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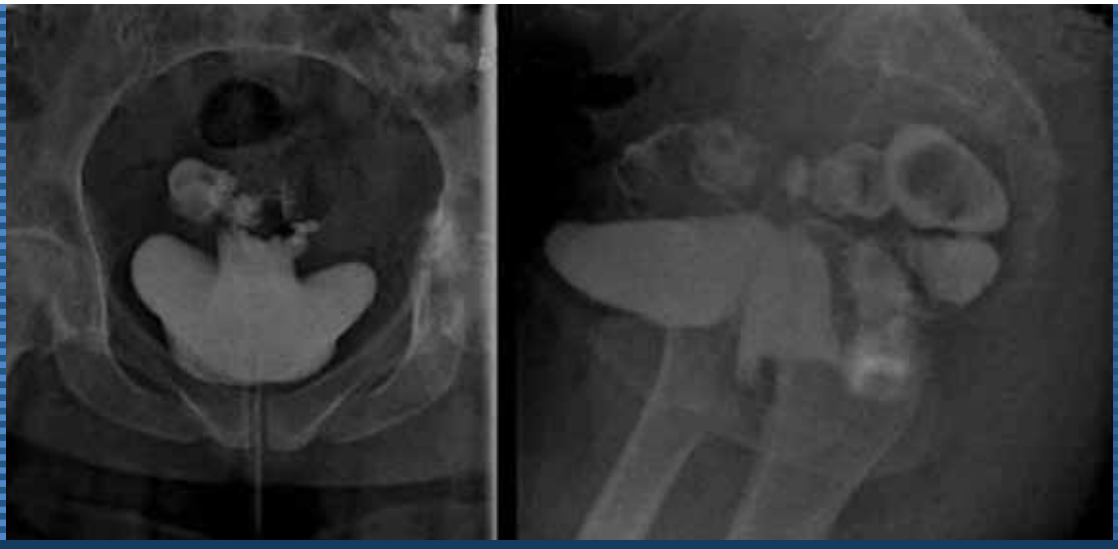

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Journal of the Turkish-German Gynecological Association is the official, open access publication of the Turkish-German Gynecological Education and Research Foundation and Turkish-German Gynecological Association and is published quarterly on March, June, September and December.

The target audience of Journal of the Turkish-German Gynecological Association includes gynaecologists and primary care physicians interested in gynecology practice. It publishes original work on all aspects of gynecology. The aim of Journal of the Turkish-German Gynecological Association is to publish high quality original research articles. In addition to research articles, reviews, editorials, letters to the editor and case presentations are also published.

It is an independent peer-reviewed international journal printed in English language. Manuscripts are reviewed in accordance with "double-blind peer review" process for both referees and authors.

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

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

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Describe the plan, the patients, experimental animals, material and controls, the methods and procedures utilized, and the statistical method(s) employed. In addition to the normal peer review procedure, all randomized controlled trials (RCTs) submitted to the journal are sent to members of a team of professional medical statisticians for reviewing.

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Present the detailed findings supported with statistical methods. Figures and tables should supplement, not duplicate the text; presentation of data in either one or the other will suffice. Emphasize only your important observations; do not compare your observations with those of others. Such comparisons and comments are reserved for the discussion section.

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Contents

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Editorial

Dear Colleagues,

It is my great pleasure to present you the first issue of the "Journal of the Turkish German Gynecological Association (JTGGA)" in the publishing year of 2015.

I would like to inform you that day by day we are getting more qualitative and quantitative submissions from the international community in addition to research studies and articles from Turkey with regards to be indexed by PubMed Central (PMC).

In this issue, you will find an opportunity to read many high quality manuscripts. One of them is an interesting research article from USA determining the impact of current video game playing on robotic simulation skills among medical students. In this issue, you will also read an attractive paper evaluating the pregnancy rates in women undergoing IVF with basal serum FSH levels between 10.0 and 11.9 IU/L. Herein is presented another highly scientific article from Russian Federation investigating the role of autonomic control of cardiovascular system in pre- and postmenopausal women. You will find a review discussing uterus transplantation as an option for uterine factor infertility. You will also read a review about multiple sclerosis; and the dilemma involving contraceptive methods. I am sure you will enjoy solving the quiz.

Our next congress - 11th Turkish German Gynecology Congress- is planned to hold on 11-15 May 2016, in Belek, Antalya. This time our congress venue will be the newly constructed Sueno Hotels Deluxe's convention center in Belek. In our forthcoming 11th congress we plan to conduct interesting pre-congress course programs, interactive live surgery presentations and also joint sessions with international associations like AAGL and NOGGO. I will inform you more about our congress preparation in the following issues.

Another good news about our foundation is that after successful projects in South Eastern Anatolia and Eastern Anatolia regions, we are determined to prepare a greater social responsibility project in Çanakkale in 2015. We are working hard to determine the best available conditions regarding the social utility and going to announce the details later on our web site and the journal.

It is also my pleasure to inform you that our foundation will restart the process of awarding scholarships to the successful colleagues studying in the field of Obstetrics and Gynecology with financial need and good academic standing. Wish you all success in your studies.

Best regards,
Cihat Ünlü, M.D.
Editor in Chief of JTGGA
President of TAJEV

Impact of current video game playing on robotic simulation skills among medical students

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Abstract

Objective: To evaluate the impact of current and prior video game playing on initial robotic simulation skill acquisition.

Material and Methods: This cross-sectional descriptive study (Canadian Task Force Classification II-1) was conducted at a medical university training center. The study subjects were medical students who currently played video games (Group I) and those who had not played video games in the last 2 years (Group II). The robotic skills of both groups were assessed using simulation.

Results: Twenty-two students enrolled in this study; however, only 21 completed it. The median age of the participants was 23 (22-24) years and 24 (23-26) years in Groups I and II, respectively. Among the participants, 15 (71.4%) were male and 6 (28.5%) were female, and 90.4% of the students started playing video games in primary school. When the 2 groups were compared according to the completion time of each exercise, Group I finished more quickly than Group II in the Peg Board-1 exercise ($p>0.05$), whereas Group II had better results in 3 exercises including Pick and Place, Ring and Rail, and Thread the Rings-1. However, none of the differences were found to be statistically significant ($p>.05$), and according to the overall scores based on the time to complete exercises, economy of motion, instrument collision, use of excessive instrument force, instruments out of view, and master workspace range, the scores were not statistically different between Groups I and II ($p>.05$).

Conclusion: According to the basic robotic simulation exercise results, there was no difference between medical students who used to play video games and those who still played video games. Studies evaluating baseline visuospatial skills with larger sample sizes are needed.

(J Turk Ger Gynecol Assoc 2015; 16: 1-4)

Keywords: Education, medical students, robotic simulation, video games

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Introduction

Minimally invasive surgery (MIS) is gaining popularity as technology advances. Robot-assisted surgery represents an increasing share of MIS in the field of gynecology as well as urology and other surgical specialties. Overall, MIS has some advantages, such as decreased blood loss, less postoperative pain, shorter hospital stay, better visualization, improved postoperative recovery, and better cosmetic outcomes, compared with open surgical cases. Robotic surgery has additional technical advantages, such as 3D viewing and better dexterity compared with conventional laparoscopy. The presence of robot-assisted surgery is projected to grow in the various surgical fields. Thus, teaching robot-assisted surgical skills is becoming part of the curriculum of surgical residency programs nationwide. To create well-structured residency training, determining future surgeons' hand-eye coordination skills is a necessity (1).

One of the main disadvantages of robotic surgery is that surgeons must operate without tactile sense. Therefore, simulation training is necessary to improve the outcome of initial hands-on experiences to avoid errors and malpractice. Video games have been discussed previously in the English medical literature for the development of laparoscopic skills to improve the learning curve in simulators and in surgery (2). The idea originated from studies that pointed out that video game playing was associated with improved reaction time, spatial visualization, and mental rotation (3, 4). Although some authors were unable to show the beneficial effects of video game playing on the ability to learn robotic suturing (5), other studies concluded that training on video games appeared to improve laparoscopic skills (6-8). Our group previously demonstrated that residents with prior laparoscopic suturing experience may learn more quickly from robotic surgery training than those with less laparoscopic surgery experience (9).

Medical schools are currently educating a generation of students who played video games from the beginning of their childhoods. They have more ability than their older counterparts to adapt to technological developments, and their experience using computers and video game consoles may afford them an advantage in their baseline eye-brain-hand coordination skills. We therefore hypothesize that these visuospatial skills acquired from playing video games can be adapted to learning robotic surgery skills. To test this hypothesis, we

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prospectively evaluated the basic robotic simulation exercise results of medical students currently playing video games and compared them with the results of medical students who previously played video games but had not played them in the last 2 years.

Material and Methods

Study design

This was a preliminary cross-sectional descriptive study comparing the effects of current or past video game playing on the ability to perform robotic simulation exercises. The study was conducted in the Department of Obstetrics & Gynecology at a State University and was approved by the Institutional Review Board (IRB) and the ethics committee. After signing the informed consent form, all participants answered questionnaires to obtain information about their histories with video games. The survey included questions about the participants' age, gender, time period of starting to play video games, and frequency of play, including the hours of gaming per day, hours per week, and duration of game playing time per session. Moreover, the type of console used [e.g., Xbox (Microsoft Corporation, Redmond, WA, USA), PlayStation (Sony Corporation, Minato, Tokyo, Japan), personal computers, or Wii (Nintendo, Kyoto, Japan)] and type of game played (first-person shooter, third-person shooter, racing games, sports games, strategy games, or other) were delineated.

Participants and outcome measures

We used the Mimic Technologies dV-Trainer™ platform (Mimic Technologies Inc., Seattle, WA, USA) for robotic simulation, which is a validated trainer for robotic surgery (10). The participants were divided into 2 groups according to their video game playing history (Figure 1): Group I included students who had played video games in the last 2 years (n=11) and Group II included students who had not played video games in the last 2 years (n=11). The participants were asked to perform 4 basic exercises: "Pick and Place," "Peg Board-1," "Ring and Rail," and "Thread the Rings-1." The objectives were to place the objects in matching colored containers, to pick up and transfer rings sequentially from peg boards to a single peg on the floor, to pick up a ring and guide the ring along a curving rail, and to pass a needle and suture through a number of flexible eyelets, respectively (Figure 2). After each exercise, the participants received overall scores out of 100 according to the time to complete the exercise, economy of motion, instrument collision, use of excessive instrument force, instruments out of view, master workspace range, and drops.

Statistical analysis

All data were initially checked for any missing variables or erroneous entries. Thereafter, data were presented as median with interquartile range. The Shapiro-Wilk test was used to check data for normal distribution. The between groups statistical analysis was performed using the Mann-Whitney rank sum nonparametric test for continuous variables and the chi-square test for categorical variables. All analyses were performed using SigmaPlot software version 12.3 (Systat software, Inc., Chicago, IL, USA). A p-value of .05 was considered statistically significant.

Results

The median age of the participants was 23 (22-24) years and 24 (23-26) years in Groups I and II, respectively. The demographic and background characteristics are shown Table 1. Among the participants, 15 (71.4%) were male and 6 (28.5%) were female. Gender distribution between the groups was not significant (p=.06). Furthermore, 90.4% of the students started playing video games in primary school. Students who continued to play video games spent 13.1±7.9 h per week on gaming. The type of game consoles used and games played by the participants are summarized in Table 2.

When we compared the 2 groups according to the completion time of each exercise, Group I finished Peg Board-1 more quickly than Group II (p>.05), and Group II finished 3 exercises more quickly, including Pick and Place, Ring and Rail, and Thread the Rings-1. However, none of the differences were found to be statistically significant (p>.05) (Table 3). According to the overall scores based on the completion time, economy of

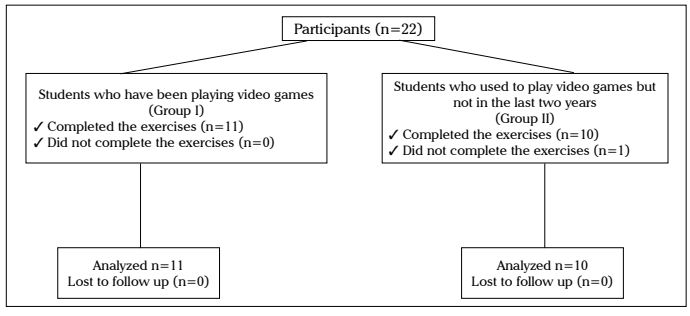

Figure 1. Participants were divided into Group I and Group II

Figure 2. a-d. Sample screen shots of the 4 basic exercises: Pick and Place (a), Peg Board-1 (b), Ring and Rail (c), and Thread the Rings-1 (d)

Table 1. Demographic and background characteristics

	Group I	Group II	p value
Median age (years)	**23 (22-24)**	**24 (23-26)**	**0.02**
Sex (n, %)			
• Male	10 (90.9%)	5 (50%)	0.06
• Female	1 (9.1%)	5 (50%)	
Starting period of playing video games (n, %)			
• Before primary school	-	-	-
• During primary school	9 (81.8%)	10 (100%)	0.47
• During secondary school or later	2 (18.2%)	-	-
Video game history in the last 2 years			
• Average hours per week (mean±SD)	13.1±7.9	-	-
• Average days per week (mean±SD)	2.9±1.8	-	-

Table 2. Type of game console used and games played by the participants*

	Group I (n=11)	Group II (n=10)
Console Type		
Xbox	6 (54.5%)	3 (30%)
Computer	4 (36.3%)	5 (50%)
PlayStation	1 (9.1%)	1 (10%)
Wii or Nintendo	-	1 (10%)
Game Type		
First-person shooter game	5 (45.4%)	-
Third-person shooter game	1 (9.1%)	-
Racing	-	2 (20%)
Sports games	1 (9.1%)	2 (20%)
Strategy games	4 (36.3%)	2 (20%)
Role-playing games	-	4 (40%)
*The respondents may have used multiple console and game types		

Table 3. Time to complete the exercises in seconds

	Group I Median (25%-75%)	Group II Median (25%-75%)	p value
Pick and Place	89 (76-116)	81 (44-104)	0.32
Peg Board-1	140 (119-227)	156 (115-227)	0.83
Ring and Rail	104 (66-118)	86 (58-140)	0.75
Thread the Rings-1	291 (229-568)	264 (211-325)	0.39

motion, instrument collision, use of excessive instrument force, instruments out of view, master workspace range, and drops, Group I had better results in 3 of 4 exercises, but none of them was statistically significant ($p>0.05$). Moreover, Group II's higher overall score in the remaining test was also not significant ($p>0.05$) (Table 4).

Table 4. Overall scores of each exercise among the participants

	Group I Median (25%-75%)	Group II Median (25%-75%)	p value
Pick and Place	80 (76-88)	86 (78-92)	0.45
Peg Board-1	61 (58-73)	52 (46-70)	0.19
Ring and Rail	76 (67-88)	74 (69-81)	0.88
Thread the Rings-1	52 (45-68)	45 (23-56)	0.14

Discussion

As MIS becomes more widespread, teaching robotic surgery will be essential to resident training programs, and video games can play a role in developing visuospatial skills. However, the present study revealed no statistically significant differences in the completion time or overall scores for the robotic simulation tests between students who used to play video games and those who still played video games.

The main strength of the study is that, to the best of our knowledge, it is the first to evaluate how past video game playing affects adoption of robotic surgical skills by comparing current players' abilities with past players' abilities, which may show whether previously acquired skills are adequate for performing robotic simulation. The study, however, has limitations. First, the main limitation is the power of the study. Although it was a prospective study, the sample size was small; thus, the results must be interpreted with caution. Nonetheless, this study was conducted as preliminary investigation and may provide a basis for future studies. The other limitation of the study is the lack of additional unmeasured variables, which may affect participants' motor skills. We cannot attribute the eye-brain-hand coordination abilities only to video games. Moreover, some types of video games may have more beneficial effects than others. In this study, we did not ask the names of video games because they may number in hundreds for the medical students and concluding their individual effects would be impossible. Lastly, gender difference may present a bias in the study. Although we aimed to avoid gender bias, female students mainly comprised the group who had not played video games in the past 2 years. Our preliminary study is inadequate to comment on gender bias, and our results must be interpreted with caution. Nevertheless, in their study, Kolozsvari et al. (11) have supported the view that gender difference does not affect performance in early fundamental laparoscopic skill training.

We previously evaluated the effect of gynecology residents' prior laparoscopic experience on the learning curve for robotic suturing techniques and found that residents with laparoscopic suturing experience may learn robotic surgery techniques more quickly than those with limited laparoscopic surgery experience (9). This transfer of laparoscopic surgery experience to robotic surgery sparked the idea of evaluating medical students' baseline abilities on a robotic simulator. Many studies in the literature suggest the possible positive effect of video games on learning laparoscopic skills (6, 8).

There are also studies evaluating the possible relationship of video games with robotic surgery skills. Shane et al evaluated

whether surgical novices exposed to previous video game exercises would acquire new surgical skills faster than nonplayers and concluded that previous video game exercises shortened the time to achieve proficiency on 2 tasks on a validated surgical simulator (12).

In contrast to these studies, Harper et al collected information about the video game experiences of 242 preclinical medical students and chose 10 students with the highest and lowest video game exposure for closer examination to assess whether prior video game experience enhances the acquisition of robotic surgical skills. They concluded that medical students' prior video game exposure did not enhance robotic surgical performance (5).

Our study evaluated the visuospatial skills of experienced video game players who currently played video games versus those who had not played video games in the last 2 years and how those previously acquired visuospatial skills may relate to robotic surgery. Because baseline ability and eye-brain-hand coordination on the 3D screen may affect future surgeons' learning curves and skill levels, we need to perform studies to determine the optimal age and best methods for developing visuospatial skills.

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Predicting pregnancy in women undergoing in-vitro fertilization with basal serum follicle stimulating hormone levels between 10.0 and 11.9 IU/L

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Abstract

Objective: To evaluate the results of the in vitro fertilization (IVF) cycle outcomes in women whose borderline basal follicle stimulating hormone (FSH) levels were between 10.0 and 11.9 IU/L and to analyze the predictors of pregnancy in this population.

Material and Methods: A prospective cohort study was performed at an academic teaching hospital; participants were infertile couples in which the women were undergoing IVF treatment and had borderline basal highest FSH levels between 10.0 and 11.9 IU/L. Statistical modeling was performed to determine risk factors for pregnancy and clinical pregnancy.

Results: A clinical pregnancy rate of 26.5% per cycle and 35% per patient was found in the study population. Among all subjects and non-intracytoplasmic sperm injection (ICSI) subjects, younger age, higher gravidity, higher number of mature follicles on day of Human Chorionic gonadotrophin (hCG) triggering, higher number of oocytes retrieved, and number of embryos produced were significant discriminators between individuals who conceived and those who did not. However, only the number of embryos predicted those who had a clinical pregnancy when compared with those who did not. Higher gravidity, and basal estradiol (E2) levels, and lower maximum basal FSH levels predicted clinical pregnancy in non-ICSI patients. Among ICSI patients, the only predictor of pregnancy was a thicker endometrium. A trend towards higher pregnancy rates was noted in ICSI patients.

Conclusion: We showed that pregnancy rates per cycle and per patient in this population were not significantly different than those in patients with a basal FSH level below 10.0 IU/L. Preliminary evidence suggests that ICSI is the fertilization method of choice in these patients.

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Introduction

In assisted reproductive technologies (ART), treatment success depends on the correct assessment of ovarian reserve. Depletion in the quantity of ovarian follicles and concurrent reduction in oocyte quality have been termed as diminished ovarian reserve and are thought to be the main reasons for declining maternal reproductive performance with age (1, 2). Various dynamic and static tests have been proposed to predict ovarian function and reserve, such as basal serum Follicle stimulating hormone (b-FSH) levels, the sonographic assessment of the ovarian antral follicle count and ovarian volume, the clomiphene citrate challenge test, the antimullerian hormone levels, the exogenous FSH stimulation test, the gonadotropin releasing hormone (GnRH) agonist stimulation test, and basal serum inhibin B levels among others (3-9). A commonly utilized test is the measurement of b-FSH levels in the early follicular phase (cycle days 2-5) (10). The use of b-FSH levels as a predictor of IVF success was first introduced in 1988 by Muasher et al. (11). There is still controversy regarding the role and accuracy of b-FSH levels in assessing ovarian reserve and counseling of patients on their chances of successful pregnancy (12, 13). However, b-FSH levels are regarded as important prognostic tests in assessing ovarian reserve and as the predictors of treatment success (1, 2, 9-11, 14-18).

Although variations in b-FSH results occured depending on the hormonal assay used for analysis, in general, b-FSH levels of less than 10 IU/L are considered to be normal (1, 14, 16). At our university, a b-FSH level of $\geq$12 IU/L is considered diminished ovarian reserve based on rare successful pregnancy rates. Pregnancy rates decline significantly as b-FSH levels become greater than 12-15 IU/L depending on the assay used at different institutions (15). The levels between 10 and 12 IU/L have been considered to be borderline (1, 14, 16, 19).

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Recently, some studies, albeit underpowered, have shown comparable results between patients under 40 years old with a b-FSH level of <10 IU/L and those with a b-FSH level between 10 and 15 IU/L, although these studies used an assay with a different cut-off (20).

An increasing number of women are delaying childbearing to a more advanced age due to various reasons (21-23). This trend has resulted in a larger number of women who search for fertility treatments at a more advanced age, and therefore, these women are at risk of elevated b-FSH levels. More women seeking infertility treatment have borderline levels of FSH and oncoming menopause (24) and have been associated with unexplained infertility (25). Success in patients with b-FSH levels between 10 and 12 IU/L, levels not yet in the abnormal range, remain poorly investigated. Thus, the purpose of our study is to describe the predictors of IVF pregnancy in women with maximum day 3 serum FSH levels of 10-11.9 IU/L, on the basis of which they are classified as having borderline ovarian reserve.

Material and Methods

A prospective cohort study was conducted at the Stanford University Hospital in the Reproductive Endocrinology and Infertility Center for 12 months. Women aged 21-43 years with borderline ovarian reserve defined as basal FSH levels of 10-11.9 IU/L and who were undergoing in vitro fertilization (IVF) were examined. The classification of subject was based on the highest serum day 2-5 FSH level. Eight hundred and sixty-six patients underwent fresh IVF cycles during the study period. Donor/recipient and frozen embryo cycles were excluded from this study.

FSH screening was performed on cycle days 2-5 in all patients. FSH levels were usually assessed at the initial infertility evaluation and were obtained within 6 months of treatment.

The controlled ovarian hyperstimulation protocol consisted of pretreatment with oral contraceptive pills with overlapping GnRH agonist downregulation, followed by FSH/human menopausal gonadotropin (hMG), microdose flare agonist, or antagonist protocols. Oocytes were inseminated conventionally or by ICSI 3-4 hours after retrieval. Embryos were cultured in groups under mineral oil in 150-μL droplets of P1 medium (Irvine Scientific, Santa Anna, CA, USA) or Quinn's Advantage Cleavage medium (Cooper Surgical, Trumbull, CT, USA) with 10% serum substitute supplement (SSS) or 10% serum protein substitute (SPS) at 37°C in a 5% O_2, 5% CO_2, and 90% N_2 environment for 72 hours. In the blastocyst transfer group, embryos were transferred on day 3 to blastocyst medium (Irvine Scientific) or Quinn's Advantage Blastocyst medium (Cooper Surgical) with 10% SSS or 10% SPS and cultured for 48 hours before transfer.

Three physicians performed the transfers; all used a similar technique. A Tefcat catheter (Cook IVF, Spencer, IN, USA) was used to deposit embryos 1.5-2 cm short of the fundus under transabdominal ultrasound guidance, with a transfer volume of 20-30 μL. Clinical pregnancies (CPs) were defined by the presence of a gestational sac on transvaginal ultrasonography.

We analyzed several patient parameters to determine their association with pregnancy, including age, gravidity, term deliveries, day 3 serum estradiol levels, maximum day 3 serum FSH levels, and accessory infertility diagnoses. In addition, cycle characteristics including stimulation protocol, total gonadotropin dose, day of stimulation, endometrial thickness on day of hCG injection, number of follicles, number of oocytes retrieved, fertilization rate, use of ICSI, use of assisted hatching, number of embryos transferred, and stage and grade of embryos at transfer were examined.

Serum b-FSH levels were determined using a solid phase two-site chemiluminescent immunometric assay, which was run on the Immulite 2500 (Siemens Healthcare Diagnostics, Inc. Tarrytown, NY, USA). The range for testing is up to 170 mIU/mL and the sensitivity is 0.1 mIU/mL. The Immulite 2500 uses a solid-phase, two-site chemiluminescent immunometric assay (sensitivity: 0.1 IU/L, intra- and interassay coefficients of variation: 4.2% and 7.9%, respectively).

All statistical analyses were performed using the statistical package for social sciences 11.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were evaluated for normal distribution using the Kolmogorov–Smirnov test. Results are reported as mean value±standard deviation (SD). The Student's t-test was used for comparison of nominal data. The Levene's test for equality of variances was applied to the data, and the corresponding t-test and p values were accepted depending on whether the variances were equal. The Chi-squared test was used to compare noncontinuous variables. Corrections were applied when the cell sizes were less than 5. For relative risk, CI denotes 95% confidence interval. Stepwise logistic regression was used to determine the predictors of pregnancy and CP while controlling for the effect of the other analyzed variables and multiplicity. Statistical significance was accepted as a two-sided $p \leq 0.05$. The university committee for the protection of human research subjects' approval of the study was obtained, and patients were consented for participation.

Results

All data were normally distributed by the Kolmogorov-Smirnov test.

Forty-nine individuals with serum b-FSH levels meeting the criteria underwent 64 IVF cycles during the study period. Cycles were cancelled in none of the patients. Thirty-two patients underwent regular IVF cycles and 32 underwent intra-cytoplasmic sperm injection (ICSI) cycles. In individuals with the highest FSH level on day 3 of the menstrual cycle being between 10 and 12 IU/L, the CP rate was 26.5% per IVF cycle and 35% per patient. At that time, the overall CP rate per cycle at the Stanford IVF clinic was 27.0% in women aged 43 years or younger and did not differ from the rate seen in the borderline FSH group. Of the cycles performed at the center during the study period, 59% were IVF cycles and 41% were ICSI cycles. Demographics of individuals with borderline b-FSH levels who conceived and failed to conceive with IVF are presented in Table 1. It can be noted that none of these parameters differed between the groups.

Table 1. Demographics of patients with b-FSH levels between 10.0 to 11.9 who achieved a clinical pregnancy and those who did not conceive

	Clinical pregnancy n=17	Not pregnant n=32	p
Age (years)	37.3±4.1	38.7±3.4	0.24
Gradivity	1.4±1.2	1.0±0.6	0.22
Previous full term pregnancies	0.5±0.8	0.3±0.6	0.36
Highest FSH (mIU/mL)	10.9±0.5	10.9±0.5	0.72

FSH: serum follicle stimulating hormone; n: number of patients

Table 2. A comparison of IVF cycle parameters in patients who achieved clinical pregnancy and those who did not

	Clinical pregnancy n=17	Not pregnant n=47	p
Gonadotropin dose IU/cycle	6203±1200	6447±1268	0.52
Number of days of stimulation	11.6±2.1	11.6±1.4	0.94
Endometrial echo at last ultrasonography prior to retrieval (mm)	10±2.1	9.7±2.7	0.62
Number of follicle with ≥15-mm diameter on day of hCG	8.6±3.3	8.0±2.7	0.49
Number of oocytes retrieved	7.9±4.5	7.1±4.1	0.48
Number of MIIs	6.9±5.8	5.3±4.8	0.27
Percent fertilization	74±21	62±21	0.07
Number of embryos	5.7±3.3	4.3±2.1	0.12
Number of embryos transferred	2.6±1.2	3.2±1.4	0.12

n: number of cycles; IU: international units; mm: millimeters; hCG: Human Chorionic Gonadotrophin; MIIs: Metaphase II oocytes

Patients were more likely to have clinical pregnancy (CP) if they had tubal factor infertility than if they did not (relative risk: 3.7, CI 1.02-14.8, p=0.05). However, male factor infertility (relative risk: 0.77, CI 0.34-1.75, p=0.51), endometriosis (relative risk: 0.69, CI 0.08-5.76, p=0.73), and recurrent pregnancy loss (relative risk: 1.50, CI 0.15-15.46, p=0.11) diagnosis did not decrease CP rates when compared with individuals without this diagnosis.

CP rates did not differ based on the stimulation protocol used. If patients had a long Gonadotropin releasing hormone (GnRh)-Agonist protocol (relative risk: 0.92, CI 0.10-8.27, p=0.94), which constituted 6% of cycles, a GnRh-antagonist cycle (relative risk: 1.09, CI 0.712-1.658, p=0.71), which constituted 61% of cycles, or a microdose GnRh-agonist flare protocol (relative risk: 0.86, CI 0.374-1.995, p=0.73), which constituted 33 percent of cycles, CP rates were similar when compared with the average CP rate of the other two protocols combined.

A comparison of parameters related to IVF stimulation between individuals with the highest serum FSH level of 10-12 IU/L who conceived with CP and who failed to conceive is presented in Table 2. None of the parameters presented differed between the two groups.

Having ICSI did not statistically improve the clinical pregnancy rate above standard IVF (45% vs. 28%, p=0.40).

As expected, individuals who had embryo quality that permitted transfer as blastocysts were more likely to have CP than individuals with day 3 embryo transfers (67% vs. 24%, p=0.003). However, embryo quality and quantity in only 14% of cycles met the criteria to enable embryos to be grown to the blastocyst stage. Based on the criteria at the IVF center, at least 4 good quality embryos were obtained on day 3 after fertilization.

Table 3. An evaluation of parameters which predicted pregnancy and clinical pregnancy in all subjects

	Pregnancy	Clinical pregnancy
Age (years)	0.03[a]	0.16
Gravity	0.04[a]	0.14
Full term deliveries	0.13	0.17
Highest FSH (mIU/mL)	0.76	0.72
Serum estradiol[b]	0.78	0.70
Gonadotropin dose per cycle	0.28	0.63
Days of stimulation	0.94	0.85
Endometrial thickness	0.13	0.46
Number of follicle ≥15 mm diameter on day of hCG	0.035[a]	0.33
Number oocytes retrieved	0.004[a]	0.30
% fertilization	0.63	0.07
Number of embryos	0.006[a]	0.03[a]
Number of embryos transferred	0.16	0.15

[a]denotes statistical significance
[b]denotes estradiol associated with the highest FSH levels
Note: stepwise logistic regression was performed which controlled for intervariable effects and multiplicity
Note: Analysis based on 64 cycles
FSH: serum follicle stimulating hormone; hCG: human chorionic gonadotrophin

Prediction of Pregnancy and CP among All Subjects

Stepwise logistic regression was performed to determine if any continuous variable predicted the likelihood of pregnancy and CP while controlling for the other variables and multiplicity. Factors that were controlled included patient age, number of previous pregnancies, number of full-term pregnancies, previous number of IVF cycles, maximum serum basal serum FSH level, basal serum estradiol level associated with that FSH level, total gonadotropin dose used, and total duration of gonadotropin stimulation and the other IVF cycle outcome parameters listed in the tables (Tables 3-5). The results are shown in Table 3. As can be noted, subject age (37±0.8 vs. 39±0.7 years), number of pregnancies (1.5±0.3 vs. 0.9±0.1), number of mature follicles on day of hCG triggering (9.0±0.7 vs. 7.7±0.4), number

Table 4. An evaluation of parameters which predict pregnancy and clinical pregnancy in ICSI cycles

	Pregnancy	Clinical pregnancy
Age (years)	0.70	0.62
Gravidity	0.75	0.80
Full term pregnancies	0.94	1.0
IVF Cycle Number	0.58	0.87
Highest FSH (mIU/mL)	0.17	0.18
Serum estradiol[b]	0.23	0.52
Gonadotropin dose per cycle	0.65	0.99
Days of stimulation	0.35	0.30
Endometrial thickness	0.049[a]	0.31
Number of follicle ≥15 mm diameter on day of hCG	0.49	0.93
Number oocytes retrieved	0.27	0.90
Number of MIIs	0.53	0.085
% fertilization	0.86	0.15
Number of embryos	0.31	0.21
Number of embryos transferred	0.94	0.62

[a]denotes statistical significance
[b]denotes estradiol associated with the highest FSH levels
Note: Analysis based on 32 cycles
FSH: serum follicle stimulating hormone; hCG: human chorionic gonadotrophin, MIIs: Metaphase II oocytes

of oocytes retrieved (9±1.0 vs. 6±0.5), and number of embryos (5.8±0.7 vs. 4.1±0.3) were significant discriminators between individuals who conceived and those who did not. However, only the number of embryos (5.7±0.8 vs. 4.3±0.3) predicted those who had CP when compared with those who did not. No other variables tested were the predictors of pregnancy or CP when controlling for the other analyzed factors.

Stepwise logistic regression was used to evaluate only subjects who underwent ICSI. The results are shown in Table 4. As can be noted, endometrial thickness predicted an increase in the pregnancy rate (p=0.049) when controlling for other factors (listed in the paragraph above) and multiplicity. However, endometrial thickness was not a predictor of CP. No other variables tested were the predictors of pregnancy or CP when controlling for the other analyzed factors among subjects who underwent ICSI.

Prediction of Pregnancy and CP among Non-ICSI Subjects

Stepwise logistic regression was used to evaluate only subjects who underwent regular IVF. The results are shown in Table 5. Individuals who conceived in comparison with those who did not were younger (36.7±1.5 vs. 40.7±0.7 years), had more previous pregnancies (2.0±0.4 vs. 0.9±0.2), had more mature follicles on the day of hCG triggering (9.5±0.8 vs. 6.9±0.6), had more oocytes retrieved (11.2±1.7 vs. 5.6±0.5), and had more embryos (6.9±0.9 vs. 3.8±0.4). In contrast, patients who had CP had a greater number of previous pregnancies (2.0±0.6 vs. 1.0±0.2), lower maximum serum FSH levels (10.6±0.2 vs. 11.0±0.08), and higher day 3 estradiol levels (61±19 vs. 35±2.4), when compared with individuals who did not achieve CP. The same previously listed factors were controlled.

Table 5. An evaluation of parameters that predict pregnancy and clinical pregnancy in patients who underwent IVF without ICSI

	Pregnancy	Clinical pregnancy
Age (years)	0.01[a]	0.26
Gravidity	0.007[a]	0.04[a]
Full term pregnancies	0.08	0.06
Highest FSH (mIU/mL)	0.16	0.03[a]
Serum estradiol[b]	0.23	0.03[a]
Gonadotropin dose per cycle	0.17	0.59
Days of stimulation	0.49	0.44
Endometrial thickness	0.48	0.89
Number of follicle ≥15 mm diameter on day of hCG	0.016[a]	0.29
Number oocytes retrieved	0.001[a]	0.31
% fertilization	0.54	0.19
Number of embryos	0.002[a]	0.06
Number of embryos transferred	0.30	0.11

[a]denotes statistical significance
[b]denotes estradiol associated with the highest FSH levels
Note: Analysis based on 32 cycles
FSH: Serum follicle stimulating hormone, hCG: Human Chorionic Gonadotrophin

Discussion

Women with borderline ovarian reserve have not been well studied in terms of the ART outcome. Due to potential negative effects of elevated b-FSH levels usually greater than at least 12IU/L on the IVF outcome, it may be reasonable to assume that there is an association of a poorer outcome in women with borderline levels of b-FSH compared with those with normal serum day 3 levels.

CP rates in women who undergo IVF under the age of 35 years have been reported to be anywhere between 30 and 45% per cycle with mostly cleavage stage transfers (26). During the study period, the CP rate per IVF- embryo transfer (ET) at the Stanford center was 27%. In our patient population with borderline ovarian reserve, overall CP rates were fairly promising, with 26.5% per IVF cycle and 35% per patient. When blastocysts were transferred in a select group of these patients, there was almost a 3-fold increase in CP rates compared with rates in cleavage stage transfers (67% vs. 24%, p=0.003). This was clearly due to a selection bias; highest quality embryos developed into blastocysts, while lower quality embryos were transferred at the cleavage stage. There was no statistical difference in mean ages between the pregnant and nonpregnant groups. Although women with slightly elevated FSH levels may have already showed a decline in their ovarian reserve,

CP rates in this study remain reassuring without significant compromise.

A variety of patient parameters were analyzed for an association with pregnancy in an IVF cycle. These data suggested that women with tubal factor infertility were more likely to achieve CP compared to those with other causes of infertility. It can be speculated that because patients with tubal factor infertility are unable to conceive without IVF, these patients differ from those with other infertility diagnoses, who have better prognosis and conceive without assistance and do not require treatment.

When many IVF cycle characteristics were examined in these women with borderline ovarian reserve, several interesting findings were noted. For example, stimulation protocols did not affect the likelihood of achieving CP in a patient. Although long protocols are usually performed in women with better prognoses, likely with lower FSH levels, we found no difference in cycle outcomes in these patients when comparing with those treated with microdose flare agonist and antagonist protocols. This may be due to the very low number of long protocols utilized in this group of women with relatively high b-FSH levels (4 cycles of 64); another reason may be that long protocols may result in similar or better stimulations than the microdose flare or antagonist protocols.

When analyzing the effects of the method of oocyte insemination on the cycle outcome in women with borderline normal b-FSH levels, having ICSI did not improve the CP rate above standard IVF (45% vs. 28%, p=ns). This trend of 45% of ICSI cycles achieving pregnancy while only 28% of standard IVF cycles did so may have been significant with a greater sample size. This nonstatistically significant trend of increased pregnancy rates with ICSI as opposed to regular IVF may be due to a reduced capability of sperm penetration of oocytes derived from women with higher b-FSH levels. De Mola et al. (27) found a significant positive correlation between b-FSH levels and zona pellucida thickness. In patients who underwent ICSI, the only parameter that predicted pregnancy was endometrial thickness. This finding coincides with the belief that the endometrium plays a pivotal role in the success of IVF. Age was not a factor that predicted outcomes of IVF cycles in women with borderline b-FSH levels who underwent ICSI.

The results differ in patients whose oocytes were not inseminated with ICSI. Age, gravidity, number of mature follicles and oocytes retrieved, and number of embryos all predicted pregnancy, while only gravidity continued to predict CP. Highest b-FSH levels and correlating estradiol levels also predicted CP.

On the other hand, assisted hatching was associated with a lower CP rate when compared with those who did not undergo this procedure. As mentioned previously, this is likely due to the fact that patients who underwent assisted hatching were older and were less likely to have had a blastocyst transfer; therefore, the outcome was skewed.

Strengths of this study include that it was performed prospectively, and it is one of the few in the literature that evaluated this cohort. Weaknesses of the study include the smaller population size. The small sample size may have affected the power to detect some significant predictors of pregnancy. However, it should be noted that several significant predictors were detected with statistical modeling, even at this small sample size, stressing the clinical significance of these predictors. Antimullerian hormone levels were measured at the discretion of the physician. Because patients clearly had borderline ovarian reserve and were offered IVF, it was not measured in most cases.

In conclusion to our knowledge, this is the first article addressing outcome predictors in infertility patients with b-FSH levels between 10.0 and 11.9 IU/L who were treated with IVF. We have shown that pregnancy rates per cycle and per patient were not significantly different from those of similar-age patients with b-FSH levels below 10 IU/L.

Ethics Committee Approval: *Ethics committee approval was received for this study from the ethics committee of Stanford University Medical Center.*

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

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Autonomic control of cardiovascular system in pre- and postmenopausal women: a cross-sectional study

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Abstract

Objective: The aim of this cross-sectional study was to assess the features of autonomic control of the cardiovascular system in pre- and postmenopausal women.

Material and Methods: We studied 185 postmenopausal women aged 59.3±8.5 years (mean±SD) and 104 premenopausal women aged 45.1±5.8 years. Standard indices of heart rate variability (HRV) (mean heart rate, coefficient of variation, standard deviation of the NN interval (the time elapsing between two consecutive R waves in the electrocardiogram with normal sinus rhythm) (SDNN), square root of the mean squared differences of successive NN intervals (RMSSD), proportion derived by dividing RR50, the number of interval differences of successive NN intervals greater than 50 ms, by the total number of NN intervals (PNN50), and power of low frequency (LF) and high frequency (HF) bands in absolute values and percentages of total spectral power) and index S of synchronization between the 0.1-Hz rhythms in heart rate and photoplethysmogram were compared between these two groups at rest. We assessed the following sex hormones: estradiol, follicle stimulating hormone, dehydroepiandrosterone sulfate, and testosterone.

Results: Mean heart rate and power of LF and HF bands were significantly different ($p<0.05$) in pre- and postmenopausal women. The autonomic indices were similar in women with natural and surgical menopause. Some indices (coefficient of variation, SDNN, RMSSD, PNN50, and power of LF and HF bands) showed weak correlation with menopause time in women with natural menopause. In women with surgical menopause, a moderate statistically significant correlation was observed only between menopause time and S index ($r=-0.41$, $p=0.039$). In premenopausal women, only testosterone correlated weakly with coefficient of variation, SDNN, PNN50, RMSSD, and power of HF band. In postmenopausal women, no correlations were found. We did not find any significant relationship between autonomic indices and hot flashes, assessed by hot flash diary.

Conclusion: We did not find a clinically important relationship between cardiovascular autonomic control and menopausal status in women. (J Turk Ger Gynecol Assoc 2015; 16: 11-20)

Keywords: Autonomic control, menopause, heart rate variability, 0.1-Hz rhythms, sex hormones, hot flashes

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Introduction

The effect of menopause on cardiovascular disease (CVD) in women has been studied by Kannel et al. (1). It has been found that autonomic dysfunction is an important factor for the evaluation of risk of cardiovascular events in CVD patients (2, 3). Age-related changes in autonomic control of the cardiovascular system (CVS) are also well known (2, 4-6). The difference of heart rate variability (HRV) indices in pre- and postmenopausal women has been reported (7, 8). Vongpatanasin W. has studied the increase of sympathetic tone and blood pressure in menopause (9). Lee et al. (10) have found a relationship between menopausal symptoms and changes in cardiovascular autonomic regulation in women. For example, hot flashes and sleep disorders are strongly associated with increased sympathetic tone (10). Moreover, a significant decrease in cardiac vagal control occurs during hot flashes (11). These signs of autonomic dysfunction may be important for cardiovascular risk assessment. The influence of sex hormones, in particular, hormone replacement therapy (HRT), on cardiovascular autonomic control is controversial (8, 12-17). Moreover, several authors reported the influence of body mass index (BMI) on autonomic control in women (18).

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Autonomic control in CVS can be assessed by HRV analysis. Various time domain and frequency domain indices are usually used for this purpose (2). The physiological explanation of these indices is known (2, 19, 20). These indices can assess cardiac autonomic regulation but not peripheral blood flow. In our previous papers, we have proposed an original method for the assessment of cardiovascular autonomic control based on synchronization between the 0.1-Hz rhythms in heart rate (HR) and photoplethysmogram (PPG) (21). The quality of 0.1-Hz rhythms synchronization was found to be higher in healthy subjects than in patients with cardiovascular disease (22). From a physiological viewpoint, the synchronization of 0.1-Hz rhythms is the result of adequate functional interaction of CVS parts (heart and peripheral vessels). The clinical importance of this diagnostic method is shown for patients with prior myocardial infarction, patients with acute coronary syndrome, and hypertensive patients (3, 23).

The physiological explanation of 0.1-Hz rhythms in PPG is a debatable point. An opto-physiological model of a finger in conjunction with a near-infrared reflectance PPG device has been proposed (24). It was shown that both oscillations in the microcirculatory bed and blood filling of digital arteries make a substantial contribution to the PPG signal. Therefore, 0.1-Hz oscillations in PPG may be associated directly with baroreceptor regulation of blood pressure (BP). At the same time, a number of authors assume that 0.1-Hz oscillations in blood microcirculation are not associated with autonomic regulation (25-28). To avoid confusion, we do not interpret the origin of 0.1-Hz oscillations in PPG in the present paper.

Thus, the features of cardiovascular autonomic control in women before and after menopause are not fully understood. Controversial results concerning this problem have been reported. The aim of the present study cross-sectional study is to assess the features of autonomic control of CVS in pre- and postmenopausal women.

Material and Methods

Patients

The study was approved by the ethics committee of the Saratov Research Institute of Cardiology in Saratov, Russia (no. 24, Sept. 12, 2013) and informed consent was obtained from all participants.

Our cross-sectional study included 185 postmenopausal women aged 59.3±8.5 years (mean±SD) and 104 premenopausal women aged 45.1±5.8 years. Both groups were investigated and treated, if necessary, in the clinic of Saratov State Medical University (Saratov, Russia). Clinical characteristics (cardiovascular, gynecological, etc.) were assessed in all women. We assessed the level of the following sex hormones: estradiol, follicle-stimulating hormone (FSH), dehydroepiandrosterone sulfate (DHEAS), and testosterone. Only patients aged between 35 and 70 years were enrolled in our study. Women with CVD were not on beta-blockers or calcium channel blockers during the 7 days before the start of the study.

Patients were not included in our study if they matched the following criteria:

i) valvular defect of the heart
ii) rhythm other than sinus that would impede analysis of HRV
iii) endocrine pathology, excluding diabetes mellitus
iv) chronic gastrointestinal diseases (hepatitis, gastric ulcer, duodenum disease, and cholecystitis), chronic diseases of the kidneys, and other chronic diseases in the stage of exacerbation

Signal recording

To examine the autonomic control of the CVS, we carried out HRV analysis and estimated the degree of synchronization between the 0.1-Hz rhythms in HR and PPG. PPG, measured on the middle finger of the subject's hand; electrocardiogram (ECG); and respiration were simultaneously recorded at rest. The signals were recorded within 10 minutes in the supine position.

All subjects were investigated after afternoon fasting under spontaneous breathing. The signals were measured in a quiet, temperature-controlled room. All signals were sampled at 250 Hz and digitized at 14 bits. The record of respiration was used to control the evenness of breathing. We excluded series with forced inspiration and delays in breathing from the analysis. For further analysis, only ECG and PPG records without artifacts, extrasystoles, and considerable trends were left.

Signal processing

We analyzed HRV in the frequency domain and time domain using HR and PPG signals simultaneously recorded within 10 minutes. We evaluated the following time domain HRV parameters: mean heart rate (mean HR), standard deviation of the NN interval (the time elapsing between two consecutive R waves in the electrocardiogram with normal sinus rhythm) (SDNN), coefficient of variation (CV), square root of the mean squared differences of successive NN intervals (RMSSD), and proportion derived by dividing NN50-the number of interval differences of successive NN intervals greater than 50 ms-by the total number of NN intervals (PNN50) (2).

High-frequency (HF) range, 0.15-0.4 Hz, and low-frequency (LF) range, 0.04-0.15 Hz, of HRV were analyzed (2). Power of LF and HF bands in the HRV power spectrum was presented in absolute values (ms^2) and in percentage of total spectral power (LF% and HF%). LF /HF ratio was also calculated (2). Very-low-frequency range of HRV was not included in our analysis to avoid questionable results, because we registered short-time ECG records (2).

To estimate synchronization between the 0.1-Hz rhythms in HR and PPG, we used the method proposed by us recently (21). Index *S* defines the relative time of synchronization between the 0.1-Hz rhythms considered.

Statistical analysis

Continuous variables are reported as medians with interquartile ranges, Me (Q1, Q3). Categorical data are presented as frequencies and percentages. The obtained estimations were considered statistically significant if $p<0.05$. For the statistical analysis, the software package Statistica 6.1 (StatSoft Inc., Tulsa, Oklahoma, USA) was used.

We applied the Shapiro-Wilk test to check whether the data were approximately normally distributed. Since these data were non-normal, their further analysis was carried out using non-parametric statistical methods. To compare the variables between patient groups, we used the Mann-Whitney test. To compare the variables within one patient group, we used the Wilcoxon test. Paired relationships between continuous variables were assessed using Spearman correlation coefficients (0.68-1.0 is high correlation, 0.36-0.67 is moderate correlation, and ≤0.35 is low correlation (29). For categorical variables, chi-square (χ^2) test was used to estimate their relationships. Multiple regression analysis with sigma-restricted parameterization was used to study multivariate effects for continuous and categorical variables.

Discriminant analysis was used to determine the set of studied parameters (clinical status, sex hormones, and cardiovascular autonomic indices) that resulted in the best separation of groups of women with hot flashes and without them.

Receiver operating characteristics (ROC) curves and corresponding area under curve (AUC) values were assessed for the binary classifier system with continuous predictors. AUC is presented with its 95% confidence interval (CI). We also assessed sensitivity (Se) and specificity (Sp) and presented them with their 95% confidence interval.

Results

Menopause, clinical status, and sex hormones

The clinical characteristics of the pre- and postmenopausal women are presented in Table 1. Postmenopausal women had a greater frequency of hot flashes assessed by hot flash diary, angina pectoris, arterial hypertension, and diabetes mellitus than premenopausal women. We revealed a strong relationship between the level of sex hormones (estradiol, testosterone, FSH, and DHEAS) and menopause (AUC tends to 1.0).

In the postmenopausal group, natural and surgical menopause occurred in 161 and 26 women, respectively. The clinical characteristics of these subgroups are presented in Table 2. Women with surgical menopause were younger than other postmenopausal women and had a greater frequency of hot flashes, greater levels of FSH and DHEAS, and lower levels of estradiol and testosterone. Also, 4.4% and 7.7% of women with natural and surgical menopause, respectively, received hormone replacement therapy. Exclusion of these patients from consideration did not change the observed differences in sex hormone levels between the subgroups studied. Menopause time was similar in women with natural and surgical menopause (Table 2).

We constructed a discriminant model based on sex hormones, age, HRT (binary), CVD (binary), and BMI for prediction of hot flashes separately in pre- and postmenopausal women. In premenopausal women, the constructed discriminant model had *Wilks' lambda* =0.72 and *approximate* F (8.98)=4.74 ($p<0.001$). The percent of correctly classified cases using the constructed model was 50.0% for women with hot flashes and 88.8% for women without hot flashes. Summary statistics for all variables of the model are presented in Table 3. The constructed model showed low discriminatory power (*Wilks' lambda* >0.5 for each variable and for the model on the whole). The main predictor of hot flashes was FSH.

In postmenopausal women, the constructed discriminant model had *Wilks' lambda*=0.55 and *approximate* F (8.17)=17.81 ($p<0.001$). The percent of correctly classified cases using the constructed model was 82.8% for women with hot flashes and 82.1% for women without hot flashes, respectively. Summary statistics for all variables of the model are presented in Table 3. The main predictors of hot flashes were estradiol and age. We did not find any relationship between smoking and sex hormones ($p>0.1$).

Correlations across cardiovascular autonomic indices

Many autonomic indices in our study correlated between themselves. Time domain indices (SDNN, CV, RMSSD, and PNN50) correlated strongly between themselves and with some frequency domain indices, but they did not correlate with HR, LF%, and *S* index. For example, SDNN had a Spearman correlation coefficient $r>0.8$, $p<0.001$ with all autonomic indices, excluding HR ($r=-0.29$, $p<0.001$), LF% ($r=0.02$, $p=0.767$), and *S* index ($r=-0.22$, $p=0.003$).

HR, LF%, and *S* index were the most independent autonomic indices in our study. We did not find any correlation between them ($r<0.1$, $p>0.05$ for all pairs). This observation was confirmed by multiple regression analysis, where adjusted R^2 took values from 0.12 to 0.15 in models for HR, LF%, and *S* index.

Menopause and cardiovascular autonomic indices

Most frequency domain and time domain parameters of cardiovascular autonomic control, excluding mean HR, were similar in pre- and postmenopausal women (Table 1). Mean HR was greater in premenopausal women. For classification of pre- and postmenopausal women, the optimal point of HR was 70 beats/min: Se=72.1% (95% CI=62.5-80.5), Sp=45% (95% CI=38.1-52.9), and AUC=0.589 (95% CI=0.530-0.646).

After the exclusion of patients with CVD (coronary heart disease, myocardial infarction, hypertension, stroke, and diabetes mellitus) from the analysis, the difference between pre- and postmenopausal women was additionally identified using the absolute values of LF and HF bands of the HRV spectrum and RMSSD (Table 1). Healthy premenopausal women had lower values of LF and HF than premenopausal women with CVD. On the contrary, healthy postmenopausal women were characterized by greater values of these indices than CVD patients. We did not reveal a significant difference in autonomic parameters in women with natural and surgical menopause (Table 2).

We also studied the correlation between cardiovascular autonomic indices and menopause time in women with natural and surgical menopause, including CVD patients (Table 4). It was shown that time domain indices (SDNN, CV, RMSSD, and PNN50) and some frequency indices (HF, HF%, and LF) correlated with menopause time in women with natural menopause ($p<0.05$). But, the values of these correlations were low. In women with surgical menopause, a moderate statistically significant correlation was observed only between menopause

Table 1. Clinical characteristics and cardiovascular autonomic indices in pre- and postmenopausal women

Parameters	Premenopausal (n=104) *(n=71)	Postmenopausal (n=187) *(n=55)	p
Age, years	46 (41, 49)	60 (53, 65)	<0.001
Hot flashes	13.6%	57.8%	<0.001
Estradiol, pmol/L	133 (121, 146)	74 (68, 84)	<0.001
FSH, IU/L	27 (24, 37)	80 (73, 85)	<0.001
Testosterone, nmol/L	1.7 (1.3, 2.0)	1.3 (1.1, 1.5)	<0.001
DHEAS, nmol/L	2.0 (1.2, 2.1)	5.7 (4.8, 5.9)	<0.001
HRT	1.9%	4.9%	0.208
Height, m	1.64 (1.60, 1.67)	1.63 (1.59, 1.65)	0.096
Waist, kg	73 (64, 86)	72 (66, 84)	0.452
BMI, kg/m^2	26.5 (24.2, 31.4)	27.1 (25.1, 31.6)	0.155
SBP, mmHg	120 (110, 135)	135 (120, 140)	0.021
DBP, mmHg	80 (70, 100)	90 (80, 100)	0.035
CHD, angina pectoris	6.7%	29.9%	<0.001
Prior myocardial infarction	0	2.7%	0.089
Arterial hypertension	26.9%	55.4%	<0.001
Prior stroke	0	2.2%	0.131
Diabetes mellitus	0	8.2%	0.032
Smoking	8.7%	6.0%	0.392
Mean HR, beats/min	75 (69, 82) *73 (69, 83)	72 (65, 80) *72 (66, 77)	0.012 *0.077
SDNN	32.8 (24.0, 48.9) *32.4 (23.4, 44.7)	33.7 (24.9, 53.9) *33.7 (24.3, 58.2)	0.371 *0.198
CV, %	4.0 (2.8, 6.0) *3.9 (2.8, 5.5)	4.1 (2.9, 6.6) *4.1 (2.9, 7.3)	0.604 *0.282
RMSSD	23.1 (13.3, 42.9) *20.9 (13.2, 41.6)	27.3 (16.4, 58.0) *26.1 (17.1, 57.9)	0.080 *0.048
PNN50	1.5 (0.2, 6.2) *1.3 (0.2, 3.9)	2.3 (0.3, 9.5) *1.9 (0.2, 11.2)	0.159 *0.309
HF, ms^2	75.2 (29.7, 204.2) *68.1 (28.9, 169.2)	102.1 (33.4, 434.5) *88.2 (50.4, 665.4)	0.055 *0.037
LF, ms^2	106.9 (54.8, 225.7) *98.5 (53.2, 188.8)	116.3 (57.8, 456.8) *143.4 (65.3, 456.8)	0.277 *0.043
HF, %	23.7 (10.2, 40.7) *21.0 (10.1, 41.5)	26.8 (14.6, 41.0) *25.1 (15.2, 38.6)	0.091 *0.301
LF, %	27.9 (20.9, 35.1) *26.7 (20.3, 34.2)	28.0 (18.2, 40.9) *28.1 (19.9, 41.6)	0.793 *0.409
S, %	46.9 (40.3, 55.9) *47.9 (40.2, 57.3)	43.6 (34.1, 55.3) *42.3 (31.3, 55.0)	0.087 *0.064

Continuous variables are presented as medians with inter-quartile ranges, Me (Q1, Q3). Categorical data are presented as percentages. FSH: follicle stimulating hormone; DHEAS: dehydroepiandrosterone sulfate; HRT: hormone replacement therapy; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; CHD: coronary heart disease; HR: heart rate; SDNN: standard deviation of the NN interval (the time elapsing between two consecutive R waves in the electrocardiogram with normal sinus rhythm); CV: coefficient of variation; RMSSD: square root of the mean squared differences of successive NN intervals; PNN50: proportion derived by dividing NN50: the number of interval differences of successive NN intervals greater than 50 ms, by the total number of NN intervals; HF: high frequency band in absolute values (ms^2); LF: low frequency band in absolute values (ms^2); HF%: high frequency band in percentage of total spectral power; LF%: low frequency band in percentage of total spectral power; S: Index S of synchronization between the 0.1-Hz rhythms
*Data in patients without CVD (CHD, hypertension, history of stroke, diabetes mellitus)

Table 2. Clinical characteristics and cardiovascular autonomic indices in women with natural and surgical menopause

Parameters	Natural menopause (n=161)	Surgical menopause (n=26)	p
Age, years	60 (54, 65)	48 (45, 60)	<0.001
Hot flashes	52.8%	92.3%	0.001
Estradiol, pmol/L	74 (68, 85)	68 (57, 74)	<0.001
FSH, IU/L	78 (70, 83)	87 (83, 88)	<0.001
Testosterone, nmol/L	1.3 (1.1, 1.6)	1.1 (0.9, 1.2)	0.024
DHEAS, nmol/L	5.5 (4.4, 5.8)	5.9 (5.8, 6.1)	<0.001
Menopause time, years	9 (3, 16)	11 (4, 19)	0.787
HRT	4.4%	7.7%	0.789
Height, m	1.63 (1.60, 1.65)	1.64 (1.58, 1.65)	0.128
Waist, kg	73 (66, 84)	67 (64, 86)	0.191
BMI, kg/m^2	27.3 (25.7, 31.6)	25.8 (24.2, 32.0)	0.233
SBP, mmHg	140 (120, 150)	120 (115, 160)	0.054
DBP, mmHg	90 (80, 100)	80 (75, 100)	0.526
CHD, angina pectoris	30.6%	26.9%	0.765
Prior myocardial infarction	3.2%	0	0.799
Arterial hypertension	56.2%	53.8%	0.847
Prior stroke	2.5%	0	0.841
Diabetes mellitus	6.9%	19.2%	0.316
Smoking	3.8%	23.1%	0.115
HR, beats/min	72.6 (65.2, 80.1)	71.8 (66.0, 75.8)	0.567
SDNN, ms	33.7 (24.9, 61.2)	35.0 (24.3, 44.0)	0.533
CV, %	4.3 (2.9, 6.9)	3.9 (3.0, 6.2)	0.486
RMSSD, ms	27.3 (16.3, 59.5)	27.3 (16.5, 44.3)	0.548
PNN50	2.3 (0.4, 9.5)	2.1 (0.5, 9.5)	0.766
HF, ms^2	102.1 (34.0, 665.4)	69.1 (33.1, 204.2)	0.317
LF, ms^2	127.8 (60.8, 456.8)	105.1 (56.3, 285.2)	0.528
HF, %	26.8 (14.7, 41.0)	23.9 (13.7, 38.3)	0.483
LF, %	28.0 (18.2, 40.9)	27.8 (18.7, 43.2)	0.781
S, %	45.2 (33.3, 55.7)	37.5 (34.7, 46.8)	0.084

Continuous variables are presented as medians with inter-quartile ranges, Me (Q1, Q3). Categorical data are presented as percentages. FSH: follicle stimulating hormone; DHEAS: dehydroepiandrosterone sulfate; HRT: hormone replacement therapy; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; CHD: coronary heart disease; HR: heart rate; SDNN: standard deviation of the NN interval (the time elapsing between two consecutive R waves in the electrocardiogram with normal sinus rhythm); CV: coefficient of variation; RMSSD: square root of the mean squared differences of successive NN intervals; PNN50: proportion derived by dividing NN50: the number of interval differences of successive NN intervals greater than 50 ms, by the total number of NN intervals; HF: high frequency band in absolute values (ms^2); LF: low frequency band in absolute values (ms^2); HF%: high frequency band in percentage of total spectral power; LF%: low frequency band in percentage of total spectral power; S: Index S of synchronization between the 0.1-Hz rhythms

time and *S* index (Spearman r=-0.41, p=0.039). The absence of a statistically significant correlation with other autonomic indices may probably be explained by the small number of patients in this subgroup.

Multiple regression analysis did not reveal a significant relationship between cardiovascular autonomic indices and menopause time. We did not find a relationship between autonomic indices and BMI in pre- and postmenopausal women, including CVD patients (p>0.05).

Sex hormones and cardiovascular autonomic indices

In our study, the correlation between cardiovascular autonomic indices and some sex hormones (FSH and testosterone) was similar to the correlation observed between the autonomic indices and menopause time. The data from all patients, including CVD patients, were analyzed.

Some cardiovascular autonomic indices showed a low correlation (Spearman r<0.18, p<0.05) with a number of sex hormones in the whole group (n=289):

Table 3. Summary statistics for all variables in the discriminant models for classification of women into two groups (with hot flashes and without hot flashes) based on sex hormones

No.		Variables	Wilks' Lambda	Partial Lambda	F-remove	p-level	Tolerance
Premenopausal women							
1		FSH*	0.76	0.95	4.80	0.031	0.15
2		Estradiol	0.75	0.97	3.37	0.069	0.16
3		Age	0.74	0.97	2.11	0.150	0.37
4		DHEAS	0.73	0.98	1.44	0.233	0.31
5		CVD	0.73	0.98	1.31	0.256	0.80
6		Testosterone	0.72	0.99	0.47	0.496	0.12
7		BMI	0.72	0.99	0.44	0.508	0.82
8		HRT	0.72	0.99	0.17	0.684	0.85
Postmenopausal women							
1		Estradiol*	0.79	0.69	78.08	<0.001	0.87
2		Age*	0.56	0.97	4.66	0.032	0.58
3		Testosterone	0.56	0.98	3.17	0.076	0.11
4		FSH	0.56	0.98	2.85	0.093	0.16
5		BMI	0.55	0.99	0.88	0.347	0.87
6		DHEAS	0.55	0.99	0.79	0.373	0.19
7		HRT	0.55	0.99	0.49	0.480	0.93
8		CVD	0.55	0.99	0.18	0.672	0.87

*Main predictor. FSH: follicle stimulating hormone; DHEAS: dehydroepiandrosterone sulfate; CVD: cardiovascular disease; BMI: body mass index; HRT: hormone replacement therapy

Table 4. Correlation of menopause time with sex hormone levels and cardiovascular autonomic indices

Parameters	Natural menopause (n=161)		Surgical menopause (n=26)	
	Spearman r	p	Spearman r	p
HR, beats/min	-0.03	0.717	-0.20	0.347
SDNN, ms	0.21	0.007	0.15	0.464
CV	0,22	0.005	0.11	0.609
RMSSD, ms	0.23	0.004	0.20	0.336
PNN50	0.24	0.002	0.06	0.791
HF, ms^2	0.22	0.005	-0.01	0.978
LF, ms^2	0.17	0.030	0.06	0.790
HF, %	0.18	0.022	-0.07	0.752
LF, %	-0.06	0.473	-0.09	0.671
S, %	-0.08	0.317	-0.41	0.039

HR: heart rate; SDNN: standard deviation of the NN interval (the time elapsing between two consecutive R waves in the electrocardiogram with normal sinus rhythm); CV: coefficient of variation; RMSSD, square root of the mean squared differences of successive NN intervals; PNN50: proportion derived by dividing NN50: the number of interval differences of successive NN intervals greater than 50 ms, by the total number of NN intervals; HF: high frequency band in absolute values (ms^2); LF: low frequency band in absolute values (ms^2); HF%: high frequency band in percentage of total spectral power; LF%: low frequency band in percentage of total spectral power; S: Index *S* of synchronization between the 0.1-Hz rhythms

i) HR and *S* index correlated with all sex hormones (estradiol ^{p}, FSH ^{n}, testosterone ^{p}, and DHEAS ^{n}), where superscripts p and n denote a positive and negative correlation, respectively

ii) RMSSD, PNN50, HF, and HF% correlated with FSH ^{p}, testosterone ^{n}, and DHEAS ^{p}

iii) SDNN, CV, LF, and LF% showed no correlation with any sex hormones

In premenopausal women, only testosterone exhibited a weak correlation with SDNN, CV, PNN50, RMSSD, HF, and HF% (Spearman R ranged from 0.16 to 0.20, $p<0.05$). In postmenopausal women, the correlations were not found.

After the exclusion of CVD patients, the correlation analysis gave the following results. In women without CVD, S index still correlated with all sex hormones (Spearman R ranged from 0.20 to 0.25, $p<0.05$), while HF correlated only with FSH and DHEAS ($r=0.18$, $p=0.039$ and $r=0.21$, $p=0.016$, respectively). Other indices showed no correlation with sex hormones. Age had no effect on the relationship between cardiovascular autonomic indices and sex hormones in the women.

Hot flashes and cardiovascular autonomic indices

We studied the relationships between hot flashes (binary parameter yes/no) and several cardiovascular autonomic indices in pre- and postmenopausal women using discriminant models. The following indices were included in the models: HR, SDNN, LF%, HF%, and *S* index. We also included age and the main predictors in the analysis. Patients with CVD were excluded from consideration to remove the uncontrolled effects of CVD on autonomic control.

We did not find any significant relationships between autonomic indices and the presence or absence of hot flashes. In premenopausal women, the constructed discriminant model (*Wilks' lambda* = 0.78 and *approximate* $F(7.62)=2.56$, $p=0.022$) showed lower predictive power than the model presented in Table 3. The percent of correctly classified cases using this model was 36.4% for women with hot flashes and 88.1% for women without hot flashes. The main predictor of hot flashes was also FSH.

In postmenopausal women, the constructed discriminant model had *Wilks' lambda*=0.62 and *approximate* $F(7.47)=4.19$, $p=0.001$. This model was also worse than the model presented in Table 3. In particular, the percent of correctly classified cases using this model was 68.8% and 73.9% for women with hot flashes and without them, respectively. The main predictor of hot flashes was estradiol.

Discussion

In our study, we found a significant difference in sex hormones between women with surgical and natural menopause. The obtained results are consistent with results reported by other authors (30, 31). Note that all women with surgical menopause included in our study were younger than 60 years. It is known that DHEAS level decreases with age (30). It is also known that smoking has an influence on steroid hormone concentrations (32). However, we did not find such an influence in our study.

The impact of sex hormones on CVD in women is discussable and attracts a lot of attention (33-36). According to our study, sex hormones and menopause time are related similarly with some autonomic indices. According to Chaudhuri et al. (37), postmenopausal women exhibit significantly decreased HRV in comparison with premenopausal women. Some other differences between these groups of women were reported in other studies (38). We did not find significant relationships between the characteristics of menopausal status and autonomic indices, which are also considered cardiovascular risk factors (2, 3). Low correlations are discussable and have no clinical importance. In our study, only HR was different in pre- and postmenopausal women, including patients with CVD. This observation contradicts the increase of sympathetic tone after menopause (10), which results in the increase of HR. In women without CVD, some spectral HRV indices (LF and HF) were also different. However, CVD masks the relationship between autonomic control and menopause.

Note that arterial hypertension was more frequent in postmenopausal women in our study, which is consistent with other studies (39-40). In the postmenopausal period, the increase of BP is associated with autonomic disturbances in the CVS, in particular, with the increase of sympathetic tone (9). Diabetes mellitus was observed only in postmenopausal women. Other authors also reported a greater frequency of glucose metabolism disturbances after menopause (41).

Moodithaya et al. (42) have shown a decrease of power of HF and LF spectral bands in the HRV power spectrum in postmenopausal women in comparison with premenopausal women. Age was the important factor responsible for the differences in all ranges of the HRV spectrum between pre- and postmenopausal women.

Tezini et al. (43) suggested the absence of a relationship between autonomic control and ovarian hormone deprivation in rats with early and physiological menopause. These results seem to be a consequence of the aging process. We confirmed this fact in postmenopausal women. The low correlation between testosterone and some autonomic indices, shown by us in premenopausal women, is a debatable point.

In postmenopausal women without prior HRT, oral estradiol therapy versus transdermal estradiol reduced HRV in the time domain (SDNN, RMSSD, and triangular index) (44). Hautamäki et al. (45) reported positive effects of estradiol-only therapy on cardiovascular control in flushing women. It was also shown that estrogen therapy has a weak attenuating effect on some nocturnal nonlinear measures of HRV (46). But, Fernandes et al. (47) did not find any effects of HRT on 24-hour HRV in postmenopausal women.

The difference in estrogen level between pre- and postmenopausal women contributed to the difference in relative values of HF and LF bands in the HRV spectrum (42). In our study, the power of HF and LF spectral bands of HRV was not significantly different in postmenopausal versus premenopausal women. However, in the analysis restricted to women without CVD, the index RMSSD and both the HF and LF bands were significantly higher in postmenopausal versus premenopausal women. The inclusion of women with CVD into the analysis led to the masking of the relationship between menopausal status and HF and LF. The results of our study may be limited by its cross-sectional design (see the Limitations section).

According to the results of cross-sectional study by Carranza-Lira et al. (48), vasomotor symptoms (hot flashes and sweats) correlate only after menopause. Da Fonseca et al. (49) reported that the age of menopause and BMI may influence the intensity of vasomotor symptoms. In our cross-sectional study, the main predictors of hot flashes were sex hormone levels (FSH and estradiol in pre- and postmenopausal women, respectively). Autonomic indices and BMI were not related with hot flashes in

the women studied. Lantto et al. (44) obtained similar results. They showed for postmenopausal women without HRT that HRV parameters are similar in subjects with hot flashes and without them. According to Hautamäki et al. (50), hot flashes and HRT were not related to the changes in HRV.

The absence of clinically meaningful relationships between cardiovascular autonomic indices and vasomotor symptoms in menopause revealed in our study agree with some other results (5, 10, 11, 44, 50). It is evident that changes in levels of sex hormones in menopause are the main factor determining vasomotor symptoms. The observed relationships between a number of autonomic indices and the level of sex hormones and menopause time indirectly indicate that autonomic indices exert an influence on the appearance of menopause symptoms. Interrelations between autonomic indices and vasomotor symptoms in menopause need further investigation.

Also, we did not find any relationship between autonomic indices and BMI, which is consistent with Moodithaya et al. (42). However, Mouridsen et al. (51) reported that weight loss seems to improve HRV. A relationship between BMI and LF and HF band of the HRV spectrum was reported only in premenopausal women (18, 52). The decrease of HF and increase of LF may be associated with central adiposity in postmenopausal women (53). According to Robillard et al. (54), healthy women with a metabolically healthy but obese (MHO) phenotype had significantly lower resting HR and higher SDNN and LF than women with obesity as a risk factor.

In our cross-sectional study, we did not reveal a clinically important relationship between cardiovascular autonomic control and menopausal status (pre- and postmenopausal period, menopausal time, sex hormones, and hot flashes) in women. A significant difference between pre- and postmenopausal women was found in a number of autonomic indices (HR, LF, and HF). In the case of CVD, there was no difference in LF and HF between the subgroups of women studied. The observed weak correlations between autonomic indices and some other parameters (hot flashes, sex hormones, menopausal time, and obesity) have no clinical impact. FSH was found to be the main predictor of hot flashes in premenopausal women in our study, while estradiol and age were found to be the main predictors of hot flashes in postmenopausal women.

Personal dynamics of sex hormone levels during menopause were not studied. The cross-sectional design of the presented study had some limitations. We can not examine individual dynamic features of the relationship between cardiovascular autonomic control and fertile status (sex hormone levels, menopause time, etc.). An additional comparative study of cardiovascular autonomic control features in pre- and postmenopausal women must be carried out during a prospective trial.

The overlap in age between pre- and post-menopausal women was small, because it was difficult to adjust for age accurately. Therefore, it was difficult to determine the influence of age on menopausal status. The small number of women with surgical menopause was a limitation of our study for the corresponding subgroup.

We did not study the duration of sleep among women. Since patients with menopause often have sleep disturbances, which can affect HRV indices, it is also a limitation of the present study. We did not assess lipids and diet in women. An influence of lipid metabolism and diet type on CVS autonomic control was shown in some studies (55). We did not identify women with the MHO phenotype among obesity subjects. The influence of BMI on autonomic indices needs further investigation.

Ethics Committee Approval: *Ethics committee approval was received for this study from the ethics committee of Saratov Research Institute of Cardiology (no. 24, 12 Sept 2013).*

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

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Determination of risk factors and perinatal outcomes of singleton pregnancies complicated by isolated single umbilical artery in Turkish population

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Abstract

Objective: To address the possible risk factors, eventual pregnancy outcomes, and probable troubles in follow-ups of pregnancies complicated by an isolated single umbilical artery and to provide data on Turkish cases in such an aspect that ethnic divergences may have influence.

Material and Methods: A total of 16568 singleton pregnancies that were delivered between May 2006 and May 2013 were retrospectively screened. Ninety-three fetuses were found to have an isolated single umbilical artery. One-hundred pregnancies that did not show any structural or chromosomal abnormalities were randomly selected from the rest of the cases to establish the control group. IBM SPSS Statistics 20.0 software was utilized for statistical analysis. Non-parametric data were analyzed with Mann-Whitney U test and were presented as means±standard deviations. P values less than 0.05 were statistically significant. For the adjustment of confounding factors, odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by multiple logistic regression analysis.

Results: The incidence of small for gestational age (SGA) fetuses and hypertensive disorders in pregnancy was found to be significantly higher in cases with an isolated single umbilical artery ($p<0.001$ and $p=0.022$, respectively). Maternal smoking was found to be independently associated with the occurrence of an isolated single umbilical artery (OR: 3.556; 95% CI: 1.104-11.45). The risk of preterm birth was not higher in the study group (OR: 0.538; 95% CI: 0.576-2.873). The incidence of cases who underwent cesarean delivery because of non-reassuring fetal heart trace was similar in the study and control groups ($p=0.499$).

Conclusion: Attention should be paid to the development of hypertensive disorders in cases with a diagnosis of an isolated single umbilical artery, and parents should be counseled properly, including the information on increased risk of SGA. Strict follow-up of pregnancies complicated with an isolated single umbilical artery in terms of preterm birth seems unfeasible except in cases with accompanying risk factors for preterm labor. (J Turk Ger Gynecol Assoc 2015; 16: 21-4)

Keywords: Isolated single umbilical artery, SGA, pregnancy outcome, hypertensive disorders, preterm birth

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Introduction

A single umbilical artery is a malformation where the umbilical cord carries one artery and one vein instead of two arteries and one vein. A two-vessel umbilical cord or single umbilical artery is seen in approximately 0.5%-1% of all deliveries, and it is the most common anomaly of the umbilical cord (1). Many risk factors have been suggested in previous studies, including maternal age, maternal smoking status, ethnicity, multiparity, and multiple gestations (2). Some studies have also indicated that risks of some adverse pregnancy outcomes such as intrauterine growth restriction, low birth weight, preterm delivery, and hypertensive disorders in pregnancy could be increased in cases with a single umbilical artery (3, 4).

A single umbilical artery is known to be associated with fetal chromosomal and structural abnormalities particularly neural tube, musculoskeletal, genitourinary, and cardiac anomalies (5, 6). The prognoses of fetuses with a single umbilical artery largely depend on the severity of the coexisting anomaly. In the absence of these additional chromosomal or structural abnormalities, a single umbilical artery is considered to be isolated. The clinical importance of a diagnosed isolated single umbilical artery is still controversial (7). Moreover, there is a meager amount of data obtained from Turkish cases in literature on the issue that divergences in ethnicity may have a significant impact (8-11). Furthermore, most of these studies were conducted on single umbilical artery cases with additional anomalies (9-11). This retrospective cohort study was conducted to evaluate the pregnancy outcomes and possible risk factors associated with an isolated single umbilical artery in a Turkish population.

Material and Methods

This retrospective cohort study was conducted in the Department of Obstetrics and Gynecology of Ankara University

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Table 1. Demographic characteristics of study and control groups

	Isolated single umbilical artery group (n=93)	Control group (n=100)	p value
Maternal age (years)	27.1±5.37	27.4±5.28	0.623
Body Mass Index (kg/m^2)	28.3±4.28	28.3±3.38	0.628
Maternal gravidity	3.91±1.96	3.84±1.04	0.653
Maternal parity	2.1±0.98	2.3±1.2	0.886

Values are compared by Mann-Whitney U test and are presented as means±standard deviations. P<0.05 is considered statistically significant

Table 2. Multiple logistic regression analysis for variables independently associated with the occurence of an isolated single umbilical artery

	Wald	OR (95% CI)	p value
Positive smoking status	4.519	3.556 (1.104-11.45)	0.034
Assited reproduction	2.540	3.76 (0.738-19.168)	0.11
Rhesus incompatibility	0.993	1.73 (0.589-5.081)	0.31
Maternal age	0.965	0.972(0.919-1.029)	0.326
Body Mass Index (kg/m^2)	0.158	1.016(0.941-1.097)	0.691
Constant	1.268	0.844	0.26

Cl: Confidence interval
OR: Odd ratio

in Ankara, Turkey. The records of women who gave birth between May 2006 and May 2013 were screened. This study was structured via retrospective data assessment and neither ethics committee approval nor patients' informed consents were obtained. The medical history and other necessary information were obtained from the patient records and by phone calls if required. The records of detailed ultrasonographic examinations and birth charts were investigated. Only singleton pregnancies were evaluated. The cases that were found to have two-vessel umbilical cords without any additional structural or chromosomal abnormalities were selected. Single umbilical arteries were diagnosed by the visualization of only one umbilical artery in the color flow mapping of the fetal pelvis as a standard component of routine detailed obstetric ultrasound examination. Detailed obstetric ultrasound examinations were performed between the 18th and 21st gestational weeks by three certified obstetric sonographers. Siemens Sonoline G50 ultrasound, Voluson E6, and Logiq 5P (GE Healthcare Company, Little Chalfont, United Kingdom) with 3.5 and 5 MHz transducers were used for the detailed obstetric ultrasound examination.

Small for gestational age (SGA) is defined as an infant that weighs below the 10th percentile because of local curves (12) and that do not have any abnormal parameters on Doppler studies. Pregnancies complicated with preeclampsia, eclampsia, or gestational hypertension were described as hypertensive disorders in pregnancy.

In our institution, non-reassuring fetal heart trace was described as a fetal heart rate pattern that was classified as either Category II (without achieving adequate reassurance) or Category III, according to National Institute of Child Health and Human Development workshop report (13). However, the retrospective nature of this study prevented us from further standardizing the term "non-reassuring fetal heart trace" and eliminating inter-physician divergences in interpretation.

Ninety-three cases of an isolated single umbilical artery were found to be diagnosed, and 100 women randomly selected among singleton pregnancies that were demonstrated to have chromosomal or structural abnormalities and that were delivered within the selected study period.

Data analysis was performed with IBM SPSS Statistics 20.0 software (IBM Corporation Software Group, New York, United States of America).

Categorical variables were expressed as numbers and percentages. Non-parametric data were compared by Mann-Whitney U test and were presented as means±standard deviations. P values less than 0.05 were considered statistically significant. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using multiple logistic regression analysis to adjust for confounding factors.

Results

A total of 17987 birth charts were screened, and 16568 of them were singleton pregnancies. Among these pregnancies, 93 fetuses (0.34%) were diagnosed to have two-vessel umbilical cords without any chromosomal or structural abnormalities, including genitourinary, cardiac, or musculoskeletal anomalies. Maternal demographic characteristics were similar in the isolated single umbilical artery and control groups in terms of maternal age, body mass index (BMI), maternal gravidity, and maternal parity (Table 1).

Through multiple logistic regression analysis, maternal smoking was found to increase the risk of occurrence of an isolated single umbilical artery (OR 4.15; 95% CI 1.104-11.45), whereas rhesus incompatibility, maternal age, maternal BMI, and assisted reproduction were unlikely to be associated with an increased risk for occurrence of a single umbilical artery (Table 2).

The mean birth weight of infants with an isolated single umbilical artery was found to be lower than infants with normal umbilical cords despite the difference not having reached statistical significance (p=0.591) after adjustment for maternal smoking status and gestational age at birth (Table 3). Both total cesarean rate and cesarean rate because of non-reassuring fetal heart trace were found to be similar between the groups (p=0.241 and p=0.499, respectively). There were 24 cases (25.8%) of SGA infants in the single umbilical artery group, whereas there were only four cases (4%) of SGA in the control group. Incidence of SGA infants was higher in the isolated single umbilical artery group even after adjusted for maternal smoking status (p<0.001). The incidence of hypertensive disorders was also higher in cases with two-vessel umbilical cords (p=0.022). No significant differences were observed between the study and control groups in terms of pregnancies

Table 3. Comparison of pregnancy outcomes in control and isolated single umbilical artery groups

	Isolated single umbilical artery group (n=93)	Control group (n=100)	p value
Mean birth weight (kg)[a,b]	2981.2±679.5	3195.7±2592.2	0.591
Cesarean section (n)	51 (56.9%)	46 (46%)	0.241
Cesarean section because of non-reassuring fetal heart trace (n)	20 (21.5%)	15 (15%)	0.499
Small for gestational age (n)[a]	24 (25.8%)	4 (4%)	<0.001
Hypertensive disorder in pregnancy (n)[a]	9 (9%)	2 (2%)	0.022
Oligohydramnon (n)	4 (4.3%)	3 (3%)	0.713
Preterm premature rupture of membranes (n)	3 (3.2%)	2 (2%)	0.673
Preterm delivery (n)[a]	15 (16.1%)	13 (13%)	0.537
Mean APGAR score at 1st minute	8.1±1.2	8.9±1.9	0.812
Mean APGAR score at 1st minute	9.2±1.1	9.8±1.0	0.523

Values are compared by Mann-Whitney U test. Categorical variables are expressed as numbers and percentages. Continuous variables are presented as means±standard deviations. P<0.05 is considered statistically significant
[a]Adjusted for maternal smoking status. [b]Adjusted for gestational age at birth

Table 4. Logistic regression analysis of pregnancy outcomes that are independently associated with isolated single umbilical artery

	Odds ratio	95% CI	p value
SGA	8.43	2.783-25.583	<0.001
Hypertensive disorder	5.250	1.104-24.975	0.018
Preterm delivery	1.287	0.576-2.873	0.538
PPROM	1.633	0.267-10.000	0.592

SGA: Small for gestational age; PPROM: preterm premature rupture of membranes

complicated by oligohydramnios, preterm premature rupture of membranes, and preterm deliveries (Table 3). The mean APGAR scores of infants at the 1st and 5th minutes were found to be similar between the groups.

Logistic regression analysis demonstrated that the cases with an isolated single umbilical artery are more likely to be complicated by hypertensive disorders in pregnancy (OR 5.25; 95% CI 1.104-24.975) and SGA infants (OR 8.43; 95% CI 2.783-25.583). However, the increase in risks of preterm delivery (OR 1.287; 95% CI 0.576-2.873; p=0.538) and preterm premature rupture of membranes (OR 1.633 95% CI 0.267-10,000; p=0.592) were unlikely to be increased in cases with a single umbilical artery (Table 4).

Discussion

A single umbilical artery is found to be associated with genitourinary, cardiovascular and musculoskeletal system anomalies in 25% of cases, and these cases are accepted to carry a higher risk of chromosomal abnormalities (14, 15). The most commonly suggested theories on the development of a single umbilical artery are primary agenesis or secondary thrombotic atrophy of one of the umbilical arteries (16). A single umbilical artery could be associated with some adverse perinatal outcomes such as growth restriction or higher fetal distress rates during the course of labor when it was described as an isolated finding. However, most studies were conducted in Western countries, and ethnic divergences may have a considerable impact on this issue. In this study, we endeavored to define the characteristics of isolated single umbilical artery cases in a Turkish population.

The results of this study indicated that fetuses with a single umbilical artery were more likely to be SGA infants. Although most of the studies indicate an association between SGA infants and an isolated single umbilical artery, this issue is not totally clarified yet (1, 4, 8, 17). A meta-analysis conducted by Voskamp et al. (17) demonstrated that larger studies on single umbilical arteries exhibited a weaker association between single umbilical artery and birth weight. Therefore, the authors indicated an evident relationship between birth weight and single umbilicalartery in smaller sample-sized studies could be the results of publication biases. Our study indicates an evident association between SGA infants and single umbilical artery after adjusting for maternal smoking status. However, the mean birth weight of the single umbilical artery and control groups was not significantly different. It could be suggested that an isolated single umbilical artery leads to SGA in some infants and has no effect on the others. Bugatto et al. (18) demonstrated a correlation between uterine artery Doppler measurements and birth weights of fetuses with an isolated single umbilical artery and suggested that growth restriction in fetuses with an isolated single umbilical artery is a consequence of disorders in maternal-placental circulation rather than placental insufficiency.

Although we lack the data on uterine artery Doppler parameters, umbilical artery Doppler parameters were all within normal limits in all cases near term in this study. Thus, placental insufficiency is unlikely to be a cause of SGA in effected fetuses. SGA could be a result of the co-existence of other factor(s) that were not contributed in this study. Demonstrating these possible factors could explain the reason why an isolated single umbilical artery leads to SGA in some infants despite not having any effect on birth weight in others.

Maternal smoking is found to be independently associated with the development of a single umbilical artery (2), whereas assisted reproduction, maternal BMI, and maternal age demon-

strated have been demonstrated to not have any effect on the development of an isolated single umbilical artery.

Cesarean rates because of non-reassuring fetal heart trace is higher in cases with an isolated single umbilical artery in a majority of previous studies (4, 7), whereas other studies have failed to demonstrate any difference (19).

Our study demonstrated similar cesarean rates because of non-reassuring fetal heart trace. Different results in literature could be a consequence of subjectivities and inter-physician differences in the interpretation of non-reassuring fetal heart trace as well as personal differences in the threshold of cesarean decision. Future studies may include more objective criteria about this aspect to cope with the query of subjectivity.

The relation between preterm birth and an isolated single umbilical artery is also a controversial issue. Some studies have shown a higher risk of preterm birth in cases with isolated single umbilical arteries (2, 4) suggesting serial cervical length assessment in these cases (20) and others have demonstrated no association (7). The study conducted by Doğan et al. (8) demonstrated similar gestational ages at birth in isolated single umbilical artery and control cases. In our study, there was no association found between the increased risk of preterm delivery and isolated single umbilical artery after adjustment for maternal smoking status. Therefore, for the Turkish population, we do not suggest a strict monitoring of patients with an isolated single umbilical artery in terms of preterm birth unless there are no other existing risk factors.

Unlike previous reports, the results of this study also showed that cases with an isolated single umbilical artery are more likely to be complicated by hypertensive disorders in pregnancy.

In conclusion, one should be cautious about the development of hypertensive disorders and growth restriction in cases with a diagnosis of an isolated single umbilical artery. Parents should be counseled properly. A strict monitoring of pregnancies complicated with an isolated single umbilical artery for preterm birth seems unfeasible. However, prospective studies with larger sample sizes could be beneficial in the further clarification of these aspects.

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Gestational diabetes mellitus screening and outcomes

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Abstract

Objective: To verify the usefulness of the World Health Organization criteria for the diagnosis of gestational diabetes mellitus in pregnant women and its effectiveness in the prevention of maternal and neonatal adverse results in women younger than 35 years without apparent risk factors for gestational diabetes mellitus.

Material and Methods: This is a retrospective study based on population involving 1360 pregnant women who delivered and who were followed-up in a university hospital in Istanbul. All women underwent the 75-g oral glucose tolerance test screening, usually in between the 24th-28th weeks of pregnancy. In all cases, the identification of gestational diabetes mellitus was determined in accordance with the World Health Organization criteria.

Results: Approximately 28% of the pregnant women aged younger than 35 years with no risk factors for gestational diabetes mellitus were diagnosed with the oral glucose tolerance test in this study. In the gestational diabetes mellitus group, the primary cesarean section rate was importantly higher than that in the non-gestational diabetes mellitus group. Preterm delivery was also associated with gestational diabetes mellitus. The diagnosis of gestational diabetes mellitus was strongly associated with admittance to the neonatal intensive care unit. Neonatal respiratory problems didn't showed any significant deviation between the groups. There was a moderate association between gestational diabetes mellitus and metabolic complications.

Conclusion: Pregnant women with no obvious risk factors were diagnosed with gestational diabetes mellitus using the World Health Organization criteria. The treatment of these women potentially reduced their risk of adverse maternal and neonatal hyperglycemia-related events, such as cesarean section, polyhydramnios, preterm delivery, admission to neonatal intensive care unit, large for gestational age, and higher neonatal weight. (J Turk Ger Gynecol Assoc 2015; 16: 25-9)

Keywords: Gestation, diabetes mellitus, pregnancy, oral glucose tolerance test, neonatal outcomes

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Introduction

Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance with onset or first recognition during pregnancy (1). GDM is currently the most frequently diagnosed metabolic disorder in pregnant women (2), and its incidence is growing (3).

GDM is associated with several adverse pregnancy outcomes with macrosomia, shoulder dystocia, and neonatal hypoglycemia being the most common serious complications.

Currently, there is no consensus on the screening criteria for GDM, and no specific universally accepted protocol exists with respect to the selective or global screening of pregnant women. Consequently, it is difficult to compare the prevalence of GDM among various populations. In particular, ethnicity has been proven to be an independent risk factor for GDM (4, 5). The goals of this study were to verify the usefulness of the World Health Organization (WHO) criteria for the diagnosis of GDM in a fragment of local population and the effectiveness of these criteria in preventing maternal and neonatal adverse outcomes in women younger than 35 years old without obvious risk factors for GDM.

Material and Methods

This was a retrospective population-based study involving 1360 pregnant women who delivered and who were observed in a university hospital in Istanbul from September 2012 to October 2013. Ethics Committee approval and informed consent has been taken.

All the subjects were younger than 35 years and had no known risk factors for GDM. Women having chronic systemic illnesses, preexisting diabetes (type 1 or type 2), or multifetal gestations were excluded. All the women underwent oral glucose tolerance test (OGTT) screening between 24 and 28 weeks of pregnancy, and ultrasound examination was made to determine gestational age. In all cases, GDM was diagnosed according to the WHO criteria (4, 5). After a minimum of 8 h of overnight fasting, blood for glucose level determination was collected, after which the patient received 75 g glucose orally. An additional blood sample was collected for glucose level determination 2 h later. The WHO criteria define GDM as a fasting blood glucose >126 mg/dL, with a 2 h post dosing value >140 mg/dL. In case of GDM diagnosis, the patients underwent individualized diet and/or insulin

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Table 1. Anthropometric, clinical, and biochemical features of all pregnant women in the study

	GDM (n=380)	No GDM (n=980)	p value
Age (year)	29.3±3.4	30.8±3.2	<0.001
BMI (kg/m^2)	22.9±1.9	21.4±1.9	<0.001
Gravida, n	2.5±0.7	2.5±0.6	0.934
Week at OGTT	27.1±1.2	27.1±0.8	0.230
Fasting glucose (mg/dL)	91.4±8.97	79.4±5.7	<0.001
2-h postprandial glucose (mg/dL)	140.5±21.8	111.6±18.9	<0.001
Weight gain at OGTT (kg)	9.8±3.4	7.0±2.7	<0.001
Weight gain at delivery (kg)	14.3±3.3	12.0±2.7	<0.001

Values are mean±SD.
GDM: gestational diabetes mellitus; BMI: body mass index; OGTT: oral glucose tolerance test

treatment with self-observing of blood glucose levels (fasting and 1 h after each meal) daily with a glucometer. Subsequent follow-ups were conducted for all patients biweekly or more frequently as indicated. Treatment outcomes were evaluated according to the American Diabetes Association recommendations (6).

All demographic characteristics (age, parity, family history of diabetes, and self-reported prepregnancy weight) of the patients were obtained from their existing records. Birth mode (cesarean or vaginal delivery) and labor induction, preterm delivery (delivery before 37 weeks of gestation), gestational hypertension, preeclampsia, polyhydramnios, and oligohydramnios were also documented from these records.

The recorded adverse fetal outcomes were infant death, stillbirth, dystocia, bone fracture, nerve palsy, admission to the neonatal intensive care unit (NICU), respiratory complications [including respiratory distress syndrome (RDS) and transient tachypnea of newborn (TTN)] that increased birth weight, macrosomy (birth weight of >4000 g), large for gestational age (LGA, defined as birth weight> the 90th percentile on standard charts), small for gestational age (SGA, defined as birth weight < the 10th percentile on standard charts), and metabolic complications including hypocalcemia, hemoglobin level ≥20 g/dL, hypoglycemia (blood glucose level ≤35 mg/dL), and hyperbilirubinemia requiring phototherapy.

Results

The present study included 1360 pregnant women who underwent screening for GDM. Out of the 1360 women screened between September 2012 and October 2013, 380 (28%) women were diagnosed with GDM, whereas the remaining 980 (72%) had no GDM. Anthropometric, clinical, and biochemical features of all pregnant women having no GDM risk factors are shown in Table 1.

Maternal age, body mass index (BMI), and weight gain at the time of 75-g OGTT and at delivery were remarkably different between the groups. Glycemic levels in both fasting samples and following the glucose load were also remarkably higher in the GDM group. Out of the 380 women with GDM, 102 (27%) received insulin, whereas the remaining 278 (73%) were treated with dietary modifications. The only adverse event in 18 of the 380 women was polyhydramnios.

Logistic regression analysis was performed to test whether the diagnosis of GDM in women younger than 35 years without risk factors influenced maternal and neonatal adverse events despite achieving adequate glycemic control. GDM was the dependent variable in this analysis. Maternal outcomes in women included in the study are shown in Table 2a.

In the GDM group, the rate of primary cesarean section (CS) was significantly higher than that in the non-GDM group [29.6% vs 15.3%; odds ratio (OR)=2.35, 95% confidence interval (CI) 1.53-3.64; p<0.001]; furthermore, the difference remained significant after correcting for age, prepregnancy BMI, and parity (Table 2a). The rate of CS after vaginal labor induction was alike in both groups. Secondary CS in women who had previously delivered via CS was strongly associated with GDM [adjusted odds ratio (AOR)=5.05, 95% CI 2.11-12.08, p<0.001]. In unadjusted analyses, the combination of gestational hypertension and preeclampsia was associated with GDM (OR=2.44, 95% CI 1.05-5.65, p=0.037), as was preterm delivery (OR=2.43, 95% CI 1.11-5.29, p=0.025); however, these associations were insignificant subsequent to adjusting for age, prepregnancy BMI, and parity (for the combination of gestational hypertension and preeclampsia AOR=2.03, 95% CI 0.83-4.97, p=0.120, for preterm delivery AOR=1.65, 95% CI 0.32-8.51, p=0.549). The diagnosis of GDM was associated with polyhydramnios even after correcting for age, prepregnancy BMI, and parity (AOR=4.48, 95% CI 1.20-16.73, p=0.025). No association was observed between fetal distress and oligohydramnios (Table 2a). Fetal/neonatal outcomes in the women included in the study are shown in Table 2b.

No stillbirth, neonatal deaths, or nerve palsy occurred among the infants in either group. The newborns of women with GDM showed a significantly higher weight (p<0.001) after correcting for maternal age, prepregnancy BMI, and gestational age at birth. Additionally, the diagnosis of GDM was strongly associated with admission to NICU following adjustment for age, BMI, parity, and neonatal weight (AOR=4.39, 95% CI 1.44-13.37, p=0.009). Nevertheless, no significant association was observed between the groups regarding other important perinatal outcomes such as shoulder dystocia and bone fracture (AOR=1.47, 95% CI 0.81-

Table 2a. Maternal outcomes in women with and without GDM

Outcome	GDM (n=380)	No GDM (n=980)	OR (95% CI)	p value	OR (95% CI)[a]	p value[a]	Power (%)
Primary cesarean section, n (%)	112 (30)	147 (15)	2.4 (1.5-3.6)	<0.001	1.9 (1.2-3.1)	0.006	>95
Secondary cesarean section, n (%)	42 (11)	37 (4)	3.9 (1.8-8.8)	0.001	5.1 (2.1-12.1)	<0.001	85.2
Cesarean section after labor, n (%)	7 (2)	27 (3)	0.6 (0.2-2.4)	0.498	0.6 (0.1-2.2)	0.401	9.7
Labor induction, n (%)	5 (1)	4 (1)	4.3 (0.4-48.1)	0.233	3.8 (0.3-53.3)	0.314	13.5
Gestational hypertension, n (%)	15 (4)	15 (2)	2.6 (0.9-7.8)	0.095	1.7 (0.7-7.2)	0.173	33.4
Preeclampsia, n (%)	10 (3)	12 (1)	2.2 (0.6-77.6)	0.223	1.7 (0.4-6.7)	0.443	18.1
Fetal distress, n (%)	11(3)	26 (3)	1.1 (0.4-3.2)	0.896	0.9 (0.3-3.0)	0.879	8
Polyhydramnios, n (%)	18 (5)	11 (1)	4.5 (1.3-14.1)	0.016	4.5 (1.2-16.7)	0.025	58.7
Oligohydramnios, n (%)	9 (2)	7 (1)	2.9 (0.6-13.1)	0.166	1.7 (0.3-8.5)	0.549	28.5
Preterm delivery, n (%)	31 (8)	33 (3)	2.4 (1.1-5.3)	0.025	1.9 (0.8-4.5)	0.116	52.3
Breech presentation, n (%)	39 (10)	81 (8)	1.2 (0.7-2.3)	0.502	1.2 (0.7-2.2)	0.563	9.9

[a]Values were adjusted for maternal age, prepregnancy BMI and parity.

Power was calculated post hoc with G*Power 3.1, entering R-squared multiple correlation coefficient obtained with regression for each trait.

OR: odds ratio; CI: confidence interval; GDM: gestational diabetes mellitus

Table 2b. Fetal/neonatal outcomes in women with and without GDM

Outcome	GDM (n=380)	No GDM (n=980)	OR (95% CI)	p value	OR (95% CI)[a]	p value[a]	Power (%)
Birth weight (kg)	3.2±0.4	3.09±0.3	-	0.002[a]	-	<0.001[b]	>95
Serious perinatal complications, n (%)	44 (12)	84 (9)	1.5 (0.8-2.6)	0.199	1.2 (0.7-2.3)[c]	0.497[c]	17.2
Dystocia, n (%)	0 (0.0)	0 (0.0)	-	-	-	-	-
Bone fracture, n (%)	4 (1.1)	0 (0.0)	-	-	-	-	-
Admission to NICU, n (%)	24 (6)	14 (2)	4.1 (1.5-11.4)	0.006	4.4 (1.4-13.4)[d]	0.009[d]	68.5
RDS, n (%)	6 (2)	4 (1)	3.3 (0.5-19.7)	0.197	2.7 (0.4-17.4)[e]	0.306[e]	26.3
TTN, n (%)	9 (3)	8 (1)	2.9 (0.7-13.1)	0.167	1.9 (0.3-10.7)[e]	0.472[e]	27.8
Macrosomia (≥4 kg), n (%)	5 (1)	16 (2)	1.5 (0.2-8.7)	0.694	0.5(0.9-2.7)[c]	0.482[c]	28.7
LGA, n (%)	33 (9)	18 (2)	4.9 (1.9-12.4)	<0.001	3.5 (1.3-9.3)[c]	0.011[c]	85.6
SGA, n (%)	10 (3)	14 (2)	1.8 (0.5-6.0)	0.331	1.9 (0.5-7.4)[c]	0.311[c]	16.5
Metabolic complications, n (%)	20 (5)	18 (2)	2.9 (1.0-7.8)	0.040	2.3 (0.8-7.1)[c]	0.137[c]	46.6
Hypoglycaemia, n (%)	3 (1)	0 (0.0)	-	-	-	-	-
Hyperbilirubinemia, n (%)	8 (2)	6 (1)	2.9 (0.6-13.1)	0.164	1.2 (0.2-5.8)[c]	0.824[c]	27.5
Hypocalcemia, n (%)	5 (1)	5 (1)	2.2 (0.3-15.5)	0.443	5.3 (0.7-41.4)[c]	0.113[c]	15.4
Polycythemia, n (%)	4 (1)	5 (1)	2.2 (0.3-15.5)	0.443	2.2 (0.3-18.7)[c]	0.474[c]	15.4

[a]Calculated by Mann-Whitney U test.
[b]Calculated by linear regression analysis after adjustment for maternal age, prepregnancy BMI, and gestational age at birth.
[c]Values were obtained by logistic regression analysis after adjustment for maternal age, prepregnancy BMI, parity, and gestational age at birth.
[d]Values were obtained by logistic regression analysis after adjustment for maternal age, prepregnancy BMI, parity, and neonatal weight.
[e]Values were obtained with logistic regression after adjustment for maternal age, prepregnancy BMI, parity, and delivery mode.
NICU: neonatal intensive care unit; RDS: respiratory distress syndrome; TTN: transient tachypnea of newborn; LGA: large for gestational age; SGA: small for gestational age
Power was calculated post hoc with G*Power 3.1, entering R-squared multiple correlation coefficient obtained with regression for each trait
OR: Odd ratio; GDM: Gestational diabetes mellitus

2.63, p=0.202). There was no remarkable difference between the groups regarding SGA or macrosomia, yet significantly more infants in the GDM group were LGA (AOR=3.53, 95% CI 1.34-9.34, p=0.011). Neonatal respiratory problems at delivery, including RDS and TTN, were not significantly different between the two groups. GDM appeared to be associated with

metabolic complications (OR=2.86, 95% CI 1.05-7.80, p=0.040), although this association was not observed after correcting for age, BMI, parity, and gestational age at birth. All significant associations were independent of BMI; however, prepregnancy BMI was correlated with primary CS (r=0.103, p=0.017), neonatal weight (r=0.122, p=0.005), and LGA (r=0.113, p=0.009) independently from GDM via Pearson's test.

Discussion

GDM is a type of diabetes and is the most common metabolic disorder seen during gestation occurring in 1%-14% of pregnancies (1). The prevalence of GDM continues to increase globally (7). GDM may cause serious morbidities both for mother and infant (8). Women with GDM have been reported to have increased rates of stillbirth, polyhydramnios, gestational hypertension, macrosomia, and cesarean delivery (9). GDM usually resolves after delivery, but it appears that the risk of recurring GDM and type 2 diabetes mellitus are increased in subsequent pregnancies, along with cardiovascular risk later in life (10, 11). Although the precise role of the risk factors related to GDM (multiparity, obesity,) has not yet been entirely defined, they may be included in the classification of pregnancy-related or maternal factors (12). Early diagnosis of metabolic disorder is highly critical for the prevention of fetal and maternal complications (5, 13).

Since the adoption of the 2 h 75-g OGTT in pregnancy, the WHO recommended the same diagnostic limit values accepted for the identification of impaired glucose tolerance in non-pregnant women (14, 15). The WHO stated in 1999 that GDM encompasses both impaired glucose tolerance and diabetes (fasting plasma glucose ≥7 mmol/dL or ≥126 mg/dL; 2 h plasma glucose ≥7.8 mmol/dL or 140 mg/dL, respectively) (16) and has maintained their recommendations to date.

With early diagnosis and good medical and obstetric care, the risks of higher perinatal mortality and infant morbidity rates associated with GDM should be minimized (17, 18). In patients with persistent maternal hyperglycemia, the use of additional oral medications, insulin treatment, and lifestyle changes has shown improved perinatal outcomes. Medical nutrition counseling and diet therapy to achieve an overall healthy lifestyle are valuable in the management of GDM (19-21) and can optimize maternal and fetal outcomes (22, 23).

In this study, our aims were to verify the effectiveness of the WHO GDM diagnostic criteria in preventing adverse maternal and neonatal outcomes in women younger than 35 years with no apparent risk factors for GDM and to verify the effectiveness of dietary modifications in those outcomes. With no prior knowledge of any risk factors, 1360 pregnant women underwent OGTT at the 24th-28th gestational weeks. Approximately 28% of them were diagnosed with GDM and subsequently treated, thus reducing the risk of adverse maternal and neonatal hyperglycemia-related events, including high rates of primary CS, polyhydramnios, preterm delivery, admission to NICU, LGA, and higher neonatal weight.

The rate of adverse events in this group was similar to all the other women with GDM. Similar findings have been recently reported (24, 25).

While women with GDM were significantly older and had a significantly higher BMI compared with their non-GDM counterparts, all observed associations remained significant after correcting for age and prepregnancy BMI, indicating that GDM was an independent risk factor. Our findings confirm and extend previous observations that GDM and increased BMI are independently associated with adverse maternal and neonatal outcomes, with their combination having a greater impact. Some adverse pregnancy outcomes in our study were correlated with prepregnancy BMI even within the normal range (<25 kg/m^2) and independently from GDM. Our results show that most cases of GDM were diagnosed at baseline and at 2 h of the OGTT timeframe.

The interpretation of the results of this study is limited by the small sample size. Higher rates of preterm delivery observed among the GDM cases together with the increase in both CS and NICU admission rates may be considered to be the result of excessive medical interventions. However, the higher rate of polyhydramnios and LGA in women with GDM accounted for the higher number of CS in this group, whereas overtreatment would not help explain the neonatal primary outcomes, such as LGA, and higher neonatal weight. All outcomes in our GDM group are remarkably lower with respect to those observed in other studies of GDM in the general population (25).

There are only a few studies on GDM prevalence reported from Turkey. In the study by Akbay et al. (26), a prevalence of 8.9% was reported, whereas Köşüş et al. (27) reported a prevalence of 8.6%. In both these studies, GDM was diagnosed after a 50-g glucose screening test followed by a 100-g glucose OGTT in two steps. While only a few studies using the 75-g OGTT according to the WHO criteria have been reported in literature, this method has the advantage of being both a screening and diagnostic test and being performed in a single step. Additional, larger studies are needed to confirm our findings.

Ethics Committee Approval: *Ethics committee approval was received for this study from the ethics committee of İstanbul Medipol University.*

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

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Author contributions: *Concept - L.H.A.; Design - L.H.A.; Supervision - L.H.A.; Resource - L.H.A., B.Y.; Materials - L.H.A., B.Y., M.A., D.U.; Data Collection&/or Processing - L.H.A., B.Y.; Analysis&/or Interpretation - L.H.A., B.Y.; Literature Search - L.H.A., B.Y., M.A.; Writing - L.H.A.; Critical Reviews - D.U., B.Y.*

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Single-incision-two port laparoscopic tubal ligation: A cost comparison and technique description

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Abstract

Objective: Laparoscopic surgery is the principal minimally invasive technique that is used for the treatment of gynecologic pathologies. The single-incision laparoscopic surgery (SILS) is another innovation in minimally invasive medicine. The cost of the procedure correlates with the fundamental materials used to access the abdominal cavity and utilize trocars.

Material and Methods: We applied the single-incision tubal ligation procedure to three patients. A 15-20-mm vertical incision was made in the umbilicus. Two trocars were inserted through the same incision at different fascial regions after insufflation of the abdomen. A 5-mm bipolar cautery was introduced through the accessory trocar, and the mid-portion of the tubes was coagulated and cut bilaterally.

Results: The postoperative periods of the three patients were uneventful. All patients were discharged on the day of surgery. No major or minor complications occurred.

Conclusion: The cost for the abdominal access will drop about 82%. When we consider the low pricing for the tubal ligation procedure, the single-incision technique will be more applicable by this method. Moreover, patients will have the advantages of single-incision laparoscopic surgery with low cost. (J Turk Ger Gynecol Assoc 2015; 16: 30-1)

Keywords: Cost, laparoscopy, single incision

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Introduction

The trend in gynecologic surgery is to be minimally invasive. Laparoscopic surgery is the principal minimally invasive technique that is used for the treatment of gynecologic pathologies. The benefits of laparoscopic surgery are less postoperative pain morbidity, shorter hospitalization duration, and shorter recovery time. The single-incision laparoscopic surgery (SILS) is another innovation in minimally invasive medicine. It was first described in 1976 by Wheeless (1) for the tubal ligation procedure and evolved with improvements in technology.

There are several techniques for female sterilization. Surgical sterilization is an effective, permanent, and safe one. Surgical sterilization could be carried out by laparoscopy, mini-laparotomy, or hysteroscopy. Laparoscopy is a widely used technique with a shorter recovery period and ease of application. Various devices are available for the execution of SILS on the market. The cost of the procedure correlates with the fundamental materials used to access the abdominal cavity and utilize trocars.

We wanted to describe an easy-to-apply and low-budget technique to execute relatively simple procedures, like tubal ligation.

Material and Methods

Three patients with the desire of permanent sterilization applied to the gynecology clinic in Namik Kemal University School of Medicine. The informed consents were obtained prior to procedures.

We applied a similar technique that was described by Podolsky et al. (2) for cholecystectomy. A single 15-20-mm vertical incision was made in the umbilicus. The Veres needle was used to maintain pneumoperitoneum at 15 mm Hg pressure. After insufflation, a 5-mm trocar was introduced into the abdomen. A 5-mm, 30-degree scope was used to confirm intraperitoneal entrance. Afterwards, another 5-mm trocar was introduced under direct observation. In other words, two trocars were inserted through the same incision at different fascial regions (Figure 1). We used a rubin cannula to elevate the uterus after maintenance of the Trendelenburg position. Then, a 5-mm bipolar cautery was introduced through the accessory trocar, and the mid-portion of the tubes was coagulated and cut bilaterally. After removal of the trocars, fascial apertures were sutured with 0 Vicryl (Ethicon, Istanbul, Turkey) suture. The skin was closed with separated 3-0 Rapid Vicyl (Ethicon, Istanbul, Turkey) sutures.

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Figure 1. The view of the umbilical 5-mm trocars after insufflation of the abdomen

Results

The postoperative periods of the three patients were uneventful (Figure 2). All patients were discharged on the day of surgery. No major or minor complications occurred. The cost of abdominal access with the SILS Port (Covidien, Istanbul, Turkey) is 1058 Turkish liras (365 euros). However, the cost of the abdominal access was 192 Turkish liras (66 euros) with the technique described.

Discussion

The options for tubal ligation are mini-laparotomy, conventional laparoscopy, and single-incision laparoscopy. The laparoscopic technique is the least invasive procedure for tubal ligation. When we compared laparotomy and laparoscopy, the laparoscopy technique has advantages, such as quick convalescence, better cosmetic results, and less pain after surgery. Thus, it is the technique of choice where available. However, laparotomy is carried out under local anesthesia with mild sedation, whereas laparoscopy mostly requires general anesthesia. Usually, two or three incisions are made for the laparoscopic procedure. On the other hand, single-port access has advantages, such as better cosmetic results, less pain, reduced complications related to trocar entry, and easier closure of the fascia with a larger incision (3). Single-port laparoscopy requires instruments that are used to maintain abdominal access. The cost of the instruments is the major limitation of single-incision laparoscopy. We use the SILS Port (Covidien, Istanbul, Turkey) for single-port laparoscopic surgery. The cost of the SILS Port was 1058 Turkish liras (365 euros). However, if we use two separate 5-mm trocars

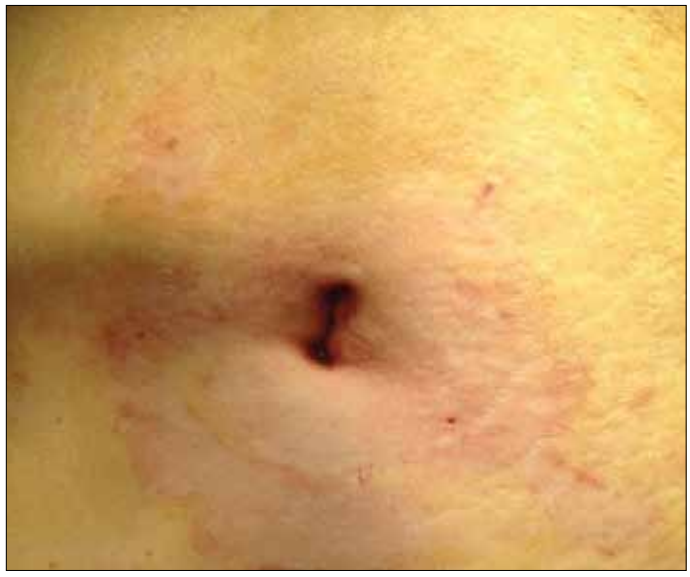

Figure 2. Early postoperative appearance of 20-mm intraumbilical incision after closure

instead of the SILS Port, as described by Podolsky et al. (2), the cost will be 192 Turkish liras (66 euros). The cost for abdominal access will drop about 82%.
Podolsky et al. (2) reported a learning curve, including 5 cases, for the three-port cholecystectomy procedure with the technique. We believe that it is not needed for the tubal ligation procedure, and a laparoscopic surgeon who is familiar with basic laparoscopy and single-port laparoscopy techniques can easily apply the technique.
The cost and effectiveness of a medical application are some of the most important aspects, and they determine the applicability of a technique. When we consider the low pricing for the tubal ligation procedure, the single-incision technique will be more applicable by this method. Moreover, patients will have the advantages of single-incision laparoscopic surgery with low cost.

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

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Juvenile granulosa cell ovarian tumor: clinicopathological evaluation of ten patients

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Abstract

Objective: We aimed to analyze the clinical characteristics and management of ten patients who were diagnosed with juvenile granulosa cell ovarian tumor (JGCOT).

Material and Methods: The records of 10 patients diagnosed with JGCOT between April 1995 and January 2014 in the Gynecological Oncology Clinic of our institution were retrospectively evaluated.

Results: The median age of the patients was 21.5 years (range; 13-36). Nine patients had stage IA disease and one had stage IC disease according to the International Federation of Gynecology and Obstetrics (FIGO) criteria. Five patients underwent pelvic and para-aortic lymph node dissection. None of them had lymph node involvement. All but two patients underwent unilateral salpingo-oophorectomy. One of the other two patients had cystectomy and the other had total abdominal hysterectomy and bilateral salpingo-oophorectomy. Three patients had adjuvant therapy after surgery. Two of these patients took chemotherapy and the other took radiotherapy. Four of the five patients who desired pregnancy achieved five term pregnancies. The median follow-up time of the patients was 58 months (range; 3-113). No recurrence was observed in the follow up period.

Conclusion: JGCOT generally occurs during childhood. The primary management of JGCOT is through surgery. The role of adjuvant therapy is controversial. Because survival is long at early stages and most of the patients are young, fertility sparing surgery could be safely suggested to these patients. (J Turk Ger Gynecol Assoc 2015; 16: 32-4)

Keywords: Juvenile granulosa cell tumor, ovary, adjuvant therapy, fertility sparing surgery

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Introduction

Ovarian granulosa cell tumors are classified into two groups based on their clinico-pathological characteristics; juvenile and adult type. Juvenile granulosa cell ovarian tumor (JGCOT) was first described by Scully in 1977 (1). JGCOT comprises 5% of all granulosa cell neoplasms. Generally, it occurs in premenarchal girls or young women (2, 3). However, it is seen in a wide age range, in a 10 month old baby as well as in a 67 year old woman (3, 4). In contrast to adult granulosa cell tumor, JGCOT has a high mitotic index and more aggressive tumor growth via via this character (5). Microscopically it is seen as diffuse and regularly distributed neoplastic cells with a wide cytoplasm and pleomorphic hyperchromatic nucleus. Follicle formation, in various sizes and shapes, is important in JGCOT. Call-Exner bodies are infrequently seen in JGCOT in contrast to the adult type (3).

The most common finding on physical examination is a palpable mass (4). Generally, the prognosis is good. Surgical stage is the most important prognostic factor and the prognosis is much more aggressive in the advanced stage than in the adult type (5, 6). Although a standard adjuvant therapy for the advanced stage or recurrent disease is not well established because of the rarity of JGCOT, adjuvant chemotherapy is recommended in the advanced stage.

Material and Methods

The cases of ovarian granulosa cell tumors that were diagnosed between April 1995 and January 2014 in gynecologic oncology department were retrospectively reviewed. Among these patients, those with JGCOT were selected. Clinicopathological characteristics including age, symptoms, primary tumor location, stage, surgery and adjuvant therapy were collected from an electronic database and medical records. The pathological evaluation was made in our pathology department. The International Federation of Gynecology and Obstetrics (FIGO) 1988 classification was used for staging.

Results

During the study period, 143 patients were diagnosed with a granulosa cell tumor, and 10 (7%) of them with JGCOT. The

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Table 1. Characteristics of the patients

Patient no:	Age	Stage	Ascites (cc)	Tumor diameter (mm)	Surgery	Adjuvant therapy	Live birth after treatment	Follow-up (month)
1	26	1A	-	110	Cystectomy	-		23
2	36	1A	-	110	TAH+BSO+BPPLND+Om	-		76
3	22	1A	100	250	USO+BPPLND+Om	-		3
4	18	1A	5000	400	USO	-	1	113
5	25	1A	-	130	USO+BPPLND+Om	-	2	29
6	20	1A	50	180	USO+BPPLND+Om+App	-		63
7	17	1A	-	150	USO+Om	6×VAC		3
8	21	1C	-	120	USO+BPPLND+Om	4×BEP	1	67
9	13	1A	200	250	USO+Om+App	RT		53
10	24	1A	-	60	USO	-	1	79

TAH: total abdominal hysterectomy; BSO: bilateral salpingo-oophorectomy; USO: unilateral salpingo-oophorectomy; BPPLND: bilateral pelvic para-aortic lymph node dissection; Om: omentectomy; App: appendectomy; RT: radiotherapy; BEP: bleomycin, etoposide, cisplatin; VAC: vincristine, adriamycin, cyclophosphamide

median age of the patients was 21.5 years (range; 13–36). The presenting symptom was bloating in five patients, abdominal pain in four, and menometrorrhagia in one. CA-125 was found in five patients and its level was normal in four of them (<35 U/mL). In a patient whose CA-125 level was 74 U/mL, cyst rupture was noted. Nine of the patients had stage IA, and one had stage IC disease. The median tumor diameter was 140 mm (range; 60-400). The tumor was resected completely in all patients. The tumor was on the right side in five patients and on the left side in the other five. Ascites was found in four patients. In patients who had stage IC disease, the cyst had ruptured preoperatively, and cytology was negative. Five of the patients underwent pelvic and para-aortic lymph node dissection. The median removed lymph node count was 54 in patients who had lymphadenectomy (range; 7-94). None of the patients had lymph node involvement. One patient was treated with total abdominal hysterectomy and bilateral salpingo-oophorectomy in another center (patient no #2). The pathology slides of this patient were re-reviewed in our pathology department, and surgical staging was performed after the diagnosis was confirmed. One patient underwent cystectomy, and eight had unilateral salpingo-oophorectomy. Infracolic omentectomy was performed in six patients, partial omentectomy in one, and appendectomy in two. No tumor was found in the omentum in these patients. Frozen/section result was available in five patients. It was diagnostic for JGCOT in two of them. Sex-cord stromal tumor was diagnosed, but the histological subtype could not be specified in two of them and lymphoma was suspected in one. Three patients underwent adjuvant therapy, two had chemotherapy, and one had radiotherapy. The chemotherapy regimen was bleomycin, etoposide, cisplatin (BEP) for four cycles in one patient and vincristine, adriamycin, cyclophosphamide (VAC) for six cycles in another.

The median follow-up duration was 58 months (range; 3-113). Recurrence did not occur in any patient. Five pregnancies occurred in 4 of the 5 patients who desired childbearing, and all these pregnancies resulted in term birth. Only one patient could not achieve pregnancy despite desiring pregnancy. This patient had stage IA disease. One of the patients who achieved pregnancy and gave birth had stage IC disease and was treated with BEP chemotherapy for four cycles (patient no : 8) (Table 1).

Discussion

JGCOT is an ovarian tumor that occurs in premenarchal girls and young women, and the mean age at diagnosis is 13 years (4). Generally, case series in literature were reported from pediatrics. In our present study, which was presented from a gynecologic oncology clinic, the mean age was 22 years. Because it is frequently seen in premenarchal girls, puberty praecox, clitoral hypertrophy, and hair in pubic and axillary areas are frequent symptoms. The most common symptoms are abdominal pain and distension (4, 5). In our study, the main symptoms were bloating and abdominal pain.

Generally, JGCOT is diagnosed in stage IA as in our study. Its management depends on the age of the patient and dissemination of the disease. However, there is no standard protocol for adjuvant chemotherapy because of the rarity of the disease. Surgery is the primary standard initial treatment. A worse prognosis and early recurrence should be expected in the case of an advanced disease (5). Unilateral salpingo-oophorectomy is the treatment for children and women in the reproductive age with stage IA disease (7). Although there are no prospective, controlled, and randomized studies, fertility sparing surgery is recommended because the disease is commonly unilateral. In addition, wedge biopsy from the contralateral ovary and chemotherapy are not recommended (8). Because lymph node metastasis is rarely observed in patients with sex-cord stromal tumor, pelvic and para-aortic lymphadenectomy may not be included in the staging surgery of these patients. Five patients underwent pelvic and para-aortic lymph node dissection. None of the patients had lymph node involvement (9). In our series,

all cases had stage I disease, and no recurrence was noted in the follow-up period. Calaminus et al. (5) reported 2 recurrences out of 20 stage IA cases in their series. These two patients had a high mitotic activity, and one of them also underwent suboptimal surgery. Additionally in that study, 4 (50%) out of 8 stage IC patients had adjuvant chemotherapy, and the disease recurred in two of them. In our study, 9 out of 10 cases were in stage IA, and eight of them underwent fertility sparing surgery. No recurrences occurred in the 5-year median follow-up period. Four out of five patients who underwent fertility sparing surgery and who desired pregnancy got pregnant. Powel et al. (10) treated two patients who had stage III disease with fertility sparing surgery and adjuvant chemotherapy and they did not observe recurrence during the follow-up period. In contrast to adult-type, most of the recurrences occur in the first year after treatment (5, 8). Although in the largest series in literature it was reported that recurrence would not be expected after three years of treatment, late recurrence was reported (4, 11). For that reason, patients should be followed-up for a long period (11). It is thought that inhibin B is a reliable marker to detect recurrence during the follow-up period (11).

Surgical and adjuvant treatments in advanced stage or recurrent diseases are unclear. The combination of taxane and platinum can be an alternative treatment option (12). For residual or recurrent adult type granulosa cell tumors, radiotherapy is recommended (13). Hirakawa et al. (12) did not obtain any response with chemotherapy in a patient with recurrent JGCOT who had multiple abdominal masses. They observed a regression in the size of the tumors and clearance of the ascites with whole abdominal external beam radiotherapy. Palliative radiotherapy can be considered in these patients.

Although JGCOT occurs frequently during childhood, it is also seen in adults. Primary management of this disease is surgery. The benefit of adjuvant therapy is unclear. Because survival is long in the early stage and most of the patients are young, fertility sparing surgery can be safely chosen in these patients.

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Gonadotropin-releasing hormone agonist triggering is effective, even at a low dose, for final oocyte maturation in ART cycles: Case series

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Abstract

Objective: To investigate the efficacy of low-dose gonadotropin-releasing hormone (GnRH) agonist for final oocyte maturation in females undergoing assisted reproductive treatment (ART) cycles.

Material and Methods: Nine females undergoing ovarian stimulation in a GnRH antagonist protocol who received triptorelin 0.1 mg to trigger final oocyte maturation were included. Treatment outcomes of these patients were compared with those of controls, matched for age and oocyte number (n=14), who received 0.2 mg triptorelin at the same time. The luteal phase was supported with vaginal micronized progesterone and oral estradiol hemihydrate 2 mg twice daily.

Results: The mean (±) numbers of retrieved, metaphase II, and fertilized oocytes were 15.66±7.82, 14±7.28, and 10.11±5.86, respectively. The implantation and clinical pregnancy rates were 46.1% and 71.4%, respectively. Of the pregnancies, 2 were live births, 1 was a preterm birth (twins), 2 are on-going, and 2 ended as miscarriages. No case of OHSS was encountered. On comparison of the results of these patients (fresh cycles; n=7) with those of matched controls, there were no significant differences in terms of retrieved mature oocytes, implantation rates, or clinical pregnancy rates (p>0.05).

Conclusion: These findings suggest that low-dose GnRH agonist triggering has similar efficacy as standard doses in terms of retrieved mature oocytes and clinical pregnancy rates in in vitro fertilization cycles. (J Turk Ger Gynecol Assoc 2015; 16: 35-40)

Keywords: Agonist trigger, triptorelin, oocyte maturation, oocyte retrieval, pregnancy rate

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Introduction

Ovarian hyperstimulation syndrome (OHSS) is the most serious complication in in vitro fertilization (IVF) cycles, with an incidence of 3%-6% for moderate and 0.1%-2% for severe cases (1). Thus, many studies have focused on avoiding this iatrogenic complication using various strategies (2). It is well established that this syndrome almost always requires the exogenous administration of human chorionic gonadotropin (hCG) or endogenous pregnancy-derived hCG stimulation (3). However, due to its luteinizing hormone (LH) homology, extended half-life, and simple manufacturing process, hCG is an excellent trigger for final oocyte maturation (3).

Nevertheless, the introduction of gonadotropin-releasing hormone (GnRH) antagonist protocols has allowed the utilization of a GnRH agonist (a) to induce final oocyte maturation. The GnRH agonist displaces the GnRH antagonist in the pituitary gland, activating the GnRH receptor and resulting in a surge of gonadotropins (flare-up) similar to the natural midcycle surge (3). Moreover, GnRH agonist triggering has been shown to retrieve more metaphase II (MII) oocytes compared with hCG triggering (4). Kol and Humaidan hypothesized that this finding may be related to the endogenous follicle-stimulating hormone (FSH) surge elicited along with the LH surge after GnRH agonist triggering (4, 5).

Several studies have investigated the optimal dose of urinary or recombinant (r) hCG to induce oocyte maturation in IVF cycles (6, 7). The minimum optimal dose of hCG was first recommended by Abdalla et al. (8). They compared the effect of 2000-, 5000-, and 10,000-IU hCG doses for successful oocyte recovery and, as a result, recommended at least 5000 IU hCG for an adequate follicular response (8). Later, several studies concluded that the clinical outcome was similar between females receiving 5000 or 10,000 IU of urinary hCG (7). A recent study found that the optimal dose of r-hCG to induce final oocyte maturation in oocyte donors was 250 μg and that a double dose of r-hCG was not associated with a higher number of retrieved MII oocytes or higher pregnancy rates among recipients (6). In contrast, the preferred GnRH agonist doses for triggering oocyte maturation have been found to be 0.2 mg for triptorelin, 0.5 mg for buserelin, and 1

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mg for leuprolide acetate (9). Several trials have explored different doses and types of GnRHa (GnRHagonists) in terms of their induction of final follicular maturation in IUI (10-12) and egg donor cycles (13). However, there are limited data in the literature about the optimal minimum doses of GnRH agonists for inducing final oocyte maturation in IVF cycles. In this report, we present a case series to show the efficacy of a low-dose GnRH agonist (0.1 mg triptorelin) for final oocyte maturation in females undergoing assisted reproductive treatment (ART).

Material and Methods

This retrospective analysis used the data of a small case series of patients (n=9) undergoing GnRH antagonist cycles using 0.1 mg triptorelin for final oocyte maturation between March 2012 and May 2013. The study was pproved by the instutional review board and informed consent was provided by each of the couples. As there is no established dose of GnRH agonist for inducing final oocyte maturation in our center, individual attending physicians determined the dose of GnRH analog and luteal phase support according to their own preference. One of the physicians (BG) in the department preferred a lower triggering dose of GnRHa (0.1 mg triptorelin) for inducing final oocyte maturation, based on the successful results of previous IUI studies (10-12). Therefore, the current study analyzed these cases retrospectively and compared the results (fresh transfers) with a control group (n=14) on the basis of the study group.

Ovarian stimulation was initiated with recombinant FSH (Puregon; Organon, Turkey and Gonal-f; Merck Serono, Turkey) from Day 2 or 3 of the cycle and continued until the day of ovulation induction. Cycles were monitored using ultrasound scanning. A GnRH antagonist, ganirelix (Orgalutran; Organon, Turkey) or cetrorelix (Cetrotide; Merck Serono, Turkey), was administered when the leading follicle reached a maximum diameter of 14 mm. When at least two follicles had reached a diameter of 17 mm, final oocyte maturation was triggered by administering 0.1 mg triptorelin (Decapeptyl; Ferring, Turkey). Oocyte pick-up was performed 35 h and 30 min after triggering. ICSI was performed in all patients. Embryos were evaluated on the second and third days, and up to two embryos per patient were transferred. For luteal phase support, all patients received micronized progesterone 90 mg vaginally (Crinone 8% vaginal gel; Merck Serono, Turkey) and estradiol hemihydrate 2 mg orally twice daily (Estrofem tb; Novo Nordisk, Turkey).

Biochemical pregnancy was detected by measuring β-hCG levels (>10 IU/L) on Day 12 after embryo transfer. Clinical pregnancy was defined as the presence of a gestational sac with a fetal heart rate present on ultrasound at Week 6 of gestation.

Statistical analysis

Statistical Package for the Social Sciences 17 (SPSS Inc., Chicago, USA) was used for the statistical analysis. Fresh transfer cycle results were compared between the groups using Fisher's exact test and Mann-Whitney U test for non-parametric conditions. The power of the study was 0.502 (∝: 0.51). A p value of <0.05 was accepted as statistically significant.

Results

a. Cycle characteristics of Group 1, including fresh and thawed transfers (n=9)

The demographic and cycle characteristics of each patient in Group 1 (n=9) are shown in Table 1. Seven patients had fresh cycle embryo transfers. The other two patients had frozen embryos; embryo transfer was performed during a subsequent artificial cycle in these patients due to OHSS risk. Seven patients in Group 1 conceived, one of whom (case 1) had a preterm delivery of twins at Week 24 due to preterm premature rupture of membranes (PPROM), one patient had a single term delivery (case 2), one patient had a term twin delivery (case 3), two patients had an on-going pregnancy (case 4- Week 25 and case 6- Week 21), while two pregnancies ended as miscarriages (case 5 and case 9). The reproductive outcomes for these patients (including both fresh and thawed transfers) were as follows: the clinical pregnancy rate was 77.7%, the on-going pregnancy+birth rate was 55.5%, implantation rate was 52.9%, and the abortion rate was 22.2% (n=2).

b. Comparison of fresh transfers (n=7) of Group 1 with Group 2 (oocyte and age-matched control group; n=14)

Only fresh embryo transfers were included in the comparative analysis; therefore, the results of patient 3 and patient 4 in group 1 were not included in the statistical analysis. The patients' characteristics and treatment outcomes are shown in Table 2. The mean ages of patients in groups 1 and 2 were 29.89+4.48 (24-37) and 28.92±3.54 (23-36) years(y), respectively (p>0.05). There were no significant differences between the groups in mean duration of infertility, previous IVF attempts, duration of stimulation, or total dose of gonadotropins required (p>0.05). There were also no significant differences in the mean number of aspirated follicles, mean number of retrieved oocytes, or mean number of metaphase II oocytes between the groups (p>0.05). Immature oocytes (MI) were significantly more numerous in group 2 than in group 1 (p<0.05). Fertilization rates were similar in both groups (72% in group 1 and 73% in group 2). The nean number of embryos was 10.11±5.86 (4-21) in group 1 and 10.79±3.14 (7-18) in group 2. The numbers of transferred embryos were 1.85±0.37 (1-2) and 1.36±0.49 (1-2) in groups 1 and 2, respectively (p<0.05). There were no significant differences between the groups in implantation rate (46.1% vs. 57.8%), clinical pregnancy rate (71.4% vs. 57.1%), and on-going pregnancy rates (42.8% vs. 42.8%) (p>0.05). There was no case of OHSS in any patient in either group.

Discussion

The major goal of studies in the field of assisted reproductive technologies is to improve the live birth rate while minimizing complications and the cost of treatment. Previous reports have claimed that GnRH agonist triggering in GnRH antagonist cycles is a new and effective modality for the most feared complication of controlled ovarian stimulation, OHSS (14). It has now been demonstrated that the flare-up effects of GnRH agonists with modified luteal support yield similar conceptual results as hCG in fresh IVF cycles (15, 16).

Table 1. Demographic and cycle characteristics of patients in Group 1 (n=9)

Case No	**1**	**2**	**3**	**4**	**5**
Age (y)	30	32.5	25	31	
BMI (kg/m^2)	28	33.5	22	24	
Cause of Infertility	Male factor+ tubal factor	PCOS	PCOS	PCOS+ endometriosis	Tubal factor
Previous IVF attempts	3	1	2	2	0
Total dose of gonadotropin (IU)	1650	1650	900	900	3150
Retrieved oocytes (n)	13	18	32	22	9
Metaphase II oocytes (MII)	13	15	30	20	9
Immature oocytes (MI-GV)	0	3	2	2	0
Fertilization rate (%)	84	66	70	90	88
2PN (n)	11	10	21	18	8
Day 3 embryos frozen (n)	6	3	13	12	0
Grade 1 embryos (n)	5	4	13	12	5
Embryos transferred (n)	2	2	Total freeze FET(2)	Total freeze FET(2)	2
IVF outcome	Pregnancy (twin) Preterm delivery (23rd week)	Live birth (single)	Live birth (twin)	Pregnancy-ongoing 22nd week-single)	Pregnancy (7th week missed abortus)
Case No	6	7	8	9	
Age (y)	25	25	34	33	
BMI (kg/m^2)	33	31.2	33.2	22.8	
Cause of infertility	Male factor	Male factor	Tubal factor+ Male factor	PCOS	
Previous IVF attempts	1	1	7	1	
Total dose of gonadotropin (IU)	1650	2875	3850	800	
Retrieved oocytes (n)	10	15	16	6	
Metaphase II oocytes (MII)	9	14	10	6	
Immature oocytes (MI-GV)	1	1	6	0	
Fertilization rate (%)	44	71	50	83	
2PN (n)	4	10	5	5	
Day 3 embryos frozen (n)	0	2	0	0	
Grade 1 embryos (n)	2	5	3	4	
Embryos transferred (n)	2	2	1	2	
IVF outcome	Pregnancy-ongoing (16th week-single)	Negative	Negative	Pregnancy (6th week missed)	

BMI: body mass index; IVF: in vitro fertilization; 2 PN: 2 pronucleus; n:number y: year; MI: metaphase I; GV: germinal vesicle; IU: international unit.

Although there are many reports about the optimal dose of hCG for inducing final oocyte maturation, there are limited data about the minimal optimal doses to trigger using GnRH agonists in IVF cycles (6, 7, 17, 18). Most previous studies have reported successful oocyte maturation with 0.2-0.3 mg triptorelin, 0.5 mg buserelin, and 1 mg leuprolide acetate (13). A similar clinical outcome was observed with 0.1 mg of triptorelin and 10,000 IU hCG in a GnRH antagonist protocol in a study that was presented during the 19th ESHRE meeting but has not yet been published (19). In a recent study of oocyte maturation using 0.1, 0.3, and 0.5 mg triptorelin, ovulation occurred in all IUI cycles (17). As there is no established dose of GnRH agonists for the induction of final oocyte maturation in IVF cycles, we hypothesized that lower doses of GnRHa may be sufficient for triggering. Herein, we report successful oocyte maturation using a lower dose of triptorelin acetate in a small case series.

As described in many reports, the main problem in GnRHa-triggered antagonist cycles is luteal phase support rather than

Table 2. Comparison of matched 0.1 and 0.2 mg triptorelin-triggered groups for fresh transfer

Variable	Group 1 (n=7)*	Group 2 (n=14)	p
Age (y)	29.89±4.48 (24-37)	28.92±3.54 (23-36)	0.256
BMI (kg/m^2)	27.78±4.98 (22-33.5)	26.45±3.98 (21-32)	0.289
Duration of infertility (y)	5±3.42 (1-9)	4.86±3.2 (1-14)	0.787
Number of Previous IVF attempts	2.0±0.68 (1-7)	1.43±0.64 (1-3)	0.306
Basal FSH (mIU/mL)	6.43±1.29 (4.1-8.1)	5.78±1.39 (3.2-8.0)	0.387
Stimulation (days)	11±4.82 (7-23)	10.38±1.39 (7-13)	0.631
Total dose of FSH (IU)	1936.11±1101.20 (800-3850)	1727.8±755.45 (750-3250)	0.481
Aspirated follicles (n)	17.55±7.71 (11-35)	18.34±6.87 (9-30)	0.704
Retrieved oocytes (n)	15.66±7.82 (6-32)	17.04±4.0 (10-26)	0.513
Retrieved oocytes per aspirated follicles (%)	89	92	0.906
Metaphase II oocytes (MII)	14±7.28 (6-30)	14.0±3.50 (9-22)	0.980
Immature oocytes (MI-GV)	1.66±1.12 (0-6)	3.04±2.32 (0-6)	<0.05
Fertilization rate (%)	72	73	0.270
2PN (n)	10.11±5.86 (4-21)	10.79±3.14 (7-18)	0.717
Embryos transferred (n)	1.85±0.37 (1-2)	1.36±0.49 (1-2)	<0.05
Implantation rate per cycle n (%)	6/13 (46.1)	11/19 (57.8)	0.471
Clinical pregnancy rate per cycle n (%)	5/7 (71.4)	8/14 (57.1)	0.290
Ongoing pregnancy + birth rate per cycle n (%)	3/7 (42.8)	6/14 (42.8)	0.433
Abortion rate per cycle n (%)	2/7 (28.6)	2/14 (14.2)	0.517
OHSS rate per cycle n (%)	0/7(0)	0/14 (0)	ns

*: Seven patients including fresh transfers.
IVF: in vitro fertilization; n: number: year; 2 PN: 2 pronucleus; MI: metaphase I; GV: germinal vesicle; IU: international unit; OHSS: ovarian hyperstimulation syndrome.

oocyte maturation, since the decrease in gonadotropins that are released from the pituitary results in corpus luteum deficiency and a defective luteal phase (20). Do lower triggering doses of GnRH agonists negatively affect the luteal phase? In a recent report, an inadequate luteal phase was observed in 34.4% of the non-conceptional cycles of patients receiving triptorelin 0.1 mg to trigger ovulation in IUI cycles; however, increasing or repeating triptorelin did not restore the luteal phase or the pregnancy rate (17). Shalev et al. (11) compared the effects of 10,000 IU hCG and 0.1 mg triptorelin on ovulation after clomiphene citrate treatment. Interestingly, midluteal progesterone concentrations (>10 ng/mL) and the mean luteal phase duration were normal in both groups. Also, there were no significant differences in pregnancy and abortion rates between groups, which may have been related to the different dynamics at midcycle in clomiphene-stimulated cycles due to a direct hypothalamic effect (10, 21). Parneix et al. (12) also investigated the effect of different doses and modes of application of GnRH agonists for triggering ovulation, finding that although ovulation occurred in all groups, shorter and inadequate luteal phases were seen in all groups. According to these findings, higher doses and different modes of GnRH agonists for triggering do not appear to improve the luteal phase in non-IVF cycles.

Standard luteal phase support after GnRH agonist triggering has been reported to be associated with lower conception rates due to corpus luteum dysfunction (22). Therefore, intensive luteal phase supplementation is recommended to achieve optimal conception rates (22). Also, since excellent pregnancy rates were reported in patients undergoing frozen embryo transfer using GnRHa suppression protocols, Engmann et al. (22) suggested that LH may not be critical for implantation. Therefore, aggressive luteal support may be another beneficial approach in agonist trigger cycles. Engmann et al. (23) reported excellent implantation and on-going pregnancy rates with intensive luteal support using intramuscular progesterone daily and estradiol patches on alternate days. Although intramuscular administration (IM) of progesterone results in higher serum levels, some studies also support the use of vaginal progesterone gel (24). In our study, all patients received micronized estradiol hemihydrate 4 mg orally combined with progesterone 90 mg vaginally twice daily for luteal support.

The main aim of this report was to demonstrate the effectiveness of lower doses of agonists to trigger final oocyte maturation, rather than pregnancy rates. Indeed, the rate of retrieved oocytes per follicle (89%) and fertilization rate (71%) seem to support the use of lower doses of GnRH agonists in clinical practice. These results also highlight the inadvertent administration of a lower dose (i.e., one instead of two ampoules) to the patients. Finally, clinicians should recognize that the cost of treatment can be reduced by using the minimum optimal dose of GnRH agonist for triggering.

Another important aspect of agonist-triggered cycles is the incidence of empty follicle syndrome (EFS). The incidence of EFS has been reported as 0.6%-3.5% in GnRHa trigger cycles, which is similar to that reported (0.1%-3.1%) after an hCG trigger (12, 19, 25-29). Therefore, EFS is not an inherent and exclusive problem to the GnRHa trigger (25) but could be related to human error, abnormalities in the *in vivo* biological activity of some batches of commercially available GnRHa, hypothalamic dysfunction, or GnRH receptor mutations (23, 26, 28-30). Elucidating the relationship between lower doses of GnRHa and EFS will require further studies including a larger number of patients. However, in our case series, there were no EFS and no reduced number of retrieved oocytes. Also, the association between BMI and the required GnRHa dose is controversial. Although Kummer et al. (25) demonstrated that a higher BMI corresponded to less of an increase in LH and lower post-trigger progesterone level, they found that BMI did not predict the oocyte yield. However, it is possible that the excess subcutaneous tissue in obese patients interferes with the absorption of medication. Only three patients in the current study were obese, and there was no reduced number of mature oocytes or EFS in these patients. However, determining the optimal GnRHa dose according to BMI will require further research.

The major limitation of our study was definitely the low number of patients. Therefore, the power of the study was relatively low to make a precise comparative analysis. However, the aim of this study was to report the effectiveness of low-dose GnRH agonist triggering in these cases.

In conclusion, the current study attempted to diagnose the effectiveness of low-dose GnRH agonist triggering in oocyte maturation. Our results suggest that 0.1 mg triptorelin acetate effectively induces final oocyte maturation in IVF cycles. However, as this was a small case series, larger randomized controlled studies are needed to determine the optimal dose for GnRH agonist triggering.

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Efficacy of a real time optoelectronic device (TruScreen™) in detecting cervical intraepithelial pathologies: a prospective observational study

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Abstract

Objective: To assess the effect of TruScreen™ (an objective optoelectronic cervical screening device) in improving the sensitivity of cervical screening programs either alone or in combination with Papanicolaou (PAP) smear or human papilloma virus (HPV) DNA screening.

Material and Methods: Our study was performed in 285 patients with abnormal Pap test results. TruScreen™ and HPV screening methods were performed in all participants. Consistency and differences between the tests were compared with cervical biopsy results.

Results: TruScreen™ was found to be an approach method in the determination of cervical pathologies (ROC curve area underlined=0.606) and with an 89.5% negative predictive value. HPV screening remains a counterpart to TruScreen™ with a 0.620 area underlined in the ROC curve and an 83% negative predictive value.

Conclusion: As determined in our study, TruScreen™ with a sensitivity of 86.1% can be used as a screening test with instant and not professional dependent results for cervical cancer screening. Avoiding from subjectivity in interpretation of Pap smears and requirement for pathologists, TruScreen™ can be a used for cervical cancer screening especially in countries with a low socio-economic status. The combination of TruScreen™ and HPV screening was not able to demonstrate a significant rise of effectiveness in screening. (J Turk Ger Gynecol Assoc 2015; 16: 41-4)

Keywords: Cervical screening, optoelectronic device, CIN

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Introduction

Cervical cancer is one of the most common gynecological cancers. It is the fourth most common cancer in women. GLOBOCAN data revealed 528,000 new cases in 2012 (1). Cervical cancer is considered as a preventable malignancy because of its close relation with the causative agent human papillomavirus (HPV) and the long period of precancerous lesions. HPV DNA was detected in 95%-100% cervical cancer patients (2). Moreover, it takes 58 months for the development of cervical intraepithelial neoplasia (CIN) 1 to carcinoma in situ and 38 and 12 months for CIN 2 and CIN 3, respectively (3).

The incidence of cervical cancer has decreased in developed countries with the aid of cervical cancer screening policies. However, in developing and under-developed countries, cervical cancer is still considered as an important public health problem. Inadequate screening programs, absence of experienced pathologists, and financial difficulties in organizing community-based screening programs seem to be the main reasons for the high incidence of cervical cancer in developing and under-developed countries. Therefore, screening programs are crucial for decreasing morbidity/mortality and for increasing the cure rate of the cervical cancer treatment. Moreover, adjunctive complementary test methods can be helpful for the improvement of detection rates of CINs and cervical cancer.

Nowadays, many methods are available for evaluating the various physical properties of human tissue. Radiation, magnetic and electrical fields, sound waves, and light can be used for the evaluation of human tissue. Optical and dielectrical impedance of human tissue is one of the potentially promising methods for the evaluation of human tissue. Because of the optical and dielectrical properties of different tissue components, human tissue has a specific intrinsic resistance and capacitance (4). Because normal or HPV infected tissues have differences in fundamental structure, it can also be assumed that optical and dielectrical impedance differences can exist between these tissues. TruScreen™ (Polarprobe; Polartechnics, Sydney, Australia) is a new real-time opto-electric screening method for cervical cancer (5). The working mechanism of this method is based on the frequency-dependent impedance spectrum. The system injects a current in different frequencies into the tissue and measures the voltage response of the tissue. There is no specification of the degree of abnormality as in a Papanicolaou (Pap) smear in the design of TruScreen™. The test detects an abnormality of the cervical tissue if present and gives results as normal or abnormal.

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Table 1. Comparison of Cervical biopsy and TruScreen results

		Cervical Biopsy		
		Positive[a]	**Negative[b]**	**Total**
TruScreen	Abnormal[c]	56 (%19.6)	143 (%50.2)	199
	Normal[d]	9 (%3.2)	77 (%27.0)	86
	Total	65	220	285

[a]Includes LSIL, HSIL, or ICC
[b]Includes normal or non-neoplastic changes
[c]Includes CIN 1, CIN 2, CIN 3, or ICC
[d]Includes normal squamous epithelium, columnar epithelium, physiologic metaplasia, or latent HPV-related changes

This real-time optoelectronic device offers the advantage of instant diagnosis, decreases the need for pathologists, and allows clinicians to counsel and manage the patient with abnormal test results in the first screening visit. These advantages can be a solution for difficulties in appropriate cervical screening programs in developing countries. We aimed to evaluate differences and consistencies between TruScreen™, Pap smear, HPV DNA screening, and pathological biopsy results in patients with cervical abnormalities in a separate manner. We also tried to determine the possible predictivity of combined methods in the early diagnosis of CINs.

Material and Methods

This prospective observational study was conducted in Zekai Tahir Burak Women's Health Education and Research Hospital in Ankara, Turkey, which is a reference center for gynecological oncology cases for the entire country. Academic approval of the study was obtained from our hospital's ethic committee. Informed written consents were obtained from all participants. The study was performed on patients who had been admitted to our hospital with abnormal cervical cytology defined by the Bethesda Classification of Cervical Cytology.

Inclusion criteria that must be met for this study were confirmed conventional Pap smear abnormality with at least atypical squamous cells uncertain significance (ASCUS), not having undergone hysterectomy before, not pregnant or not been pregnant for the last 3 months, not having undergone any cervical intervention or treatment for any diseases, and not having undergone pelvic radiotherapy treatment. Demographic features such as age, gravity, parity, abortion, and pregnancy history of all the participants were recorded. A total of 285 of 305 patients were recruited for the study.

Polartechnics' TruScreen™ device was used to perform TruScreen™ screening for the patients who were chosen according to the inclusion criteria. The TruScreen™ screening procedure was performed by a single trained physician with the method defined by Copellson et al. previously. The operator placed the tip of the probe (TruScreen™) with its single-use sensor. The operator targeted different points of the cervix using a predetermined protocol and topographical scanning path, which is defined in the manual of the device. After the completion of the examination, the result was calculated by the device and printed out from the console. The results are defined as "normal" for normal squamous epithelium, columnar epithelium, physiological metaplasia, or latent HPV-related changes or "abnormal" for CIN 1, 2, and 3 and invasive cervical carcinoma (6).

After TruScreen™ screening, specimens were also taken for HPV screening test from all participants. HPV DNA tests were evaluated via NucleoSpin® Blood kit (manufactured by Pharmatech©, New Jersey, USA).

Colposcopic investigations of all participants were performed by a single gynecologist with Allyn Videopath Colposcope (Medical Device Depot©, Ellicot City, MD, USA) after the application of 3% acetic acid to the cervix. After the colposcopic investigation, cervical biopsies were obtained from suspected areas, and pathological investigations were performed in our hospital's pathology laboratory. In order to avoid variability issues in the interpretation of pathological specimens, the specimens were investigated by a single expert pathologist.

Statistical analysis was performed with SPSS version 19.0 (SPSS, IBM, Chicago, USA). To evaluate the efficacy of TruScreen™, HPV DNA testing, and conventional Pap smear with the cervical biopsies, the sensitivity, specificity, and positive and negative predictive values were calculated. Because of the values identified as nominal, Chi-square test was used to evaluate differences between screening tests; kappa test was used to evaluate the consistency of tests. ROC curve analysis was used to evaluate the adequacy of tests in screening the cervical cytopathologies.

Results

This prospective observational study was performed in 285 patients who had abnormal Pap smear results. From a total of 285 participants, Pap smear results included 175 (61.4%) cases with ASCUS, 66 (23.4%) with low-grade squamous intraepithelial lesions (LGSIL), 13 (4.6%) with high-grade squamous intraepithelial lesions (HGSIL), 20 (7.0%) with atypical glandular cells of undetermined significance, 6 (2.1%) with malignant squamous carcinoma, and 5 (1.8%) with atypical squamous cells cannot exclude HSIL.

The colposcopic biopsy results showed 65 (22.3%) patients with abnormal results (LSIL, HSIL or Carcinoma). Among these pathological results, 42 (14.7%) cases had LGSIL, 15 (5.3%) had HGSIL, and 8 (2.8%) had squamous carcinoma. There were 56 cases with positive results for both biopsy and TruScreen™, including 33 cases with LGSIL, 15 with HGSIL, and 8 with invasive carcinoma. TruScreen™ did not miss any case of HGSIL or invasive carcinoma (Table 1). Nine patients with LSIL in the pathological investigation were reported as normal by TruScreen™.

The positivity rate of TruScreen™ was 69.8% (199/285). The sensitivity and specificity of the TruScreen™ test were found as 86.1% (56/65) and 35% (77/220), respectively. Additionally, positive and negative predictive values were 28.1% (56/199) and 89.5% (77/86), respectively. In the ROC curve analysis, the area underlined value was 0.606, and there was a consistency between the TruScreen™ and pathological biopsy results (Figure 1).

HPV DNA positivity was determined in 85 participants. Subtypes of HPV infection were also exhibited, and the most common sub-types that were examined in all participants (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) were included the study. The positivity rate of HPV screening was 29.8% for all participants. The sensitivity and specificity of the HPV screening test

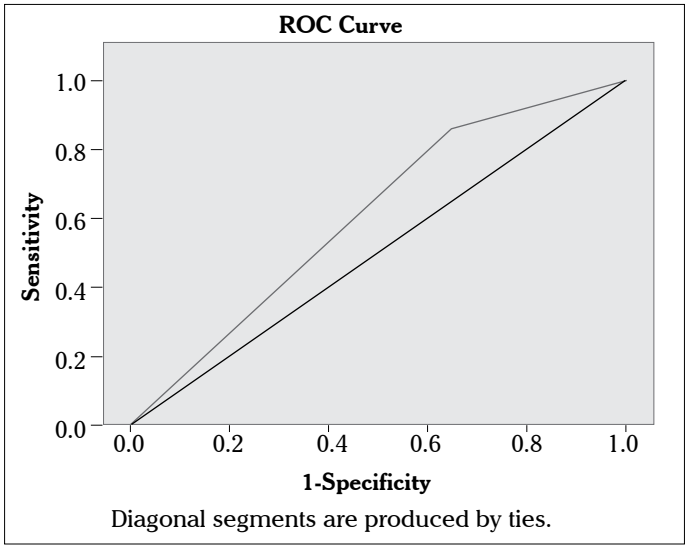

Figure 1. ROC curve analysis of TruScreen™ with pathological results in patients with cervical histological abnormalities

Table 2. Comparison of Cervical biopsy and HPV DNA results

		Cervical Biopsy		
		Positive[a]	Negative[b]	Total
HPV DNA	Positive[c]	31 (10.9%)	54 (18.9%)	85
	Normal[d]	34 (11.9%)	166 (58.2%)	200
	Total	65	220	285

[a]Includes LSIL, HSIL, or ICC
[b]Includes normal or non-neoplastic changes
[c]Includes positive for High Risk HPV DNA Type 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68
[d]Includes negative result for High Risk HPV DNA DNA Type 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68

Table 3. Sensitivity, specificity, false positive, and false negative results for each screening regime

	TruScreen™	HPV DNA
Sensitivity for abnormal cervical biopsy results[a]	86.1%	47.7%
Corresponding false negative rate for abnormal cervical biopsy results	89.5%	83%
Specificity for abnormal cervical biopsy results	35%	75.4%
Corresponding false positive rate for abnormal cervical biopsy results	28.1%	36.4%

[a]Include CIN 1, CIN 2, CIN 3 or ICC

were found as 47.7% (31/65) and 75.4% (166/220), respectively, in our study. The positive and negative predictive values were 36.4% (31/85) and 83% (166/200), respectively (Table 2). In the ROC curve analysis, the area underlined value was 0.616, and it demonstrated a consistency between HPV screening and pathological biopsy results (Figure 2). The sensitivity, specificity, and negative and positive predictive values of both tests are mentioned in Table 3.

Because the combination of TruScreen™ and HPV screening did not demonstrate better results in the ROC curve analysis

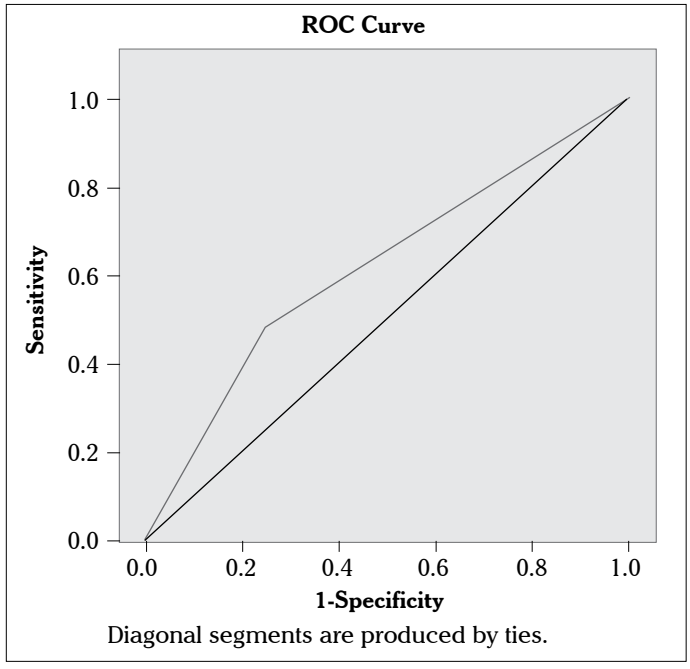

Figure 2. ROC curve analysis of HPV screening with pathological results in patients with cervical histological abnormalities

(area underlined value=0.614) and negative predictive value evaluation (negative predictive value 86%), we concluded that the combination of HPV DNA test and TruScreen™ cannot provide significant enhancement in the screening program. For this reason, we did not consider the combination as an efficient screening regime.

Discussion

In a recent study including 176 women, a difference between impedance spectrum of cancerous and normal cervical tissue was demonstrated. The results indicated screening with this method could detect CIN II/III with a sensitivity of 74% and a specificity of 53% (7).

Pap smear is the standard screening test for cervical cancer and premalignant cervical lesions. It was determined that approximately 50% of women who have cervical cancer have no history of regular cervical screening (8). According to the report from Agency for Health Care Policy and Research, the conventional Pap smear has a sensitivity of 51% and a negative predictive value of 47% (9). On the other hand, according to a study in 2000, 47% of women who develop cervical cancer may report an adequate screening history (10). They indicated that the complementary tests can improve detection rates for high grade CINs and can also increase the overall sensitivity for cervical cancer screening. These data reveal that new screening methods should be developed for patients who cannot be determined by conventional screening methods. The objective of the study was to assess the efficacy of TruScreen™ in improving the sensitivity of cervical screening programs either alone or in combination with another test.

Including our country, most countries have difficulties in cervical cancer screening that covers the entire population. Despite

the presence of a large number of people to be screened, a lack of experienced cytopathologists makes a proper population-based screening program challenging. Moreover, subjectivity in the interpretation of Pap smear tests and need for consecutive doctor visits in case of abnormal results reveal an urgent need for additional, cost-effective methods for better results in the early diagnosis of cervical carcinoma. A multicenter trial by Singer et al. that was performed in 671 patients in 10 centers showed sensitivities for histologically confirmed CIN 2/3 lesions by TruScreen™, Pap, and a combination of these two techniques as 70%, 69%, and 93%, respectively (11). In the same study, the sensitivities of the TruScreen™, Pap, and the combined test for CIN 1 positive (+) patients were 67%, 45%, and 87%, respectively. Two recent studies also describe TruScreen™ as a good and objective method for cervical screening with high sensitivity results (12, 13). In our study, the sensitivity of TruScreen™ was 86.1% and the negative predictive value was 89.5%, which is similar to Singer et al. (11) results.

Screening with HPV DNA seems to be more reliable for screening cervical pathologies in our study. The negative predictivity rate and specificity of HPV DNA testing were found to be 83% and 75.4%, respectively, in our study. In a meta-analysis, the specificity HPV DNA testing was calculated as 71% for ASCUS and LSIL and as 77% for HSIL lesions on screening, which is similar to our results (14). As an objective, standardized test HPV DNA test is a promising screening modality; however, in daily circumstances, there are some doubts about the test's cost-effectivity especially for larger populations. Morin et al. (15) suggested that even HPV should be tested first; the repetitive cytological tests should be performed in the management of cervical screening. An increase in the effectiveness of a cervical cancer prevention program is related to women's participation, test's acceptability, affordability, accuracy, and rapidity (16). Conventional cytology needs not only special equipment and supplies but also trained specialists for interpretation. The obligation of second doctor visit for results can be defined as another factor that decreases the acceptability and increases the affordability of the screening program with the Pap smear. In contrast, TruScreen™ would minimize training requirements and assist in the standardization of results (13).

In conclusion, with a sensitivity of 86.1% and advantages such as being and objective and real-time test, makes TruScreen™ an accepted valuable screening test for detecting preinvasive cervical lesions especially in areas where Pap screening cannot be effectively performed. TruScreen™ can be an alternative way for cervical screening, especially in under-developed and developing countries that have a lack of experienced pathologists and have difficulties in patient follow-up. The combination of TruScreen™ and HPV screening was not able to demonstrate a significant rise of effectiveness in screening, although only HPV screening was able to demonstrate an acceptable efficacy. However, the combination of TruScreen™ with Pap smear can be effective in enhancing the sensitivity of cervical cancer screening. Because of limited cases and deficiency in cervical biopsy results of patients with normal Pap smear, the significance of TruScreen™ needs further investigation with larger cases.

Ethics Committee Approval: *Ethics committee approval was received for this study from the ethics committee of Zekai Tahir Burak Women's Health Education and Research Hospital, Educational Planning and Coordination Decision 09/2009- 17.*

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

Peer-review: *Externally peer-reviewed.*

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Might uterus transplantation be an option for uterine factor infertility?

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Abstract

Current data on uterus allotransplantation research has been reviewed and summarized. Over the past 15 years, progress in uterus transplantation research has increased dramatically. As a consequence, the first pregnancy and delivery following uterus allotransplantation in rats have been reported. The technique has been better defined. Although clinical pregnancy and delivery following uterus allotransplantation has been reported in humans, there are still many questions to be answered before clinical application. Gestational surrogacy still remains an important option for being a genetic parent in selected cases with uterine factor infertility. (J Turk Ger Gynecol Assoc 2015; 16: 45-8)

Keywords: Uterus transplantation, uterine factor infertility, gestational surrogacy

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Introduction

Uterine-related infertility is one of the main unresolved causes of infertility, and it affects around 3-5% of the general population (1-7). It might be congenital (agenesis or malformation) or acquired (Asherman syndrome, myoma uteri, adenomyosis, or hysterectomy). Research on uterus transplantation started in rabbits and dogs in 1896 (8, 9). Clues on the transplantation technique and improvements in immunosuppressive agents have enabled progression to the clinical research phase in the last two decades (8, 9). Currently, uterine factor infertility patients can conceive through gestational surrogacy (10). Other indications of gestational surrogacy are history of recurrent miscarriage and implantation failure and deteriorating maternal diseases such as severe systemic lupus erythematosus, cardiac disorders, Takayasu's arteritis, history of breast cancer, hematological condition, pulmonary hypertension, residual pituitary macroadenoma, and brain tumor (10, 11). Results of many studies have shown that children born through vital organ tissue transplantation and immunosuppression or gestational surrogacy are healthy (12-14). Attitudes toward gestational surrogacy can be affected by religious, cultural, ethical, and legal factors (15, 16). Gestational surrogacy is not allowed in Australia (South and West), Austria, the Czech Republic, Denmark, Egypt, France, Germany, Ireland, Italy, Japan, Jordan, Norway, Poland, Saudi Arabia, Singapore, Spain, Sweden, Switzerland, Taiwan, and Turkey (17). Solving the legal and ethical issues and increasing public awareness regarding gestational surrogacy may increase the acceptance rate (18, 19).

Uterus transplantation research

Uterus transplantation research has been conducted in several animal models (mouse, rat, sheep, pig, baboon, and macaque) (Table 1) (8, 9). The allogeneic uterus transplantation technique has been better defined with either end-to-end anastomosis of the uterine arteries and veins or anastomosis of an aortacaval patch to the external iliacs (20, 21). Progress in composite tissue transplantation has been achieved with the development of new immunosuppressive therapy regimens (22). The first attempt in human uterus transplantation was performed by Fageeh et al in 2000 (23).

The graft has to be removed on 99th day due to thromboses in the anastomosis site. International Federation of Gynecology and Obstetrics (FIGO) advised that the human clinical experimentation stage should take place only after significant and adequate research in appropriate, large animal models, including primates (24). Since FIGO's statement in 2009, numerous animal studies, including studies using primates, have been performed (25). Akdeniz University is a well-known transplantation center that has also performed the first double hand and face transplantations in Turkey (26). A transplantation center's experience with microsurgery, immunosuppression, and infection control should be the most important factors determining success when attempting a new composite tissue transplantation procedure. Following surgical uterus retrieval experience with cadavers for checking the feasibility of this surgical procedure, and taking institutional review board approval and discussing the procedure with the organ transplantation team and the recipient candidates, our team performed the first uterus transplantation from a multiple organ donor (27). The anonymous details of the

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Table 1. Uterus transplantation studies in animals

Reference	Species	Vascular supply	Transplanted organ	Immuno-suppression regimen	Study population	Viable grafts	Pregnancy/ delivery
Knauer 1896	Rabbit(a)*	-	Ovaries	-	1	yes	
Zhordonia 1964	Sheep(a)	Omentopexy	Uterus &	- Ovaries		yes	20/12
Eraslan 1966	Dog(a)	Anastomosis	Uterus & Ovaries	-	18	10 normal function	Not tested
Yonemoto 1969	Dog(h)**	Anastomosis	Uterus & Ovaries	Azathioprine& prednisolone	14	7 rejection by 17-45 days	
Oleary 1969	Dog(a)	Omentopexy	Uterus & Ovaries	-	32		
Mattingly 1970	Dog(a/h)	Anastomosis	Uterus & Ovaries	Azathioprine	7 a 50 h	6a normal function 13h rejection by 6-21 days	2(autot)/1
Scott 1970	Dog(a/h)	Omentopexy	Segmented Uterus	Azat&pred (5 homot)	10 a	7a normal function	Not tested
Scott 1971	Primate (a/h)	Omentopexy	Uterus & tubes	-	10 h 4 a	10h rejection 4a normal function	Normal menst and mating
Barzilai 1973	Dog(a)	Omentopexy Anastomoses	Uterus & Ovaries	-	13 oment 12 anast	9 total necrosis 10 Normal function By 40 days	1(anast)/1
Confino 1986	Rabbit (a/h)	Sutured to the broad lig	Unilat uterus & Ovary	Cyclosporine	8 autot 10 homot	3a 3h preserved by 30 days	Not tested
Lee 1995	Rat& (h)	Anastomosis	Uterus & Ovaries	-	24	Normal function From 1-180 days	Not tested
Diaz Garcia 2010	Rat(allo)	Anastomosis	Uterus	- Tacrolimus	10	Normal function	Delivery
Ramirez 2011	Sheep (allo)	Anastomosis	Uterus		1 allo-transplant	Normal function	Delivery
Mihara M 2012	Monkey (h)	Anastomosis	Uterus	-	2 syngeneic	2 viable graft	1 spontan pregnancy
Diaz Garcia 2014	Rat	Anastomosis	Uterus	Tacrolimus	10 allo-transplant	6 viable graft	5 delivery

a* autotransplantation
h** homotransplantation
ATG***antithymocyte globulin

patient, her condition, the rationale and background for the use of this procedure, exactly what was performed, and adequate details regarding the relevant outcomes have been reported automatically as advised (personal communication with Dr Mats Brännström, October 2011). The better recording of surgical training and the experience of participating surgeons have also been defined by our group (28). Full and clear informed consent had also been obtained from the recipient following long-term consultation. We reported the first clinical pregnancy 18 months after uterus transplantation (29). Unfortunately, this pregnancy resulted in miscarriage (30). Brännström's team has performed nine uterus transplantation surgeries from live donors (31). They have recently reported the first live birth after uterus transplantation, which is a very important step forward (32). The outcomes of their seven cases, as well as our case, will provide very important information for the future of uterus transplantation (Table 2).

Safety concerns associated with uterus transplantation

Following the first live donor uterus transplantation attempt, FIGO stated that the harvesting of the donated uterus, if removed from a living donor, necessitates relatively major surgery with its own risk of complications (33). They further considered the procedure ethically inappropriate and advised surgeons to not perform the procedure using organs from live donors, given the lack of data on the safety and hazards for live

Table 2. Uterus transplantation studies in humans

Reference	Species	Vascular supply	Transplanted organ	Immuno-suppression regimen	Study population	Viable grafts	Pregnancy/ delivery
Fageeh W 2000	Human	Anastomosis	Uterus	Cyclosporine Azathioprine Prednisolone Antithymocyte globulin	1 allotransplant	Normal function for 3 months	Not tested
Ozkan and Akar M 2013	Human	Anastomosis	Uterus (multiple organ donor)	ATG*** Tacrolimus Mycophenolate mofetil Azathioprine Prednisolone	1 allotransplant	1 viable graft	Spontaneous abortion
Brannstrom M 2014	Human	Anastomosis	Uterus	ATG Tacrolimus Mycophenolate mofetil Azathioprine Prednisolone	9 allottransplant	7 viable graft	1 delivery

donors. Risks for the live donor and recipient are defined as the complications of hysterectomy, sequelae associated with the removal of vascular pedicles, probable ovarian dysfunction, and decreased quality of life (34).

Conclusion

Uterus transplantation should be performed by a team comprising transplant surgeons, gynecologists, plastic surgeons, transplant internists, infection specialists, and transplant psychiatrists. Any team planning to perform human uterus transplantations in the future should undergo extensive training and methodological development with the use of large animal models or cadavers. In addition, all aspects of transplantation, including immunosuppression protocols and the follow-up of transplant patients and pregnancies, are fundamental parts of the training process, because the procedure carries major surgical risks to the live donor and recipient, and no definitive conclusions can be made regarding uterus transplantation. Regenerative medicine also holds significant promise for transplantation in the future (35). Concerning the surgery and immunosuppression-related risks, congenital anatomical variations in the genitourinary system of the recipient, such as solitary pelvic kidney, gestational surrogacy policies should be established in parallel with clinical and experimental uterus transplantation studies.

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Multiple sclerosis; a disease of reproductive-aged women and the dilemma involving contraceptive methods

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Abstract

Multiple sclerosis (MS) is an autoimmune disorder characterized by chronic inflammation in the central nerves system. Because the disease predominantly affects women of reproductive ages, having knowledge about contraception options for MS patients can make clinicians provide better counseling. Although most contraceptive methods are generally accepted as safe and effective in MS patients, recent studies have raised questions about their potential adverse effects on the disease. The use of contraceptive methods to avoid unintended pregnancies is crucial in MS patients, particularly during the relapse phase of the disease or the time when the disease is not completely under control. This review investigates the contraception options and their effects on female MS patients.

Providing appropriate contraception options to multiple sclerosis patients will be one of the most challenging issues for clinicians to deal with. Recent studies have raised questions that the use of hormonal contraceptives may at least partly contribute to the rise in incidence of MS in women. This review investigates the contraception options and their effects on female MS patients.

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Introduction

Multiple sclerosis (MS) is an autoimmune disorder characterized by chronic inflammation in the central nerves system and subsequent demyelination of nerves (1).The disease predominantly affects women of reproductive ages in the 3rd and 4th decades; 62% of these women use contraceptive methods (2, 3). There are recent conflicting studies about the effect of oral contraceptive (OC) use on MS and MS-like symptoms in the literature (4, 5). Therefore, it is important to understand the effects of hormonal contraceptives in MS patients.

In addition, the medical treatments of MS such as through the use of interferons (IFNs), fingolimod, dimethyl fumarate, and, natalizumab may compromise the pregnancy in patients with this disease (6). The ongoing use of IFNs in women planning pregnancy may also be relatively contraindicated because of possible abortifacient properties (6). Therefore, the use of contraceptive methods to avoid unintended pregnancies will be extremely important in MS patients, particularly during the relapse phase of the disease or the time when the disease is not completely under control.

Therefore, clinicians usually try to provide contraceptive counseling to these young MS patients for addressing the question regarding the most appropriate contraceptive method. Providing an appropriate contraception options to MS patients is one of the most challenging issues for clinicians to deal with. However, most contraceptives methods are hormonal methods, and recent studies have raised questions about their potential adverse effects on the disease.

We start this review by discussing the use of hormonal contraceptives in MS patients. To understand the effect of hormonal contraceptives on MS, the effects of sex steroids on this disease are discussed initially.

MS, sex steroids, hormonal contraceptive methods

Although the strong interaction between the pathogenesis of MS and the immune system and sex steroids is well known for a long time, the exact mechanism through which the disease develops is yet to be identified completely. Hormonal contraceptives are effectively used by many young women to prevent unintended pregnancies.

Most women use this method, particularly in their middle reproductive years, in which MS is mostly detected. The well-recognized problem in the pathogenesis of MS is inflam-

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mation of the myelin and the defects in the regeneration of the myelin sheaths. The defective regeneration of myelin sheaths as a result of inflammation shows up as a white region causing plaque appearance in the nerve system (7).

Observations such as the alleviation of the symptoms of MS during pregnancy when the progesterone level becomes high, the increase in the frequency of attacks after the delivery when progesterone levels rapidly decrease (7), the aggravation of the symptoms of the disease during the premenstrual period (8), and the increase in relapses following the end of progesterone treatment during the assisted reproductive treatment (9) suggest that progesterones can provide a mitigating effect against the development of MS attacks. Based on the aforementioned observations, it was recommended that nomegestrol acetate (NOMAC), a highly selective progestogen with the ability to cross the blood-brain barrier easily, may be used to help prevent the relapse of the disease.

NOMAC, derived from 19-nor-progesterone, suppresses the secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus and inhibits the production of progesterone from ovaries (10). It was shown in animal studies that NOMAC increases the production of ALLOPREG, which plays an important role in the coordination between neurons and supporting cells, which are required for producing myelin sheaths (11).

It is well documented that the mechanism of action of progestin only pills (POPs) is basically related to their progestogenic effect of thickening the cervical mucus, and thinning of the endometrium causes it to become involuted. Thus suppressant effect of progesterones on the endometrium prevents the implantation of the product of conception (12). POP is usually preferred during the postpartum period for its minimally suppressive effect on lactation. Considering the effect of progesterone on the myelin sheaths, it can be argued that POP can be an effective choice of contraception for MS patients during the postpartum period.

Based on this discussion, it can be expected that other progesterone preparates such as medroxyprogesterone acetate injection (Provera, Depo-Provera) and the progestin preparates etonogestrel subdermal implant (Implanon) or levonorgestrel implants (Norplant and Jadelle) will have a similar progestogenic effect on the neuronal system in MS patients. However, rising rumors about the presence of MS-like symptoms in women with levonorgestrel-releasing intrauterine devices (LNG-IUDs) increasingly cast doubts on the use of progestins as contraceptive methods (13).

The effect of progestin in LNG-IUD is mainly local, e.g., causing glandular atrophy and decidualization of the endometrium, resulting in thickening of the cervical mucus, and creating a barrier to sperm penetration (12). The contraceptive effect of LNG-IUD basically depends on its spermicidal effect and partially depends on the inhibition of follicle maturation and the inhibition of ovulation (12). At present, two LNG-IUDs, Mirena® (Schering Health, Berlin, Germany) and Skyla (Bayer, Pittsburgh, Pennsylvania) are on the market. In this review, LNG-IUD refers to the Mirena® IUD because little clinical research currently exists regarding the Skyla® IUD. Levonorgestrel in Mirena® is released into the blood circulation minimally, approximately 20 mcg per day, and its amount tends to decrease with THE duration of use (12). In addition to the supposed protective the effect of progestins against demyelination in MS patients, the negligible amount of levonorgestrel found in the bloodstream of LNG-IUD users does not support the argument that LNG-IUD causes MS or MS-like symptoms in women. However, in recent years, a growing number of cases regarding the development of MS symptoms in women using Mirena® have prompted significant concern by both MS patients and clinicians (13). In a recent study, 62,517 female participants were directed to fill out web-based questionnaires regarding the use of Mirena® and MS diagnosis. It was reported that out of 62,517 registered women with Mirena®, 31 were diagnosed with MS. In total, 20% of these women were diagnosed with the disease within a month of IUD insertion, while 30% developed MS between 1-6 months, 10% between 2-5 years, and 10% between 5-10 years. While the incidence of MS among women without Mirena® was 0.01%, this rate increased to 0.05% among women with Mirena® (13). The overall incidence rate of MS in women was found to be 0.036% in another study (14). However, it is hard to interpret the aforementioned results because of the lack of prospective controlled studies and the limited data regarding women who may have early MS symptoms that are vague and undiagnosed at the time of the insertion of LNG-IUD. Nevertheless, one should always take into account the possibility of exacerbation of the disease in patients diagnosed with MS while recommending Mirena® or possibly Skyla.

There are a number of experimental studies regarding the effect of estrogens on the development and progression of MS. In one of the most typical of these studies, experimental autoimmune encephalomyelitis was induced in mice, and estradiol and ethynil estradiol were administered to investigate the effect of estrogens on neurons (15). This and other related studies have shown that estrogens decrease the production of tumor necrosis factor-α (TNF α) and other chemokines (15, 16), inhibit major histocompatibility complex-II (MHC-II) expression (17), and protect dendritic cells from inflammation (18). After the administration of estrogens in the study, the decrease in the production of TNF-α, interferon gamma (IFN-gamma), and interleukin-12 (IL-12) in dendritic cells; the decrease in antigen presentation to T cells (19); and a shift from T helper-1 (TH-1) to T helper-2 (TH-2) cells were observed (19). Moreover, both estrogen- and progesterone-containing OCs have been shown to promote the survival and growth of neurons and myelin formation (20). In addition, it is reported that the alleviation of symptoms of MS during pregnancy is related to enhanced immune response arising from high estrogen levels (21). Based on these studies, it was concluded that estrogens can prevent patients from developing MS symptoms by affecting the immune response and inflammation. Based on these findings, it was suggested that estrogen-containing agents can be the choice of both contraceptive methods and treatment for MS in young women with this disorder. However, this hypothesis is not supported by clinical studies. Moreover, the question of why more women have MS than men if estrogen prevents the disease has remained unanswered.

There are four large prospective studies performed regarding OCs and their effects on MS. One of those studies, the Oxford

Family Planning Association Study (4) was conducted between 1968-1974 on a total of 17,032 female patients aged between 25-39 years who presented to family planning clinics requesting contraceptive counseling. The main aim was to investigate the efficacy of contraceptive methods and their effects on the general health. In total, 56% of the women were using OCs for birth control. No correlation between the use of OC and MS was detected in the study (4). Another study named the Royal College of General Practitioners' Oral Contraception Study (22) investigated 46,000 women, half of whom used OCs as contraceptive methods in 14 months of the study period. The previous OC users, new OC users, and nonusers were compared in terms of the risk of developing MS, and no correlation was found between these variables (22). Furthermore, no significant association was observed between the risk of MS and OC medicines that contain a different combination of active ingredients (<50 μg estrogen, >50 μg estrogen, progesterone only) in the study.

In the Nurses' Health Study (NHS), 121,700 OC user patients aged between 30-55 years were followed up for at least 6-7 years. The Nurses' Health Study II (NHSII) included 116,671 women aged between 25-42 years who used OCs as contraceptive methods (23). In total, 181 women in NHS and 134 women in NHSII developed MS during the 6-7-year follow-up. Although the increase in the risk of the development of MS was found in OC users, no correlation between the duration of OC use and the risk of MS was detected (23).

In the study of General Practice Research Database (24), the study group consisted of 106 women with MS and the control group consisted of 1001 healthy women. They found that women who previously used OCs and had just stopped it had a decreased risk of developing MS in comparison with nonusers (24). They showed that the incidence of MS was 40% lower in OC users than in nonusers during the previous 3 years. The risk of MS increased in the 6 months after pregnancy. However, conclusions derived from the short-term study were not valid in the long term (24). None of these studies were convincing enough to reveal that the use of OCs increases the incidence of MS. Based on these studies, it was previously concluded that hormonal contraceptives were used as contraceptive options for patients with MS or MS-like symptoms. However, the findings of the study presented in the 66th Annual Meeting of American Academy of Neurology in 2014 have changed the general concept about the effects of hormonal contraceptives on MS patients (5). In this population-based nested case-control study, 305 incident female cases with MS and 3050 matched controls were identified. It was observed that 29.2% of women with MS and 23.5% of control patients had used hormonal contraceptives for at least 3 months within the 3 years prior to the onset of symptoms. The majority of women used estrogen/progestin combination preparations. Women who used any hormonal contraceptive in the 3 years prior to the onset of symptoms, particularly those who had stopped the use at least 1 month prior to the beginning of symptoms, had a slightly increased risk of MS (5). Based on their findings, they suggested that the use of hormonal contraceptives at least partly contributes to the rise in the incidence of MS in women (5).

It seems that the opinion about the use of hormonal contraceptives in MS patients tends to change after this study. These contraceptive methods may not be as innocent as they seem in MS patients. Therefore, clinicians should be aware of the potential harmful effect of hormonal contraceptives in patients with known or suspected MS. If they have undiagnosed MS symptoms, they may be more likely to avoid pregnancy and to use hormonal contraceptives. If they have vague symptoms while on a pill prior to the diagnosis of MS, they may stop the pill to see whether their symptoms are related to the use of hormonal contraceptives.

It is also expected that certain drugs used to treat MS may reduce the effectiveness of OCs in these patients. It should be kept in mind that there is an increased risk of thrombosis associated with immobility in MS patients. In the presence of these conditions, other alternative contraceptive options should be recommended to MS patients.

The observations that MS is rare among men in general suggest the possible protective effects of androgens against the disease (25). The recent experimental study has revealed that testosterone treatment efficiently stimulates the formation of new myelin and reverses myelin damage in chronic demyelinated brain lesions in organotypic culture (25). In addition to the strong effect of testosterone on myelin repair, the authors of that study observed that the number of activated astrocytes and microglial cells returned to low control levels, indicating a reduction of neuroinflammatory responses. They have also identified the neural androgen receptor as a novel therapeutic target for myelin recovery (25). They concluded that androgens can be used as remyelinating agents and the brain androgen receptors can be promising drug targets for remyelination therapy in male MS patients (25).

It is well known that some OCs, LNG-IUDs, and LNG implants contain progesterone derivatives, which have more potent androgenic effects than the others. This feature may prove helpful in deciding the type of OCs in women with MS. Needless to say, to demonstrate the effect of the androgenic progestins on MS, future prospective studies should be performed.

In conclusion, given the lack of clarity regarding the use of hormonal contraceptives in MS patients and their potential risk of adversely affecting MS or MS-like symptoms in female patients, contraceptive methods should be carefully selected after considering the balance between their advantage and disadvantage.

MS and nonhormonal contraception

Inflammation plays an important role in the pathogenesis of MS. Vascular endothelial growth factor (VEGF), an angiogenic growth factor, promotes the resistance against neuronal damage and regulates the proliferation of neuroprogenitor cells, migration, differentiation, and survival of oligodentrocyte precursor cells, and migration to demyelinated lesions (26). However, in chronic MS, angiogenesis induced by inflammation seems to be limited because of a counterbalancing effect of vasoconstrictive mechanisms (26). During the chronic phase of MS, responsiveness to VEGF lessens and the regenerative process becomes disrupted (26). Angiogenesis in MS brings about

neovascularization and causes a rise in the vascular supply of nutrients and migration of inflammatory cells to demyelinating lesions (27). Copper-containing IUDs are among the most commonly used contraceptive options. The mechanism of action of the copper IUD is based on the direct effect on the oocytes via lessening or inhibiting their fertilization capacities (28, 29). This device has also an effect on the uterine cavity, endometrium, and cervical mucus, resulting in the immobilization of sperms and prevention of sperms to migrate to the fallopian tubes (28). Copper-containing IUDs release free copper and copper salts into the uterine cavity without increasing serum copper levels in women with IUDs (30). Early analyses suggested that IUDs cause pelvic inflammatory disease (PID) in women. However, more recent studies have found no increased risk of PID in monogamous women with IUDs (31-33). It can be assumed that MS attacks can be triggered by the presence of infection in the genital tract. Based on the data in literature, it can be concluded that copper-containing IUDs can be safely used by MS patients. However, this hypothesis should be supported by prospective controlled studies. It is well known that the use of diaphragms increases urinary tract infections in women (34). The presence of infections can induce MS symptoms with mechanisms similar to those mentioned above.

Conclusion

Because MS is usually observed among women of the reproductive age, the question about the most reliable contraceptive option for these patients will always be the first one for clinicians to answer. While the earlier research did not oppose the idea of using hormonal contraceptives in MS patients, a recent study has suggested that certain hormonal methods may increase the risk of developing MS or MS-like symptoms. Based on recent findings, we recommend that clinicians should prescribe selective nonhormonal contraceptives such as copper-containing IUDs in all phases of MS disease to be on the safe side. In addition, when counseling about contraception methods for MS patients, each case should be individually evaluated on the basis of the severity of the disease and patient's lifestyle instead of steering away from this issue on the basis of inconclusive data. Further studies are required to arrive at a definitive conclusion regarding the identification of potential adverse effects of various hormonal and nonhormonal contraceptive methods.

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COMET, TUNEL, and TEM analysis of an infertile male with short tail sperm

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Abstract

Male infertility is correlated with sperm morphology and sperm DNA damage, which are completely different from that of fertile individuals. An accurate sperm DNA damage analysis and ultrastructural examination of the ejaculate provide important support in the clinical evaluation. It is supposed that in the near future, the fertilization rate, pregnancy rate, and miscarriages could be predicted using the combination of these types of tests in assisted reproductive technologies (ARTs). For this purpose, we report a very rare case of an infertile man having short tail sperm. The infertile man and his wife underwent in vitro fertilization (IVF) with intracytoplasmic sperm injection (ICSI). During this process, we examined the ultrastructure of the ejaculated sperm with transmission electron microscopy (TEM) and calculated the sperm DNA damage with terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) and COMET assays. Then, we evaluated the association between sperm DNA damage and embryo quality. (J Turk Ger Gynecol Assoc 2015; 16: 54-7)

Keywords: Short tail sperm, sperm DNA damage, transmission electron microscopy

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Introduction

Sperm chromatin structure and sperm DNA integrity are important parameters for successful fertilization, embryo development, and heritage of the genome to the next generation. Abnormal spermatozoa contain high levels of damaged DNA and reactive oxygen species (ROS); also, they show alterations in protamination, chromatin packaging, and depleted antioxidant profile. The cumulative effect is demonstrated as poor semen quality and poor reproductive outcome in infertile men (1, 2). We report here a very rare case of an infertile man who has short tail sperm. The infertile man and his wife underwent *in vitro* fertilization (IVF) with intracytoplasmic sperm injection (ICSI). During this process, we examined the ultrastructure of the ejaculated sperm with transmission electron microscopy (TEM) and calculated the sperm DNA damage with terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) and COMET assays. Then, we evaluated the association between sperm DNA damage and embryo quality.

Case Presentation

A 39-year-old Turkish male gold mine worker was referred to Ege University Family Planning and Infertility Research and Treatment Center for evaluation of infertility associated with severe asthenoteratozoospermia. The patient and his wife had not achieved a pregnancy for 18 years of unprotected coitus. He reported that he had been smoking 10 cigarettes a day for the last 10 years and he did not drink alcohol. He has 2 sisters who have children. He does not have any brothers but has 2 male cousins (his uncle's son) who could not have any children either. Our patient does not have any idea whether the cousins received any treatment for *in vitro* fertilization. The lymphocyte karyotype of the patient was 46; XY and Y chromosome microdeletion was not detected. The lymphocyte karyotype of his wife was 46,XX. The wife's clinical and biological analysis did not reveal anything particular except her age (40 years old). Microbiological investigations did not show any urogenital infection.

The patient was involved in this study within the framework of decision ♯ 5 of the Ethics Committee of Çukurova University Faculty of Medicine, dated June 12, 2007. He was informed about the study and gave written permission for the analysis related to the study.

A semen sample was collected by masturbation after 4 days of sexual abstinence. The ejaculate was fully liquefied, and the semen analysis was performed in our laboratory according to standard World Health Organization (WHO) criteria.

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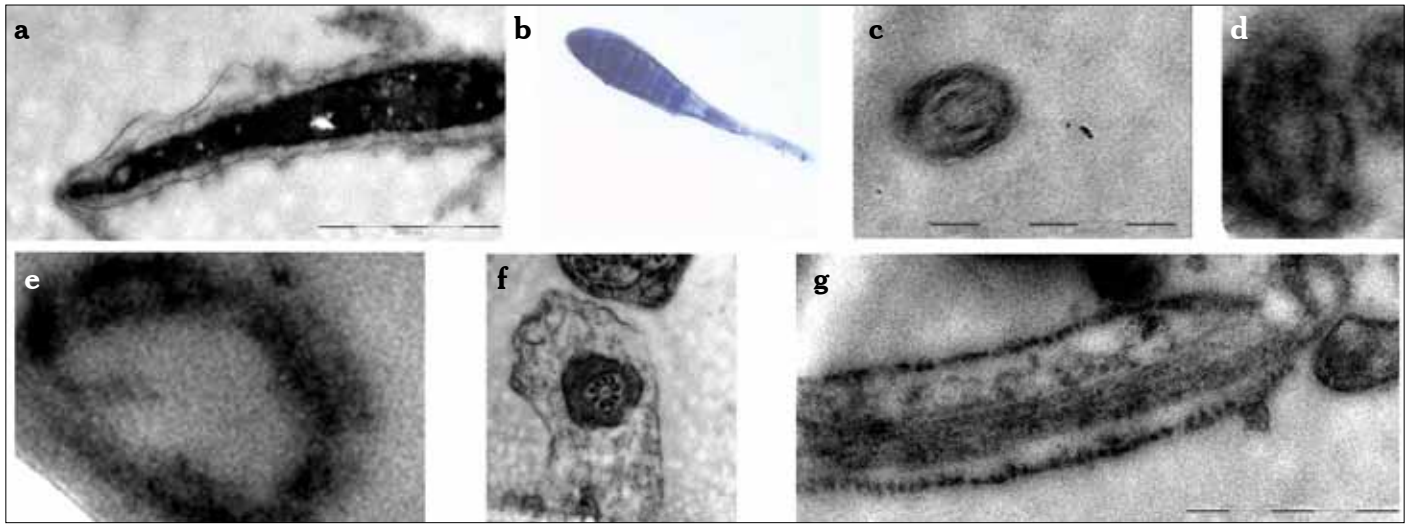

Figure 1. a-g. Transmission electron microscopy (TEM) micrograph of a longitudinal section of a sperm head showing a normal acrosome and nucleus structure. A: Acrosome, N: Nucleus (a). Semi-thin section with stained Toluidine blue and examined by light microscopy. Short tails were observed compared the long head (b). TEM micrographs of cross-sections of tails: the fibrous sheath was disorganized and the axoneme and outer dense fibers were missed (black arrow) (c-e). Fibrous sheath was disorganized (asterisk) and outer dense fibers are disorganized (white arrow) (f). TEM micrographs of cross-sections of tails at midpiece: microtubules were disorganized (Mt), and the head and neck junction had irregular and incomplete cytoplasm (IS) (g) (Bars: a, c, d, e, f, g: 5000 nm, b:X100)

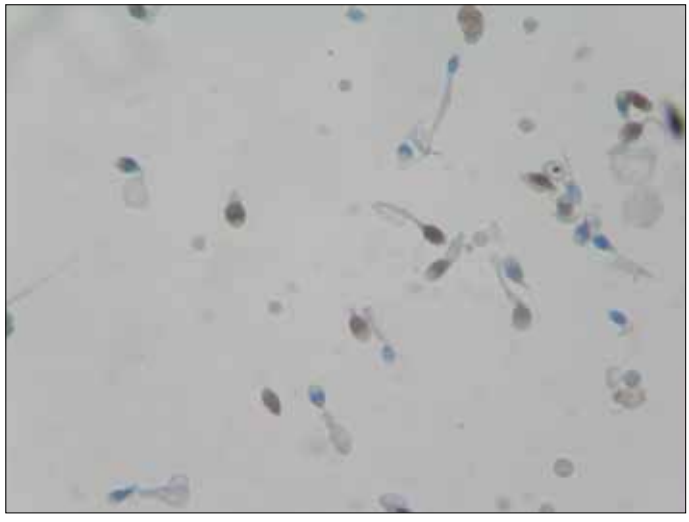

Figure 2. TUNEL-positive sperm was detected as a brown precipitate in the head of the sperm after TUNEL assay. Scale bar: 25 μm

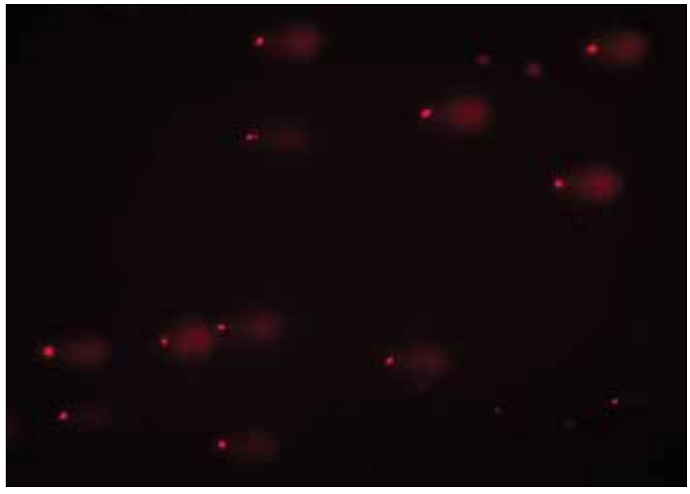

Figure 3. DNA damage in sperm as measured by the Comet assay. Scale bar: 25 μm

After semen analyses, the sample was divided into three groups for ultrastructural sperm evaluation using the TEM, TUNEL, and COMET assays.

After light microscopic evaluation, semen parameters revealed an asthenoteratozoospermia profile (sperm count: 15x10^6/mL), with 90% of spermatozoa being immotile and 10% of spermatozoa only just moving slightly; there was no progressive motility. Morphology analysis revealed teratozoospermia, with all spermatozoa showing abnormal head morphology and 85% with a short tail phenotype. Eosin staining revealed that 70% of the sperm cells were alive.

After electron microscopic analysis, the sperm heads were observed to have a normal acrosomal structure and cell nucleus. The junction of the head and neck on the transverse section was irregular, and the cytoplasmic microtubules were missing and disorganized. Deficiencies in the structure of the cross-sections were examined axoneme queues, and the mitochondrial fibrous sheath was found to be irregular. Irregular structure of mitochondria was observed in the midpiece of the tail (Figure 1).

After TUNEL analyses, the TUNEL-positive cells were detected as brown precipitates in the heads of the sperm (Figure 2), and the percentage of the TUNEL-positive sperm was 59.5%. The mean level of DNA fragmentation is 13.1±7.3% in fertile individuals (Table 1) (3).

Results of the Comet assay showed an index of damaged DNA (percentage tail DNA) and undamaged DNA (percentage head DNA). In this case, the patient's sperm DNA damage was calculated as 59.15% and is shown in Figure 3. At present, clini-

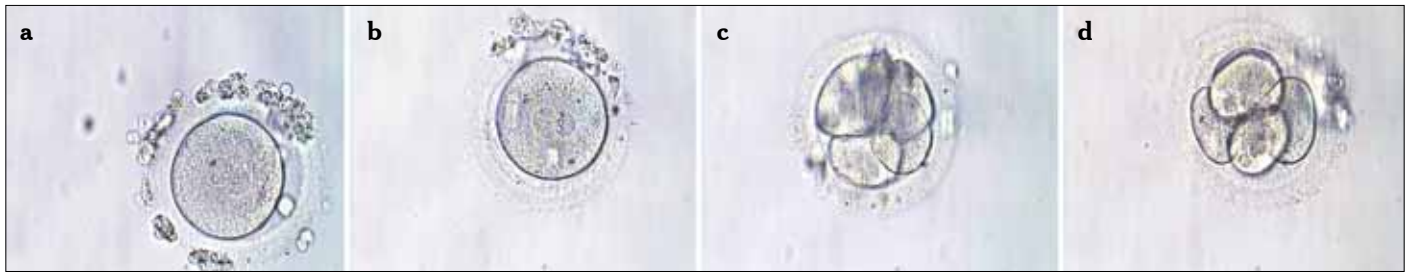

Figure 4. a-d. Diploid zygote (2PN) (a). Triploid zygote (3PN) (b). Day 2 embryo that was transferred (c). Day 2 embryo that was transferred (d)

Table 1. Sperm DNA damage analysis with TUNEL and COMET assays

	COMET Assay (Percentage tail DNA)	TUNEL Assay (%)
Normospermic volunteers	7.21±7.51	13.10±7.30
Case with short tail	59.15	59.50
TUNEL: terminal deoxynucleotidyl transferase dUTP nick end labeling		

cally useful thresholds have not been established for sperm DNA damage analysis using the Comet assay. So, each laboratory has established its own normal values. According to our previous study, which was unpublished and consisted of 20 normospermic fertile men, the mean percentage of damaged DNA in the normospermic group was calculated as 7.21±7.51% (Table 1).

IVF

Due to the severe asthenoteratozoospermia and high DNA damage, the couple underwent IVF with ICSI. Six oocytes were picked from his wife on day 0, and all oocytes were mature (MII). During the ICSI procedure, we preferred ejaculated spermatozoa that moved slightly and had long tails. After 16-18 hours from microinjection, fertilization check was performed, and 5 of them had two pronuclei (2PN) (Figure 4a). The other one had three pronuclei; so, it was evaluated as 3PN (Figure 4b). On the second day after microinjection, cleavage was observed in all embryos, although their grades were poor. The two embryos (Figure 4c, d) were transferred on day 2, but pregnancy did not occur because of low levels of βhCG after 15 days of transfer.

Discussion

The mammalian flagellum is composed of a number of cytoskeletal elements whose proper assembly is critical for sperm motility. These elements are the axoneme, outer dense fibers, and fibrous sheath, which are essential for flagellar development and movement (4, 5). In this case, ultrastructural analysis of the sperm showed that the fibrous sheath in the midpiece and principal piece was irregular. Due to this defect, sperm motility was decreased, and it was recorded around 10%.

Sperm DNA integrity and sperm morphology are essential parameters for successful fertilization and embryogenesis. According to the electron microscopic evaluation, the sperm heads were observed to have a normal acrosomal structure and cell nucleus. But, the sperm DNA damage was calculated as 59.5% and 59.15% with the TUNEL and COMET assays, respectively. Because of the normal structure of the sperm heads, DNA damage can not prevent the pronuclei formation. However, it is clear that severe asthenoteratozoospermia has a positive correlation with increased sperm DNA damage, which is detected with the TUNEL and COMET assays, which were correlated to each other, consequently affecting embryo quality and pregnancy negatively. These results are strengthening the previous findings that claimed that DNA-damaged sperm can form pronuclei at fertilization (6) and allow for normal embryo development (7). But, the risk of failure to achieve a pregnancy increases when the sperm DNA fragmentation exceeds the value of 52% by alkaline Comet assay (8).

A negative pregnancy result does not essentially depend on the paternal genome. Oocytes also have to be considered. Human oocytes have the capacity to repair paternal DNA abnormalities. This capacity is largely based on its cytoplasmic and genomic quality but also on age, ovarian environment, and fertility level. However, this capability deteriorates with age. When this repair tool is not adequate, embryonic genome activation may fail. At this point, development of the embryo may end, and blastocyst formation may not be achieved.

In our case, due to the highly damaged sperm DNA and advanced age of the wife (40 years old), the capacity of the oocytes to repair was not sufficient; thus, the pregnancy was deteriorated.

Ethics Committee Approval: *Ethics committee approval was received for this study from the ethics committee of Çukurova University.*

Informed Consent: *Written informed consent was obtained from patient who participated in this case.*

Peer-review: *Externally peer-reviewed.*

Author contributions: *Concept - A.D., S.V.; Design - A.D., C.G., N.D.; Supervision - E.T., E.N.T.G., N.D.; Materials - A.D., N.D., C.G.; Data Collection&/or Processing - A.D., S.M., E.T.; Analysis&/or Interpretation - A.D., S.M., H.A.B.; Literature Search - A.D., S.V.; Writing - A.D., E.N.T.G., E.T.; Critical Reviews - A.D., S.M., H.A.B.*

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

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Osseous metaplasia of the cervix: A rare transformation

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Abstract

Although numerous cases of endometrial osseous metaplasia appear in the literature, only 6 cases of osseous metaplasia of the cervix have been reported since 1982.A 30 years old nulligravida women was referred to our colposcopy clinic with cervical mass. General, gynecologic and colposcopic assessments were done. The patient had an excision biopsy. Diagnosis of cervical osseous metaplasia was confirmed on histologic examination.The cervical epithelium has the potency to differentiate to multiple types of epithelium including osseous epithelium.

(J Turk Ger Gynecol Assoc 2015; 16: 58-9)

Keywords: Osseous metaplasia, cervix, colposcopy

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Introduction

Cervical metaplasia represents the replace of the endocervical epithelium with tubal, intestinal, squamous, endometrial, transitional, cartilaginous or osseous (1).

We are presenting a case of osseous metaplasia of the cervix which is a rare pathological transformation. The etiology of osseous metaplasia has given rise to controversies; various theories of the uterine bone formation have been discussed (2, 3).

Some studies showed that osseous metaplasia might be generated from stromal tissue by differentiation of fibroblast into osteoblastes. Other studies hypothesized that it is secondary to abortion and retention of fetal bone, a tissue that may initiate osteogenesis (4-6).

Most patients having osseous metaplasia present with menstrual irregularities, pelvic pain, bloody vaginal discharge, infertility and sterility (7).

Case Presentation

30 years-old nulligravida woman was referred to our colposcopy service because of an incidental finding of cervical mass whilst investigating infertility. She had a history of primary infertility for 2 years. She was also complaining of postcoital, contact bleeding and dyspareunia for 1.5 year. The patient was non-smoker. She denied any previous history of cervical or uterine trauma. The patient was medically free. She had no history of previous surgeries. General and abdominal examination revealed no significant findings. Inspection of the vulva revealed no abnormality. On speculum examination: a cervical whitish solid mass was noted. It was approximately 2.5 cm x 1.5 cm on the Anterior lip of cervix. A smear was taken. A high vaginal swab and ectocervical and endocervical smears were taken as well. On palpation, the cervix was hard as well as the mass. Colposcopic examination was performed (Zeiss, Germany) (Figure 1). On applying the acetic acid, no acetowhite changes were noted. Taking a punch biopsy was attempted but unfortunately it failed due to the hardness of the mass. The patient had an excisional biopsy in the theatre under regional anaesthesia. The smear result showed no abnormality. The vaginal and endocervical swaps revealed no evidence of infection. Microscopic examination of the excised cervical mass showed mature bone tissue of metaplastic origin (Figure 2).

Blood tests were taken to exclude metabolic disorders that can lead to calcification such as hypercalcemia, hypervitaminosis D, and hyperphosphatemia. Hysteroscopy and endometrial sampling were performed and revealed no abnormality. Informed consent was obtained.

Discussion

Osseous metaplasia (OM) is defined by the presence of heterotopic normal bone tissue in a soft tissue (8).

Overall, osseous metaplasia occurs in approximately 0.3 per 1000 women (9). The pathogenesis is still not clear. Inflammatory and traumatic processes had been incriminated. Injury to the cervix either by surgical trauma or by recurrent infection may cause the mesenchymal cells to undergo osseous metaplasia (9).

The women with osteoid metaplasia may be presented with dyspareunia, postcoital bleeding, infertility and leucorrhea (6, 10). Osteoid metaplasia of the uterus is a rare disease that affects the uterus and was reported after abortion, in chronic endo-

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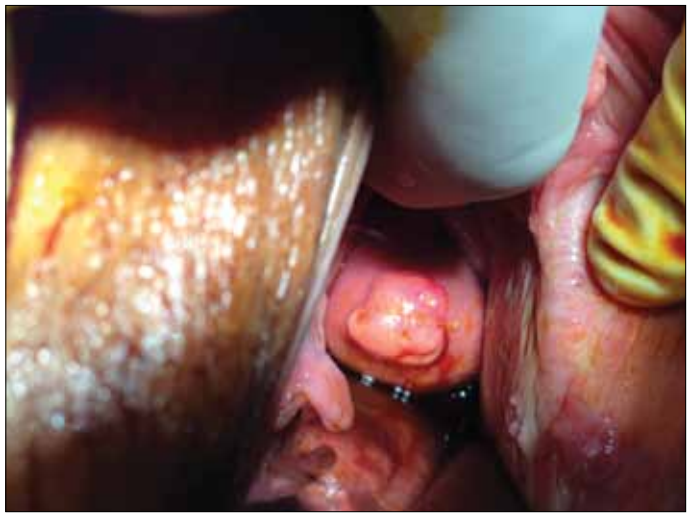

Figure 1. Shows the colposcopic examination of the cervical mass

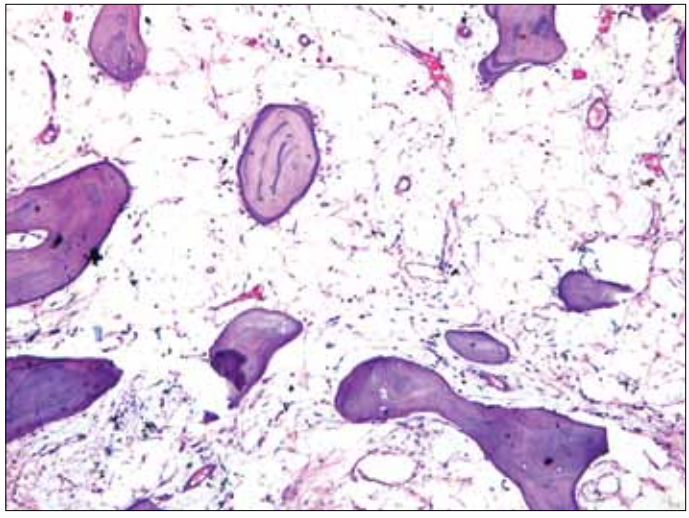

Figure 2. Shows the histopathology of the cervical mass after excision

metritis, metabolic disorders, and electro excision of the cervix (e.g. for severe cervical dysplasia). Retention of the fetal parts should be excluded. Bedaiwn et al. (4) reported a case of a woman that developed osseous metaplasia of the cervix shortly after loop electrosurgical excision procedure (LEEP) for severe cervical dysplasia. In this case the bone formation rapidly recurred after initial removal (4). There were previous 6 reported cases of Osseous metaplasia of the cervix in the literature. Physicians investigated the endometrium in only 3 of 6 cases, and in 2 of these, concomitant endometrial osseous metaplasia was found. In these 2 patients, chronic inflammation secondary to tissue damage was thought to be the principal cause. Therefore, because cervical osseous metaplasia can be associated with endometrial metaplasia, an evaluation of the endometrial cavity would be useful (11, 12).

We are reporting a very rare case of osseous metaplasia of the cervix. The aetiopathogenesis remains unclear. Although there was no concomitant osseous metaplasia in the uterine cavity, it may worth examining its effect on potential fertility.

Ethics Committee Approval: *Ethics committee approval was received for this study from the ethics committee of Cairo University.*

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

Peer-review: *Externally peer-reviewed.*

Author contributions: *Concept - E.E., M.A.; Design - E.E., M.A.; Supervision - M.A.; Resource - H.A., E.A., D.S., H.K.; Materials - E.E., H.A., E.A., D.S., H.K.; Data Collection&/or Processing - E.E.; Analysis&/or Interpretation - E.A., D.S.; Literature Search - E.E., H.A., E.A.; Writing - E.E., H.A., E.A.; Critical Reviews - E.E., H.A., E.A.*

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What is your diagnosis?

A 65-year-old-woman who complained of uncontrollable passage of gas and feces from the vagina without fever or abdominal pain was referred to the Obstetrics and Gynecology Department. She was in good health and had previously undergone total hysterectomy by laparotomy 20 years earlier for uterine leiomyomata. The symptoms began 5 months after an acute sigmoiditis and were accompanied by vulvovaginal burns and itching. She had undergone several gynecological examinations, which failed to identify the etiology. Rectosigmoidoscopy and magnetic resonance imaging (MRI) also failed to establish a diagnosis. A subsequent workup by vaginography resolved the etiological investigation (Figure 1, 2).

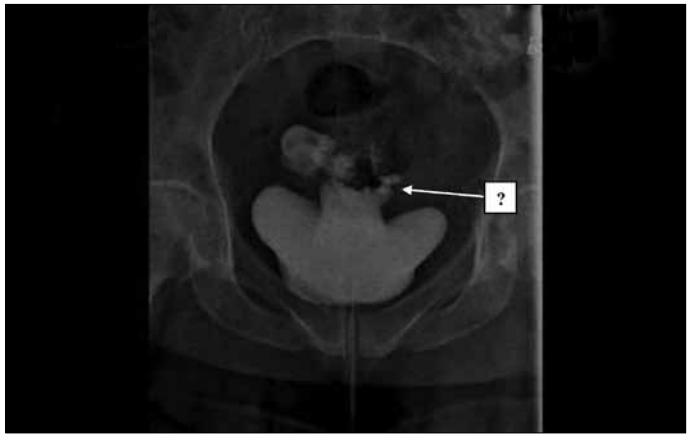

Figure 1. Vaginography-frontal view

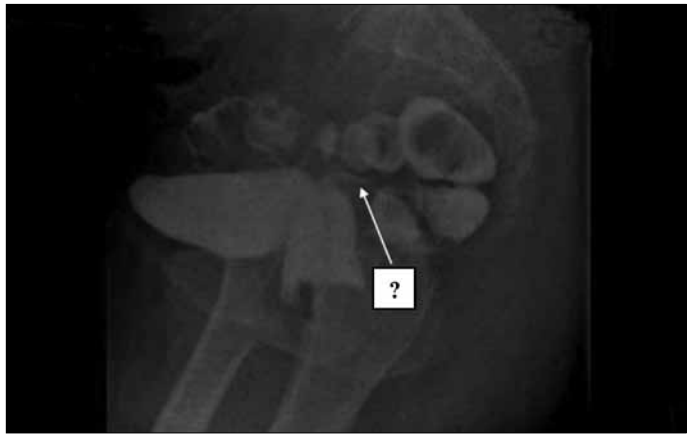

Figure 2. Vaginography-view in profile

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Answer

Among cologenital fistulae secondary to sigmoid diverticulitis, sigmoidovaginal fistulae are the most frequent type, and they are suspected in elderly women with a history of total hysterectomy and with the complaints of malodorous vaginal discharge, continuous or temporary fecal diversion, and flatus vaginalis (1, 2). They are usually investigated by lower gastrointestinal contrast radiology, frequently with a failure to detect the vaginal fistula (VF). Despite the current focus on modern imaging means, vaginography can appear as a valuable diagnostic test and an attractive alternative (3). In this case, vaginography showed a reflux of contrast medium from the vagina into the sigmoid colon, revealing a fistulous tract (Figure 3, 4). To perform it, we used a Foley® catheter (Bard Urological CO, Covington, GA; which is usually used for bladder drainage) for instillation of water-soluble contrast medium. A large-sized balloon (30 mL) must be used to permit definite sealing of the vagina and avoid contrast medium leakage to the outside. The catheter was positioned in the vagina, and the procedure proved to be painless. Once the balloon was inflated (with water and smoothly), it was necessary to apply gentle traction on the catheter to further seal the introitus. Vaginography showed a fistulous tract. However, it was noteworthy that we observed retrograde filling of the bladder insofar, as the urethra had a high enough opening (contrast medium had instilled it in limit of balloon). Vaginography is indicated to identify the presence and anatomy of high VF. The pressure of contrast medium can unveil fistulous tracts that are not visible with frozen and simply observational imaging techniques. Indeed, some fistulae act as dampers and are visible only through this increase in pressure. However, for fistulae resulting from obstetrical trauma with a lower location, it may be ineffective seeing that the fistula's orifice can be hidden and occluded by the inflated Foley® catheter balloon. The use of an endoscopic device (used in the emergency treatment of digestive hemorrhages) has also been reported to determine the location of vaginodigestive and ureterovaginal fistulae (4). Different operative modalities can be performed for VF (5). It is essential to emphasize that the use of a barium-containing contrast agent is absolutely contraindicated due to the risk of the intraperitoneal passage of barium. In this case, nonvisualization of the fistula did not permit the use of the endoscopic clipping method as described by John et al. (6). Surgical repair via the abdominal approach consisting of fistulectomy and omentum interposition between the colon and the vagina permitted the resolution of the symptoms (Figure 5). The patient's postoperative course was uneventful, and she has remained free from any complaints during follow-up for 35 months.

VF appears to be extremely distressing and remains a major contributor to morbidity in terms of physical, sexual, psychological, and social consequences. It can cause problems of anatomical location. Visualization of the fistula is essential to its successful repair in as much as it allows the surgeon to choose the most appropriate approach. Vaginography has long been the standard examination for the identification of VF. Since then, the progress made in the endoscopic explorations and medical imaging such as MRI or computed tomography has

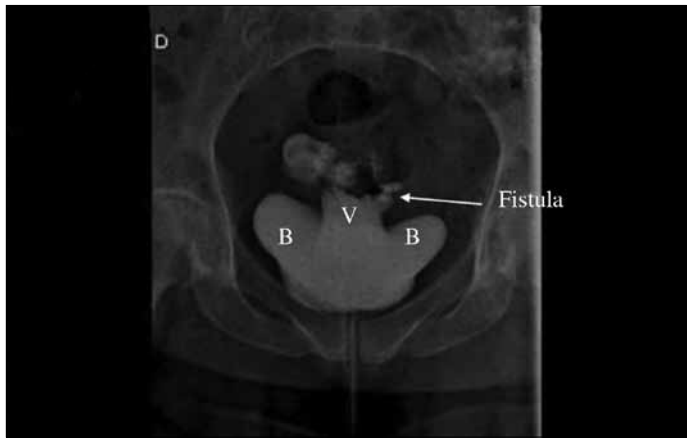

Figure 3. Vaginography revealed a reflux of contrast medium into sigmoid colon (white arrow)

B: Bladder; V: Vagina-frontal view

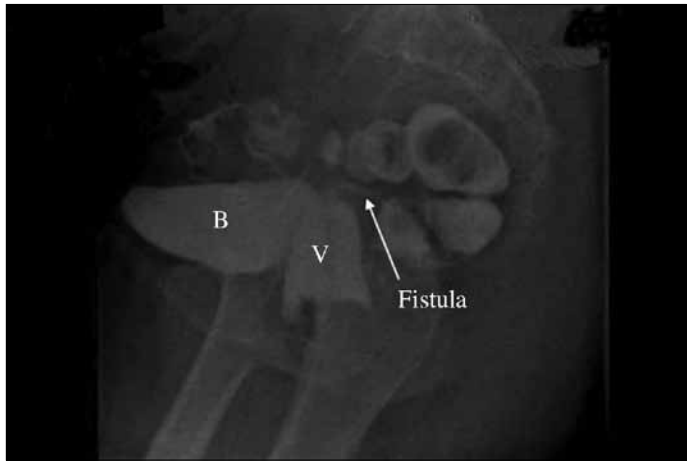

Figure 4. Fistulous tract from the vagina to the sigmoid colon (white arrow)

B: Bladder; V: Vagina-view in profile

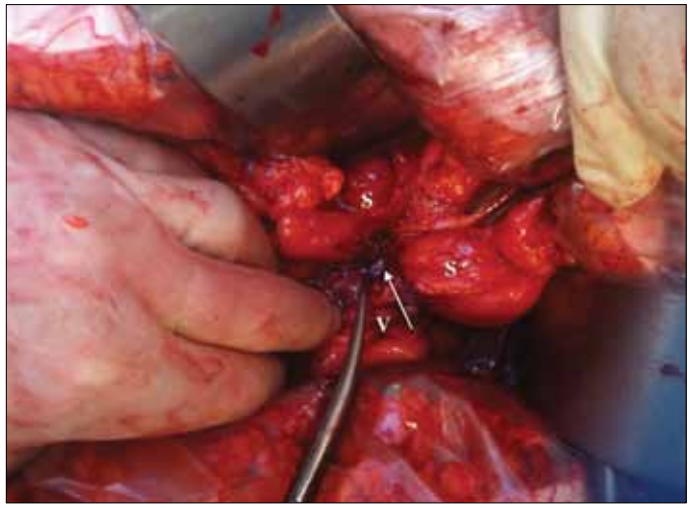

Figure 5. Intraoperative view of the sigmoidovaginal fistula (white arrow)

V: Vagina; S: Sigmoid colon

somewhat relegated this exploration to the second line. Thus, vaginography must be considered as an alternative method during the workup of female patients with a clinically suspected colovaginal fistula, especially when other imaging modalities fail to identify the etiology. According to Giordano et al., it should be considered as the initial investigation method of choice in such cases (7). Moreover, vaginography offers some advantages seeing that it appears to be an accessible, accurate, sensitive, and economic examination (7, 8).

In the past, vaginography had been traditionally used for detection congenital abnormalities such as ectopic insertion of ureters into the vagina as well as for VF diagnosis. In such cases, female patients complained of continuous urinary incontinence without dry time. Son et al. (9) used intravenous urography, ultrasonography, and radionuclide, which failed to identify vaginal ectopic ureters in 61% of cases, while vaginography permitted a diagnosis in the most other cases. In another study, magnetic resonance urography failed to establish a diagnosis, whereas vaginography permitted the discovery of the ectopic ureter in all cases (10). Thus, vaginography should be typically considered in the situation of continuous urinary incontinence in young female patients, especially when other diagnosis and imaging modalities have not established the etiology. More recently, in the same way as MRI, cystourethrography, peritoneography, or defecography, vaginography has been used in the diagnosis and evaluation of pelvic floor disorders (11, 12). Some authors have also reported a method performed by ultrasonography consisting of the use of three-dimensional saline infusion vaginography as an adjunctive modality in the same indications (13). Vaginography has also been described to allow the indirect visualization of an intravaginal foreign body in childhood (14).

We can draw the following conclusions from this case: VF represents a condition with profound and devastating consequences for the patient. VFs pose significant challenges in terms of the diagnosis, which determine their successful therapeutic management (1, 2). Because it targets clinically suspected fistulae and identifies their occult forms, vaginography should win its letters of nobility. Moreover, the procedure causes little or no discomfort to the patient and should also be considered easy to perform, cost-effective, and more conclusive. Thus, the simplest explorations may prove to be the most effective. The authors declare no conflict of interest.

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Bleeding and fetal Doppler parameter

To the Editor,

The report on “bleeding and fetal Doppler parameter” is very interesting (1). Iskender et al. reported that “bleeding during genetic amniocentesis did not change umbilical artery and middle cerebral artery Doppler parameters (1).” The finding might not applicable to all cases. In cases with pathology, an aberration might be possible. For example, in the case with intrauterine growth restriction (IUGR), of which the parameter is usually abnormal (2, 3), the effect should be specifically studied. A similar consideration for the case with polyhydramnios (4) should be mentioned as well.

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Author’s Response

We thank the authors for their valuable comments on our study. The main concern raised by the authors is that our findings may not be applicable to all patients, particularly those with obstetrical complications such as intrauterine growth restriction (IUGR) or polyhydramnios. Additionally, the authors suggested that the effects of amniocentesis should be studied specifically under these circumstances. While these suggestions are worthwhile to consider, they seem to miss the point of the present study because of a number of reasons. The sole purpose of this observational study was to investigate whether midtrimester amniocentesis through the transplacental route had any significant effect on fetal hemodynamic parameters (1). To eliminate potential confounders, patients with aneuploidy were excluded. In our cohort, there were no cases of very early IUGR, which is a relatively rare condition with a diverse etiology. The majority of cases are associated with fetal anomalies, aneuploidies, or infections (2). Considering the etiological diversity of very early IUGR, we doubt whether the impact of placental manipulation during amniocentesis in these patients would be of any clinical significance without a proper methodology. A similar consideration is also valid for polyhydramnios, which is related to a higher incidence of associated fetal abnormalities especially when related to IUGR or preterm birth (3).

Having stated that, we would like to mention that we totally agree with the authors who suggested that the effects of amniocentesis should be studied specifically under these circumstances. As suggested by our findings and other studies (1, 4), amniocentesis is a safe procedure with minimal and short-term consequences on fetal hemodynamics. We hope these findings provide a basis for relevant future research.

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CONGRESS CALENDAR

INTERNATIONAL MEETINGS

5-7 March, 2015	**Best of ESHRE & ASRM - A joint meeting of the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine** New York, USA http://www.asrm.org
18-20 March, 2015	**16th World Congress on Human Reproduction** Berlin, Germany http://www.humanrep2015.com/congress
8-12 April, 2015	**3rd Annual Middle East Society for Gynecologic Endoscopy (MESGE) Congress & 6th Annual Congress of Turkish Society of Gynecological Endoscopy (TSGE) Conjoint Meeting** Antalya, Turkey www.mesge2015.org
15-18 April, 2015	**8th International DIP Symposium on Diabetes, Hypertension, Metabolic Syndrome & Pregnancy** Berlin, Germany http://www.comtecmed.com/dip/2015
11-13 June, 2015	**7th Annual SERG Meeting on Robotic Gynaecological Surgery** İstanbul, Turkey www.sergs2015.org
14-17 June, 2015	**31st Annual Meeting of ESHRE** Lisbon, Portogual http://www.eshre.eu
16-19 June, 2015	**11th AAGL International Congress on Minimally Invasive Gynecology & 15th Annual Meeting of the Israeli Society of Gynecologic Endoscopy - ISGE IL Conjoint Meeting** Jerusalem, Israel www.aagljerusalem2015.com

NATIONAL MEETINGS

5-8 March, 2015	**12th Uludağ Obstetrics and Gynecology Winter Congress** Bursa, Turkey www.uludagkadindogum.org/
23-25 April, 2015	**Perinatal Medicine 2015 (TMFTP and SEESPM)** İstanbul, Turkey www.perinatalmedicine2015.org
11-15 May, 2015	**13th TJOD National Obstetrics and Gynecology Congress** Antalya, Turkey http://www.tjodkongre2015.org/
15-18 September, 2015	**7th Annual Urogynecology Congress** http://www.urojinekoloji.org/
15-18 October, 2015	**15th National Congress of Perinatal Medicine** Muğla, Turkey www.perinatoloji2015.org
12-14 November, 2015	**12th Traditional Zekai Tahir Burak Days** Ankara, Turkey http://www.ztbgunleri2015.org/

JTGGA CME/CPD CREDITING

Questions on the article titled *"Multiple sclerosis; a disease of reproductive-aged women and the dilemma involving contraceptive methods"* within the scope of CME/CPD

1. Which of the following is not an effect of progesterons on multiple sclerosis?
   a) Agravating MS attacks
   b) Mitigating the effect against developing MS attacks
   c) The decrease of relapses during assisted reproductive treatment
   d) The decrease in relapses during pregnancy
   e) The increase in the remission phase of MS patients

2. Which of the following is true for MS?
   a) More men have MS than women
   b) More women have MS than men
   c) More common in women in the postmenopausal period
   d) MS is not characterized by plaques on white region
   e) MS isn't characterized with plaque on white region

3. Which of the following is not true for MS and contraceptive methods?
   a) IUDs can be used by MS patients safely
   b) The use of diaphragms increases urinary tract infection in MS female patients
   c) The use of hormonal contraceptives may be a contributing factor, at least in part, to the increase in the incidence of MS in women
   d) One should always take into account the possibility of exacerbation of the disease in patients diagnosed with MS while recommending Mirena® or possibly Skyla.
   e) There is a significant correlation of MS with the time of using oral contraceptives

4. Which of the following is not a contributing factor to the significance of contraception with MS patients?
   a) MS is more common during the reproductive period
   b) MS is more common in women
   c) IFN, fingolimod, dimethyl fumarate, and natalizumab may compromise pregnancy rates in MS patients
   d) The disease may be ongoing with severe relapse phases
   e) All contraceptive methods are safe for MS patients

5. Which of the following drugs will be used in the treatment of MS in the future?
   a) Oral contraceptives
   b) Mirena® or Skyla
   c) NOMAC
   d) Progestin-only pills
   e) Depo-Provera

6. Which of the following is true for oral contraceptive in MS patients?
   a) The use of oral contraceptives may be a contributing factor, at least in part, to the increase in the incidence of MS in women
   b) A significant association exists between estrogen dosage in oral contraceptive and the MS relapse rate
   c) A significant association exists between oral contraceptive using time and the MS relapse rate
   d) Previous oral contraceptive users are more prone to MS development than past users
   e) Users of more androgenic progestin-containing oral contraceptives are more prone to MS development than users of less androgenic progestin-containing oral contraceptives.

JTGGA CME/CPD CREDITING

Answer form for the article titled *"Multiple sclerosis; a disease of reproductive-aged women and the dilemma involving contraceptive methods"* within the scope of CME/CPD

1st Question	A	B	C	D	E

2nd Question	A	B	C	D	E

3rd Question	A	B	C	D	E

4th Question	A	B	C	D	E

5th Question	A	B	C	D	E

6th Question	A	B	C	D	E

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Türkçe Özler – Mart 2015

Özgün Araştırma

J Turk Ger Gynecol Assoc 2015; 16: 1-4 • DOI: 10.5152/jtgga.2015.15188

Tıp Fakültesi ögrencileri üzerinde bilgisayar oyunlarının robotik cerrahiye katkisi

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ÖZ

Amaç: Şimdi ve daha önceki video oyunu oynamanın robotik similasyon becerileri kazanmadaki etkisini araştırmak.
Gereç ve yöntemler: Bu kesitsel deskriptif çalışma (Canadian Task Force Classification II-1) tıp fakültesi eğitim merkezinde yapılmıştır. Çalışma katılımcıları tıp fakültesinden halen video oyunu oynayanlar ile (Grup I) son iki yılda video oyunu oynamayan (Grup II) öğrencilerdir. Smilasyon ile her iki grubun robotik becerileri değerlendirilmiştir.
Bulgular: Yirmi iki öğrenci çalışmaya dahil edildi fakat 21'i çalışmayı tamamladı. Katılımcıların median yaşları Grup I ve Grup II için sırasıyla 23 (22-24) ve 24 (23-26) idi. Katılımcıların 15 tanesi (%71.4) erkek, 6'sı (%28.5) kadındı ve öğrencilerin %90.4'ü video oyunları oynamaya ilkokulda başlamıştı. Her iki grup her bir egzersizi tamamlama zamanı yönünden karşılaştırıldığında Grup 1 Peg Board 1 egzersizini Grup 2'den daha erken bitirmiş ($p>0.05$) ancak, Grup II Pig and Place, Ring and Rail ve Thread the Rings egzersizlerinde daha iyi sonuç almıştır. Bu farkların hiçbiri istatistiksel olarak anlamlı bulunmamıştır ($p>0.05$) bunun yanında egzersizleri tamamlama zamanı, hareket ekonomisi, enstrüman çarpışması, enstrümana aşırı güç uygulanması, enstrümanların görüntü alanı dışına çıkması ve çalışma alanı büyüklüğü skorları Grup I ve II arasında istatistiksel olarak farklı değildi ($p>0.05$).
Sonuç: Temel robotik simülasyon egzersiz sonuçlarına göre önceden video oyunu oynamış ve halen oynamakta olan tıp öğrencileri arasında fark bulunmadı. Bazal uzaysal bakı becerisini araştıran daha geniş örneklemli çalışmalar gereklidir.
Anahtar kelimeler: Eğitim, tıp öğrencisi, robotik similasyon, video oyunları

Özgün Araştırma

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İn vitro fertilizasyon uygulanan ve bazal serum folikül stimüle edici hormon düzeyi 10.0 ve 11.9 IU/L arasında olan kadınlarda gebeliğin öngörülmesi

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ÖZ

Amaç: Bazal folikül stimüle edici hormon (FSH) seviyeleri sınırda 10.0 ve 11.9 IU/L arasında olan kadınlarda in vitro fertilizasyon (IVF) döngüsü sonuçlarını değerlendirmek ve bu popülasyonda gebelik prediktörlerini analiz etmek.
Gereç ve yöntemler: Bir akademik eğitim hastanesinde prospektif kohort çalışması yapıldı; katılımcılar, kadınların IVF tedavisi gördüğü ve bazal en yüksek FSH düzeyleri 10.0 ve 11.9 IU/L arasında sınırda olan infertil çiftlerdi. İstatistiksel modelleme gebelik ve klinik gebelik için risk faktörlerini belirlemek amacıyla yapıldı.
Bulgular: Çalışma popülasyonunda klinik gebelik hızı döngü başına %26.5 ve hasta başına %35 olarak bulundu. Tüm bireyler ve intrasitoplazmik sperm enjeksiyonu (ICSI) yapılmayan bireyler arasında; genç yaş, yüksek gravida, insan koryonik gonadotropin (hCG) tetikleme gününde olgun folikül sayısı yüksekliği, toplanan oosit sayısının yüksekliği ve üretilen embriyoların sayısı gebe kalan ve kalmayan bireyler arasında anlamlı ayırt ettiricilerdi. Bununla birlikte, klinik gebeliği olanlarda olmayanlara kıyasla yalnızca embriyo sayısı prediktördü. Yüksek gravida ve bazal östradiol (E2) düzeyleri ve daha düşük maksimum bazal FSH seviyeleri ICSI yapılmayan hastalarda klinik gebelik prediktörü idi. ICSI yapılan hastalar arasında tek gebelik prediktörü daha kalın endometrium idi. ICSI hastalarında daha yüksek gebelik oranlarına doğru bir eğilim dikkat çekti.
Sonuç: Bu popülasyonda siklus başına ve hasta başına gebelik hızlarının 10.0 IU/L altında bazal FSH düzeyi olan hastalardakinden belirgin farklı olmadığı gösterilmiştir. Ön kanıtlar bu hastalarda ICSI'nin tercih edilecek fertilizasyon metodu olduğunu göstermektedir.
Anahtar kelimeler: FSH 10-12 IU/L, sınırda over rezervi, IVF, ICSI, istatistiksel modelleme.

Özgün Araştırma

J Turk Ger Gynecol Assoc 2015; 16: 11-20 • DOI: 10.5152/jtgga.2015.15201

Menopoz öncesi ve sonrası kadınlarda kardiyovasküler sistemin otonomik kontrolü: kesitsel bir çalışma

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ÖZ

Amaç: Bu kesitsel çalışmanın amacı menopoz öncesi ve sonrası kadınlarda kardiyovasküler sistemin otonomik kontrolünün özelliklerini değerlendirmekti.

Gereç ve yöntemler: Yaşı 59.3±8.5 yıl (ortalama±SD) olan 185 menopoz sonrası kadın ve yaşı 45.1±5.8 yıl olan 104 menopoz öncesi kadın ile çalıştık. Kalp hızı değişkenliği (KHD)'nin standart indeksleri; [ortalama kalp hızı, varyasyon katsayısı, NN intervali (normal sinüs ritmi olan elektrokardiyogramda iki ardışık R dalgası arasında geçen süre)'nin standart sapması (SDNN), ardışık NN intervallerinin farklarının kareleri ortalamasının karekökü (RMSSD), 50 ms'den daha büyük ardışık NN intervallerinin interval farklılıklarının sayısı olan RR50'nin NN intervallerinin toplam sayısına bölünmesi ile elde edilen oran (pNN50), toplam spektral gücün mutlak değerlerinde ve yüzdelerinde düşük frekans (LF) ve yüksek frekans (HF) bantlarının gücü] ve kalp hızında 0.1-Hz ritimleri arasındaki senkronizasyonun S indeksi ve fotopletismogram bu iki grup arasında istirahatte karşılaştırıldı. Şu seks hormonları değerlendirildi: Östradiol, folikül stimüle edici hormon, dehidroepiandrosteron sülfat ve testosteron.

Bulgular: Ortalama kalp hızı ve LF ve HF bantlarının gücü menopoz öncesi ve sonrası kadınlarda anlamlı olarak farklıydı ($p<0.05$). Otonomik indeksler, doğal ve cerrahi menopoz olan kadınlarda benzerdi. Bazı indeksler (varyasyon katsayısı, SDNN, RMSSD, PNN50, LF ve HF bantlarının gücü), doğal menopoz olan kadınlarda menopoz süresi ile zayıf korelasyon gösterdi. Cerrahi menopoz olan kadınlarda, istatistiksel olarak orta düzeyde anlamlı ilişki sadece menopoz zamanı ve S indeksi ($r=-0.41$, $p=0.039$) arasında gözlendi. Menopoz öncesi kadınlarda, sadece testosteron varyasyon katsayısı, SDNN, PNN50, RMSSD ve HF bandı gücü ile zayıf korelasyon gösterdi. Menopoz sonrası kadınlarda, hiçbir korelasyon saptanmadı. Sıcak basması günlüğü ile değerlendirdiğimiz sıcak basması ve otonomik indeksler arasında anlamlı bir ilişki bulamadık.

Sonuç: Kadınlarda kardiyovasküler otonomik kontrol ve menopoz durumu arasında klinik olarak önemli bir ilişki bulamadık.

Anahtar kelimeler: Otonomik kontrol, menopoz, kalp hızı değişkenliği, 0.1-Hz ritimleri, seks hormonları, sıcak basmaları

Özgün Araştırma

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Türk popülasyonunda izole tek umbilikal arter görülen tekil gebeliklerde perinatal sonuçlar ve risk faktörlerinin belirlenmesi

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ÖZ

Amaç: Etnik farklılıkların etkileyebileceği bir konu olan tek umbilikal arter görülen gebeliklerde perinatal sonuçların, gebelik takibende karşılaşılabilecek olası sorunların ve tek umbilikal arter görülme riskini artıran durumların Türk popülasyonunda değerlendirilmesi.

Gereç ve yöntemler: Mayıs 2006 ve Mayıs 2013 tarihleri arasında doğum ile sonuçlanmış 16568 tekil gebelik retrospektif olarak taranmıştır. Doksan üç fetüste izole tek umbilikal arter görüldüğü saptanmıştır. Yapısal yada kromozomal bir anomalisi olmayan üç damarlı kordu olduğu gösterilmiş olan 100 gebelik kontrol grubu olarak belirlenmiştir. İstatistiksel analiz IBM SPSS 20.0 ile yapılmıştır. Non-parametrik veriler Mann Whitney U testi kullanılarak analiz edilmiş, ortalama±standart sapma olarak verilmiştir. ,005'ten küçük p değerleri anlamlı kabul edilmiştir. Etki eden diğer faktörler açısından düzeltmede odds ratio (OR) ve %95 güven aralığı çoklu lojistik regresyon analizi ile hesaplanmıştır.

Bulgular: Gebelik yaşına göre küçük fetüsler ve hipertansif bozukluklar ile komplike olan gebelik insidanslarının tek umbilikal arter grubunda artmış olduğu gözlenmiştir (sırasıyla p<0,001 ve p=0,022). Maternal sigara kullanımı tek umbilikal arter oluşumu açısından bağımsız bir risk faktörü olarak bulunmuştur (OR:3,556 95%CI: 1,104-11,45). Tek umbilikal arter grubunda erken doğum riskinin artmadığı görülmüştür (OR:0,538 95%CI:0,576-2,873). Güven vermeyen fetal kardiyotokografi nedeniyle sezaryene alınan hasta oranlarının çalışma ve kontrol gruplarında aynı olduğu görülmüştür (p=0,499).

Sonuç: Tek umbilikal arter tanısı alan gebeliklerde, takiplerde hipertansif olayların gelişimi açısından dikkatli olunması ve fetal gelişimin gebelik yaşına göre küçük olabileceği hakkında ebeveynlerin bilgilendirilmesi akılcı bir yaklaşım olabilir. Erken doğum için başka risk faktörü bulunmayan tek umbilikal arterli gebeliklerin, erken doğum açısından diğer gebeliklerden daha sıkı takip edilmesi gereksiz gibi görünmektedir.

Anahtar kelimeler: İzole tek umblikal arter, gebelik sonuçları, erken doğum, hipertansif bozukluk, düşük doğum ağırlığı

Özgün Araştırma

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Gestasyonel Diyabet Melitus Taraması ve Sonuçları

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ÖZ

Amaç: Gestasyonel Diabetes Mellitus için belirgin risk faktörü olmayan 35 yaşından genç kadınlarda, maternal ve neonatal olumsuz sonuçların önlenmesinde, Dünya Sağlık Örgütü kriterlerinin Gestasyonel Diabetes Mellitus tanısını koymaktaki fayda ve etkinliğini gerçeklemektir.

Gereç ve yöntemler: İstanbul'da bulunan üniversite hastanesinde takip edildikten sonra doğum yapan 1360 gebeyi kapsayan, retrospektif nüfus-bazlı bir çalışmadır. Bütün kadınlara, hamileliklerinin 24-28›inci haftaları arasında, 75 gr.lık Oral Glükoz Tolerans Testi yapıldı. Tüm vakalarda, Gestasyonel Diabetes Mellitus tanısı Dünya Sağlık Örgütü kriterine göre konuldu.

Bulgular: Bu çalışmada, Gestasyonel Diabetes Mellitus için risk faktörü taşımayan <35 yaş gebe kadınların yaklaşık %28›ine Oral Glükoz Tolerans Testi ile tanı konuldu. Gestasyonel Diabetes Mellitus grubunda, primer sezaryen oranının belirgin şekilde yüksek çıktığı görüldü. Erken doğumların da Gestasyonel Diabetes Mellitus ile ilişkili olduğu tespit edildi. Gestasyonel Diabetes Mellitus tanısının, Yenidoğan Yoğun Bakım Ünitesi'ne alınmayla sıkı bir bağlantısı olduğu görüldü. Yeni doğan solunum problemleri, gruplar arasında belirgin bir farklılık göstermedi. Gestasyonel Diabetes Mellitus ve metabolik komplikasyonlar arasında orta düzeyde bir ilişki görüldü.

Sonuç: Belirgin bir risk faktörü taşımayan gebelere Dünya Sağlık Örgütü kriteri kullanılarak Gestasyonel Diabetes Mellitus tanısı konuldu. Bu kadınların tedavisi primer sezaryen, polihidramniyon, erken doğum, Yenidoğan Yoğun Bakım Ünitesi'ne alınması, gebelik yaşına göre büyük olma ve doğum ağırlığı yüksek yeni doğan gibi, maternal ve neonatal hiper glisemi ile ilişkili olumsuzlukların riskini potansiyel olarak azalttı.

Anahtar kelimeler: Gestasyon, diyabet, melitus, gebelik, oral glukoz tolerans test, neonatal sonuçlar

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Özgün Araştırma

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Tek insizyondan iki portla laparoskopik tüp ligasyonu: Maliyet karşılaştırması ve teknik tanımlaması

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ÖZ

Amaç: Laparoskopik cerrahi jinekolojik patolojilerin tedavisinde kullanılan temel minimal invaziv tekniktir. Tek insizyondan gerçekleştirilen laparoskopik cerrahi (SILS) ise minimal invaziv tıptaki bir başka yeniliktir. İşlemin maliyeti abdominal kaviteye ulaşmak ve trokarları kullanmak için gereken temel teçhizatın maliyeti ile orantılıdır.

Gereç ve yöntemler: Üç hastaya tek insizyondan tubal ligasyon işlemi uygulandı. Umblikusa 15-20 mm uzunluğunda dikey bir kesi yapıldı. Abdomen şişirildikten sonra iki adet trocar aynı insizyondan fakat farklı fasyal bölgelerden yerleştirildi. Aksesuar trokardan yerleştirilen bipolar koter ile tubaların orta kısımları koterize edildikten sonra kesildi.

Bulgular: Hastaların postoperatif takipleri olağandı. Tüm hastalar ameliyat edildikleri gün taburcu edildi. Major veya minor komplikasyon gelişmedi.

Sonuç: Batına giriş maliyeti %82 oranında düştü. Tubal ligasyon için yapılan geri ödemenin düşüklüğünü göz önünde bulundurursak, bu yöntemle tek insizyon tekniği daha uygulanabilir hale gelmektedir. Dahası hastalar, tek insizyon laparoskopinin avantajlarından daha düşük maliyet ile faydalanabileceklerdir.

Anahtar kelimeler: Laparoskopi, maliyet, tek insizyon

Özgün Araştırma

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Juvenil granüloza hücreli tümör: 10 hastanın kliniko-patolojik değerlendirilmesi

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ÖZ

Amaç: Çalışmamızda 10 adet juvenil granüloza hücreli tümörlü (JGHT) hastanın klinik özelliklerini ve yönetimini inceledik.
Gereç ve yöntemler: Hastanemizin Jinekolojik Onkoloji kliniğinde, Nisan 1995-0cak 2014 tarihleri arasında JGHT tanısı almış 10 olgu retrospektif olarak değerlendirildi.
Bulgular: Hastaların medyan yaşı 21.5 (13-36) olarak bulundu. FIGO evreleme sistemine göre hastaların 9 tanesi evre IA, bir hasta evre IC olarak sınıflandırıldı. Hastaların 5'ine pelvik-para-aortik lenf nodu diseksiyonu yapıldı. Hiçbir hastada lenf nodunda tümöral tutulum tespit edilemedi. İki hasta dışındakilere unilateral salpingo-ooferektomi yapıldı. Diğer iki hastanın birine kistektomi diğerine total abdominal histerektomi ve bilateral salpingo-ooferektomi yapıldı. Üç hasta cerrahi tedaviden sonra adjuvan tedavi aldı. Bu hastaların 2 tanesi kemoterapi ve diğer hasta radyoterapi tedavisi aldı. Hastaların tedaviden sonra 5 tanesi çocuk isteminde bulundu ve bu 5 hastanın 4 tanesinde toplam 5 adet term gebelik elde edildi. Hastaların medyan takip süresi 58 aydı (3-113 ay). Takip süresinde hiçbir hastada rekürrens izlenmemiştir.
Sonuç: JGHT daha çok çocukluk yaş grubunda gözlenmektedir. Primer tedavisi cerrahidir. Adjuvan tedavinin yeri tartışmalıdır. Hastaların çoğu genç olduğu ve erken evrelerde sağkalım yüksek olduğu için bu hastalarda fertilite koruyucu cerrahi güvenli olarak önerilebilir.
Anahtar kelimeler: Juvenile granüloza hücreli tümör, Over, Adjuvan tedavi, Fertilite koruyucu cerrahi

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Özgün Araştırma

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Yardımcı Üreme sikluslarında gonadotropin serbestleştirici hormon agonist ile oosit maturasyonu tetiklemesi düşük dozda bile etkindir: Vaka serisi

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ÖZ

Amaç: Yardımcı üreme tedavisi uygulanan kadınlarda oosit maturasyonu için düşük-doz gonadotropin serbestleştirici hormon (GnRH) agonist kullanımının etkinliğini araştırmak.
Gereç ve yöntemler: GnRH antagonist protokol uygulanan ve oosit maturasyonu için 0.1 mg triptorelin kullanilan dokuz kadın çalışmaya dahil edildi. Hastaların çalışma sonuçları oosit maturasyonu için 0.2 mg triptorelin kullanılan benzer yaş ve oosit sayısı (n=14) olan kontrol grubuyla da karşılaştırıldı. Luteal faz günde iki kez vajinal mikronize progesteron ve 2 mg oral estradiol hemihidrat ile desteklendi.
Bulgular: Ortalama (±) oosit, matür (MII) oosit ve fertilize oosit sayıları sırasıyla 15.66±7.82, 14±7.28 ve 10.11±5.86 idi. İmplantasyon ve klinik gebelik oranları sırasıyla %46.1 ve %71.4 idi. Gebeliklerin iki tanesi canlı doğum, bir tanesi preterm doğum (ikiz), iki tanesi devam eden gebelik ve iki tanesi de düşükle sonuçlandı. Hiç bir olguda ovarian hiperstimulasyon sendromu (OHSS) izlenmedi. Kontrol grubuyla karşılaştırıldışında elde edilen oosit sayısı, implantasyon oranları ve klinik gebelik açısından anlamlı farklılık saptanmadı ($p>0.05$).
Sonuç: Bu bulgular in vitro fertilizasyon sikluslarında düşük-doz GnRH agonist ile tetiklemenin matür oosit sayısı ve klinik gebelik oranları açısından benzer etkinlikte olduğunu düşündürmektedir.
Anahtar kelimeler: Agonist tetikleme; triptorelin; oosit maturasyonu; oosit toplanması; gebelik oranı

Özgün Araştırma

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Servikal intraepitelyal neoplazilerin saptanmasında gerçek zamanlı optoektronik cihazın (truscreen) etkinliği; Prospektif gzölemesel çalışma

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ÖZ

Amaç: Bu çalışmada Truscreen (objektif optoelektronik sevikal kanser tarama cihazı)'nın servikal kanser tarama programlarının etkinliğini arttırmada tek başına kullanımı veya PAP smear yada HPV DNA testi ile kombinasyonunun etkinliğinin incelenmesi amaçlanmaktadır.
Gereç ve yöntemler: Çalışma PAP testi sonucu anormal olarak rapor edilen 285 hasta üzerinde gerçekleştirilmiştir. TruScreen ve HPV DNA taraması tüm hastalara uygulanmış, testlerin tutarlılığı ve farklılıkları servikal biyopsi sonuçları ile karşılaştırılmıştır.
Bulgular: TruScreen servikal patolojilerin saptanmasında %89,5 'lik negatif prediktif değeri ile kullanılacak bir yaklaşım olabileceği sonucuna varılmıştır. (ROC Eğri altında kalan alan=0,606).HPV DNA taraması %83 negatif prediktif değeri ve 0,620 eğri altında kalan alan değeri ile TruScreen taraması ile benzer sonuçlar göstermiştir.
Sonuç: Çalışmamızdaki veriler ışığında TruScreen %86,1 sensitivite değeri ile ve anında, kullanıcı bağımsız sonuç verebilme özellikleri ile servikal kanser taramasında kullanılabilecek bir yöntem olarak dikkat çekmektedir. PAP testin patolog ihtiyacı ve yorumlamadaki kişi bağımlı farklılıklarının Truscreen ile taramada ortadan kalkması sebebiyle özellikle düşük sosyo ekonomik düzeydeki ülkelerde kullanılabileceğini düşünmekteyiz. Ayrıca, TruScreen ve HPV taraması kombinasyonu ise taramada belirgin bir etkinlik artışı sağlamadığı gözlemlenmektedir.
Anahtar kelimeler: Servikal tarama, optoelektronik cihaz, CIN

Derleme

J Turk Ger Gynecol Assoc 2015; 16: 45-48 • DOI: 10.5152/jtgga.2015.15107

Uterus transplantasyonu uterin faktöre bağli infertilitede tedavi seceneği olabilir mi?

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ÖZ

Uterus transplantasyon arastirmalari ile ilgili guncel literatur gozden gecirilip, ozetlendi. Son yillarda uterus transplantasyonu arastirmalarinda buyuk ve onemli gelismeler sonucunda, sicanda uterus allotransplantasyonu sonrasi ilk gebelik ve dogum bildirildi. Transplantasyon teknigi daha iyi tanimlandi. Insanda da uterus allotransplantasyonu sonrasi gebelik ve dogum bildirilmis olmasina ragmen, klinik uygulama oncesi halen cevaplanmasi gereken bircok soru mevcuttur. Secilmis uterin faktor infertilite vakalarinda , tasiyici annelik halen onemli bir tedavi secenegi olmaya devam etmektedir.

Anahtar kelimeler: Uterus transplantasyonu, uterin faktor infertilitesi, gestasyonel tasiyicilik

Derleme

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Multipl skleroz; üreme çağı kadınlarını etkilediği için kontraseptif yöntem tartışmasını gerektiren bir hastalık

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ÖZ

Multipl Sklerozis (MS) Santral Sinir Sisteminde kronik inflamasyon ile karakterli otoimmün bir hastalıktır. Hastalık başlıca üreme çağındaki kadınları etkilediğinden MS hastaları için kontrasepsiyon seçenekleri hakkında bilgi sahibi olunması klinisyenin daha iyi danışmanlık vermesini sağlayabilir. Kontraseptif yöntemlerin çoğunun MS hastaları için genellikle güvenli ve etkili kabul edilmesine rağmen son zamanlarda yapılan çalışmalar bu yöntemlerin hastalık üzerine olası zararlı etkileri hakkındaki soruları artırmıştır.
MS hastalarında istenmeyen gebelikten kaçınmak için kontraseptif yöntemlerin kullanılması özellikle hastalığın alevlenme döneminde veya hastalık tam olarak kontrol altında olmadığında kritiktir. Bu derleme MS li kadın hastalarda kontraseptif seçenekleri ve onların etkilerini incelemektedir.
Anahtar kelimeler: Multipl sklerozis, kontrasepsiyon, kontraseptifler

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Olgu Sunumu

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Kısa kuyruklu spermi olan infertil erkekte COMET, TUNEL ve TEM analizleri

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ÖZ

Erkek infertilitesi fertil bireylerinkinden tamamen farklı olan sperm morfolojisi ve sperm DNA hasarı ile ilişkilidir. Doğru bir sperm DNA hasar analizi ve ejakülatın ultrastrüktürel incelemesi klinik değerlendirmede önemli bir destek sağlar. Yakın gelecekte yardımcı üreme tekniklerinde (ART) bu tip testlerin kombinasyonları kullanılarak fertilizasyon oranı, gebelik oranı ve düşüklerin öngörülebileceği umulmaktadır. Bu amaçla, çok nadir görülen kısa kuyruklu spermi olan infertil erkek vakası rapor ediyoruz. İnfertil erkek ve eşine intrasitoplazmik sperm enjeksiyonu (ICSI) ile in vitro fertilizasyon (IVF) uygulandı. Bu işlem sırasında, ejakülat olan spermin ultrastrüktürünü transmisyon elektron mikroskopi (TEM) ile inceledik ve terminal deoksinükleotidil transferaz dUTP çentik uç işaretleme (TUNEL) ve COMET analizleri ile sperm DNA hasarını hesapladık. Daha sonra, sperm DNA hasarı ve embriyo kalitesi arasındaki ilişkiyi değerlendirdik. (J Turk Ger Gynecol Assoc 2014; 15(0): 000-000)
Anahtar kelimeler: Kısa kuyruklu sperm, sperm DNA hasarı, transmisyon elektron mikroskopi

Olgu Sunumu

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Serviksin osseöz metaplazisi: Nadir bir dönüşüm

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ÖZ

Literatürde çok sayıda endometrial osseöz metaplazi vakası görülmesine rağmen 1982'den beri serviks osseöz metaplazisi olan sadece 6 olgu bildirilmiştir. 30 yaşında nulligravida bir kadın servikal kitle ile kolposkopi kliniğimize sevk edildi. Genel, jinekolojik ve kolposkopik değerlendirmeler yapıldı. Hastaya bir eksizyon biyopsisi uygulandı. Servikal osseöz metaplazi tanısı histolojik inceleme ile doğrulandı. Servikal epitel kemik epiteli dahil olmak üzere birçok epitel tipine farklılaşma kapasitesine sahiptir.
Anahtar kelimeler: Osseöz metaplazi, serviks, kolposkopi