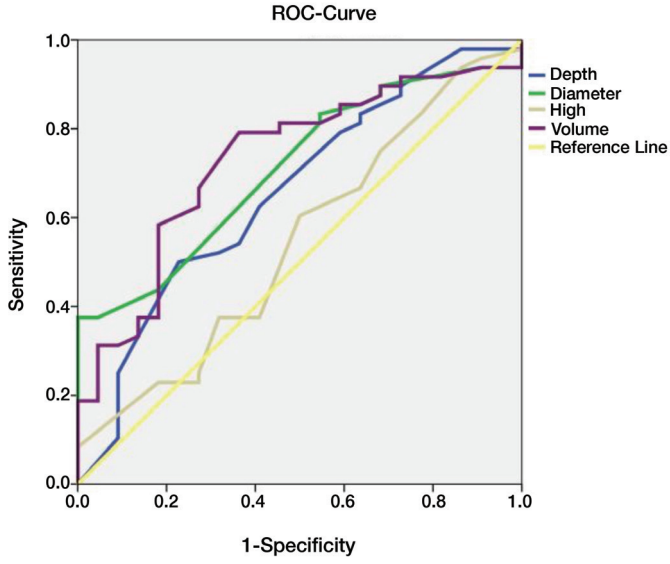

Figure 3. ROC analysis

Table 2. Results of LEEPs

	LEEP total (n=75)	
Result	**%**	**n**
Normal	2.7	2
Cervicitis	0.0	0
CIN 1	5.3	4
CIN 2	13.3	10
CIN 3	77.3	58
Cervical cancer	1.3	1
LEEP: loop electrosurgical excision procedures; CIN: cervical intraepithelial neoplasia		

Table 3. Legend for ROC analysis

Area under the Curve					
				95% CI	
Parameters	**Area under the curve**	**Standard error**	**Asymptotic significance**	**Lower limit**	**Upper limit**
Depth	0.657	0.071	0.035	0.517	0.796
Diameter	0.709	0.062	0.005	0.587	0.831
High	0.544	0.074	0.552	0.397	0.691
Volume	0.730	0.063	0.002	0.606	0.855

cone. Best safety was achieved for a depth equal or larger than 20 mm.

Previous studies investigating resection depth and margin status found conflicting results. Some studies found optimal depth for 10 mm resections (7), or confirmed 20 mm as the optimal depth (6), whereas the study of Öz et al. (6) found no correlation between resection depth and margin status. The use of cold-knife excisions might have influenced the results of the studies of Öz et al. (6) and Kliemann et al. (7), which makes a comparison with the results of the present study difficult.

For positive margins of cones from LEEPs, a previous meta-analysis showed a relative risk of 6.1 for recurrence of cervical dysplasia (CIN 2/3), which stresses the importance of negative margins of LEEP samples (10). Therefore, from this point of view, LEEPs should aim at great depth of cones (>20 mm) to maximize safety for patients.

On the other hand, Noehr et al. (5) described an estimated 6% increase in risk for preterm delivery with every additional millimeter of excised cervical tissue. Because the average age for family plannung has risen it is becoming increasingly important to resect only as much tissues as necessary to achieve a negative margin.

The results of the current study suggest a depth ≥20 mm for best safety. However, the estimated odds ratio (OR) for preterm delivery is already significantly elevated (OR ≈1.5) for a depth of ≈13 mm and is increasing to around OR ≈3.0 for depths around 20 mm (4). This illustrates the dilemma for surgeons and emphasizes the need for detailed patient education about risk of positive margins versus risk of preterm delivery in a latter pregnancy.

In conclusion, this study suggests a resection depth of ≥20 mm to achieve histologic negative margins of cones from LEEPs for cervical dysplasia. On the other hand, patients need to be educated about the increased risk for preterm delivery that comes with a greater depth.

Study limitations

The retrospective design and low number of patients with positive margins (n=20) limit this study. Following the recommendation of operative therapy, 2 patients refused surgery and 26 patients had insufficient data about demography or on the histologic report (n=6), which could create a selection bias.

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Retrospective analysis of episiotomy prevalence

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Abstract

Objective: This study was performed to determine the rate of episiotomy.

Material and Methods: This retrospective was conducted in 3 state hospitals located in 3 cities in the Central Anatolia region of Turkey. Ethics committee approval was received for this study. Also, institutional permissions from the institutions where the study was conducted were obtained before the study. The sample of the study consisted of 8587 women. The data of the study were collected by analyzing birth records in archive records.

Results: The average age of the women was 26.16±5.9 years, the average number of deliveries was 2.19±1.2, and 52.0% of the women who gave birth via vaginal delivery underwent episiotomy. The rate of episiotomy was found to be 93.3% in primipara women and 30.2% in multipara women. It was determined that neonatal weight did not affect the episiotomy rate, and that neonatal height was higher in deliveries with episiotomy and suture. Also, it was determined that as the age and parity of the women decreased, the rate of episiotomy increased.

Conclusion: The rate of episiotomy was observed to be high, especially in primipara women. (J Turk Ger Gynecol Assoc 2017; 18: 190-4)

Keywords: Episiotomy, prevalence, vaginal deliveries

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Introduction

Episiotomy is a surgical incision applied to the bulbocavernosus muscle in the second phase of labor in order to make the delivery easier by enlarging the vaginal opening, to protect the tonus of the perineum, to prevent undesired vaginal fissures, and to enable easy, fast and safe delivery of the head of the fetus (1).

Surgical opening of the perineum was suggested for the first time in 1714 in order to prevent serious tears of the perineum (2). A significant increase in episiotomy rates was observed around the world (3). Despite being one of the most frequently administered surgical procedures in the world, the efficacy of episiotomy was introduced without strong scientific evidence (2). The World Health Organization (WHO) suggested that episiotomy should not be administered as routine practice (4), and in a bulletin published by the American College of Obstetricians and Gynecologists, episiotomy was reported to be restricted (5). Despite these suggestions, prevalence of episiotomy varies significantly between countries (6). The rate of episiotomy varies between 9.7% (the lowest) (Sweden) and 100% (the highest) (Taiwan) in both primipara and multipara women (7).

Episiotomy is suggested to be administered in conditions such as complicated vaginal deliveries (breech, shoulder dystocia, forceps, vacuum), incision-related scars in the genital area, poorly healed or 4th degree tears, and fetal distress (8). There are different opinions about the applicability of episiotomy in addition to protecting maternal and infant health. While opinions about episiotomy's increasing Apgar score of the baby or decreasing perinatal asphyxia by shortening the second phase of delivery are not definite, there are also views that it does not prevent, or even increases, defects in the perineum (9). Also, in a comparison of limited use of episiotomy and routine episiotomy in deliveries without any complication, the WHO reported that episiotomy decreased posterior perineal

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trauma risk and prenatal trauma repair need, and that there was no difference between the two groups in terms of risks of vaginal and perineal trauma, pain, dyspareunia, and urinary incontinence (10).

It is indicated that routinely administered episiotomy causes postpartum early perineal complications and higher perineal pain scores (11-13), urinary inconsistencey is higher in the postpartum 3rd month in women undergoing episiotomy (13), and the amount of blood loss is higher in the delivery (14). In another study, it was stated that with a decrease of episiotomy administration, anal sphincter lacerations decreased in vaginal deliveries (15).

The rate of perineal trauma is indicated to be high in countries where episiotomy is frequently administered (16-18). Moreover, perineal trauma caused due to episiotomy can affect the sexuality and self-confidence of women (19,20), and lead to perineal pain and infections (21,22). There are also studies emphasizing that episiotomy has a protective role against the formation of 3rd degree tears (14,23-25).

The study was conducted to retrospectively analyze the prevalence of episiotomy in vaginal deliveries in 3 state hospitals located in the Central Anatolia region of Turkey.

Material and Methods

Study design and participants

This retrospective study was conducted in state hospitals in 3 cities in the Central Anatolia region of Turkey. The records of 8649 women who gave birth between January 1st, and December 31st, 2013, were examined retrospectively. The data of 62 women were excluded due to a lack of information and 8587 women were included in the study. The data of the study were collected by examining birth registrations from archive records. The birth registrations involved information concerning the ages of the women, delivery methods, number of births, and the height and weight of the infants.

Ethical aspect of the study

Ethics committee approval was received for this study. Also, institutional permissions from the institutions where the study was conducted were obtained before the study.

Statistical analysis

The Statistical Package for Social Sciences (SPSS) 20 package programme was used to assess the data. Categorical measurements are given as number and percentage, and numerical measurements are given as mean and standard deviation. The chi-square and ANOVA test were used. Statistical significance was accepted as $p<0.05$.

Results

It was determined that average age of the women was 26.16±5.9 years, the average number of births was 2.19±1.2, 34.6% were primipara, 76.4% of all women had vaginal deliveries, and 52.0% of the women who had vaginal deliveries gave birth with episiotomy. Also, 99.2% of the deliveries were live births (Table 1).

The rate of episiotomy was determined as 93.3% in primipara women and as 30.2% in multipara women. The rate of suture delivery without episiotomy was 0.6% in primipara women, whereas this rate was 7.4% in multipara women. In the statistical analysis, a significant difference between the groups was determined ($p<0.05$) (Table 2).

It was determined that neonatal weight did not affect the episiotomy rate, and neonatal height was higher in deliveries with episiotomy and suture. Moreover, as the age of the women decreased, the episiotomy rate increased. The episiotomy

Table 1. Distribution of the women based on demographic and obstetric characteristics

Variables	**Mean ± standard deviation**	
Age (years)	26.16±5.9	
Number of births	2.19±1.2	
Obstetric history	**Number**	**%**
Primipara	2971	34.6
Multipara	5616	65.4
Delivery method		
Cesarean section	2026	23.6
Vaginal	6562	76.4
Vaginal delivery (n=6562)		
Delivery with episiotomy	3415	52.0
Delivery without episiotomy	2818	42.9
Suture delivery without episiotomy	329	5.1

Table 2. Distribution of vaginal delivery-related characteristics of the women in terms of gravida number

Delivery related characteristics	**Gravida**				χ^2	**p**
	Primipara		**Multipara**			
	n	**%**	**n**	**%**		
Delivery with episiotomy	2116	93.3	1299	30.2	2366.8	**<0.001**
Delivery without episiotomy	138	6.1	2680	62.4		
Suture delivery without episiotomy	13	0.6	316	7.4		

rate of women with a low number of births was high and the difference between the groups was statistically significant ($p<0.05$) (Table 3).

Discussion

The WHO reported that episiotomy should be restricted in deliveries without complications. In the same study, it was also stated that restrictive episiotomy was more advantageous compared with routine episiotomy, and there was less posterior perineal trauma, and fewer sutures and complications in restrictive episiotomy (2).

In addition to the WHO and other authorities, patients for whom episiotomy should be administered are clearly defined in the safe motherhood module published by the General Directorate of Maternal and Infant Health and Family Planning and used in in-service training of personnel. Episiotomy is suggested in order to step up the delivery in cases with fetal distress, in order to prevent intracranial hemorrhage with forceps, vacuum applications, premature or breech delivery, and in cases where excertion of the mother's strength during delivery should be prevented (i.e. cardiac failure), and if there is a risk of 3rd degree perineum tears (especially when 3rd degree tears occurred during a previous delivery) (26).

Table 3. Distribution of vaginal delivery characteristics in terms of different variables

Variables	Mean ± standard deviation	F	p
Neonatal weight (grams)			
Delivery with episiotomy	3252.04±966.13	0.44	0.639
Delivery without episiotomy	3238.92±742.58		
Suture delivery without episiotomy	3281.52±50.01		
Neonatal height (cm)			
Delivery with episiotomy	50.07±1.47	4.85	**0.008**
Delivery without episiotomy	49.91±2.50		
Suture delivery without episiotomy	50.02±2.78		
Age of the women (years)			
Delivery with episiotomy	23.62±5.18	623.33	**0.001**
Delivery without episiotomy	28.49±5.78		
Suture Delivery without episiotomy	27.37±5.74		
Number of births			
Delivery with episiotomy	1.53±0.8	1632.46	**0.001**
Delivery without episiotomy	3.01±1.3		
Suture delivery without episiotomy	2.42±0.8		

In the present study, it was determined that more than half of the women (52.0%) having vaginal deliveries underwent episiotomy, and 93.3% of the primipara women and 30.2% of the multipara women received episiotomy. The suture delivery rate was determined to be higher in multipara women.

In a study conducted by Çalışkan et al. (27) (2003), it was reported that the episiotomy rate was 74.2%. In another study conducted in Turkey by Karaçam et al. (12), it was reported that episiotomy was performed in 64% of vaginal deliveries (95% of first deliveries, 48% of second deliveries, 12% of third and subsequent deliveries). In another Turkish study, episiotomy was reported to be administered in 92% of primipara women and 72% of multipara women (28).

In some countries, the episiotomy rate has decreased over the years. The episiotomy rate was 60.9% in all vaginal deliveries in 1979 in the United States of America, but the rate decreased to 24.5% in 2004; (15) in a study conducted in Thomas Jefferson University Hospital, the episiotomy rate decreased from 69.6% in 1983 to 19.4% in 2000 (29), and in a study conducted in Hong Kong, the rate decreased from 73% in 2003 to 27% in 2008 (30). However, the ideal rate of episiotomy is still not clear (15). There are differences between episiotomy rates depending on the countries. In a study conducted in primipara women in Nigeria, the rate of episiotomy was determined as 62.1% (6). In contrast, the rate of episiotomy was 40.6% in primipara women in a study conducted in Italy (31). Trinh et al. (32) (2013) evaluated the rate of episiotomy among women born in Vietnam and Australia between 2001 and 2010. In Australia, they found that the episiotomy rate was 27% in Australian-born primipara women, and 48% in Vietnamese-born women. In a study conducted in Oman, the rate of episiotomy was 66% (33).

Perineal trauma is described as damage that occurs in the genital region or due to a surgical incision or episiotomy during delivery (20,34). Even though there are a number of studies indicating that episiotomy is defined as a cause of birth trauma, as well as disadvantages of its administration, the episiotomy rate was high in the present study, as it is in developing countries. Episiotomy is administered in almost all primipara women regardless of the presence/absence of complications with delivery, it is almost a routine administration for primipara women. In Turkey, deliveries performed at hospitals are performed in the lithotomy position and practices providing flexibility to the perineum are applied

in very few clinics. Episiotomy administration procedures should be adapted to all healthcare personnel who assist delivery through in-service training and the necessity of avoiding routine administration should be emphasized. In addition, increasing alternative practices such as massage and restricting episiotomy in vaginal deliveries will enable a decrease in the episiotomy rate.

Ethics Committee Approval: *Ethics committee approval was received for this study from the ethics committee of Nevşehir Hacı Bektaş Veli University (No: 2014.02.02).*

Informed Consent: *Written informed consent wasn't obtained from patients who participated in this study because it's a retrospective study.*

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Does size matter? Retrospective analysis of large gynecologic tumors

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Abstract

Objective: To evaluate the characteristics of patients who underwent surgery due to the presence of a large pelvic-abdominal mass over a 5-year period in a university clinic.

Material and Methods: Among 3476 gynecologic operations, intraoperative findings were evaluated retrospectively. Uterine and/or adnexal masses smaller than 20 cm were excluded to refine "large" tumors and 74 patients with large tumors were enrolled in the study group. Demographic characteristics, intraoperative findings, and results of histopathologic examinations were recorded. Moreover, preoperative and intraoperative findings were compared among tumors with adnexal origin according to their final histopathologic results.

Results: The mean age of the patients was 46 years. The most common symptom was abdominal pain, as recorded in 38 (51.4%) patients. Among all patients, 31 (41.9%) had coexisting illness and 13 (17.6%) had a history of surgery. The mean tumor diameter was 25.9±8.6 cm (20-60) and 60 (78.9%) tumors were of adnexal origin. The ratios of malignancy for large adnexal and uterine tumors were 34.4% and 12.5%, respectively. When the large adnexal tumors were re-evaluated, the mean cancer antigen (CA) 125 level was significantly higher, and ascites was more frequently detected in malignant tumors ($p<0.01$) then in benign and borderline tumors.

Conclusion: Benign and borderline tumors are more common among large abdominopelvic masses, although the presence of ascites and elevated CA 125 may present malignancy in large gynecologic tumors. Further studies with larger sample sizes are needed to define the characteristics of large tumors and their malignant potentials. (J Turk Ger Gynecol Assoc 2017; 18: 195-9)

Keywords: Big gynecologic tumors, borderline tumors, leiomyoma, ovarian cysts

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Introduction

Managing pelvic masses, which may result from benign or malignant conditions of gynecologic and non-gynecologic diseases, is routine daily practice for outpatient clinic gynecologists. However, due to its rarity, large-sized pelvic tumors that reach the upper abdomen may sometimes be confusing for physicians (1,2). The size of the adnexal mass is one of the important factors in making decisions for the clinical management, and therefore some indexes have to be taken into account (3-7). Although "giant", "huge," and "large" tumor descriptions are not very clear, and the cut-off sizes of these explanations are inconclusive, gynecologists and oncologists can diagnose large pelvic-abdominal masses that require treatment.

To our knowledge, although the English literature consists of case reports including large gynecologic tumors of ovarian, tubal, and uterine origin, there is lack of data regarding a series of large tumors (8-10). From this point of view, we aimed to evaluate the characteristics of patients who were diagnosed as having and underwent surgery for large pelvic-abdominal masses over a 5-year period in a university clinic.

Material and Methods

After obtaining approval from the local ethics committee, the surgical and pathologic reports of patients who underwent surgical procedures due to suspected adnexal masses between 2011 and 2016 were retrospectively reviewed in our university clinic.

All patients underwent detailed pelvic examination, ultrasonographic evaluation and computerized tomography

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or magnetic resonance imaging (MRI) if needed. Thereafter, all patients were evaluated by the tumor board and surgery indications were approved. After preoperative medical evaluations, all patients underwent laparotomy through a midline incision. Adnexal masses with suspected malignancies were sent for frozen section. According to frozen section histopathologic evaluations, patients with malignant masses underwent debulking surgery, and patients with benign disease underwent conservative surgery or total hysterectomy and salpingo-oophorectomy. Among 3476 gynecologic operations, intraoperative findings were evaluated and uterine and/or adnexal masses smaller than 20 cm were excluded to refine "large" tumors, and 74 patients with large tumors were enrolled in the study group. A flow chart of the patients is shown in Figure 1.

Demographic characteristics including age, gravidity, parity, medical history, symptoms, physical and pelvic examination, ultrasonographic evaluations, cancer antigen (CA) 125 levels, intraoperative findings, and results of the histopathologic examinations of the patients were recorded. In addition, preoperative and intraoperative findings were compared among tumors with adnexal origin according to their final histopathologic results.

Statistical analysis of the collected data was performed using IBM Statistical Package for Social Sciences (SPSS) 23.0 software. The normality of distribution was checked initially using Shapiro-Wilk's test and parametric or non-parametric tests were applied to data with normal or non-normal distribution, respectively. One-way analysis of variance (ANOVA) with Tukey's honest significant difference post hoc test and Kruskal-Wallis (ANOVA on Ranks) tests with Dunn's post hoc tests were applied to determine the differences among benign, borderline, and malignant adnexal masses. Chi-square tests were applied for categorical variables. The results are expressed as mean ± standard deviation and median (interquartile range Q1 and Q3); p values <0.05 were considered statistically significant.

Results

The mean age of the patients was 47 years. Of the patients, 54.1% (n=40) were premenopausal and 45.9% (n=40) were postmenopausal. Two of the premenopausal patients were adolescents. The most common symptom was abdominal pain, which was recorded in 38 (51.4%) patients. Among all patients, 31 (41.9%) had coexisting illness and 13 (17.6%) had a history of surgery. The patients' demographic characteristics, preoperative CA 125, and hemoglobin levels are summarized

Table 1. Patient characteristics

Age, (years)	47.3±14.6
Gravida, (n)	2.5±2.3
Parity, (n)	1.8±1.5
Symptoms, (n)	
Abdominal pain	38 (51.4%)
Abdominal distension	16 (21.6%)
Abdominal mass	15 (19%)
Menometrorrhagia	5 (6%)
Coexisting illness, (n)	
Hypertension	16 (21.6%)
Hypothyroidism	6 (8%)
Diabetes mellitus	5 (6%)
Asthma bronchial	4 (5%)
History of surgery (n)	
Cesarean section	7 (9%)
Other	6 (8%)
CA 125 (U/mL)	98.4±165
Preoperative hemoglobin (g/dL)	12.3±1.8
Data are given as mean ± standard deviation or No (%)	

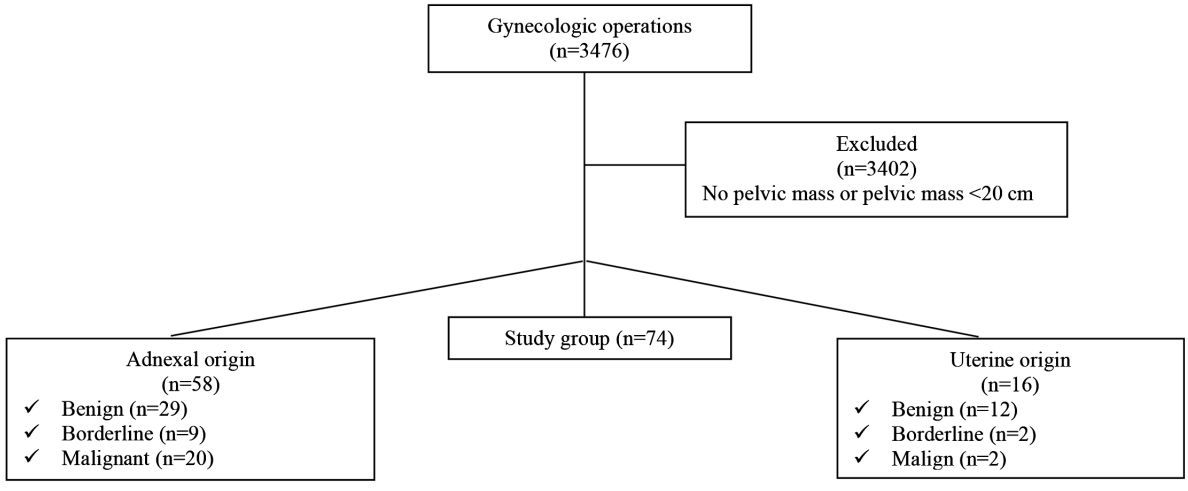

Figure 1. Flow chart of the patients

in Table 1. According to the operation findings, the mean tumor diameter was 25.9±8.6 cm (20-60) and 60 (78.9%) of the tumors were of adnexal origin. During the operations, adhesiolysis was performed in 30 (40.5%) operations, 4 small bowel lacerations, 1 bladder, and 1 sigmoid perforation occurred, all were repaired in the same session. Exploration findings during laparotomy are summarized in Table 2. Among 74 operations, 58 of 60 adnexal masses were sent for frozen section analysis. None of the large tumors of uterine origin (n=14) were evaluated using frozen section analysis. Frozen section examination revealed benign, borderline, and malignant tumors in 29 (50%), 9 (15.5%), and 20 (34.4%) patients with adnexal masses, respectively. Histopathologic examination revealed leiomyosarcoma in 2 (12.5%) of 16 patients with gynecologic tumors of uterine origin. When patients were classified according to menopausal status, final histopathologic examinations revealed malignancy in 13 of the 34 (38.2%) menopausal patients, and 9 of the 40 (22.5%) pre-menopausal patients. Moreover, 2 of the pre-menopausal patients were adolescents and their evaluations were regarded as benign disease. The ratios of malignancy for large adnexal and uterine tumors were 34.4% and 12.5%, respectively. Detailed final histopathologic examination distributions are shown in Table 3.

When the adnexal big tumors were re-evaluated, the mean CA 125 level was significantly higher, and ascites was more frequently detected in malignant tumors ($p<0.01$) than in benign and borderline tumors. The characteristics of the large adnexal tumors according to final histopathologic results are summarized in Table 4.

Discussion

In the present study, we aimed to evaluate and share our experience of large abdominopelvic tumors that underwent surgery in a university gynecology clinic. Of the tumors with adnexal and uterine origin, 34.4% and 12.5% were found to be malignant, and 15.5% and 12% of tumors were diagnosed as borderline ovarian and uterine smooth muscle tumors of uncertain malignant potential, respectively. The mean size and weight of tumor were not statistically different between benign, borderline, and malignant large tumors; however, CA 125 was found to be elevated, and the presence of ascites was significantly detected in large malignant tumors.

One of the limitations of this study is its retrospective design. All operation notes were evaluated but there may still have been

Table 2. Exploration findings during laparotomy

Site of tumor, (n)	
Adnexa	60 (81.1%)
Uterus	14 (18.9%)
Diameter of tumor, (cm) (minimum - maximum)	25.9±8.6 (20-60)
Weight of tumor, (g) (minimum - maximum)	5555±2241 (3500-14600)
Presence of ascites, (n)	
Yes	57 (77%)
No	17 (23%)
Frozen section results, (n)	
Benign	29 (50%)
Borderline	9 (15.5%)
Malignant	20 (34.5%)
Data are given as mean ± standard deviation or No (%)	

Table 3. Final histopathologic results

	n (%)
Benign	
Mucinous cystadenoma/fibroma	14 (18.9%)
Simple/functional cysts	4 (5.4%)
Fibroma	4 (5.4%)
Endometrioma	3 (4%)
Serous cystadenoma/fibroma	2 (2.7%)
Teratoma	2 (2.7%)
Leiomyoma	12 (16.3%)
Borderline	
Borderline mucinous cystadenoma	7 (9.5%)
Borderline serous cystadenoma	2 (2.7%)
STUMP*	2 (2.7%)
Malignant	
Mucinous adenocarcinoma	6 (8.2%)
Serous adenocarcinoma	5 (6.7%)
Endometrioid adenocarcinoma	5 (6.7%)
Clear cell carcinoma	2 (2.7%)
Metastatic carcinoma	2 (2.7%)
Leiomyosarcoma	2 (2.7%)
Total	**74 (100%)**
STUMP: Smooth muscle tumors of uncertain malignant potential	

Table 4. Characteristics of big tumors with adnexal origin according to final histopathologic results

	Benign	Borderline	Malignant	p
Age, (years)	45.8±17.4	48.7±15.3	50.3±13.3	>0.05
CA 125 (U/mL)	28 (17-43)	18 (17-27)	122 (42-294)	**<0.01**
Hb (g/dL)	12.5±1.7	12.3±1.6	12.1±1.6	>0.05
Presence of ascites, (n)	3 (19%)	2 (13%)	11 (68%)	**<0.01**
Diameter of tumor, (cm)	25 (20-35)	20 (20-26)	25 (20-30)	>0.05
Weight of tumor, (g)	5000 (4200-6700)	6000 (4650-7200)	4550 (4100-5000)	>0.05

CA 125: Cancer antigen 125; Hb: Hemoglobin
Data are given as mean ± standard deviation for normally distributed variables, median (25%-75%) for non-normally distributed variables, or No (%); a p value <0.05 was considered statistically significant

patients who did not undergo surgery or were lost before the operation. Moreover, our cut-off limit may be questionable; however, to our knowledge, there is no consensus for the size of tumors to call them large, huge, or giant. Therefore, after searching the literature and our patients' charts, we set out cut-off level for "large" tumors at 20 cm, and evaluated the operative characteristics of the patients in order to share our experience of large tumors. Also, we included all uterine and adnexal tumors in our study because we aimed to evaluate all large-sized tumors. Before surgery, all patients underwent ultrasonography and there was no question as to whether the origin was uterus or adnexa. Another limitation of this study is the sample size, even though large tumors are not very common. Our sample size was very small for large tumors with uterine origin; therefore, we only compared the operative characteristics of patients with large adnexal tumors.

During gynecology and gynecologic oncology practice, physicians usually diagnose adnexal masses and the most important issue it to exclude malignancy during the management. Ultrasonographic evaluation, menopausal status, and tumor markers such as CA 125 and HE4 are important predictors for malignancy (4,11). Moreover, the presence of a multilocular cystic lesions, solid areas, bilateral lesions, ascites, and intra-abdominal metastases are also known to be important parameters during ultrasonographic evaluations. These features are known to be important morphologic features of adnexal masses. In addition, unilocular tumors, smooth multilocular tumors and no intra-tumoral blood flow in color or power Doppler are simple rules to predict benign disease, whereas irregular solid tumor, ascites, at least 4 papillary projections, and strong intra-tumoral blood flow in color or power Doppler may predict malignancy (12). Efforts are ongoing to standardize ultrasonographic evaluations for optimal patient management (13). For larger tumors, computed tomography (CT) or MRI may be required to determine the origin of the tumor. In the present study, 64 (86.4%) patients were evaluated using CT or MRI for the differential diagnose. MRI was preferred especially for suspected masses of uterine origin in 10 (13.5%) patients, whereas 54 (72.9%) patients were evaluated using CT to discriminate the origin of the tumor, possible metastasis, and predict optimal cytoreduction.

In addition, some scoring systems such as the Rajavithi-Ovarian Cancer Predictive Score [risk of ovarian malignancy algorithm and risk of malignancy index (RMI)] have been introduced to discriminate benign and malignant cases (3,4,6). RMI is the one of the most common methods using the knowledge of menopausal status (M), ultrasound findings (U), and the serum CA 125 level, and is calculated as M × U × CA 125; (a total ultrasound score of 0 yields U=0, a score of 1 yields U=1, and a score of 2 yields U=3. Premenopausal status yields M=1, and post-M yields M=3. The serum level of CA 125 is applied directly to the calculation (6,7). RMI is then developed as RMI 1, RMI 2, and RMI 3 using the same formula, but scoring differently, and RMI 4 where size (S) is taken into account in a formula as S × M × U × CA 125. RMI 4 takes tumor size <7 cm as S=0, and ≥7 cm as S=2 in the formula, and was introduced to be more reliable than RMI 1, RMI 2, and RMI 3. However, the diagnostic accuracy is still inconclusive in large tumors and new studies are needed to evaluate this issue.

Although there are some protocols or indexes for the management of adnexal masses, frozen section analysis is usually mandatory for large tumors. Large tumors typically require a midline incision reaching the upper abdomen, and need extra care during operations, but the role of minimally invasive surgery cannot be ignored. In some studies, laparoscopy was suggested a feasible and safe treatment for women with large ovarian cysts with proper patient selection (14-16). However, surgeons should carefully consider the potential risk of malignancy in such patients, and surgeon experience may still be a limitation with large tumors.

Mucinous tumors are more likely present in large masses averaging 16 to 30 cm in diameter (17,18). A retrospective study evaluating mucinous borderline tumors reported the median tumor size as 20 com (range, 4-40 cm) (19). In the present study, of the 9 borderline tumors, 7 (77%) were mucinous, the mean diameter was 26 cm. Although mucinous ovarian cancer is an uncommon subtype of malignant ovarian tumors and accounts for approximately 5% to 10% of ovarian carcinomas, we found that the most frequent histologic type was mucinous adenocarcinoma. This finding may be due to our selection criteria, only choosing masses 20 cm and above.

To conclude, physicians should be aware of the malignancy potential and plan the optimal surgical team and procedure because large gynecologic tumors require surgical treatment. Benign and borderline tumors are more common among large abdominopelvic masses although the presence of ascites and elevated CA 125 may present malignancy in large gynecologic tumors. Further studies with larger sample sizes are needed to define the characteristics of large tumors and their malignant potentials.

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

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Concept - T.Ö., E.Ö., Ö.T.Y.; Design - T.Ö., E.Ö., Ö.T.Y.; Supervision - T.Ö., Ö.T.Y.; Materials - T.Ö., E.Ö.;*

Data Collection and/or Processing - T.Ö., E.Ö.; Analysis and/or Interpretation - T.Ö., E.Ö.; Literature Review - T.Ö., E.Ö., Ö.T.Y.; Writer - T.Ö., E.Ö., Ö.T.Y.; Critical Review - T.Ö., E.Ö., Ö.T.Y.

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Diagnostic and treatment guidelines for gastrointestinal and genitourinary endometriosis

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Abstract

Endometriosis is commonly misdiagnosed, even among many experienced gynecologists. Gastrointestinal and genitourinary endometriosis is particularly difficult to diagnose, and is commonly mistaken for other pathologies, such as irritable bowel syndrome, interstitial cystitis, and even psychological disturbances. This leads to delays in diagnosis, mismanagement, and unnecessary testing. In this review, we will discuss the diagnosis and management of genitourinary and gastrointestinal endometriosis. Medical management may be tried first, but often fails in cases of urinary tract endometriosis. This is particularly important in cases of ureteral endometriosis because silent obstruction can lead to eventual kidney failure. Thus, we recommend complete surgical treatment in these cases. Bladder endometriosis may be managed more conservatively, and only if symptomatic, because these rarely lead to significant morbidity. In cases of bowel endometriosis, we recommend medical management first in all cases, and the least invasive surgical management only if medical treatment fails. This is due to the extensive nervous and vasculature supply to the lower rectum. Injury to these nerves and vessels can cause significant complications and postoperative morbidity. (J Turk Ger Gynecol Assoc 2017; 18: 200-9)

Keywords: Laparoscopy, endometriosis, general surgery, gynecology

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Introduction

Endometriosis affects up to 10% of all reproductive-age women, and affects approximately 35-50% of women with pelvic pain and infertility (1). It can manifest as deeply infiltrative endometriosis (DIE) or superficial lesions of the peritoneum and serosa. Endometriosis predominantly affects the pelvic reproductive organs, but can also be found in non-reproductive organs, known as extragenital endometriosis. The most common site of extragenital endometriosis is the gastrointestinal and urinary tract (2). Gastrointestinal endometriosis is found in 3.8-37% (3,4) of women with a known diagnosis of endometriosis, and urinary tract endometriosis is found in 1-6% of these women (2). The wide range reported in the literature is likely due in part to the difficulty in diagnosis of this enigmatic disease.

Pathogenesis

There are numerous theories regarding the pathophysiology of endometriosis. One of the earliest and most instinctive theories proposed is that of retrograde menstruation, which describes the retrograde spillage of menstrual blood from the fallopian tubes during menstruation. Endometrial cells implant in the peritoneal cavity causing pain, inflammation, and fibrosis. Some observations supporting the retrograde menstruation theory are that;

1) Women with genital tract obstructions are more likely to have endometriosis (5),

2) The distal ureter is affected more often than the proximal ureter, possibly due to its closer proximity to the uterus and dependent location (6),

3) The left ureter is affected more commonly than the right (7,8), which may be due to obstruction of peritoneal flow by the sigmoid colon on the right (9,10),

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4) Bladder endometriosis is found less commonly in women with a retroverted uteruses, potentially due to the larger space for endometrial cells to disseminate rather than implant on the bladder (11).

However, this theory is not all encompassing because 90% of women have retrograde menstruation, but only 10% of women develop endometriosis. Thus, further steps are necessary for endometrial cells to transform into endometrial implants (9,12). The second theory has an immunologic basis. It has been observed that there is a high incidence of endometriosis in women with autoimmune disorders, such as systemic lupus erythematosus, thyroid disease, 4 rheumatoid arthritis, Sjogren syndrome, asthma, and eczema (13). Dysregulation of the immune system may prevent normal clearance of ectopic endometrial cells, facilitating their implantation (10). Another commonly held theory is that of coelomic metaplasia. In this theory, normal peritoneum or residual embryonic müllerian tissue is stimulated by exogenous or endogenous hormones and transforms into endometriosis. This theory is supported by cases of endometriosis found in patients with müllerian agenesis. Other theories include metastasis of endometrial cells through lymphatic or hematologic dissemination to distant sites of the body (10). With the exception of the spleen, endometriosis has been found in every site in the body including the brain and lymph nodes. Endometriosis may also be iatrogenic and has been found in trocar sites and incisional scars. Almost 50% of bladder endometriosis is found in women with a prior cesarean section (14). Finally, there is a genetic component to the disease; first-degree relatives have a 7% risk of endometriosis (15). In summary, although there are numerous theories, the true pathogenesis of endometriosis is still unknown, complex, and likely a combination of all the above processes. In the following manuscript, we describe the two most common types of extragenital endometriosis: genitourinary and gastrointestinal, and discuss the diagnosis and management of this disease.

Gastrointestinal endometriosis

Diagnosis

Gastrointestinal endometriosis is most commonly found on the rectosigmoid colon (90% of cases of intestinal endometriosis), followed by the rectum, ileum (12%), appendix (8%), and cecum (6%) (2,16) (Figures 1 and 2). There have also been case reports of endometriosis found on the transverse colon (17) and stomach (18). Gastrointestinal endometriosis should be suspected in patients who report deep dyspareunia, dyschezia, catamenial diarrhea, hematochezia, constipation, pain with sitting, and pain radiating to the perineum. Lesions of the enteric nervous system may cause nausea, vomiting, and bloating if they involve Aurbach's plexus, Meisner's plexus, or the interstitial cells of Cajal (19).

Medical management

Medical therapy is the first-line treatment for bowel endometriosis because of the potential morbidity of surgical treatment. However, it may not provide long-term improvement, and these patients may eventually require surgical management. It may also be used in patients who are not surgical candidates or prefer to avoid surgery. It has been shown to be effective by significantly alleviating symptoms in patients with less than 60% bowel stenosis (20). Hormonal suppression may also be used pre-operatively to reduce the disease burden, or post-operatively to prevent disease progression and recurrence (21). Medical treatment options are the same as those used for pelvic endometriosis, and include progesterone only, estrogen-progesterone combination contraceptives, the Mirena intra-uterine device, gonadotropin-releasing hormone (GnRH) agonist with or without add-back therapy, aromatase inhibitors, and danazol (22). Although medical management can significantly improve symptoms in 53% of patients, 33% of patients (23) eventually opt for surgical management after a 12-month period owing to persistent symptoms.

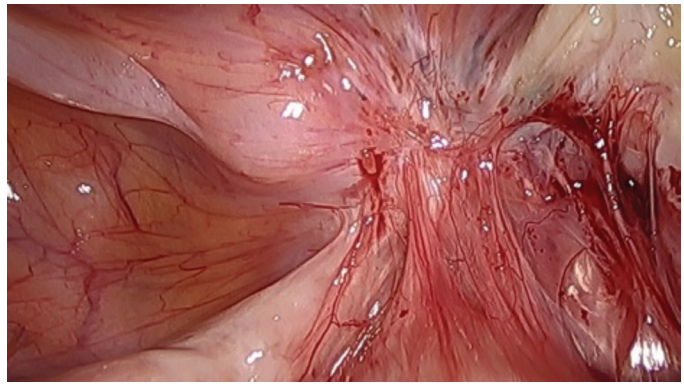

Figure 1. Endometriosis involving the rectum

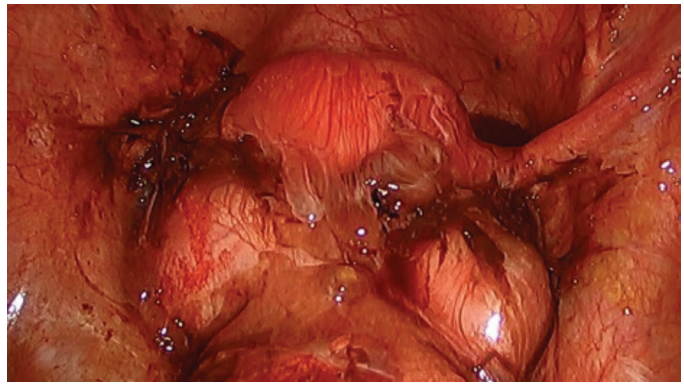

Figure 2. Ruptured bilateral endometriomas causing complete obliteration of the posterior cul-de-sac

Surgical management

Surgical management is recommended for symptomatic patients who are refractory to medical therapy, or in whom medical therapy is contraindicated. The recommended surgical approach depends largely on the location and number of lesions, size and depth of the lesion, degree of circumferential involvement, and the presence or absence of stricture (24-26). Of these, location is the most important in dictating surgical procedure choice. We recommend a laparoscopic approach, whenever feasible, due to the numerous advantages of video-assisted laparoscopy with or without robotic assistance (VALRA) over laparotomy, including lower blood loss, less adhesion formation, less postoperative pain, shorter hospital stays, fewer postoperative complications, and improved fertility rate (27-32). The optimal surgical approach to lesions involving the rectum and sigmoid colon is controversial. The most important factor is the location of the lesion because lower rectal lesions require extensive dissection of the retro-rectal space and pelvic sidewall. Dissection of this space risks injury to the superior and inferior hypogastric plexuses, parasympathetic and sympathetic nerves, and vasculature (Figure 3). Injury to these structures may result in bowel, bladder or sexual dysfunction. Generally, the lower the lesion, the higher the risk of complications. Other complications involving dissection of the retrorectal space may include fistula, anastomotic leakage or stricture, bowel obstruction, bowel perforation, bowel and bladder incontinence, bowel stenosis or ischemia, bleeding, infection, constipation, and urinary retention (28,29,32-37). While some advocate complete resection of bowel endometriosis because of the risk of recurrence, we recommend a conservative surgical approach with shaving excision, particularly for lesions located 5-8 cm from the anal verge (38). Although shaving excision is associated with higher recurrence rates, there are multiple reported cases of bowel endometriosis recurrence even after radical segmental resection, possibly due to occult microscopic endometriosis, which can be found in 15% of specimen margins (39,40). Roman et al. (32) estimated that to prevent the risk of a single recurrence of bowel endometriosis that would necessitate repeat surgery, 23 patients would need to be treated initially with segmental bowel resection. In our experience, shaving excision provides high success rates with the lowest complication rates.

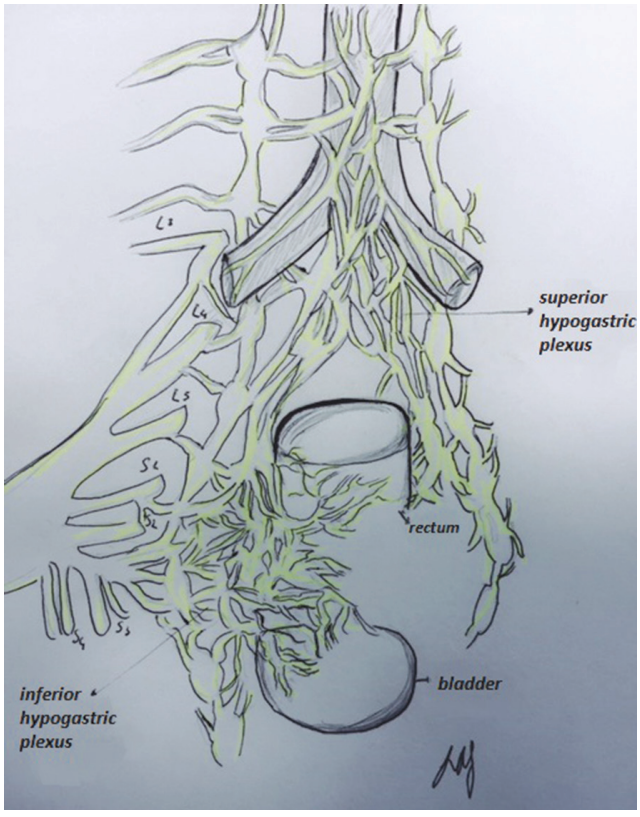

Figure 3. Innervation of the bowel

Techniques

The three surgical approaches, from least conservative to most aggressive, are described below (Video 1. Bowel Endometriosis: Safe Endoscopic Excision of Deep Infiltrating Extragenital Endometriosis, https://www.youtube.com/watch?time_continue=2&v=inUVHCLzrQQ, Feb 8, 2107):

Shaving excision

Shaving excision is the most conservative approach to surgical management of bowel endometriosis. It is performed through progressive layer-by-layer removal of diseased bowel until underlying healthy tissue is reached. It can be performed via ablation or excision. The aim is to remove as much endometriosis and fibrosis as possible, and restore a normal anatomic architecture without entering the bowel lumen (41-46). This technique is associated with lower complication rates compared with the other two techniques (44-47), and is recommended for lesions below the sigmoid colon owing to the abundant vasculature and nervous plexi supplying the lower rectum (38).

Disc excision

Disc excision removes the full thickness of the diseased portion of bowel, and is indicated in patients with DIE of the bowel, which may involve the mucosa (48-50). The defect is repaired either by suturing or stapling (28,41,43,48,49,51-55). To be a candidate for disc excision, the patient's lesion must be smaller than 3 cm and involve less than 1/3 of the circumference of the bowel, in order to prevent stricture and stenosis (31). Suturing should be performed perpendicular to the long axis of the bowel to avoid shortening the length of bowel. Disc excision has good outcomes, with less risk of postoperative

complications compared with segmental resection, but more than shaving excision (24-26,38,46,48).

Segmental resection

Segmental bowel resection has been reported in the medical literature since 1907. It is indicated for multifocal or obstructive lesions, lesions larger than 3 cm, or lesions involving more than one-third of the bowel lumen (27,49,56-58). It involves complete resection of the diseased segment of bowel with primary end-to-end or side-to-side anastomosis. It can be performed via laparotomy or laparoscopically by surgeons trained in advanced laparoscopic techniques. Given the potential complications, it should be reserved for patients who fail medical management, or those with persistent symptoms after more conservative surgery. It is important to ensure well-vascularized and tension-free anastomoses to minimize the risk of anastomotic leakage (2,37). Recently, injection of intravenous (i.v) indocyanine green has been proposed as a method to ensure well-vascularized margins. Surgeons can immediately visualize perfusion to the colon at the site of re-anastomosis at the time of surgery (38).

Location

Lesions can be categorized into four locations:
1) Above the sigmoid,
2) Sigmoid,
3) Rectosigmoid, and
4) Rectal.

Lesions above the sigmoid colon

Lesions above the sigmoid colon generally do not require extensive retroperitoneal dissection. Segmental or disc resection is performed preferentially along the antimesenteric surface of the bowel to spare the vascular and nervous plexuses located in the mesentery. Lesions of the small bowel, ileocolic region, right hemicolon, and appendix are removed via segmental resection (2). The appendix should be inspected carefully for endometriosis and removed if abnormal because endometriosis commonly coexists on the appendix. There may be a benefit to removing the appendix even if it appears normal due to the high incidence of occult appendiceal endometriosis (38,59-61).

Lesions along the sigmoid colon

Segmental resection at or below the sigmoid should be avoided whenever possible due to the risk of postoperative morbidity associated with dissection of the retrorectal space (34,62,63). Even disc excision involving dissection laterally and posteriorly risks injury to the nerves and vasculature, potentially leading to anastomotic leak, and bowel and bladder dysfunction necessitating long-term self-catheterization or colostomy. We prefer shaving excision for lesions at or below the sigmoid colon. When this technique is used, a thorough evaluation of the bowel thickness should be performed to assess the bowel wall integrity and thickness, and significant defects reinforced with suture. Disc excision or segmental resection may be performed, if indicated (38).

Lesions along the rectosigmoid colon

Surgeons must exercise extreme caution when excising lesions at the level of the rectosigmoid colon; segmental resection at this level is often approached through the rectum or vagina (27,64-66). Segmental resection of lesions in this location often requires significant lateral mobilization and dissection of the retrorectal space. We recommend shaving excision, even in cases with lesions larger than 3 cm unless the patient has failed prior surgical management. Disc excision is possible, but must be performed with caution (38).

Lesions along the rectum

We exclusively recommend shaving excision for lesions in this region except in cases of acute obstruction due to the extensive dissection required, which will inevitably compromise the surrounding neurovascular structures (38).

Ureteral endometriosis

Diagnosis

The most common sites of urinary tract endometriosis are the bladder, ureter, and kidneys, with a ratio of 40:5:1, respectively (67-69). Ureteral endometriosis can be difficult to diagnose because it is asymptomatic in over 50% of patients (70-72). This can be dangerous because it can cause silent kidney loss if it results in ureteral stricture and obstruction (71,72). If symptoms are present, patients usually present with the usual symptoms of pelvic endometriosis: dysmenorrhea, pelvic pain, dyspareunia. Few present with specific urinary tract symptoms (e.g., flank or abdominal pain, dysuria, hematuria) (70). Ureteral endometriosis can be divided into extrinsic or intrinsic disease. Extrinsic, or superficial disease, is 4-5 times more common than intrinsic disease (68,70,73). It is caused by superficial endometriosis of the serosa of the ureter that compresses the ureter from fibrosis of the overlying peritoneum (Figure 4). It may also be caused by a large endometrioma adherent to the pelvic sidewall causing compression of the ureter. Intrinsic disease invades deeply into the ureteral wall, muscularis, or mucosa, and requires pathologic confirmation (Figure 5). It accounts for 20% of ureteral endometriosis. It is more commonly symptomatic with some patients reporting cyclic flank pain,

but still less than 15% of patients will present with cyclic hematuria (70).

Imaging

There are numerous imaging modalities that may be used to diagnose ureteral endometriosis: computed tomography urogram, magnetic resonance imaging (MRI), i.v pyelogram/retrograde pyelogram (RVP), and transvaginal ultrasound. Ultrasound is best for detecting ovarian and bladder endometriotic lesions, and frequently fails to detect ureteral endometriosis (74). It is highly dependent on the skill and expertise of the sonographer. A renal ultrasound is indicated to evaluate for hydronephrosis in women with suspected urinary tract endometriosis, and may be used to measure the degree of hydroureter and point of constriction (75). i.v pyelogram can be particularly useful in diagnosing intrinsic disease and to evaluate the degree and level of obstruction. It can also be used to evaluate ureteral patency after surgical treatment. If i.v contrast is contraindicated, a RVP can provide the same results. MRI is a sensitive modality in cases of DIE. However, a 2016 Cochrane review concluded that no imaging modalities were superior to surgery in the diagnosis of endometriosis, although it notably excluded bladder and ureteric endometriosis in the study. The goal of treatment is to relieve ureteral obstruction and compression from endometriosis, thus preserving renal function (73,76). Although a pre-operative renogram is unable to predict the return of kidney function after surgical decompression of obstruction, it may be considered if hydronephrosis or the hydroureter is present. A kidney is considered salvageable if more than 10% of renal function remains. If the glomerular filtration rate is less than 10%, a nephrectomy may be considered after consultation with a urologist.

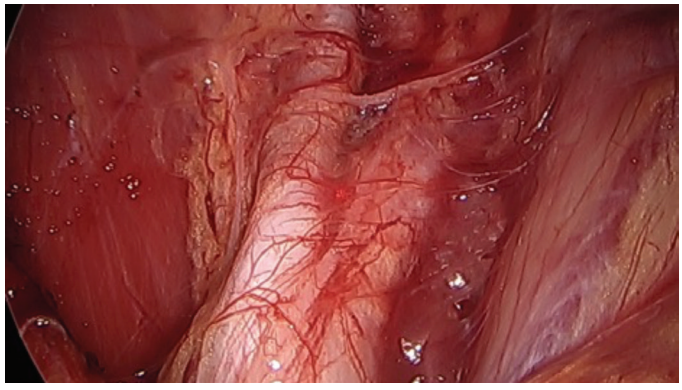

Figure 4. Extrinsic endometriosis of ureter causing ureteral obstruction and hydroureter

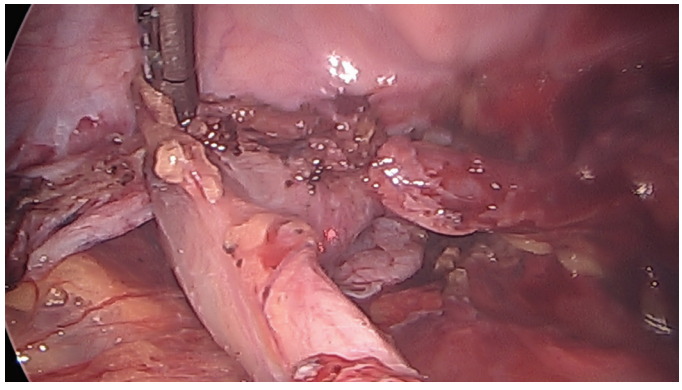

Figure 5. Intrinsic endometriosis of ureter causing stricture and hydroureter

Medical management

Medical management of ureteral endometriosis is not recommended due the serious permanent sequelae of disease progression, high risk of failure, and risk of recurrence (77). It can, however, be considered for mild disease, or if a patient is not a candidate for surgery, and after careful discussion with the patient regarding the risks/benefits of conservative therapy. It is contraindicated when ureteral obstruction or hydronephrosis is present due to the risk of kidney loss. The goal of treatment is to induce regression of endometrial tissue, prevent endometriosis proliferation, and progression to ureteral obstruction.

Surgical management

Laparoscopic treatment of endometriosis with complete excision of fibrotic lesions is the treatment of choice (67,71,78-83). VALRA offers numerous advantages over laparotomy, in particular improved visualization and magnification of endometriotic lesions, less blood loss, and less adhesion formation. The carbon dioxide laser or plasma jet energy with hydrodissection is our preferred technique, as it is much more precise and is associated with less thermal spread compared to electrocautery. This, in turn, may prevent unintentional injury to the ureters and surrounding vasculature (Figure 6). The retroperitoneum is injected with saline or dilute vasopressin using a laparoscopic needle to lift the peritoneum away from the underlying structures. The ureters and vessels are protected from the laser beam because the laser beam is unable to penetrate fluid. A peritoneal incision is made in an unaffected area using the laser to create a 0.5 cm opening. Lactated ringers or normal saline solution is then injected into this space by inserting the suction irrigator tip into the peritoneal opening. The endometriosis lesion is excised with 1-2 cm margins and the overlying peritoneum is peeled away while using the suction irrigator as a backstop to the laser (46) (Video 2: Laparoscopic Treatment of Genitourinary Endometriosis with and without Robotic Assistance, https://www.youtube.com/watch?v=zFdWu-wvM2E, Feb 8 2017). Laparoscopic ureterolysis has been shown to be successful in 90% of cases of hydroureter caused by ureteric endometriosis. The type of

procedure performed depends on the location and depth of the lesion. For intrinsic disease or if hydroureter persists after ureterolysis, ureteral resection is indicated (68). If the lesion is located in the lower third of the ureter, close to the bladder, a ureteroneocystostomy with or without Psoas hitch may be performed. A larger distance may require a Boari flap, ileal interposition, or autotransplantation (78). Lesions in the middle or upper third of the ureter may require a ureteroureteral anastomosis (67,70,78,84). It is important to ensure that all anastomoses remain free of tension to prevent leakage and fistula formation (83).

Bladder endometriosis

In contrast to ureteral endometriosis, bladder endometriosis is usually symptomatic. Patients may present with dysuria, hematuria, suprapubic pain, urinary urgency and frequency (70,79). Fortunately, it is usually associated with less morbidity compared with ureteral endometriosis. However, if an endometriosis lesion implants at the ureteral orifice and causes obstruction, it can also theoretically lead to hydroureter, hydronephrosis, and eventual kidney failure. Ultrasound and MRI both have high specificity for the detection of bladder endometriosis for lesions larger than 3 cm (7). Cystoscopy can identify deeply infiltrating endometriosis, seen as bluish lesions in the bladder mucosa. It can also estimate the distance from the lesion to the ureteral orifice, which is important in counseling patients on the risk of reimplantation if the lesion is less than 2 cm from the ureteral orifice. i.v pyelogram may show a filling defect if a bladder endometriotic lesions is present.

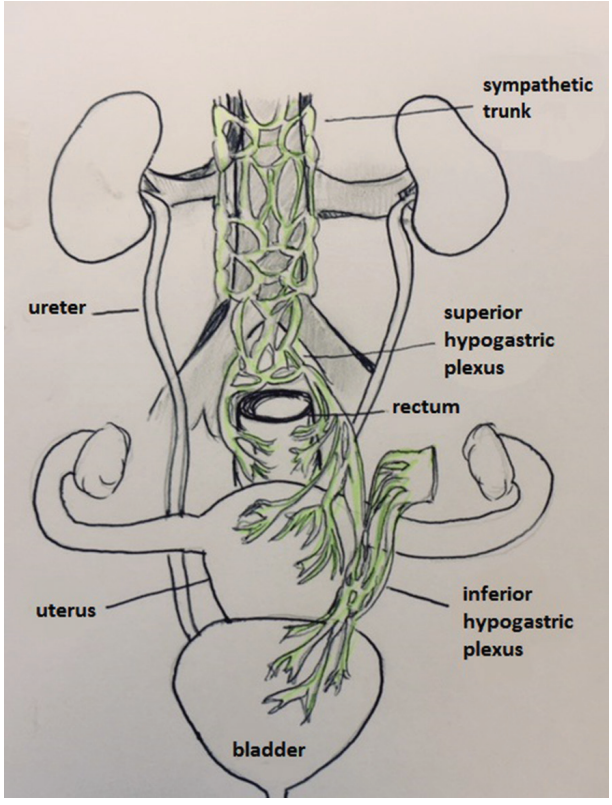

Figure 6. Innervation of the ureter

Medical management

Medical therapy is generally considered a temporary solution because symptoms invariably return after discontinuation of medical therapy, and must be continued until menopause. It is preferred if asymptomatic, or if the lesion lies very close to the trigone, because excision can cause postoperative neurogenic bladder and retrograde bladder reflux due to disruption of the nerve and blood supply (83). Medical therapy options are the same as those for pelvic endometriosis. GnRH agonists can cause superficial bladder lesions to regress and have been found to be more effective than combined oral contraceptives. The typical treatment length is limited to 6 months because of bone loss with prolonged GnRH agonist use. If the symptoms persistent despite conservative medical management, surgical excision can be considered.

Surgical management

Laparoscopic surgical management is the treatment of choice (11,85). The specific procedure depends on the location and depth of invasion. For superficial bladder lesions or extrinsic disease, either excision or fulguration is acceptable (26,82). Excision is preferred to remove the entire lesion, reduce the risk of recurrence, for pathologic confirmation, and to rule out malignancy (83).

For detrusor muscle involvement, bladder endometriotic lesions or intrinsic disease, a segmental bladder resection may be required (70). Fortunately, laparoscopic segmental bladder resection usually heals well owing to the abundant vascularization. It provides the best results in terms of symptomatic relief, disease progression, and recurrence risk. Laparoscopic excision should be performed concurrently with cystoscopy to ensure correct margins and complete excision. One- or two-layer closure using barbed sutures for bladder closure showed improved efficacy and more secure wound closure compared with monofilament sutures in one study (86). It is important to ensure a water-tight closure to prevent fistula or uroma formation. Ureteral stents should be placed when the lesion is near the trigone or within 2 cm of the ureteral orifice to maintain ureteral patency during the healing process. A ureteroneocystostomy may be required if the lesion is less than 2 cm from the ureteral orifice or close to the interureteric ridge (79). (Video 3: Robotic Assisted Laparoscopic Segmental Bladder Resection for Infiltrative Endometriosis, https://www.youtube.com/watch?time_continue=2&v=VPjCMhJoxuI, Sept 12, 2016). A catheter should be placed and left in situ for 1-2

weeks to decompress the bladder. A routine cystogram should be performed prior to catheter removal to confirm there is no urine leakage (73,75,87).

Deeply infiltrating endometriosis

DIE is defined as the presence of endometriosis lesions more than 5 mm below the peritoneal surface. DIE is commonly found in the posterior cul-de-sac, the most dependent location for menstrual blood to collect. DIE behaves differently compared with superficial peritoneal endometriosis and has been found to express a higher level of invasive mechanisms such as matrix metalloproteinases and activins (88), which allow it to resist the suppressive effects of peritoneal fluid (89,90). An Allen-Masters peritoneal defect may act as a pathway for DIE in rectovaginal endometriosis. Physical exam findings may be particularly helpful at the time of menstruation when lesions may be more inflamed, tender, and palpable. Findings may include palpable nodules or thickening of the uterosacral ligaments, uterus, vagina, or rectovaginal septum (21). The presence of palpable nodules on rectovaginal exam indicates likely DIE and should prompt an evaluation for gastrointestinal and genitourinary endometriosis because these are more commonly found in patients with coexisting DIE (68). Transvaginal ultrasound is the initial imaging of choice for the diagnosis of DIE. A meta-analysis by the IDEA group showed transvaginal sonography had a high sensitivity and specificity for diagnosis of uterosacral, rectovaginal, vaginal, and bladder endometriosis (75). Renal ultrasound is also recommended in cases of DIE to evaluate for hydroureter/hydronephrosis. Much like gastrointestinal or genitourinary endometriosis, medical treatment of DIE is often ineffective and temporary - symptoms tend to recur once therapy is discontinued (7).

Nerve-sparing surgery

Many surgical complications are a result of disruption of the superior and inferior hypogastric nerve plexus, which may be difficult to avoid in cases of DIE, which frequently involve these structures (91). Dissection in this area and disruption of this nerve supply may cause worsening or new-onset urinary dysfunction, such as urinary retention, dysuria or incontinence (36,92). Nerve-sparing surgery has been proposed as a method to reduce the risk of injury to these vital structures (58,93). The Tokyo method is a procedure in which the surgeon separates and ligates the vascular portion of the cardinal ligament while preserving the branches of the pelvic splanchnic nerves (94). Kockel described a technique sparing pelvic ligaments containing peripheral pelvic nerves and using liposuction to expose the autonomic pelvic nervous system. Possover (95) described a technique using electrostimulation to identify and avoid the parasympathetic pelvic nerves, known as the LANN technique. In a prospective study by Ceccaroni et al (58), which compared laparoscopic resection vs. laparoscopic nerve-sparing surgery, the authors found a significant reduction in bladder, rectal, and sexual dysfunction with nerve-sparing techniques. Furthermore, both groups had similar rates of intra-operative complications (58).

Risk of malignant progression

The risk of developing endometriosis-associated neoplasm is estimated to be up to 1%, with 25% of these cases involving extra-ovarian tissue (96). Endometriosis is associated with an increased risk of endometrioid and clear cell adenocarcinoma (97,98). Thus, excision of endometriosis has the additional benefit of potentially reducing the risk of progression to cancer.

Conclusion

Extragenital endometriosis is relatively rare, but may be more common than many realize due to its difficulty in diagnosis. Thus, it is important to thoroughly evaluate the patient for gastrointestinal and genitourinary endometriosis, especially if DIE is present on physical exam. When advanced stage disease is suspected, imaging with ultrasonography, MRI, or i.v pyelogram is necessary. Ultrasound is sufficiently sensitive for diagnosis of pelvic DIE and bladder endometriosis; however, MRI or i.v pyelogram is often needed to evaluate the intestines or ureter. Alternatively, a kidney ultrasound is indicated in cases of suspected genitourinary endometriosis to look for hydroureter or hydronephrosis. For gastrointestinal endometriosis, medical management should be tried first due to the risk of postoperative complications associated with injury to the nervus plexi supplying the lower rectum. Surgery should be considered as a second-line treatment only if medical management fails, and a conservative approach with shaving excision is preferred over disc or segmental excision when indicated. The recommended surgical approach depends largely on the patient's symptoms, the location of disease, and the size and depth of the lesion. Nerve-sparing surgery, such as the Tokyo method, Kockel or LANN technique have been suggested to reduce the risk of nerve damage and subsequent complications, resulting in bowel, bladder, or sexual dysfunction. VALRA is recommended over laparotomy owing to the numerous advantages of laparoscopy, such as less postoperative pain, lower blood loss, less adhesion formation, magnification of lesions, and faster postoperative recovery. For ureteral endometriosis, complete surgical excision is preferred due to the permanent and serious sequelae of silent kidney failure associated with disease progression to ureteral stricture and obstruction. For bladder endometriosis, a trial of medical therapy may be appropriate if the patient is symptomatic because bladder endometriosis is not associated with kidney failure unless the lesion is

located near the ureteral orifice and is causing obstruction. Medical management is usually temporary, less effective, and best used pre-operatively to reduce the disease burden, if the patient is unsuitable for surgery, or for post-operative hormonal suppression. Surgical excision and complete removal of lesions has the additional advantage of preventing malignant transformation because endometriosis has been associated with clear cell and endometrioid ovarian cancer.

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Role of hormones in hypoactive sexual desire disorder and current treatment

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Abstract

Over the decades, female sexual dysfunction (FSD) has grown to be an increasingly potential problem that complicates the quality of life among women. In the current review, FSD refers to recurrent and persistent problems with sexual orgasm, desire, or response. One of the most common subtypes of FSD that has evoked increased research interest in the scientific community is hyposexuality. Today, there is a consensus that hyposexuality is a multifactorial condition that manifests with reduced sexual desire resulting in significant interpersonal distress. The objective of the current review was to examine how hormonal profile triggers propagate hypoactive sexual desire disorder (HSDD), and to highlight effective treatment interventions that can be used to manage the condition. The current review describes HSDD as a sexual dysfunction characterized by the absence or lack of sexual desire and fantasies for sexual activities. The review argues that even if the role of sexual hormones is essential in modulating HSDD through therapeutic interventions, an effective comprehension of the biologic mechanisms underlying HSDD is necessary. There is a consensus in the literature that HSDD still poses significant challenges due to the lack of properly formulated treatment regimens and absence of clear clinical guidelines. That is, a better intervention consisting of both psycho-relational and biologic aspects is compulsory if tailored management and accurate diagnosis of HSDD in clinical practice are to be realised. The review concludes that, to date, a reliable clinical intervention to manage hyposexuality is still absent and more interventions, in terms of safety and efficacy, are required. Thus, additional investigation is required to document precise hormonal or non-hormonal pharmacotherapeutic agents for individualised care among patients with HSDD. (J Turk Ger Gynecol Assoc 2017; 18: 210-8)

Keywords: Hyposexuality, hormone, women, menopause, hypoactive

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Introduction

The problem of low sexual desire affects women of all ages, which contributes to potential negative outcomes including reduced well-being and quality of life (1,2). Over the years, low sexual desire has been widely regarded as part of broader female sexual dysfunction (FSD) conditions (3), of which HSDD is more prevalent (4,5). According to the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), HSDD is defined as a persistent absenteeism of sexual craving for sexual activities (6). However, the International Classification of Disease by the World Health Organization (7) and the DSM-IV tool (6) have reached a consensus that the definition of HSDD must include several aspects of accurate diagnosis. These include the presence of interpersonal difficulties and/or personal distress, in addition to the lack of sexual desires or fantasies for sex-related activities (6,7). A similar claim has also been supported by the American Foundation for Urologic Disease, on the basis that both sexually-related individual distress and low sexual desire should be observed for a person to be positively diagnosed as having HSDD (7,8).

Often, when cases of low sexual desire are reported, the most common diagnosis is assumed to be generalised acquired HSDD. HSDD is mostly not reliant on a specific situation, and often develops at a time when the desire for sex is assumed to be ordinary (8). As such, the presence of HSDD may manifest as a comorbidity in addition to a dysfunctional sexual experience, even if no exclusive connection can be made with the physiologic effects of a therapeutic agent or medical conditions (9). Recently, the International Consultation on Sexual Medicine (10) recommended the need to redefine HSDD because of the diverse heterogeneity among women

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and their sexual responses. As such, according to Sand and Fisher (11), a new definition for HSDD is set to be taken into consideration in the upcoming DSM-V.

Today, the aetiology of HSDD has not been holistically agreed upon, although scholars and researchers agree that the condition is multifactorial (12). To elaborate, HSDD has been elucidated to be triggered by factors such as psychiatric issues (12), behavioural components (13), and neuroendocrine changes (14,15). Previous studies largely centred on understanding how biologic and behavioural aspects contribute to HSDD, with a primary focus on assessment tools; the use of hormonal assays and validated behavioural questionnaires (12). Irrespective of their use, however, these methods have not completely helped in resolving the puzzle and yielding satisfactory elaboration for the development and cause of FSD conditions, and specifically HSDD.

The next section discusses how ageing factors, such as menopause, are associated with HSDD. Second, the correlation between hormonal profile and HSDD will be detailed, taking into account medical factors that can result in a hormonal imbalance. Third, the psychological and psychosocial factors and their effect on HSDD are also outlined. Fourth, the current treatment plans for HSDD are discussed before offering concluding remarks on the current review issue.

Ageing factors, menopause, and HSDD

Despite the current consensus in the literature that FSD can manifest at any age in a woman's life, researchers such as Sarrel (16) documented that during menopause, up to 40% of women experience reduced sexual libido. Moreover, this claim has been supported by a survey (17) undertaken on 31,581 women aged 18 years and above in the United States of America. The study found that the higher prevalence of HSDD was in women above the age of 45 years, and distress was reported to be a major concern among younger women (12.3%) compared with older women (7.4%) aged ≥65 years.

Although sexuality is essential to both young and older women, lack of a satisfying sexual life negatively impacts on the overall quality of life (18). The trend is particularly reflected among female groups that experience an unexpected rapid decline in hormone levels as a result of chemical menopause or even post-surgical events. Figure 1 shows hormone production as a function of age, both before and after menopause (19). As evident, between the age of 20 and 40 years, there is an increase in the production of sex hormones, before a gradual decline is experienced during menopause and post-menopause years of 45 years and above.

On the contrary, other scholars argue that based on longitudinal findings, relationship issues and other non-biologic factors can strongly impact on the overall sexual experience of women other than menopausal changes alone (20). For example, research from the Massachusetts Women's Health Survey reported that the onset of menopause contributes to reduced sexual desire. Nonetheless, anxiety, depression, and other relationship changes including conflict in the family, the condition of the relationship, sexual function, and health of a partner can contribute to substantial FSD (21). The common assumption is that menopause contributes to reduced sexual desire as a result of low production of hormones from the ovaries, resulting in loss of oestrogen and reduction in testosterone. The next subsections elaborate on the relationship between low testosterone and oestrogen levels on HSDD.

Low testosterone and HSDD

Scholars have reported that low production of testosterone plays a central role in HSDD. One of the key reasons in support of this claim is that testosterone initiates sexual activities and proliferates sexual desire and behaviour. In addition, testosterone is essential in modulating clitoral and vaginal physiology to facilitate genital lubrication, sensation, and engorgement (22). Therefore, a lack of testosterone has been reported to contribute to low libido and to reduced sexual pleasure and receptivity (23). Also, low levels of testosterone have been correlated with lack of sexual motivation, fatigue, distress, and overall reduce the sense of well-being (24). Figure 2 shows that there is a significant decline in the production of testosterone four years before menopause, during menopause, and two years into menopause.

It is not unusual for women in their pre-menopausal years with functional ovulatory cycles to report HSDD. One of the main causes of such reduced sexual expression can be attributed to low levels of testosterone, which start to reduce in the mid-30s among women and continue to reduce at a constant rate of about 50% of their highest levels by the time they reach menopause. A recent report on women's sexuality and

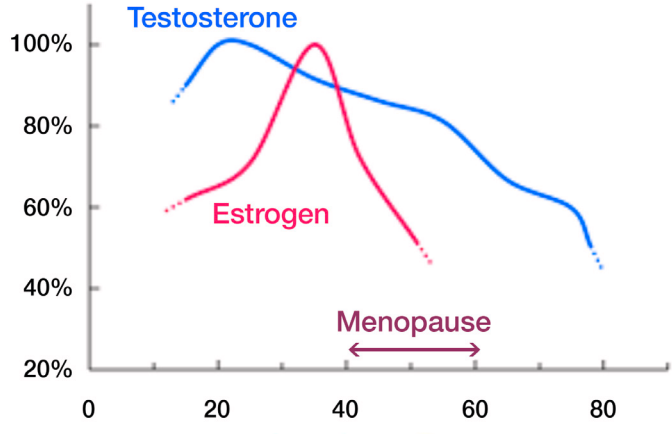

Figure 1. Hormone production before and after menopausal years (19)

health found that young women who had undergone surgical procedures reported high levels of HSDD resulting from the effects of bilateral oophorectomy where both ovaries are removed. Such procedures have been noted to contribute to about 50% reduction in the levels of testosterone (25). Hence, there seems to be a close relationship between the production of testosterone and reduced sexual desire, with more effects felt among older women in their post-menopause years and women who have undergone oophorectomy compared with younger ladies and those in their premenopausal years (26).

Figure 3 further shows that with increasing age, the levels of testosterone reduce and by the time a woman reaches menopause, the levels of testosterone are almost a quarter of what they were in their early 20s. According to Simon et al. (26), such a severe reduction in testosterone levels makes women gain weight, feel depressed and tired, and completely blocks most of their sex drive.

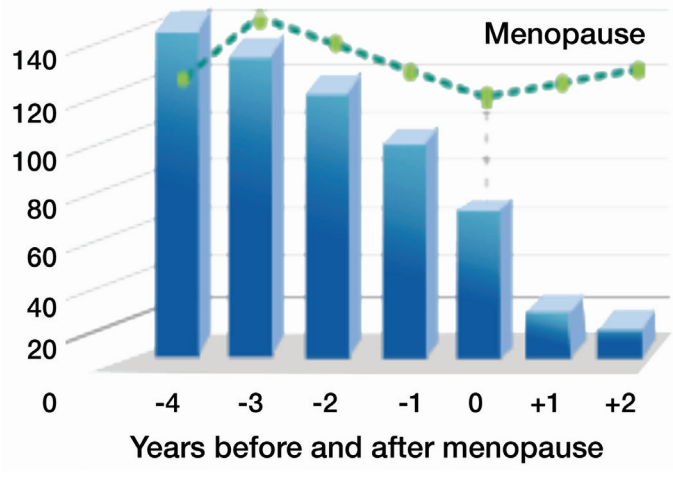

Figure 2. The change in testosterone levels during menopause (24)

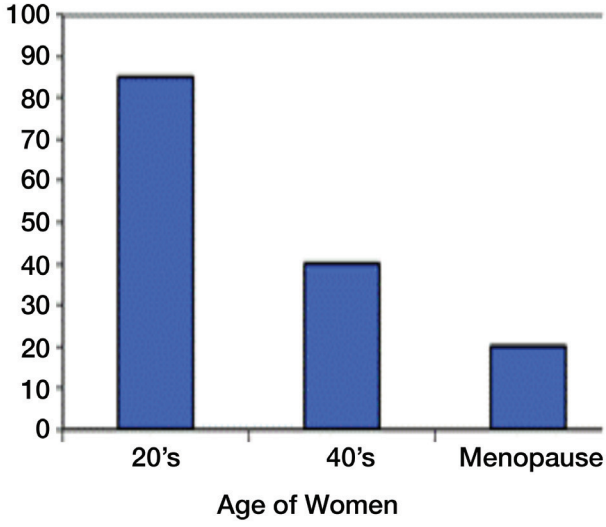

Figure 3. Declining levels of testosterone in women (26)

Low oestrogen levels and HSDD

Besides low testosterone levels, low sex drive among women can also be affected by reduced levels of oestrogen during postmenopausal years. Low levels of oestrogen results in vulvovaginal dryness and atrophy in addition to initiating changes of genital function through reduced sensory perception and decreased clitoral blood flow (27). As such, it becomes apparent that lack of oestrogen is associated with vaginal discomfort due to dryness and genital insensitivity, making it difficult for an individual to actively respond to sexual expression and cues, considering a reduced impact on desire (28). Researchers have recommended the use of oestrogen therapies to treat dyspareunia and vaginal dryness resulting from vulvovaginal atrophy (28). However, oestrogen-based therapies have been questioned as to whether they contribute to the effect after precise use in managing low sexual desire, in the event that low sexual events results from issues such as loss of genital pleasure, sensation, or as a consequence of pain (29). Figure 4 shows the variation in oestrogen production during years of fertility, perimenopause, menopause, and post-menopause.

As evident from Figure 4, there is a high variation in oestrogen production during menopause, and these fluctuations levels contribute to decreased sex libido among women. Besides, both peri- and post-menopausal individuals can experience HSDD due to low levels or deficiency in oestrogen hormone production (30,31). Laumann et al. (32) argued that menopause results when the levels of circulating oestrogen reduce, and this reduction leads to vaginal dryness, painful intercourse (dyspareunia), and inability to lubricate. In this case, oral oestrogen therapy is often recommended as a replacement to relieve mood changes, hot flashes, and alleviate irregular sleep patterns and improve the quality of life among women (33-35). However, a study by Laumann et al. (36) on sexual dysfunction

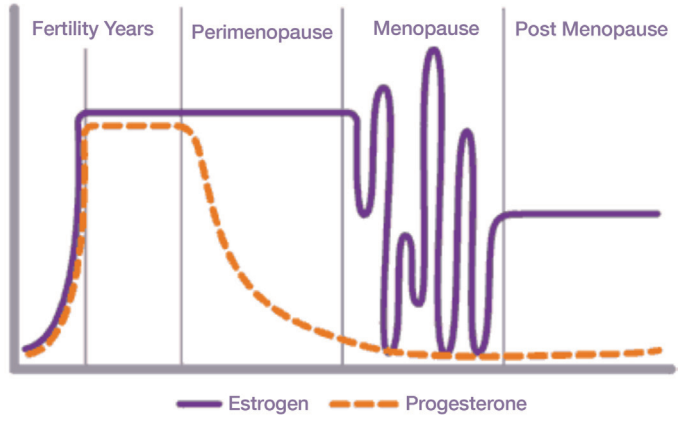

Figure 4. The variation in production of oestrogen and progesterone hormones throughout the female's life (30)

among American women reported that even if oestrogen replacement could assist in treating the symptoms linked to menopause, it would potentially have negative impacts on the levels of testosterone and further lead to HSDD. One of the reasons for this is that oral oestrogen can increase the levels of circulating sex hormone-binding globulin (SHBG) among menopausal women (37-39). O elaborate, SHBG has been reported as a protein that can bind testosterone and as a result, lead to lowering of free testosterone levels in the blood (40). Therefore, if the levels of SHBG are high, the level of free testosterone in plasma will be lower. In addition, Simon et al. (26) reported that oral oestrogen reduced both luteinizing hormone (LH) and follicle-stimulating hormone, thereby lowering total testosterone levels and reducing ovarian synthesis (26,31). Warnock et al. (14) also noted that birth control pills could lower the levels of testosterone as a result of the exogenous oestrogen found in birth control pills, which can further reduce LH and hinder ovulation (41,42). As such, the ovarian release of oestrogen is suppressed, and as a result, sexual libido is also affected. However, the levels of SHBG can be reduced using testosterone replacement therapy, which works by raising the levels of free testosterone and potentially decreasing potential signs and symptoms of HSDD (43,44). The next section elaborates on how hormonal influence affects FSD and contributes to HSDD in women.

Hormonal influence and androgen deficiency

In women, androgens are C19 steroids generated from cholesterol, where the main sources of release are from the adrenal glands, peripheral tissues, and the ovaries. Figure 5 shows steroidogenesis of androgens in women. Androgens are released from peripheral tissues such as cutaneous, muscle, and adipose tissues. Figure 1 shows that testosterone (T) represents the final product in the androgen pathway and it results from the conversion of androstenedione (A) present in plasma. Half of the androgens come from the ovaries, 25% of the androgens are produced in the adrenal glands, and the other 25% comes from the conversion of androstenedione in peripheral tissues. In addition, the principal precursor of both androstenedione and testosterone androgens is dehydroepiandrosterone (DHEA), half of which is produced in the adrenal glands and 20% is generated from the ovaries; 30% is derived from dehydroepiandrosterone sulphate (DHEAS) that circulates in the blood. During post-menopause, DHEA, which is the main source of androgens, experiences an up to 60% decline resulting in hypoandrogenism, which can affect the normal sexual response in women (45).

As noted from the ageing factors associated with FSD, women can experience the effcets before and after menopause as a result of androgen hormone deficiency (46). Long before menopause, and specifically from the second half of the pre-menopausal years when a woman is aged between 30 and 50 years, the development of androgen hormones reduces from the ideal rate observed during puberty and up to the late 20s or early 30s (47,48). However, from the mid-30s, the normal activities of the ovaries reduce, and the process of ovulation becomes irregular.

As shown in Figure 6, in irregular ovulation cycles, there is less progesterone release, and in cycles where there is no ovulation, there is no release of progesterone (49). As such, as the levels of progesterone start to fall, the menstrual cycle becomes shorter and the lack of progesterone results in a hormonal imbalance where there is oestrogen dominance. The oestrogen dominance is shown in Figure 3, in relation to progesterone levels that are lower than normal among pre-menopausal women (49). Some of the symptoms linked to increased production of oestrogen at this age include depressive mood and anxiety. As an individual transitions into menopause (perimenopausal age), the irregular release of androgen hormones become longer, and women may have reduced sexual desire for prolonged months because they receive irregular menstrual cycles (50-52). At the age of 50 years, most women experience a significant reduction in the amounts of androgen, while the values for testosterone and oestrogen reach their minimum levels (53-55).

The process is characterised by the loss of androgen hormones with the situation reported to be worse in persons

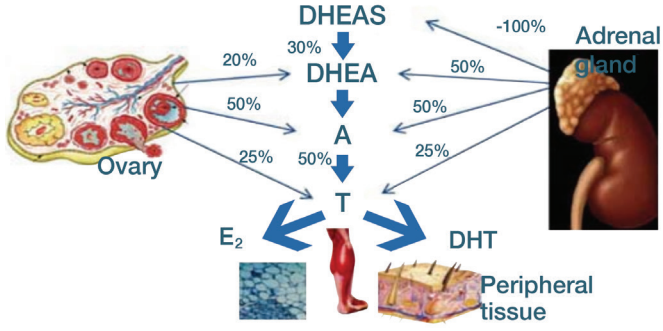

Figure 5. Production of androgens in the adrenal glands, peripheral tissues, and in the ovaries (45)

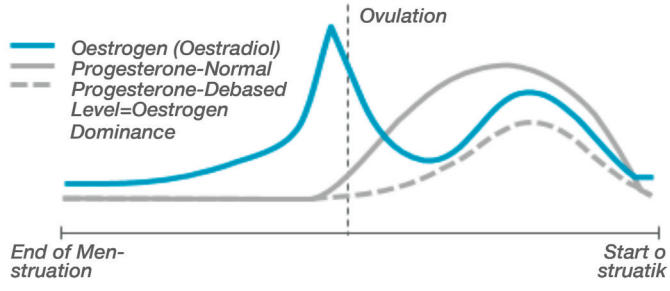

Figure 6. Oestradiol and progesterone cycle-dependent variations are showing oestrogen dominance (49)

with hypopituitarism, bilateral oophorectomy, and Addison's disease. Even so, the natural development of menopause can also result in reduced production of androgens (56,57). In most cases, androgen deficiency is difficult to identify, and most women correlate their reduced sexual desires with lifestyle issues or psychological distress as opposed to biologic changes in their bodies (58). Some of the experiences can result in an inexplicable lack of energy, tiredness, low self-motivation, disturbed sleep, a complete lack of sexual desire, and low self-esteem or poor general well-being (59,60). Low levels of androgens in women and reduced sexual desire can be diagnosed by examining levels of SHBG and testosterone because initial findings reported from women that have undergone surgery are as elaborated below.

Oophorectomy, hysterectomy, and HSDD

Even if the changes in hormone profile among young women who have undergone hysterectomy and oophorectomy might not entirely affect sexual expression, the increased prevalence of HSDD in young women compared with pre- and post-menopausal women is a strong indicator for the affect of hormonal levels on sexual desire (61-63). The age-associated reduction in androgen hormones parallels the age-linked increase in HSDD among women, mainly in those who have reached natural levels of menopause with low sexual desire compared with pre-menopause women, further indicating the central role that hormones play in HSDD (64,65). As discussed earlier, low levels of oestrogen are largely associated with dyspareunia and vulvovaginal mucosa changes, a move that can contribute to reduced sexual desire among affected women (46,47).

In past studies, women who have undergone oophorectomy have shown to have associated low levels of sexual desire and increased distress or poor overall well-being. One study found lower levels of androgen hormones in healthy pre-menopausal women who reported having low sexual desire compared with women without a similar problem (66). The marked decline in low levels of testosterone after surgery has been linked to low sexual desire (67,68), because most studies have focused on safety, efficacy, and testosterone-route therapy to treat reduced sexual desire. Women who undergo bilateral oophorectomy experience a decline in testosterone between 40% and 50% from pre-surgical levels, and reduced libido between 30% and 50% (69,70). In addition to surgical procedures, a number of medical factors can also affect hormonal levels in women and contribute towards HSDD as discussed in the next section.

Medical factors linked to HSDD

A number of studies have also found a positive relationship between hypersexuality and medical factors. Some researchers reported that some treatments and medical conditions could negatively affect sexual desire among women. Table 1 summarises some diseases that have possible negative impacts on sexual libido. Medical interventions and diseases can change the physiology of sexual response both peripherally and centrally (71,72). Moreover, the presence of sexual disorders, including loss of sensitivity and pain, can trigger negative responses that can make such women lose interest in sexual expression (73).

Besides the chronic conditions that contribute to HSDD, Table 2 lists some common medicines reported to cause reduced sexual urge among women. For example, drugs that give healing benefits for diseases may negatively impact on sexual response among women (77). In most gynaecologic conditions, oral contraceptives are often used together in pregnancy prevention. For years, the combination and type of progestin and oestrogen have closely been reported in dealing with benign gynaecologic diseases and pregnancy prevention (78,79). However, notwithstanding the existing literature findings, the impact that these drugs have on women's sexual changes still remain controversial (80).

Furthermore, there is increased connection between the oral contraceptive prescription in some women with vulvar vestibular pain. In patients with depression, serotonin-norepinephrine reuptake inhibitors (SNRI) and selective serotonin reuptake

Table 1. Long-term medical conditions that lead to hyposexuality in women

Condition	Example
Mood disorders (74)	Bipolar disorder, major depression
Psychotic disorders (75)	Schizophrenia
Cancer treatment (76)	Gynaecological cancer and breast cancer
Gynaecologic disorders (77)	STIs, chronic pelvic pain, vulvovaginal atrophy, dyspareunia, pelvic organ prolapse
Urologic disease (78)	Urinary tract infection, renal failure

STIs: Sexually transmitted infections

Table 2. Some medications that affect sexual desire among women

Antiandrogen agents/ hormones (74)	Gonadotropin-releasing hormone agonists, oral contraceptive pills, spironolactone
Antihypertensive agents (76)	Beta-blockers, angiotensin II antagonists, angiotensin-converting enzyme inhibitors
Antidepressants (76)	Selective serotonin re-uptake inhibitors, antipsychotic drugs
Others (77,80)	Chemotherapeutic agents, Narcotics, Antiepileptic drugs, amphetamine

inhibitors (SSRI) medications are commonly prescribed antidepressants, although they commonly result in adverse events, including arousal difficulties, absent orgasm, delayed orgasm, and decreased desire. However, there continue to be few outcome studies evaluating the most effective agents in the management of FSD (80). The next section discusses some treatment approaches in the management of hormone-induced HSDD among women.

Testosterone treatment and desire

Poor awareness of FSD and the complex issues linked to HSDD development have largely reduced the formulation and research of therapeutic interventions for persons with low sexual desire (81). Several studies have been undertaken to assess the impact that sex hormones (androgens) have in HSDD management among affected women in menopause (82,83). Nevertheless, a proper understanding of the pathophysiology and physiology has triggered positive research progress in both pre- and post-menopausal female populations. The research process has also been encouraged by the need to have appropriate exclusion and inclusion criteria for FSD in clinical research using better analytical tools to examine primary outcome measures suitable in medication interventions (84-86).

In most cases, hormone therapy (using oestrogen alone) as indicated in oestrogen-progestin therapy (OPT) is widely used among menopausal women that have an intact uterus. Thus, the use of EPT is limited to women who report early symptoms (mainly hot flashes) as the first line of defence throughout the menopausal transition phase (80). Local and systemic use of oestrogen alone (OT) or with EPT has been reported as being an effective intervention in suppressing symptoms of vulvovaginal atrophy. The intervention has been reported to improve the sexual life of affected populations as a result of better lubrication (82,86). However, despite the reduction in dyspareunia, some women with FSD have been reported to be unresponsive because the OPT/OT does not have a consistent effect on the increase in sexual activity or desire, mainly among women grouped under surgical menopause (87,88).

Greenblatt et al. (89) conducted a randomised clinical trial and found that low sexual desire responded highly effectively to androgen therapies (AT). The authors also pointed out that low sexual desire responded even better to a combination of OT/AT, as opposed to using OT alone in ovariectomised women. Since this research, several studies have also demonstrated that androgens have an important role to play in terms of improving arousal and suppressing the negative impacts of FSD among women who have attained menopause. However, most studies have been based on supra-physiologic doses of hormone administration with testosterone (90).

Some Cochrane reviews have recently explored the risks and benefits of therapy, in addition to OPT+ OPT alone for both pre-menopausal and post-menopausal women where researchers included 35 studies with about 4800 participants. Most of the trials, which had several therapy regimens (including subcutaneous implants, intramuscular injections, gels or transdermal patches, and oral tablets), recruited only post-menopausal women–both surgically and naturally menopausal–with low sexual desires. The medium intervention period was six months and ranged from one and half months to 24 months. A pooled approximation from the examined clinical trials indicated that by adding therapy to hormone therapy, the women's sexual response improved and led to improved satisfaction in sexual incidents among post-menopausal women. These beneficial effects were reported and measured for coital frequency, desire, responsiveness, and sexual activity (91,92).

However, some adverse effects were also reported, including increased cases of acne and excess hair growth and reduced levels of high-density lipoprotein. When this intervention was discontinued, the outcome was similar for both groups. Among the perimenopausal women, however, there was insufficient evidence about the efficacy of this treatment or for additional outcomes that were explored, including body composition, cognition, menopausal symptoms, fatigue, and well-being. Another study examined the effect of transdermal T patch in post-menopausal women with HSDD. The randomised, double-blind, and placebo-controlled research was evaluated over a 24-week period with over 1200 participants who were surgically menopausal with HSDD and received affiliated oestrogen therapy (93-95).

The baseline research reported that women had three episodes of increased sexual desire during the first four weeks when the 300 μg T patch was used compared with a single satisfying event among the placebo group. Nonetheless, a 450 μg T patch had no benefits compared with a non-intervention placebo group, indicating the absence of dose-response from additional T patch intervention (94). Besides increased sexual activity, there were also improvements in domains of sexual functions among women who received T patches and those from the placebo group including pleasure, orgasm, distress, sexual self-image, responsiveness, concerns, and desire. As a result, there was an increase in sexual episodes with the use of the therapy compared with placebo (95). As such, the use of hormone therapy shows significant improvement of sexual response and suppression of HSDD among women with the condition.

In conclusion FSD, grouped either as HSDD, has been shown to be a highly prevalent sexual condition, which has negative outcomes on the women's well-being and sexual life. Despite

this, HSDD remains a common underdiagnosed condition by physicians, and it also has few treatment regimens. Even so, a number of factors have recently converged to create a suitable shift toward greater awareness and attention. For instance, increased focus on hypoactive sexuality as a topic in menopause research has increased interest in the field of female fertility and further changed the previous focus on the topic. The shift has also resulted from a change in societal perception about women's privilege to a healthy sexual lifestyle, even if most post-menopausal women still possess the perception that sexuality is a taboo subject.

Today, the increased search for effective pharmacologic agents to manage various biologic causes of HSDD is a primary indicator of the strong forces that are currently initiating more attention on the topic among physicians and researchers. Most studies have now weighed in by including FSD as a disease area that deserves unique and separate research focus. In addition, a number of pharmacologic agents have been designed to target HSDD and are in various stages of clinical trials. However, the field still continues to face some hurdles including a lack of information, confusion over medications and management, and the discomfort associated with addressing the subject of sexuality. Therefore, the value of the current review will be enhanced by addressing the current barriers to the topic and committing more resources to understanding the role that hormones play in HSDD.

Ethics Committee Approval: *Department of Obstetrics and Gynaecology; University of Saarland; 66421 Homburg/Saar, Germany.*

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What is your diagnosis?

A 31-year-old patient presented for routine first trimester antenatal screening at 11 weeks 5 days. On ultrasonographic examination, crown-rump length: 58 mm, nuchal translucency: 1.3 mm, and nasal bone and tip were present. The lower limbs were observed as fused (Figure 1, 2). A single umbilical artery, and an intra-abdominal septated cystic mass was seen.

The patient (gravida 3, para 1, abortion 1) had no history of diabetes mellitus. There was no consanguinity. She did not use alcohol or illicit drugs, but consumed tobacco (5 cigarettes per day). She had a child with Wilms' tumor, with no mutations of the WT1 gene. Hematologic and biochemical parameters were all within the normal range. The combined test result of the patient was normal. Chorionic villus sampling was performed, and the result reported as normal.

The patient was hospitalized at 13 weeks and 4 days for termination of the pregnancy. Misoprostol was used for medical abortion. On physical examination, the fetus had fused lower limbs with no feet like a tail, absent external genitalia, imperforate anus, and a single umbilical artery (Figure 3, 4). The upper extremities were morphologically normal. Autopsy was performed. At autopsy, the external examination revealed imperforate anus, absent external genitalia, single umbilical cord, and fusion of lower extremities. Bilateral renal agenesis was also noted at autopsy.

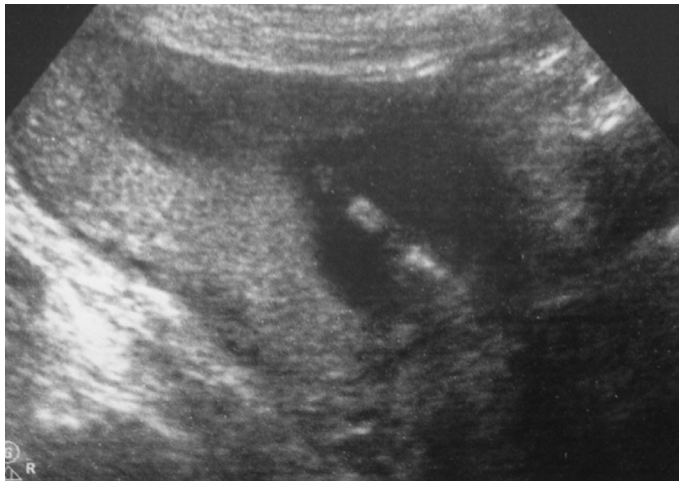

Figure 1. The lower limbs observed as fused

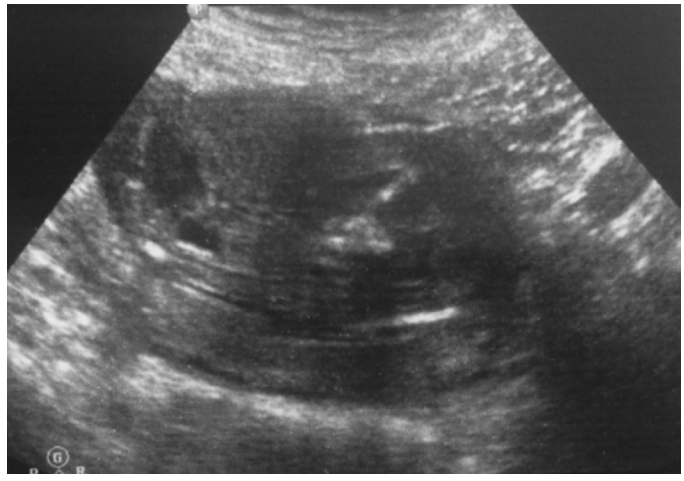

Figure 2. Sagittal view of the fused lower limbs

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Note: *This study has previously been presented as a poster at Maternal-Fetal Medicine and Perinatology Association X. National Congress, İstanbul, Turkey, 27-30 October 2016.*

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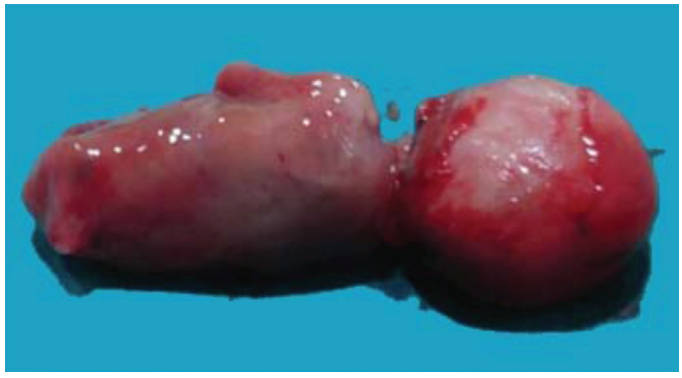

Figure 3. Photography of the fetus showed imperforate anus

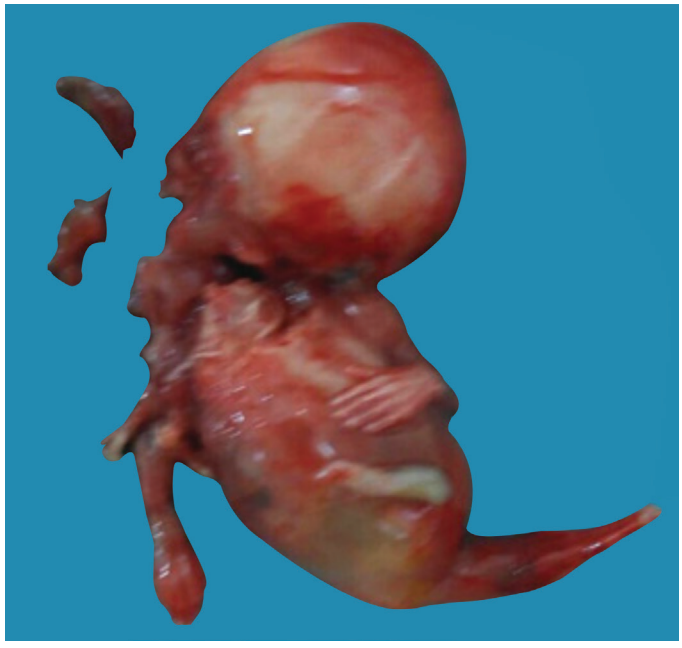

Figure 4. Photography of the fetus showed fused lower limbs, like a tail with no feet, absent external genitalia, and single umbilical artery

Answer

Sirenomelia or mermaid syndrome, is a congenital deformity. The prevalence is estimated to be one in 100.000 live births (1). Sirenomelia is a fatal congenital defect with characteristic features of partial or complete fusion of the lower limbs accompanying various other anomalies such as bilateral renal agenesis or dysgenesis, an imperforated anus and absence of the rectum, absence of the sacrum and other vertebral defects, absence of both external and internal genitalia, and oligohydramnios. Oligohydramnios is usually the first sign of this syndrome in the second trimester. Early detection of this syndrome prenatally is very rare (2,3).

Although rare cases of sirenomelia may survive for a short time (4-6), sirenomelia is a fatal congenital defect, and pregnancy termination should be offered to the parents. Sirenomelia can be associated with diabetes mellitus (7), teratogen exposure (8), and drug abuse (5). In our case, the patient used tobacco during pregnancy. Diagnosis of sirenomelia is usually made during the second trimester of pregnancy, the alerting sign is mostly oligohydramnios. Due to oligohydramnios, evaluation of fetus is more difficult than in the first trimester. First trimester diagnosis of sirenomelia is more important because this is a fatal anomaly. Accordingly, first trimester screening of limb defects is important to catch sirenomelia. Our literature search demonstrated that only a few cases of sirenomelia have been diagnosed in the first trimester. We suggest routine screening of extremities in the first trimester.

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Hysterectomy
A Comprehensive Surgical Approach

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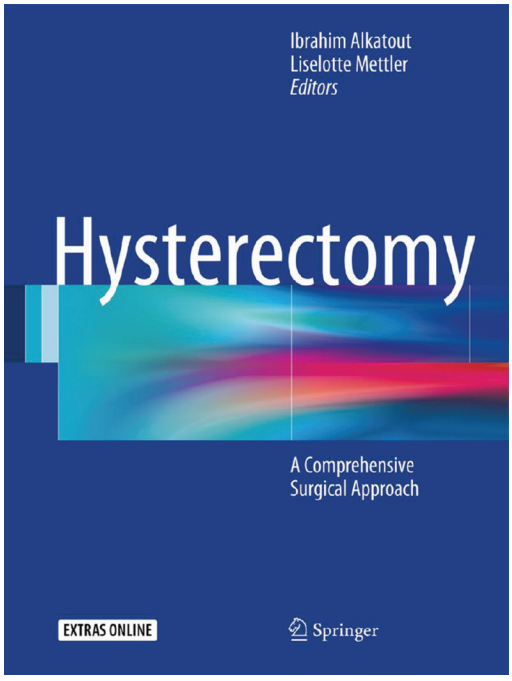

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Abstract

This book presents a step-by-step surgical description of vaginal hysterectomy, abdominal hysterectomy, conventional laparoscopic hysterectomy, and robotic-assisted hysterectomy. It brings into balance theoretical background, clinical experience, and scientific findings in a readily comprehensible form with numerous illustrations and tables. The book contains a large proportion of interdisciplinary aspects that make a substantial contribution to meeting the growing requirements of interdisciplinary medical treatment. It offers related disciplines the opportunity to describe areas of common overlap and how these can be treated.

Verschiedene chirurgische Verfahren einschließlich vaginaler Hysterektomie, abdominaler Hysterektomie, konservativer laparoskopischer Hysterektomie und roboterassistierter Hysterektomie werden in diesem englischsprachigen Lehrbuch schrittweise beschrieben. In ausgewogener Art und Weise werden theoretische Hintergründe, klinische Erfahrungen und wissenschaftliche Erkenntnisse in leicht verständlicher Form mit zahlreichen Abbildungen und Tabellen dargestellt. Indem es verschiedene interdisziplinäre Aspekte behandelt, wird das Buch den wachsenden Anforderungen der interdisziplinären medizinischen Therapie gerecht. Benachbarte medizinische Fachbereiche kommen zu Wort und haben die Möglichkeit, überlappende Krankheitsbilder und deren Behandlung zu erläutern.

Keywords: Hysterectomy, laparoscopy, robotic surgery, vaginal hysterectomy, abdominal hysterectomy

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Introduction

This comprehensive surgical approach to hysterectomy rests on the pillars erected by the great masters in gynecology and obstetrics. The first hysterectomy was performed as a vaginal hysterectomy and dates back to ancient times. The procedure was performed in the time of Soranus of Ephesus, 120 years after the birth of Christ. There were many reports of its use in the Middle Ages, nearly always for the extirpation of an inverted uterus, and the patients rarely survived. Hysterectomy became safer with the introduction of anesthesia, antibiotics and antisepsis, blood transfusions, and intravenous therapy. Apart from the transverse abdominal incision introduced by Johannes Pfannenstiel in the 1900s, there was little advance in hysterectomy techniques until the advent of endoscopic surgery and the performance of the first laparoscopic hysterectomy by Kurt Semm in Kiel in 1984, and Harry Reich in Kingston, Pennsylvania in 1988 (1). Stimulated by technical advances, the first hysterectomy with a robotic surgical system was performed after Food and Drug Administration approval in 2005 (2).

In this age of global communication, it seems more than appropriate to publish a specialist surgical book on hysterectomy that features leading surgeons, researchers and teachers from around the globe as contributing authors. With the assistance of over 200 multi-disciplinary authors, the editors have been able to compile a book that meets the requirements of a broad base of readers from beginners to specialists in gynecology. The book at hand also addresses specialists in other surgical fields, such as urologists, visceral surgeons, pathologists, radiologists, anesthesiologists, and conservative gynecologists, dealing with the interdisciplinary challenges associated with hysterectomy.

Although there is a flood of literature on this topic, this comprehensive approach to hysterectomy is unique in that it includes the historical background of the leading surgical techniques of the present day and the future perspectives as seen by the leading, contemporary, multi-disciplinary authors.

Outline of the book content

The main part of the book provides a balance of theoretical background, broad clinical experience, and scientific findings in a readily comprehensible and well-described manner, enriched with extensive illustrations and tables. For the beginner, this masterpiece serves as a reliable companion, providing background information and assistance for all procedures associated with hysterectomy. This includes abdominal, vaginal, conventional laparoscopic, and robotic-assisted surgical procedures for benign and malignant indications. Experienced surgeons in particular will be able to broaden their spectrum and learn experimental and innovative surgical approaches because this textbook is unique in offering traditional, up-to-date, and innovative surgical methods for hysterectomy. The associated medical fields, such as general surgery, urology, pathology, anesthesiology, radiology, and general /internal medicine, will benefit from the structured organization of the book and the integration of all interdisciplinary aspects.

After beginning with the historical background, there follows a section on topographic anatomy for hysterectomy procedures. This section was written by a renowned clinical anatomist and provides new insights into the female anatomy. The next section comprises five chapters dealing with imaging and diagnostics, followed by a section examining extended, and often controversial, aspects regarding indications and contraindications. Even the often underrepresented aspects of communication and training have a firm place in the book (3). Further topics covered include macroscopic and microscopic pathology, the involvement of antithrombotic therapy, and anesthesiology.

The main aspects of the book deal with the practical performance of hysterectomy with conventional laparoscopic, robotic-assisted, abdominal, and vaginal surgical techniques. In addition to all types of hysterectomies for benign and malignant indications, concomitant procedures such as urogynecologic procedures, lymphadenectomy, and omentectomy are featured in the book.

The book has several unique features. The historical chapters were written by world-renowned and respected contemporary witnesses of pioneering surgical developments (4). The imaging of the anatomic and radiologic chapters is a brilliant realization of current requirements. The chapter on sarcoma and morcellation covers an on-going, far-reaching, health-related policy debate. Innovative and reproducible surgical techniques regarding embryologic resection margins in oncologic cases are presented in different approaches. The initial abdominal approach is compared with the laparoscopic and robotic-assisted surgical approach; such a comprehensive compilation of all surgical techniques has never before been collected together in one book (5). Finally, surgical procedures that are on the verge of becoming lost are reexamined and improved in a brilliant and up-to-date fashion (6).

Evaluation of the book

The book examines many interdisciplinary aspects and the editors believe it will make a substantial contribution to meeting the growing requirements of interdisciplinary medical treatment. It offers related disciplines the opportunity to describe the areas of common overlap and how these can be treated.

The wide range of contents developed in the course of the conception of the book. Extended hysterectomy procedures

cannot be separated from pre- and postsurgical aspects or from procedures on the internal genital organs or those involving the anatomic and functionally-relevant surrounding area. This book gives access to the most advanced treatment concepts of our time. Furthermore, the eBook version meets global demands of unlimited exchange and gives access to the worldwide community interested in this topic. This text book is an important addition to the literature on hysterectomy techniques, accessible to gynecologists worldwide, and thereby contributes towards the global improvement of healthcare for women.

Peer-review: *Externally peer-reviewed.*

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

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2017 Referee Index

Acknowledgements for the Year 2017
(Reviewers contributed at the review process in 2017)

On behalf of the office staff and the Editorial Board of the *Journal of The Turkish German Gynecological Association*, we would like to thank to all of our reviewers of the past year for their outstanding contributions. Their thorough reviews and expertise enable our journal to improve its scientific quality. We certainly look forward to their ongoing support, suggestions and recommendations as to how to continue to advance the overall quality of the *Journal of The Turkish German Gynecological Association*.

Prominent Reviewers in 2017

We would like to acknowledge, with special thanks and appreciation, the following reviewers for their remarkable contributions to peer review process of the Journal of *The Turkish German Gynecological Association* in 2017. We extend our sincere gratitude for their timely, scholarly and critically evaluations.

Ali Kolusarı	Mustafa Kara	Taner Usta
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Mehmet Kağıtçı
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Murat Bakacak
Murat Dede
Murat Doğan
Murat Ekin
Murat Muhcu
Murat Öz
Murat Seval
Mustafa Albayrak

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Nafiye Yılmaz
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Numan Çim
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Yavuz Emre Şükür
Yavuz Tokgöz
Yusuf Üstün
Zeliha Selamoğlu Talaş

2017 Subject Index

2017 Subject Index

2017 Author Index

2017 Author Index

CONGRESS CALENDER

INTERNATIONAL MEETINGS

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

Progress and Controversies in Gynecologic Oncology Conference 2018

- **Venue** : Crowne Plaza Barcelona - Fira Center
- **Location** : Barcelona
- **Start Date** : January 19, 2018
- **End Date** : January 20, 2018

12th Congress of Turkish German Gynecology Association

- **Venue** : Elexus Hotel and Convention Center in Kyrenia, Cyprus
- **Location** : Cyprus
- **Start Date** : April 27, 2018
- **End Date** : May 1, 2018

NATIONAL MEETINGS

February 21-25, 2018	**Minimal İnvaziv Jinekolojik Cerrahi Kongresi** (http://minimalinvazivjinekolojikcerrahi.org//)
March 1-4, 2018	**Palandöken Kadın Doğum Kongresi, Erzurum** (http://palandokenkadindogum.com/)
March 8-11, 2018	**7. Jinekoloji Endoskopi Sempozyumu ve Çalıştayı, Bursa** (http://www.infertilitendoskopi.org/)
April 27-May 1, 2018	**12. Türk Alman Jinekoloji Kongresi, Kıbrıs** (http://www.tajev2018.org/)

TGGF

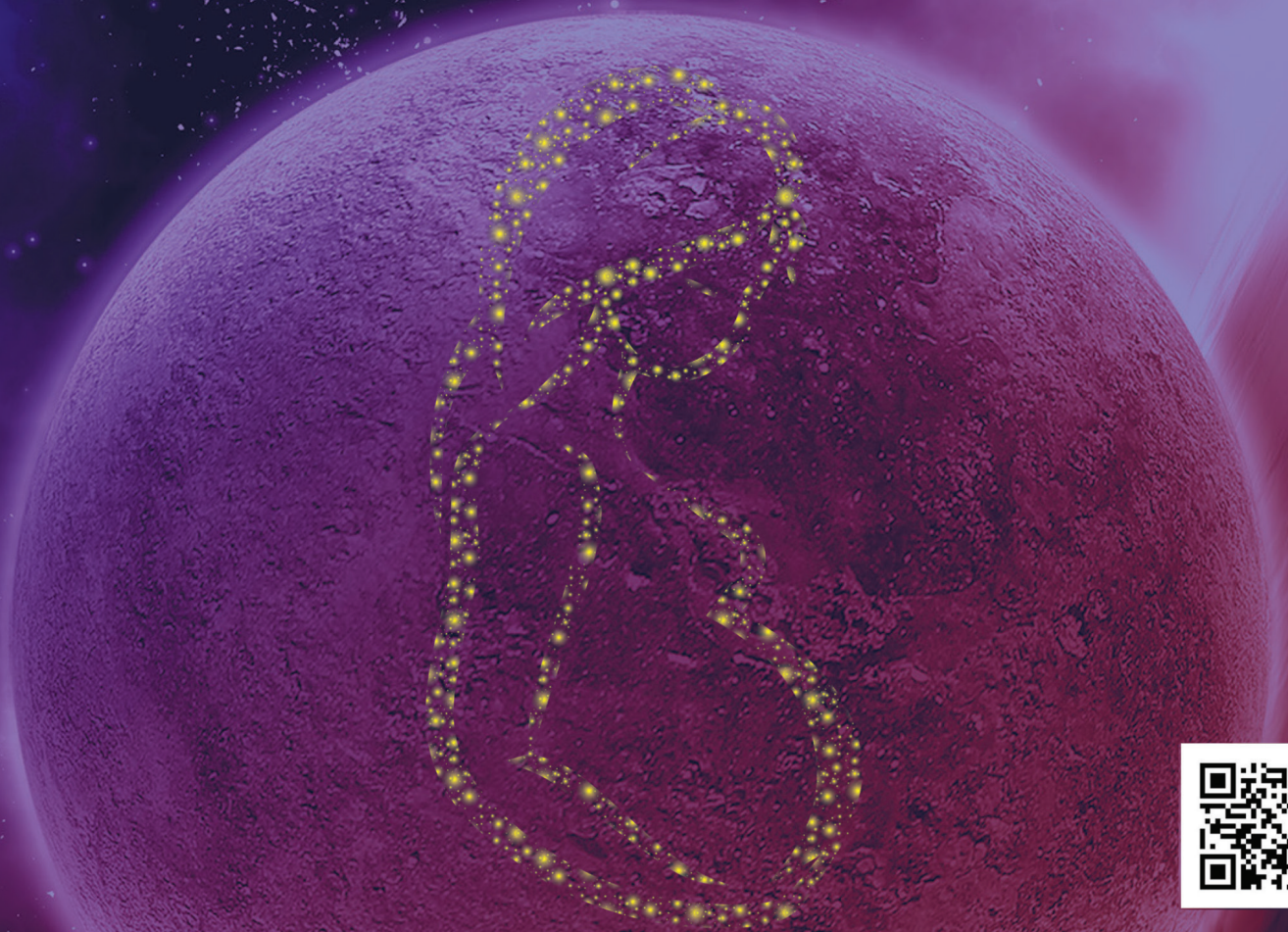
TURKISH - GERMAN GYNECOLOGICAL
EDUCATION and RESEARCH FOUNDATION

XII. TURKISH GERMAN GYNECOLOGIC CONGRESS

www.tajev2018.org

April 27 - May 01, 2018

Elexus Hotel, Kyrenia / TRNC



Drosetil

Etinilestradiol 30 mcg
Drospirenon 3 mg

Drospera

Etinilestradiol 20 mcg
Drospirenon 3 mg

Dienille

Etinilestradiol 30 mcg
Dienogest 2 mg

Güç ve güvenle birleşen güzellik...

DİENİLLE KÜB ÖZETİ: ÜRÜN ADI: DİENİLLE 2 mg/0.03 mg Film Kaplı Tablet. **FORMÜL:** 2 mg dienogest/0.03 mg etinilestradiol (Her bir film kaplı tablet). **FARMAKOLOJİ:** ATC kodu: G03FA15. DİENİLLE dienogest (progestojen) ve etinilestradiol (östrojen) içeren, antiandrojenik etkili bir kombine oral kontraseptif (KOK)'tir. **ENDİKASYONLAR:** Hormonal kontrasepsiyon. **KULLANİM ŞEKLİ VE DOZU:** Tabletler her gün aynı zamanda ve birbirini izleyen 21 gün boyunca alınır. Bir önceki ay hormonal kontraseptif kullanımı yoksa, tabletler kanamanın ilk günü alınmaya başlanmalıdır. Bir sonraki pakete 7 günlük tabletsiz aradan sonra devam edilir, genellikle ara kanama bu dönemde meydana gelir. Tipik olarak kanarna, son hapı aldıktan 2-3 gün sonra başlar ve bir sonraki paketten ilk tablet alınana kadar devam edebilir. **UYGULAMA ŞEKLİ:** Oral. **KONTRENDİKASYONLAR:** İçeriğindeki maddelerden herhangi birine karşı aşırı duyarlılık; venöz tromboz veya pozitif hasta öyküsü; arteriyel tromboz veya pozitif hasta öyküsü veya prodromal olayların varlığı; arteriyel tromboz için ciddi ya da birçok risk faktörünün varlığı, venöz veya arteriyel trombozun kalıtsal veya edinilen yatkınlığının göstergesi olabilecek biyokimyasal faktörler, ağır karaciğer hastalığı veya pozitif hasta öyküsü (karaciğer fonksiyon değerleri normale dönmemişse), karaciğer tümörü veya pozitif hasta öyküsü; steroid bağımlı tümörler; tanı konulmamış vajinal kanama; fokal nörolojik belirtili migren öyküsü; geçmişte yaşanan pankreatit veya ağır hipertrigliseridemi; ağır veya akut böbrek yetmezliği. **ÖZEL KULLANİM UYARILARI VE ÖNLEMLERİ:** DİENİLLE kullanımından önce olası dolaşım bozukluğu risklerine karşı KOK tedavisi dikkatlice tartışılmalıdır. Herhangi bir KOK kullanımı, kullanılmadığı durum ile karşılaştırıldığında venöz tromboemboli riski artar. Bazı epidemiyolojik çalışmalarda uzun süre KOK kullanımının servikal kanser riskinde artışa neden olabileceği bildirilmiştir, ancak bu bulguların KOK kullanımının hangi etkilerine bağlı olabileceği halen tartışılmaktadır. Kendisinde ya da aile öyküsünde hipertrigliseridemi olan kadınlarda, KOK kullanımı sonucu pankreatit riski artabilir. **İLAÇ ETKİLEŞİMLERİ VE GEÇİMSİZLİKLER:** Herhangi bir geçimsizlik yoktur. Diğer ilaçlar ile arasındaki etkileşmeler ara kanamaya ve/veya kontraseptif potansiyel kaybına yol açabilirler. Bu etkiler karaciğer enzim indüksiyonunu arttıran hidantoin, barbitüratlar, primidon, karbamazepin ve rifampisin durumunda gösterilmiş olup; rifabutin, efavirenz, nevirapin, okskarbazepin, topiramat, felbamat, ritonavir, nelvinafir, griseofulvin ve St. John's wort içeren bitkisel ilaçlar için geçerlidir. **GEBELİK VE EMZİRME:** Gebelik döneminde kontrendikedir. Kullanımı sırasında gebelik meydana gelirse kullanım durdurulmalıdır. Emzirme döneminde kullanılmaması tavsiye edilir. **ARAÇ VE MAKİNE KULLANIMI:** Herhangi bir etkisi bulunmamaktadır. **İSTENMEYEN ETKİLER:** KOK kullanan kadınlarda venöz ve arteriyel tromboemboli riski vardır. Sigara, hipertansiyon, kan pıhtılaşması ve lipid metabolizması bozuklukları, ağır obezite, varis, gelişmiş flebit ile tromboz gibi faktörler venöz ve arteriyel tromboemboli riskini artırabilir. **RAF ÖMRÜ VE SAKLAMA KOŞULLARI:** 36 ay-25°C'nin altındaki oda sıcaklığında saklayınız. **TİCARİ TAKDİM ŞEKLİ:** PVC/PVDC-Alu blisterde, 21 film kaplı tablet. **FİYATI:** 34,28 TL (Şubat 2017 itibariyle). **ÜRETİM YERİ:** Laboratorios Leon Farma S.A.La Vallina s/n. Polígono Industrial Navatejera 24008, Leon İSPANYA. **RUHSAT SAHİBİ:** Exeltis İlaç San. ve Tic. A.Ş. Kültür Mah. Nisbetiye Cad. No:56 Akmerkez B Blok Kat: 6 D: 574 Etiler, Beşiktaş/İstanbul. **RUHSAT TARİH/NO:** 16.02.2015-2015/136.

DROSPERA KÜB ÖZETİ: ÜRÜN ADI: DROSPERA 3 mg/0.02 mg film kaplı tablet. **FORMÜL:** 3 mg drospirenon ve 0.02 mg etinilestradiol içeren 24 adet aktif ve 4 adet plasebo beyaz film kaplı tablet. **FARMAKOLOJİ:** ATC kodu: G03AA12. DROSPERA drospirenon (progestojen) ve etinilestradiol (östrojen) içeren, antimineralokortikoid ve antiandrojenik etkili bir kombine oral kontraseptif (KOK)'tir. **ENDİKASYONLAR:** Kontrasepsiyon, hormona bağlı su tutulması ve buna bağlı belirtilerin gözlendiği durumlar, orta derecede akne vulgaris ve premenstruel disforik bozukluk semptomlarının tedavisi. **KULLANIM ŞEKLİ VE DOZU:** Tabletler gösterilen sırayla, her gün yaklaşık aynı zamanda, bir miktar su ile ve birbirini izleyen 28 gün boyunca alınır. Bir önceki ay hormonal kontraseptif kullanımı yoksa, tabletler kanamanın ilk günü alınmaya başlanmalıdır. Tablete 2. ile 5. günler arasında başlanması da kabul edilebilir, bu durumda tablet alımına başlanması itibariyle yedi gün boyunca ilave bir koruma yöntemi kullanılmalıdır.Bir sonraki pakete önceki kutudaki son tablet alımının ertesi günü başlanır. Çekilme kanaması genellikle plasebo tablet alımına başlanmasından 2-3 gün sonra başlar ve bir sonraki pakete başlandığında devam edebilir. Doğru şekilde kullanıldıklarında başarısızlık oranı yılda yaklaşık % 1 kadar olup, bu oran hap alımı unutulduğunda veya doğru alınmadığında artabilir. **UYGULAMA ŞEKLİ:** Oral. **KONTRENDİKASYONLAR:** Venöz veya arteriyel trombotik/tromboembolik olayların veya serebrovasküler bir olayın varlığı ya da öyküsü, bir tromboz prodromunun varlığı veya öyküsü, venöz veya arteriyel tromboz için ciddi ya da birçok risk faktörünün varlığı, fokal nörolojik belirtili migren öyküsü, ağır karaciğer hastalığı (karaciğer fonksiyon değerleri normale dönmemişse) varlığı, ağır veya akut böbrek yetmezliği, karaciğer tümörü varlığı veya öyküsü, steroid bağımlı tümörler, tanı konulmamış vajinal kanama, bilinen gebelik veya gebelik şüphesi, içeriğindeki maddelerden herhangi birine karşı aşırı duyarlılık, pankreatit ya da ağır hipertrigliseridemi öyküsü. **ÖZEL KULLANIM UYARILARI VE ÖNLEMLERİ:** KOK kullanımı ile ender olarak ortaya çıkan arteriyel ve venöz trombotik/tromboembolik hastalıkların risk artışı arasında ilişki bildirilmiştir. Venöz tromboembolizm riski kullanımın ilk yılında en yüksek olup, bir KOK'a başlarken ya da aynı veya farklı bir KOK'a tekrar başlarken (4 hafta ya da daha uzun aradan sonra) mevcuttur. Servikal kanser için en önemli risk faktörü süregelen human papilloma virus (HPV) enfeksiyonudur. Bazı epidemiyolojik çalışmalarda, uzun süre KOK kullanımının servikal kanser riskinde artışa neden olabileceği bildirilmiştir, ancak bu bulguların KOK kullanımının hangi etkilerine bağlı olabileceği halen tartışılmaktadır. Risk faktörlerinin veya bu durumlardan herhangi birinin ilk kez ortaya çıkması ya da artması halinde hemen doktora başvurulmalıdır. Tedavinin devamlılığı hakkındaki karar doktor vermelidir. **İLAÇ ETKİLEŞİMLERİ VE GEÇİMSİZLİKLER:** Herhangi bir geçimsizlik yoktur. Oral kontraseptifler ve diğer ilaçlar (HİV proteaz inhibitörleri ve antibiyotikler gibi) arasındaki etkileşmeler ara kanamaya ve/veya kontraseptif başarısızlığa yol açabilirler. Antibiyotik tedavisi (rifampisin ve griseofulvin dışında) alan kadınlar, ilacın sonlanmasını takiben 7 gün boyunca bariyer yöntemi kullanmalıdırlar. **GEBELİK VE EMZİRME:** Gebelik döneminde kontrendikedir. Kullanımı sırasında gebelik meydana gelirse kullanımı durdurulmalıdır. Emzirme döneminde genellikle önerilmemelidir. **ARAÇ VE MAKİNE KULLANIMI:** Herhangi bir etkisi bulunmamaktadır. **İSTENMEYEN ETKİLER:** Oral kontraseptif olarak ya da orta düzeyli akne vulgaris tedavisinde kullanıldığında en sık bildirilen advers reaksiyonlar bulantı, memelerde ağrı, öngörülmeyen uterin kanama ve daha ileri belirtilmemiş genital sistem kanamasıdır.Bu etkiler kadınların ≥ %3'ünde gözlemlenir. PMDD tedavisi için kullanıldığında en sık bildirilen advers reaksiyonlar: bulantı, memelerde ağrı ve öngörülmeyen uterin kanama. Bu etkiler kullanıcıların ≥ %10'unda gözlemlenir. Ciddi advers olaylar arteryel ve venöz tromboembolizmdir. **RAF ÖMRÜ VE SAKLAMA KOŞULLARI:** 36 ay-25°C'nin altındaki oda sıcaklığında saklayınız. **TİCARİ TAKDİM ŞEKLİ:** PVC/PVDC-Alu blisterde, 24 aktif ve 4 plasebo film kaplı tablet. **FİYATI:** 27,06 TL (Şubat 2017 itibariyle). **RUHSAT SAHİBİ:** Exeltis İlaç San. ve Tic. A.Ş. Kültür Mah. Nisbetiye Cad. No:56 Akmerkez B Blok Kat: 6 D: 574 Etiler, Beşiktaş/İstanbul. **ÜRETİM YERİ:** Laboratorios Leon Farma S.A.La Vallina s/n. Polígono Industrial Navatejera 24008, Leon İSPANYA. **RUHSAT TARİH/NO:** 24.02.2015-2015/208.

DROSETİL KÜB ÖZETİ: ÜRÜN ADI: DROSETİL 3 mg/0.03 mg Film Kaplı Tablet. **FORMÜL:** 3 mg drospirenon/0.03 mg etinilestradiol (Her bir film kaplı tablet) **FARMAKOLOJİ:** ATC kodu: G03AA12. DROSETİL drospirenon (progestojen) ve etinilestradiol (östrojen) içeren, antimineralokortikoid ve antiandrojenik etkili bir kombine oral kontraseptif (KOK)'tir. **ENDİKASYONLAR:** Kontrasepsiyon, hormona bağlı su tutulması ile buna bağlı belirtiler, akne ve sebore tedavisi. **KULLANIM ŞEKLİ VE DOZU:** Tabletler gösterilen sırayla, her gün yaklaşık aynı zamanda, bir miktar suyla ve birbirini izleyen 21 gün boyunca alınır. Bir önceki ay hormonal kontraseptif kullanımı yoksa, tablet alımına kanamanın ilk günü başlanmalıdır. Tabletlere 2. ile 5. günler arasında başlanması da kabul edilebilir, bu durumda tablet alımına başlanması itibariyle yedi gün boyunca ilave bir koruma yöntemi kullanılmalıdır. Bir sonraki pakete 7 günlük, sıklıkla çekilme kanamasının izlendiği ve tablet alınmayan dönemi takiben geçilir. Bu kanama, genellikle son tabletin alınmasını takiben 2.-3. gün başlar ve bir sonraki pakete başlandığında devam edebilir. KOK'lar doğru şekilde kullanıldıklarında başarısızlık oranı yılda yaklaşık % 1 olup, ilaç unutulduğunda ya da yanlış kullanıldığında oran artabilir. **UYGULAMA ŞEKLİ:** Oral. **KONTRENDİKASYONLAR:** Venöz veya arteriyel trombotik/tromboembolik olayların veya serebrovasküler bir olayın varlığı ya da öyküsü, bir tromboz prodromunun varlığı veya öyküsü, venöz veya arteriyel tromboz için ciddi ya da birçok risk faktörünün varlığı, fokal nörolojik belirtili migren öyküsü, ağır karaciğer hastalığı (karaciğer fonksiyon değerleri normale dönmemişse) varlığı, ağır veya akut böbrek yetmezliği, karaciğer tümörü varlığı veya öyküsü, steroid bağımlı tümörler, tanı konulmamış vajinal kanama, bilinen gebelik veya gebelik şüphesi, içeriğindeki maddelerden herhangi birine karşı aşırı duyarlılık (enzim indükleyiciler ve antibiyotikler gibi) arasındaki etkileşmeler, ara kanamaya ve/veya kontraseptif başarısızlığa yol açabilirler. Antibiyotik tedavisi (rifampisin ve griseofulvin dışında) alan kadınlar, ilacın sonlanmasını takiben 7 gün boyunca bariyer yöntemi kullanmalıdırlar. **GEBELİK VE EMZİRME:** Gebelik döneminde kontrendikedir. Kullanımı sırasında gebelik meydana gelirse kullanım durdurulmalıdır. Emzirme döneminde genellikle önerilmemelidir. **ARAÇ VE MAKİNE KULLANIMI:** Herhangi bir etkisi bulunmamaktadır. **İSTENMEYEN ETKİLER:** KOK kullanan kadınlarda venöz ve arteriyel tromboemboli riski vardır. Sigara, hipertansiyon, kan pıhtılaşması ve lipid metabolizması bozuklukları, ağır obezite, varis, gelişmiş flebit ile tromboz gibi bazı faktörler venöz ve arteriyel tromboemboli riskini artırabilir. **RAF ÖMRÜ VE SAKLAMA KOŞULLARI:** 36 ay-25°C'nin altındaki oda sıcaklığında saklayınız. **TİCARİ TAKDİM ŞEKLİ:** PVC/PVDC-Alu blisterde, 21 film kaplı tablet. **FİYATI:** 24,92 TL (Şubat 2017 itibariyle). **ÜRETİM YERİ:** Laboratorios Leon Farma S.A.La Vallina s/n. Polígono Industrial Navatejera 24008, Leon İSPANYA. **RUHSAT SAHİBİ:** Exeltis İlaç San. ve Tic. A.Ş. Kültür Mah. Nisbetiye Cad. No:56 Akmerkez B Blok Kat: 6 D: 574 Etiler, Beşiktaş/İstanbul. **RUHSAT TARİH/NO:** 24.02.2015-2015/205.
REÇETE İLE SATILIR.

Daha geniş bilgi için firmamıza başvurunuz. Tel: 0 212 365 93 30, infoTR@exeltis.com . Herhangi bir şüpheli advers reaksiyon ile karşılaşılması halinde TÜFAM'a bildiriniz. (www.titck.gov.tr; e-posta:tufam@titck.gov.tr) Tel:0 800 314 00 08; Faks: 0 312 218 35 99.

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