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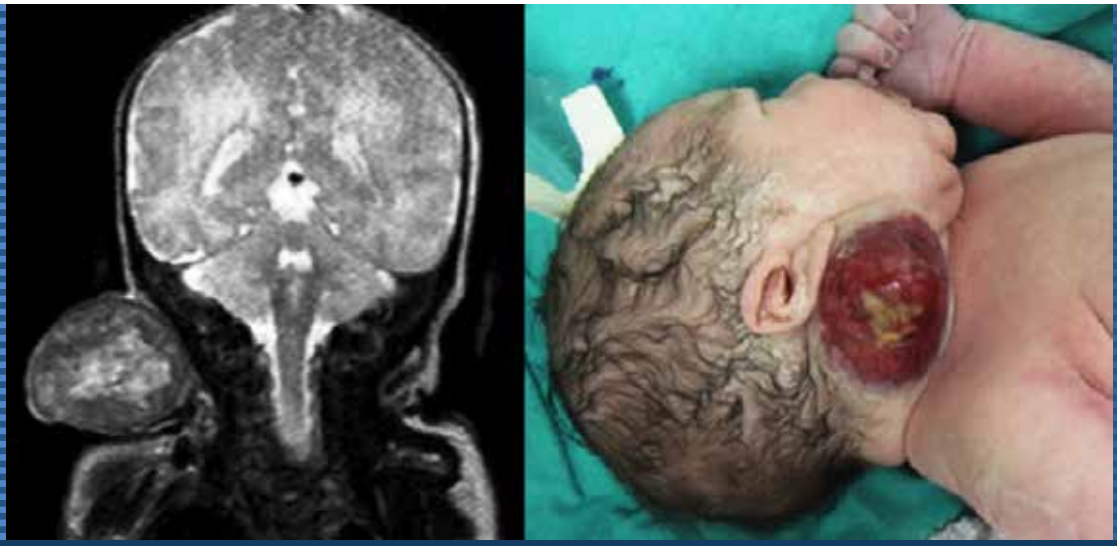

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Cover Picture: A fetal neck mass. Doğer et al. (Page: 119)

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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.

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

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State concisely the purpose and rationale for the study and cite only the most pertinent references as background.

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

The main text of case reports should be structured with the following subheadings: Introduction, Case Presentation, Discussion.

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Contents

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Editorial

Dear Colleagues,

I am delighted to introduce the second issue of the "Journal of the Turkish German Gynecological Association (JTGGA)" in the publishing year of 2015.

Many interesting articles are included in this issue from Turkey and other countries. One of them is a research article from Thailand investigating the correlation between ultrasound measured placental volume and collected umbilical cord blood volume in term pregnancy. In this issue, you will also read an attractive paper evaluating the clinical presentation, laboratory findings, and response to treatment in girls with labial adhesion younger than 23 months. As you know, male live births slightly exceed female live births by approximately 3%. The ratio of male to total live births is conventionally represented as M/F. Privation, toxins, and stress have been shown to affect M/F, all of which reduce M/F. You will find an interesting paper conducted to ascertain whether the onset of the "Great Recession" (2007) was associated with changes in M/F in the United States. You will also read a review discussing impact of obesity on infertility in women.

Turkish - German Gynecological Education and Research Foundation (TAJEV) and German-Turkish Gynecological Association (DTGG) Joint Meeting was conducted in Istanbul on May 22nd – May 24th, 2015 with a high scientific quality. More than 100 experts from Germany with different institutional background have shared their knowledge and experiences with the all the participants and Turkish colleagues. The Joint Meeting organized by the foundation has also the privilege of being the first meeting in which German language has been used as the official language in Turkey. During the meeting majority of the topics in the field of obstetrics & gynecology has been debated.

I would also like to inform you about the fifth Social Responsibility Project of our foundation - Turkish German Gynecological Education and Research Foundation (TAJEV) which will be held on September 11-12, 2015, in Çanakkale. The project is traditionally organized in four steps; public awareness meeting with participation of the locals, the scientific meeting with participation of health professionals, performing of the advanced operations and medical examination / screening to local women, and finally a medical device donation to a local hospital. We would be excited to have our colleagues join us in these intense scientific activities.

Wish you all a sunny holiday.

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

Correlation of ultrasound estimated placental volume and umbilical cord blood volume in term pregnancy

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Abstract

Objective: To investigate the correlation between ultrasound measured placental volume and collected umbilical cord blood (UCB) volume in term pregnancy.

Material and Methods: An observational cross-sectional study of term singleton pregnant women in the labor ward at Maha Chakri Sirindhorn Medical Center was conducted. Placental thickness, height, and width were measured using two-dimensional (2D) ultrasound and calculated for placental volume using the volumetric mathematic model. After the delivery of the baby, UCB was collected and measured for its volume immediately. Then, birth weight, placental weight, and the actual placental volume were analyzed. The Pearson's correlation was used to determine the correlation between each two variables.

Results: A total of 35 pregnant women were eligible for the study. The mean and standard deviation of estimated placental volume and actual placental volume were 534±180 mL and 575±118 mL, respectively. The median UCB volume was 140 mL (range 98-220 mL). The UCB volume did not have a statistically significant correlation with the estimated placental volume (correlation coefficient 0.15; p=0.37). However, the UCB volume was significantly correlated with the actual placental volume (correlation coefficient 0.62; p<0.001) and birth weight (correlation coefficient 0.38; p=0.02).

Conclusion: The estimated placental volume by 2D ultrasound was not significantly correlated with the UCB volume. Further studies to establish the correlation between the UCB volume and the estimated placental volume using other types of placental imaging may be needed.

(J Turk Ger Gynecol Assoc 2015; 16: 64-7)

Keywords: Umbilical cord blood volume, placenta parameters, ultrasound

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Introduction

Umbilical cord blood (UCB) is an established source of hematopoietic stem cells for transplantation (1, 2). It has become more popular in the new era of transplantation medicine (3).

In cord blood banking, the qualified cord blood unit was determined by the number of the total nucleated cell count (TNC) and the cluster of differentiation 34+ (CD34+) cell concentration that is adequate for engraftment (4). For an efficient banking system, some researchers look for a reliable method to predict UCB cell yield from volunteer cord blood donors (5-7). Several maternal and neonatal factors may influence the quantity and quality of UCB collection; for example, gestational age, neonatal birth weight, placental weight, route of delivery, and length of umbilical cord (7-9). The method of UCB collection also has an influence on the volume collected (10).

UCB volume is a simple, rapid, and cost-effective parameter to estimate the blood forming potential of cord blood units. The volume collected correlates well with TNC and CD34+ cell measures; the high yield of hematopoietic cells were found in a greater volume of cord blood (11). Therefore, UCB volume is used as a criterion for UCB donor selection in many centers. The minimum threshold of volume needs at collection to bank units is 50 mL (12, 13).

Placenta is a connector between maternal and fetal circulation, and it is a reservoir for passing the blood to the fetus. Thus, placental volume should be another important factor that correlates to UCB volume. There are many modalities to estimate placental volume (EPV) prenatally such as two-dimensional (2D) ultrasound (14), three-dimensional (3D) ultrasound (15), and magnetic resonance imaging (MRI) measurement (16). The 2D ultrasound is mainly used for placental measurement in the prenatal period, and these specific placental parameters can calculate placental volume using the mathematic model with good correlation (17).

The purpose of the study is to find a correlation between ultrasound EPV and UCB volume. The ability to predict the UCB volume would help in selecting UCB donors before delivery.

This research was presented as oral presentation in the 29th annual meeting of The Royal Thai College of Obstetricians and Gynecologists, 14-17 October 2014, Dusit Thani Hotel, Pattaya, Chonburi, Thailand.

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Material and Methods

This study is a cross-sectional study. The study population was singleton term pregnant women who had spontaneous vaginal delivery in our hospital from January 2014 to April 2014. The study protocol was approved by the ethical review board.
A pilot study of 10 pregnant women was performed. After data collection, the sample size was calculated using the expected correlation coefficient (r) of 0.74. This study required at least 35 participants.

Inclusion and exclusion criteria
A total of 50 Thai pregnant women in the labor room were recruited by the simple sampling method. The inclusion criteria were as follows: maternal age of >18 years, term singleton pregnancy, plan for a vaginal delivery, and consent to participate in the study. The exclusion criteria were as follows: any antenatal obstetrics complications, having any blood-borne transmission diseases such as viral hepatitis B or syphilis, history of hematopoietic malignancy, suspected fetal anomaly/fetal distress, abnormal amniotic fluid volume, rupture of amniotic membranes, and abnormality of placenta and umbilical cord. The authors also excluded cesarean delivery cases because the route of delivery may affect the collected UCB volume.

Placental volume measurement
Estimated placental volume (EPV)
All patients underwent ultrasound scans at hospital admission in the latent phase of labor using an ultrasound machine (Aloka®SSD900; BJC Healthcare, Bangkok, Thailand) with a 5 MHz 2D curvilinear abdominal transducer. After establishing a correct positioning according to the landmarks as previously described by Azpurua et al. (17), the measurement of placental height, width, and thickness were made on the same sonographic plane by the first author. Briefly, the placental location and cord insertion was identified. The ultrasound beam must be placed vertically to the placenta. The thickest non-folding part of the placenta was measured perpendicularly. The maximal placental width was measured in the range of between both edges of placenta. The placental height was the distance from the level of the width measurement to the base of the placenta vertically, as shown in Figure 1. All scans were performed during the uterine contraction-free period. After the complete linear measurement of three placental parameters, placental volume was later calculated using the convex–concave shell mathematic equation, $V=\left(\pi\frac{T}{6}\right)\times\{4H(W-T)+W(W-4T)+4T^2\}$ (17).

Actual placental volume (APV)
The placenta was examined after delivery by a standard method (18). The membranes were trimmed at the placental edge, and all of the placental mass was wrapped up with a plastic bag and put in a bucket full of water to instead of water. The spilled water was measured for its volume using a scientific glass beaker as the principle of the water volume displacement. The APV was the spilled water volume plus UCB volume.

Umbilical cord blood (UCB) volume collection
Following delivery, the baby was placed in the same level of the placenta.The umbilical cord was clamped at 7 and 12 cm from the baby's side within 2 min after birth and then cut in the usual manner. A 16-gauge needle was inserted into the umbilical vein to allow drainage of UCB from the placenta to a standard 350 ml blood collecting bag, TERUMO® blood bag with Citrate Phosphate Dextrose Anticoagulant-1 (CPDA-1) (TERUMO Thailand Co. Ltd., Bangkok, Thailand), by gravity until blood flow stopped (19). The blood collection was monitored by a blood bag weighing machine (BIOMIXER® -323; Ljungberg & Kogel AB, Helsingborg, Sweden). The UCB volume was defined as the volume of blood in the collecting bag, excluding the pre-existing anticoagulant, measured in milliliters.

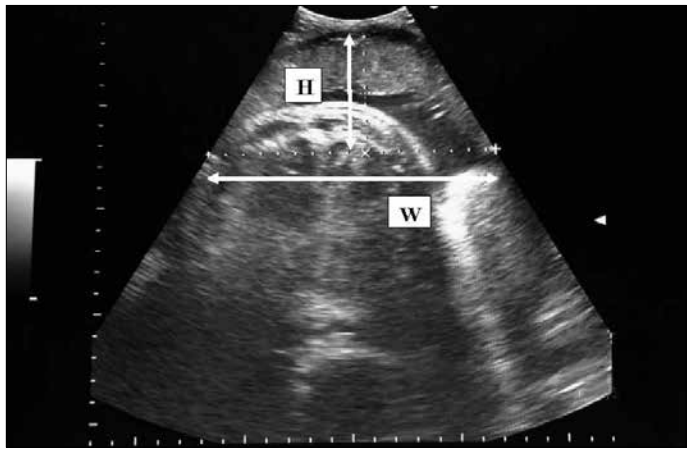

Figure 1. A two-dimensional ultrasound scan showing the measurement of placental width (W) and placental height (H) in centimeters

Statistical analysis
Statistical analysis was performed using SPSS IBM (Registration number 1975-01566-C) (Singapore Pte. Ltd., Singapore, China). The data was tested for a normal distribution. Continuous data was presented as mean and standard deviation (SD) or median and interquartile range (IQR) when appropriate. The Pearson's correlation coefficient (r) or the Spearman's rho correlation coefficient was calculated. Variable p-values <0.05 was considered statistically significant.

Results

A total of 50 pregnant women met the inclusion criteria. Five cases were excluded because the entire placental width could not be measured using ultrasound, and 10 cases were excluded because of poor visualization of the placenta due to its location. The median and interquartile range of maternal age and gestational age was 29 (IQR 26, 33) years and 38 (IQR 38, 39) weeks, respectively. The demographic and significant obstetrical parameters of the 35 participants were shown in Table 1. All the babies were healthy and showed no signs of respiratory distress. The mean and standard deviation of EPV and APV were 534±180 mL and 575±118 mL, respectively. The minimum, maximum, and mean of UCB collected were 98, 220, and 140 mL, respectively.
Figure 2 and 3 demonstrated the scatter plot of EPV, APV, and collected UCB volume in 35 participants. The APV was significantly correlated with UCB volume ($r=0.62$; $p<0.001$), where-

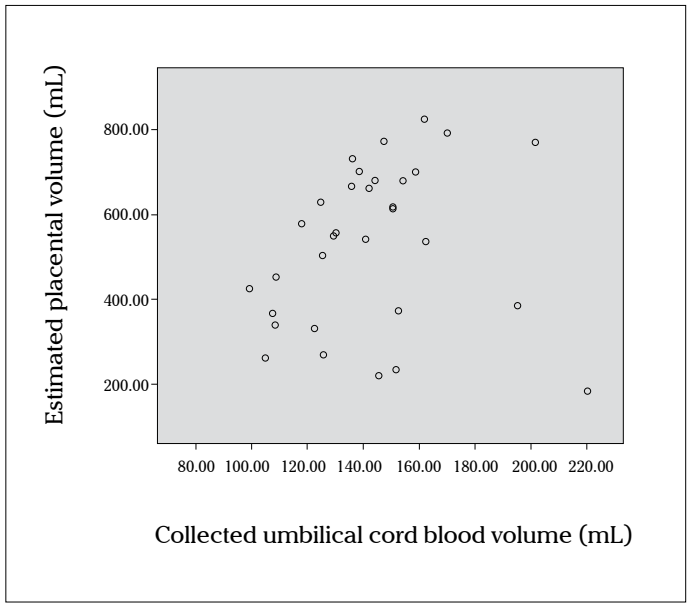

Figure 2. Scatter plot of estimated placental volume and umbilical cord blood volume. The correlation coefficient was 0.15; p=0.37

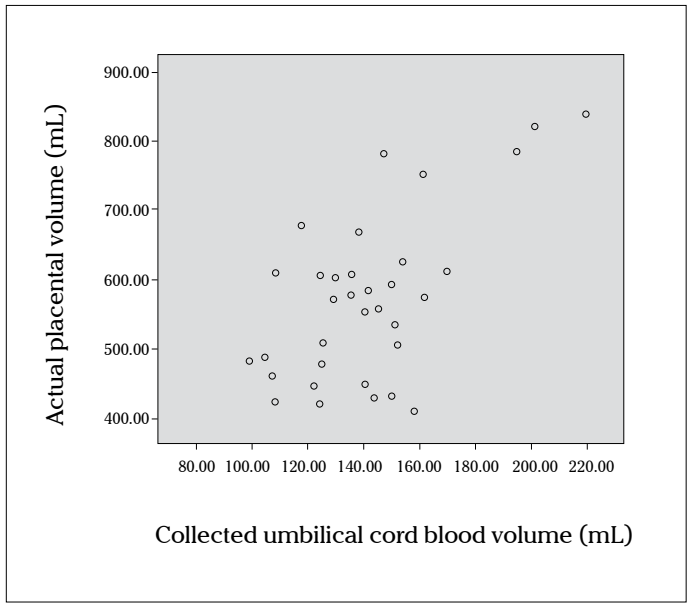

Figure 3. Scatter plot of actual placental volume and umbilical cord blood volume. The correlation coefficient was 0.62; p<0.001

Table 1. Demographic data of the participants (n=35)

	Median	(1st and 3rd interquartile range)
Age (year)	29	(26, 33)
Gestational age (week)	38	(38, 39)
Maternal BMI (kg/m^2)	25	(24, 29)
Neonatal birth weight (gram)	3090	(2890, 3300)

BMI: body mass index
n=number of patients
kg/m^2=kilogram per meter square

Table 2. Correlation of umbilical cord blood volume to other factors (n=35)

Factors	Correlation (r)	p value
Estimated placental volume	0.15	0.37
Actual placental volume	0.62	<0.001
Placental weight	0.57	<0.001
Neonatal birth weight	0.38	0.02

n=number of patients
r=correlation coefficient

as the EPV had no statistically significant correlation (r=0.15; p=0.37). The neonatal birth weight correlated with the UCB volume (r=0.38; p=0.02) as shown in Table 2.

Discussion

The collection of UCB for transplantation is still a good source of stem cell therapy. Currently, Thailand has only one public cord blood bank. The National Blood Center at Thai Red Cross Society serves the need of UCB transfusion for all of the Thai recipients. Because the UCB donors are limited by many factors, the UCB unit storages have never met its demand (20). Several factors play a role in the quality of the UCB unit, such as its volume, TNC, CD34+concentration, and sterility control (21). In this study, the authors focused primarily on UCB volume collected and its correlation with placental measurements. Because the placenta is the reservoir for the blood to be transferred to the baby, a larger placental volume should result in a higher volume of cord blood collected.

Interestingly, the authors found that EPV measured by the 2D ultrasound was not statistically correlated with UCB volume. The authors used 2D placental parameters to calculate its volume with a specific mathematic model (14, 17). Although this mathematical formula has been validated in previous studies and the authors limited the inter-operator variability, it is still possible that there were some errors in the EPV measurement. Another possibility that may have influenced the results with the EPV is a uterine contraction. More placental blood is shifted from the placenta into the baby during labor. This contributes to the poor correlations with the EPV measurement. A few limitations that may affect the reliability of the measurement included placental location, shape of the placenta, size of the placenta, and poor image quality. Differences in patients' demographics and a few number of participants also has an influence on the result. On the other hand, the method of UCB collection may interfere with the volume collected; therefore, the authors chose a simple technique based on gravity, which is commonly used in clinical practice. The mean volume of UCB collected in this research was >50 mL. This finding suggested that we can get enough UCB volume with our current technique.

In accordance with Wen SH et al. (9) and Urciuoli P et al. (22), the authors observed the positive correlation of placental weight and UCB volume. The APV and the UCB also show a

high correlation in this study. These findings support the theory that the larger the placenta, the higher volume of cord blood will be collected. Therefore, the problem lies within what is the accurate method for antenatal estimation of the placental volume. Future studies are needed to explore a reliable modality for antenatal placental volumetric measurement. Other types of placental imaging such as a 3D ultrasound or placental MRI may be the interesting options.

Our data also demonstrated that the neonatal birth weight was correlated with the UCB volume. A previous study in the Italian population suggested that sonographic parameters such as fetal abdominal circumference and femur length may be used to predict UCB unit bankability (6). A further research in the Thai population to validate fetal biometric measurement for predicting UCB volume could also be beneficial.

The limitations of the study were a small number of participants, lack of sterility control, and no cell count report that may reflect the UCB transplant efficiency.

In conclusion, the EPV by 2D ultrasound is not correlated with UCB volume and cannot be used for prenatal selection of UCB donor. Other measures for estimation of placental volume should be further studied to improve the UCB bank efficiency.

Ethics Committee Approval: *Ethics committee approval was received from the ethical review board, Srinakarinwirot University (SWUEC/EX-23/2556, SWUEC/X-020/2557).*

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

Peer-review: *Externally peer-reviewed.*

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

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References

1. Metheny L, Caimi P, de Lima M. Cord Blood Transplantation: Can We Make it Better? Front Oncol 2013; 3: 238. [CrossRef]
2. Yu X, Gu Z, Wang Y, Wang H. New strategies in cord blood cells transplantation. Cell Biol Int 2013; 37: 865-74. [CrossRef]
3. Oran B, Shpall E. Umbilical cord blood transplantation: a maturing technology. Hematology Am Soc Hematol Educ Program 2012; 2012: 215-22.
4. George TJ, Sugrue MW, George SN, Wingard JR. Factors associated with parameters of engraftment potential of umbilical cord blood. Transfusion 2006; 46: 1803-12. [CrossRef]
5. Nakagawa R, Watanabe T, Kawano Y, Kanai S, Suzuya H, Kaneko M, et al. Analysis of maternal and neonatal factors that influence the nucleated and CD34+ cell yield for cord blood banking. Transfusion 2004; 44: 262-7. [CrossRef]
6. Cobellis L, Castaldi MA, Trabucco E, Imparato G, Perricone F, Frega V, et al. Cord blood unit bankability can be predicted by prenatal sonographic parameters. Eur J Obstet Gynecol Reprod Biol 2013; 170: 391-5. [CrossRef]
7. Page KM, Mendizabal A, Betz-Stablein B, Wease S, Shoulars K, Gentry T, et al. Optimizing donor selection for public cord blood banking: influence of maternal, infant, and collection characteristics on cord blood unit quality. Transfusion 2014; 54: 340-52.
8. Solves P, Perales A, Moraga R, Saucedo E, Soler MA, Monleon J. Maternal, neonatal and collection factors influencing the haematopoietic content of cord blood units. Acta Haematol 2005; 113: 241-6. [CrossRef]
9. Wen SH, Zhao WL, Lin PY, Yang KL. Associations among birth weight, placental weight, gestational period and product quality indicators of umbilical cord blood units. Transfus Apher Sci 2012; 46: 39-45. [CrossRef]
10. Dennopporn S, Wacharaprechanont T. Comparison of three methods in umbilical cord blood collection for hematopoietic stem cell transplantation. Thai J Obstet Gynaecol 2002; 14: 183-92.
11. Chandra T, Afreen S, Kumar A, Singh U. Correlation of umbilical cord blood volume with CD34+ cells concentration. Int J Blood Transfus Immunohematol 2011; 1: 11-5. [CrossRef]
12. O-Charoen R. Cord blood bank in Thailand. Thai J Hematol Transfus Med 2006; 16: 239-42.
13. Allan D, Petraszko T, Elmoazzen H, Smith S. A review of factors influencing the banking of collected umbilical cord blood units. Stem Cells Int 2013; 2013: 463031. [CrossRef]
14. Arleo EK, Troiano RN, da Silva R, Greenbaum D, Kliman HJ. Utilizing two-dimensional ultrasound to develop normative curves for estimated placental volume. Am J Perinatol 2014; 31: 683-8.
15. Hata T, Tanaka H, Noguchi J, Hata K. Three-dimensional ultrasound evaluation of the placenta. Placenta 2011; 32: 105-15. [CrossRef]
16. Derwig IE, Akolekar R, Zelaya FO, Gowland PA, Barker GJ, Nicolaides KH. Association of placental volume measured by MRI and birth weight percentile. J Magn Reson Imaging 2011; 34: 1125-30. [CrossRef]
17. Azpurua H, Funai EF, Coraluzzi LM, Doherty LF, Sasson IE, Kliman M, Kliman HJ. Determination of placental weight using two-dimensional sonography and volumetric mathematic modeling. Am J Perinatol 2010; 27: 151-5. [CrossRef]
18. Baergen RN. Macroscopic examination of the placenta immediately following birth. Journal of Nurse-Midwifery 1997; 12: 393-403. [CrossRef]
19. Martin PL, Kurtzberg J, Hesse B. Umbilical cord blood: a guide for primary care physicians. Am Fam Physician 2011; 84: 661-6.
20. Mancinelli F, Tamburini A, Spagnoli A, Malerba C, Suppo G, Lasorella R, et al. Optimizing umbilical cord blood collection: impact of obstetric factors versus quality of cord blood units. Transplant Proc 2006; 38: 1174-6. [CrossRef]
21. Wacharaprechanont T, O-Charoen R, Vanichsetakul P, Sudjai D, Kupatawintu P, Seksarn P, et al. Cord blood collection for the National Cord Blood Bank in Thailand. J Med Assoc Thai 2003; 86: S409-16.
22. Urciuoli P, Passeri S, Ceccarelli F, Luchetti B, Paolicchi A, Lapi S, et al. Pre-birth selection of umbilical cord blood donors. Blood Transfus 2010; 8: 36-43.

Labial adhesion and bacteriuria

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Abstract

Objective: The purpose of this study is to evaluate the clinical presentation, laboratory findings, and response to treatment in girls with labial adhesion younger than 23 months.

Material and Methods: A retrospective chart review of all girls younger than 23 months with the diagnosis of labial adhesion was referred to Dr Sheikh children's clinic in Mashhad in northeast Iran between 1998 and 2013.

Results: Sixty-three patients were diagnosed with labial adhesion during the review period. Most patients were diagnosed by physicians during the physical examination or during the evaluation for their voiding problems. The most prevalent symptom among patients was dysuria and restlessness while voiding. Twenty-one (33.3%) patients had a history of urinary tract infection. 17 (26.9%) patients had sterile pyuria and 69.8% showed presence of bacteria in their urine samples.

Conclusion: Physicians may frequently encounter pre-pubertal girls whose urinalysis may show sterile pyuria or presence of bacteria with colony counts <105 in the absence of urinary tract infection symptoms. In these cases, labial adhesion should always be suspected and genital examination should be performed. (J Turk Ger Gynecol Assoc 2015; 16: 68-9)

Keywords: Labial adhesion, bacteriuria, urinary tract infection, topical estrogen

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Introduction

Labial adhesion is a common pediatric gynecological problem which occurs in 0.6%–5% of pre-pubertal girls (1). Its prevalence may be even greater because many patients with this condition are asymptomatic and may go undetected. Its peak incidence is between 3 and 23 months and is rarely observed after the age of 6 years (2).

Although the exact etiology of labial adhesion is not known, it is probably associated with hypoestrogenism in pre-pubertal girls (3). Vulvar inflammation and irritation due to various conditions such as vulvuvaginitis, diarrhea, and dermatological problems are also a suspect (4).

Labial adhesion may be asymptomatic and is found accidentally by a physician or a caretaker or it may cause symptoms such as urinary tract infection and pain during activity, postvoid dripping, and abnormal urinary stream (2, 3). It may rarely present as urinary retention (5).

Asymptomatic patients with minor adhesions may need no treatment, and they can only be observed because this condition can resolve spontaneously, particularly with the onset of puberty and the resultant estrogen production (4). Symptomatic patients and those with a complete adhesion should be treated (6). The treatment includes nonsurgical and surgical methods. Topical estrogen in combination with vulvar hygiene is generally the first-line treatment with a success rate between 50% and 88% (7, 8). The use of topical betamethasone is an alternative (8, 9), and surgical separation should be considered in refractory cases that are not responsive to conservative management (10).

Material and Methods

This research work is a retrospective study. The medical records of all children under the age of 2 years who had been admitted to Dr Sheikh Children's clinic in Mashhad, in the northeast of Iran, between 1998 and 2013, with the diagnosis of labial adhesion were reviewed. The study was approved by the medical ethics commitee of Mashhad University of Medical sciences prior to the start of the study.

Sixty-three patients met the inclusion criteria and were analyzed. Demographic information included the age at the time of diagnosis and the place of residence (Table 1).

Adhesions were viewed as involving more or less than 50% of the vestibule.

Patients' symptoms and the history of urinary tract infection were also evaluated.

Patients were also evaluated for the presence of urinary tract infection and bacteriuria.

Statistical analysis

All statistical analysis was performed using SPSS for Windows, Version 16.0 statistical package (SPSS Inc., Chicago, IL, USA). The results are expressed as mean and percents.

Results

All our patients in this study were under the age of 2 years and were in diapers. Most of the patients (73%) were between 6 and 12 months. Three of the patients were diagnosed by their parents because of their abnormal genital appearance.

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Table 1. Demographic charachteristics of patients with labial adhesion

Age at diagnosis	1-6 months	16 (25.4%)
	6-12 months	29 (46%)
	12-24 months	18 (28.6%)
Place of residence	Urban	45 (71.4%)
	Rural	18 (28.6%)

Twenty-four patients were diagnosed by their primary care physicians and 36 patients were diagnosed during evaluation for their voiding problems.
Forty-three patients at the time of referral had adhesion of greater than 50% of the vestibular opening.
Twenty-one patients had a history of urinary tract infection and 38 patients had complaints such as dysuria or restlessness while voiding. Twenty patients had a history of altered urinary stream or post-void dripping.
None of our patients complained about urinary retention.
Urinalysis and urine culture was performed for all patients. Seventeen patients had pyuria [white blood cell (WBC) >5/hpf] in their urinalysis and the urine culture of three patients was positive for *Esherishia coli* (*E. coli*) with a colony count of $>10^5$. The urinalysis of 44 (69.8%) patients showed a presence of moderate to severe bacteria.
All 63 patients were treated with topical estrogen therapy in this study. Seventeen patients responded to treatment after 2 weeks, 29 patients in 2–3 weeks, and three patients received topical estrogen therapy for >3 weeks. Fourteen patients were lost in the follow-up.

Discussion

Labial adhesion is a common urologic condition in pre-pubertal girls (1) and is considered as an acquired condition (11). Physicians may often receive referrals for the evaluation and treatment of this condition.
Patients in our study generally match those classically reported in the pediatric literature. This condition was most prevalent between 6 and 12 months, which is similar to previous studies (4, 9, 10).
All patients were treated with the traditional topical estrogen therapy. Most of them responded to this treatment. In a study, all 20 girls (up to 3 years of age) responded to treatment with estrogen therapy and had minimal recurrence rate (12). Another study from Turkey reported a success rate of 66% among 49 girls (13). Another study with 107 patients reported successful separation in 79% of patients; however, almost 40% of these patients had recurrence and needed repeated treatments (14). However, one study has reported a success rate of <50% with topical estrogen therapy; 262 girls were studied in this study and a recurrence rate of 11% was reported (15).
The patients with pyuria was 26.9%, and 69.8% showed a presence of moderate to severe bacteriuria. Leung and Robson found that asymptomatic bacteriuria is quite prevalent in girls with labial fusion and have recommended that a urine culture be performed in girls with labial fusion and girls with bacteriuria be checked for labial fusion (16), which is similar to the results of our study.
In conclusion we strongly recommend physicians to perform genital examination in girls who show sterile pyuria or significant bacteriuria in their urinalysis.

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

Informed Consent: *This was a retrospective chart review. Informed consent was not received due to the retrospective nature of the study.*

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

Author Contributions: *Concept - A.A., M.E., Y.R.; Design - A.A., S.B.; Supervision - A.A., M.E.; Resource - M.M., S.B.; Materials - A.A., M.M., S.B.; Data Collection & /or Processing - A.A., Y.R., M.M.; Analysis & /or Interpretation - Y.R., S.B.; Literature Search - S.B.; Writing - A.A., S.B.; Critical Reviews - A.A., M.E., Y.R.*

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References

1. Omar HA. Management of labial adhesions in prepubertal girls. J Pediatr Adolesc Gynecol 2000; 13: 183-5. [CrossRef]
2. Bacon JL. Prepubertal labial adhesions: evaluation of a referral population. Am J Obst Gynecol 2002; 187: 327-31. [CrossRef]
3. Girton S, Kennedy C. Labial adhesion: a review of etiology and management. Postgraduate Obstet Gynecol 2006; 26: 1. [CrossRef]
4. Leung AK, Robson WL, Tay-Uyboco J. The incidence of labial fusion in children. J Pediatr Child Health 1993; 29: 235-6. [CrossRef]
5. Norbeck J, Ritchey M, Bloom D. Labial fusion causing upper urinary tract obstruction. Urology 1993; 42: 209-11. [CrossRef]
6. Erouglu E, Yip M, Oktar T, Kayiran SM, Mocan H. How should we treat prepubertal labial adhesions? Retrospective comparison of topical treatments: estrogen only, betamethasone only, and combination estrogen and betamethasone. J Pediatr Adolesc Gynecol 2011; 24: 389-91. [CrossRef]
7. Soyer T. Topical estrogen therapy in labial adhesions in children: therapeutic or prophylactic. J Pediatr Adolesc Gynecol 2007; 20: 241-4. [CrossRef]
8. Mayoglou L, Dulabon L, Martin Alguacil N, Pfaff D, Schober J . Success of treatment modalities for labial fusion: a retrospective evaluation of topical and surgical treatments. J Pediatr Adolesc Gynecol 2009; 22: 247-50. [CrossRef]
9. Myers J, Sorensen C, Wisner BP, Furness PD, Passamaneck M, Koyle MA. Betamethasone cream for the treatment of pre-pubertal labial adhesions. J Pediatr Adolesc Gynecol 2006; 19: 407-11. [CrossRef]
10. Nurzia M, Eickhorst K, Ankem M, Barone JG. The surgical treatment of labial adhesions in pre-pubertal girls. J Pediatr Adolesc Gynecol 2003; 16: 21-3. [CrossRef]
11. Griton S, Kennedy CM. Labial adhesion: a review of etiology and management. Postgraduate Obstet Gynecol 2006; 26: 1-5. [CrossRef]
12. Leung AK, Robson WL, Kao CP, Liu EK, Fong JH. Treatment of labial fusion with topical estrogen therapy. Clin Pediatr (Phila) 2005; 44: 245-7. [CrossRef]
13. Soyer T. Topical estrogen therapy in labial adhesions in children: therapeutic or prophylactic? J Pediatr Adolesc Gynecol 2007; 20: 241-4. [CrossRef]
14. Schober J, Dulabon L, Martin-Alguacil N, Kow LM, Pfaff D. Significance of topical Estrogens to labial fusion and vaginal introital integrity. J Pediatr Adolesc Gynecol 2006; 19: 337-9. [CrossRef]
15. Muram D. Treatment of prepubertal girls with labial adhesions. J Pediatr Adolesc Gynecol 1999; 12: 67-70. [CrossRef]
16. Leung AK, Robson WL. Labial fusion and asymptomatic bacteriuria. Eur J Pediatr 1993; 152: 250-1. [CrossRef]

The Great Recession of 2007 in the United States and the male: female ratio at birth

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Abstract

Objective: Male live births slightly exceed female live births by approximately 3%. The ratio of male to total live births is conventionally represented as M/F. Many factors have been shown to affect M/F, mainly privation, toxins, and stress, all of which reduce M/F. Population stress may be engendered by natural phenomena such as earthquakes and man-made events such as short wars, terrorist attacks, and contracting economies. This study was conducted to ascertain whether the onset of the "Great Recession" (2007) was associated with changes in M/F in the United States (US).

Material and Methods: Annual monthly live births by gender for January 2006 to December 2008 were obtained from United States Centres for Disease Control and Prevention.

Results: In 2007, there were 4316233 live births [M/F: 0.51157; 95% confidence intervals: 0.51110–0.51205). M/F rose between January and June, and then fell sharply between August and December. M/F was statistically significantly lower in the second half of 2007 (p=0.007). The dip in M/F from June to July was also significant (p=0.02). These findings were not replicated in the amalgamated data for 2006 and 2008.

Conclusion: The United States housing boom of the mid-2000s was fueled by rising house prices and cheap mortgages given to credit-poor buyers. A halt in rising house prices resulted in defaults and foreclosures, triggering the worst financial crisis since the Great Depression. The associated stress appears to have decreased M/F in the US. (J Turk Ger Gynecol Assoc 2015; 16: 70-3)

Keywords: United States, economic recession, birth rate/trends, infant, newborn, sex ratio

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Introduction

Male live births slightly exceed female live births by a difference of approximately 3% (1). The ratio of male to total live births is conventionally (albeit technically erroneously) represented as M/F.

Many factors have been shown to affect M/F, and the principal factors include privation (2), toxins (1, 3), and stress (4), all of which tend to reduce M/F.

Population stress may be engendered through a variety of occurrences, including natural phenomena such as earthquakes (5), flooding, and the great London Smog (6). Man-made events have also been shown to reduce M/F, and these include short duration wars (7) and terrorist attacks (8).

The latter was famously shown after the September 11 attacks on the United States in 2001, where M/F dipped not only in New York(4) but also across the country in California (8). The M/F drop occurred 3–4 months after the event (4, 8) and was shown to be associated with an excess of male fetal losses (9).

Contracting economies have also been shown to reduce M/F, as was witnessed in East Germany in 1991, the year following this country's reunification (10). However, not all studies are in agreement, with some failing to demonstrate significant M/F reductions in response to parental stress (11).

The "Great Recession" is a term used to describe the worldwide economic decline that occurred at the end of this century's first decade. The International Monetary Fund stated that this was the worst global recession since the second world war (12-14).

The United States National Bureau of Economic Research has defined the recession as lasting 18 months, from December 2007 to June 2009. This was preceded by a subprime mortgage crisis wherein lenders who had offered home loans to individuals with poor credit lost these high-risk mortgages as the borrowers went into default (13, 14).

This study was conducted to ascertain whether these events were associated with changes in M/F.

Material and Methods

Annual monthly live births by gender between January 2006 and December 2008 were obtained from the website of the United States (US) Centers for Disease Control and Prevention (15). The amalgamation of monthly data for the two years adjacent to 2007, i.e., 2006 and 2008, were chosen for the purpose of comparison. Longer stretches were avoided as M/F is known to undergo secular changes, which this study aimed to avoid (16). This comparison was made to gauge whether any changes in M/F were greater than those normally expected by seasonality in M/F, which is known to rise in the US from February to June, followed by a drop in December (17, 18).

Excel was used for data entry, overall analysis, and charting.

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Table 1. Male/Female comparisons for the United States in 2006, 2007, and 2008

	2006	2007	2008		Jul–Dec	2006	2007	2008	
Male	1634031	2208071	1644413		Male	578860	1131438	571877	
Female	1556227	2108162	1567747		Female	551583	1082984	544805	
Total	3190258	4316233	3212160		Total	1130443	2214422	1116682	
UCI	0.51274	0.51205	0.51248		UCI	0.51299	0.51160	0.51305	
M/F	0.51219	0.51157	0.51193		M/F	0.51206	0.51094	0.51212	
LCI	0.51165	0.51110	0.51139		LCI	0.51114	0.51028	0.51119	
chi		2.8	1.0		chi		3.79	4.14	
p		1.0	0.3		p		0.052	0.042	
2007	**Jan–Jun**	**Jul–Dec**	**Jul**	**Aug**	**2006+2008**	**Jan–Jun**	**Jul–Dec**	**Jul**	**Aug**
Male	1076633	1131438	194754	199240	Male	2127707	2229919	381128	389510
Female	1025178	1082984	184862	191138	Female	2027586	2128037	362190	371621
Total	2101811	2214422	379616	390378	Total	4155293	4357956	743318	761131
UCI	0.5129	0.5116	0.5146	0.5119	UCI	0.51253	0.51216	0.51388	0.51288
M/F	0.5122	0.5109	0.5130	0.5104	M/F	0.51205	0.51169	0.51274	0.51175
LCI	0.5116	0.5103	0.5114	0.5088	LCI	0.51157	0.51122	0.51160	0.51063
chi		7.29		5.42	chi		1.09		1.47
p		0.007		0.020	p		0.296		0.226
% males	51.22	51.09	51.30	51.04	% males	51.20	51.17	51.27	51.18
Difference		0.13		0.27	Difference		0.04		0.10
2006	**Jan–Jun**	**Jul–Dec**	**Jul**	**Aug**	**2008**	**Jan–Jun**	**Jul–Dec**	**Jul**	**Aug**
Male	1055171	578860	188772	198576	Male	1072536	571877	192356	190934
Female	1004644	551583	179162	189222	Female	1022942	544805	183028	182399
Total	2059815	1130443	367934	387798	Total	2095478	1116682	375384	373333
UCI	0.51295	0.51299	0.51468	0.51363	UCI	0.51251	0.51305	0.51402	0.51304
M/F	0.51226	0.51206	0.51306	0.51206	M/F	0.51183	0.51212	0.51242	0.51143
LCI	0.51158	0.51114	0.51144	0.51049	LCI	0.51116	0.51119	0.51082	0.50983
chi		0.12		0.75	chi		0.24		0.74
p		0.732		0.385	p		0.623		0.390
% males	51.23	51.21	51.31	51.21	% males	51.18	51.21	51.24	51.14
Difference		0.02		0.10	Difference		−0.03		0.10

M/F: male divided by total live births; UCI: upper 95% confidence intervals; LCI: lower 95% confidence intervals

The quadratic equations of Fleiss were used for exact calculation of 95% confidence intervals for ratios (19). Chi tests and chi tests for trends for annual male and female births were used throughout using the Bio-Med-Stat Excel add-in for contingency tables (20). A p-value ≤0.05 was taken to represent a statistically significant result. The analysis was of a large and anonymous dataset. Ethical approval was therefore not required. Informed consent was also not required for the same reason.

Results

This study analyzed 12829482 live births (6257104 males and 6572378 females) between 2006 and 2008. There was no statistically significant change in M/F between 2007 and the previous and following years (Table 1).

In 2007, there were a total of 4316233 live births with 2208071 males and 2108162 females (M/F 0.51157; 95% confidence intervals: 0.51110–0.51205). Monthly M/Fs are shown in figure 1. M/F rose from January to June and then fell sharply from August to December.

M/F was statistically significantly lower in the second half of 2007 when compared with that in the first half (p=0.007; Table 1). The dip in M/F from July to August was also statistically significant (p=0.02). The percentage changes in M/F in 2007 are shown in Table 1, with a 0.13% decrease in male births from the first to the second halves of the year, and a 0.27 reduction between July and August; this occurred despite a rise in total births. For the amalgamation of 2006 and 2008 data, the declines were 0.04 and 0.10%, respectively, and these declines were not statistically significant (Table 1).

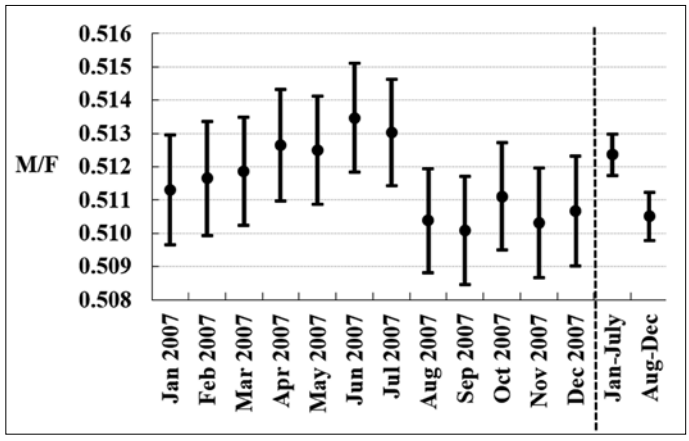

Figure 1. Monthly M/F for the United States in 2007, as well as the first and second halves of 2007

M/F was statistically significantly lower in the second half of 2007 when compared with that of the following year and was almost significantly lower when compared with that of the previous year (Figure 1).

Discussion

The United States housing boom of the mid-2000s was fueled by several factors. These were low mortgage interest rates, low short-term interest rates, relaxed standards for mortgage loans, and "irrational exuberance" (21). These factors prompted lenders to recklessly offer home loans to individuals with poor credit ratings, with the argument being that because house prices had not decreased nationwide since the Great Depression, then this trend would inevitably continue. Government regulators felt no need to attempt to control escalating home prices, not recognizing this as a bubble in the making (21).

In fact, the situation was such that mortgages would only continue to have interest rates if house prices kept rising, which was an unwarranted assumption. Furthermore, these mortgages were used to back securities, which would only continue to perform well if house prices continued to ascend. Furthermore, credit rating agencies continued to give AAA ratings to securities backed by subprime, but potentially adjustable, mortgage rates. This also encouraged foreign investors to heavily invest in these unreliable securities. All these factors made the housing bubble more extreme and fragile and the ensuing credit crisis more severe (21). When the real estate bubble burst, many borrowers were unable to make payments on their subprime mortgages and were unable to refinance them, resulting in defaults and foreclosures. This initiated the eventual cascade that continued as the "Great Recession," the worst financial crisis since the Great Depression (13, 14).

As a result of these influences, housing prices peaked in early 2006 and started to decline in late 2006 and 2007. The result was profound and affected not only the US economy but also international banks and the global economy. Warning signs commenced early in 2007. In February, the Hongkong and Shanghai Banking Corporation issued a warning of substantial losses in its mortgage arm because of subprime losses (13, 14).

The Federal Home Loan Mortgage Corporation (Freddie Mac, Fairfax County, Virginia), a public government-sponsored enterprise started tightening standards in February after a surge in subprime mortgage defaults publicly stating that it would stop entering into risky home loans (13, 14). In April, the subprime lender New Century Financial filed for bankruptcy with billions of dollars worth of bad loans, making over 3000 employees redundant and piling pressure on other US mortgages banks (13, 14).

In June 2007, Standard and Poor's and Moody's Investor Services downgraded over a 100 bonds backed by subprime mortgages. In the following month, Standard and Poor's placed 612 securities (backed by subprime mortgages) on a credit watch, and Countrywide Financial Corporation warned of upcoming difficult conditions. Bear Stearns also liquidated two hedge funds that invested in various mortgage-backed securities. Credit markets completely seized up in August when Banque Nationale de Paris, a large international bank, announced that two of its hedge funds were frozen (13, 14).

All this was associated with significant stress (22), leading to even suicides, not only in the US but also globally (23-25). Warning signs of the looming disaster emerged in February 2007, before spiraling out of control in August. This occurred four months after April, the midpoint between February and August.

While some studies failed to show a diminution in M/F in response to parental stress (11), many other studies have shown that M/F is acutely affected 3–4 months after such events, as evidenced in the United States after the September 11 attacks (4, 8) with an excess of male fetal losses (9). The disagreement between findings in different papers and peoples may stem from the fact that different populations may require not only different stimuli but also stimuli of different strengths to manifest statistically significant changes in M/F.

This accords with the Trivers–Willard hypothesis of parental investment, which proposes that natural selection has favored parents who bias M/F toward sons when in good condition and toward daughters when in poor condition (26). In this case, economic depression as a result of a contracting economy was the cause of substantial stress (22-26).

Contracting economies have also been shown to result in a drop in M/F, putatively for the same reasons. This was seen in East Germany after the region's reunification with West Germany. The ensuing economic turmoil in the first year after reunification was associated with a drop in M/F in East Germany (10) where workers experienced the full effect of market forces and free competition, resulting in a 20% unemployment rate and another 20% reduced working days (27), factors that were attributed to have caused the decline (10).

Further evidence that stress reduces M/F also comes from the observation that extrauterine pregnancies also result in a reduction in M/F probably because of the hostile gestational environment (28).

The Great Recession induced significant stress worldwide; stress is known to reduce M/F. These factors may have been the cause of the M/F drop witnessed in the second half of 2007 in the United States.

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References

1. James WH. The human sex ratio. Part 1: A review of the literature. Hum Biol 1987; 59: 721-52.
2. Song S. Does famine influence sex ratio at birth? Evidence from the 1959-1961 Great Leap Forward Famine in China. Proc Biol Sci 2012; 279: 2883-90. [CrossRef]
3. James WH. The human sex ratio. Part 2: A hypothesis and a program of research. Hum Biol 1987; 59: 873-900.
4. Catalano R, Bruckner T, Marks AR, Eskenazi B. Exogenous shocks to the human sex ratio: the case of September 11, 2001 in New York City. Hum Reprod 2006; 21: 3127-31. [CrossRef]
5. Fukuda M, Fukuda K, Shimizu T, Møller H. Decline in sex ratio at birth after Kobe earthquake. Hum Reprod 1998; 13: 2321-2. [CrossRef]
6. Lyster WR. Altered sex ratio after the London smog of 1952 and the Brisbane flood of 1965. J Obstet Gynaecol Br Commonw 1974; 81: 626-31. [CrossRef]
7. Zorn B, Sucur V, Stare J, Meden-Vrtovec H. Decline in sex ratio at birth after 10-day war in Slovenia: brief communication. Hum Reprod 2002; 17: 3173-7. [CrossRef]
8. Catalano R, Bruckner T, Gould J, Eskenazi B, Anderson E. Sex ratios in California following the terrorist attacks of September 11, 2001. Hum Reprod 2005; 20: 1221-7. [CrossRef]
9. Bruckner TA, Catalano R, Ahern J. Male fetal loss in the U.S. following the terrorist attacks of September 11, 2001. BMC Public Health 2010; 10: 273. [CrossRef]
10. Catalano RA. Sex ratios in the two Germanies: a test of the economic stress hypothesis. Hum Reprod 2003; 18: 1972-5. [CrossRef]
11. Khashan AS, Mortensen PB, McNamee R, Baker PN, Abel KM. Sex ratio at birth following prenatal maternal exposure to severe life events: a population-based cohort study. Hum Reprod 2009; 24: 1754-7. [CrossRef]
12. National Bureau of Economic Research. Business Cycle Dating Committee. Available from: http://www.nber.org/cycles/sept2010.html
13. Verick S, Islam I. The great recession of 2008-2009: causes, consequences and policy responses. Discussion paper series// Forschungsinstitut zur Zukunft der Arbeit 2010; 4934: 1-63.
14. Baldwin R. The great trade collapse: Causes, consequences and prospects. Geneva; Centre for Trade and Economic Integration: 2009.
15. Centers for Disease Control and Prevention. National Center for Health Statistics. Available from: http://www.cdc.gov/nchs/data_access/vitalstats/VitalStats_Births.htm
16. Gini C. Sulla probabilita che termini di una serie erratica sieno tutti crescenti (o non decrescenti) ovvero tutti decrescenti (o non crescenti) con applicazioni ai rapporti dei sessi nascite umane in intervalli successivi e alle disposizioni dei sessi nelle fratellanze umane. Metron 1955; 17: 1-41.
17. Orwig GH. A statistical analysis of seasonal differences in human live birth sex ratios. Univ Chicago Masters Thesis 1948.
18. Slatis HM. Seasonal variation in the American live birth sex ratio. Am J Hum Genet 1953; 5: 21-33.
19. Fleiss JL. Statistical methods for rates and proportions. New York: John Wiley and Sons; 1981. p. 14-5.
20. Slezák P. Microsoft Excel add-in for the statistical analysis of contingency tables. Int J Innovation Educ Res 2014; 2: 90-100.
21. Holt J. A Summary of the Primary Causes of the Housing Bubble and the Resulting Credit Crisis: A Non-Technical Paper. Journal of Business Inquiry 2009; 8: 120-9.
22. Mulia N, Zemore SE, Murphy R, Liu H, Catalano R. Economic loss and alcohol consumption and problems during the 2008 to 2009 U.S. recession. Alcohol Clin Exp Res 2014; 38: 1026-34. [CrossRef]
23. Reeves A, McKee M, Gunnell D, Chang SS, Basu S, Barr B, Stuckler D. Economic shocks, resilience, and male suicides in the Great Recession: cross-national analysis of 20 EU countries. Eur J Public Health 2014.pii: cku168.
24. Phillips JA, Nugent CN. Suicide and the Great Recession of 2007-2009: the role of economic factors in the 50 U.S. states. Soc Sci Med 2014; 116: 22-31. [CrossRef]
25. Houle JN. Mental health in the foreclosure crisis. Soc Sci Med 2014; 118: 1-8. [CrossRef]
26. Trivers RL, Willard DE. Natural selection of parental ability to vary the sex ratio of offspring. Science 1973; 179: 90-2. [CrossRef]
27. Neumann M. German unification: Economic problems and consequences. Carnegie-Rochester Conference Series on Public Policy 1992; 36: 163-209. [CrossRef]
28. Masukume G. Live births resulting from advanced abdominal extrauterine pregnancy, a review of cases reported from 2008 to 2013. WebmedCentral Obstet Gynecol 2014; 5: WMC004510.

The impact of intrahepatic cholestasis of pregnancy on fetal cardiac and peripheral circulation

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Abstract

Objective: The aim of this study was to evaluate changes in fetal cardiac and peripheral circulation in pregnancies complicated with intrahepatic cholestasis.

Material and Methods: The Doppler examination results of 22 pregnant subjects complicated with intrahepatic cholestasis of pregnancy (ICP) and 44 healthy controls were compared. The parameters of fetal cardiac circulation were pulmonary artery and aortic (Ao) peak systolic velocity (PSV), pulmonary vein (Pv), peak velocity index (PVI) and pulsatility index (PI), mitral valve (MV) and tricuspid valve (TV), early diastole (E)- and atrial contraction (A)-wave peak velocity ratio (E/A), and isthmus aortic peak systolic velocity (IAo PSV). The parameters of fetal peripheral circulation were middle cerebral artery (MCA) and umbilical artery (UA) PI, resistance index (RI), systolic/diastolic (S/D) ratio. Fetal obstetric Doppler monitoring was conducted weekly before 36 weeks and biweekly after that, and the results were compared with the normal reference values for gestational age.

Results: The Doppler parameters of fetal cardiac and peripheral circulation did not significantly differ between the two groups. S/D ratio readings in the ICP group were significantly above 2 SD before 35 weeks of gestation. Women with ICP had increased risks of preterm delivery, neonatal unit admission, and meconium-stained amniotic fluid compared with those in the controls.

Conclusion: Fetuses of pregnant women with ICP showed no differences in the evaluation of cardiac and peripheral Doppler measurements compared with fetuses of healthy mothers. The Doppler investigation of the umbilical artery may be useful in monitoring of pregnancies complicated by early onset intrahepatic cholestasis. (J Turk Ger Gynecol Assoc 2015; 16: 74-9)

Keywords: Intrahepatic cholestasis of pregnancy, fetal Doppler, fetal cardiac circulation

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Introduction

The characteristic features of intrahepatic cholestasis of pregnancy (ICP) include abnormal liver function and maternal pruritus that most frequently occur in the third trimester. Adverse fetal outcomes such as spontaneous pre-term labor, fetal distress, and even intrauterine death are frequently associated with ICP (1-3). The pathophysiology and epidemiology of fetal morbidity are not well characterized. Intrauterine death may occur without prior symptoms, such as uteroplacental insufficiency or intrauterine growth restriction, with no significant findings during fetal autopsy (4, 5). Non-specific pathology suggestive of hypoxia has been reported in placental histological samples; however, hypoxia has not been established as a primary pathophysiological process in ICP (6). Several studies have reported that fetal complications of ICP occur more commonly in pregnancies where the mother displays elevated levels of serum bile acids (7, 8). It is postulated that raised levels of fetal serum bile acids may be cardiotoxic to the fetus (9).

There are currently no methods present for predicting the risks for the fetus in pregnancies complicated with ICP. Abnormal heart rate (≤100 or ≥180 bpm) is associated with an elevated risk in some studies, although cardiotocograph monitoring cannot reliably predict the risk of complications, and normal cardiotographs are observed within 24 h of intrauterine demise (10-12). Furthermore, fetal heart rate tracing does not correlate with disease severity (13). The results of a study using the fetal biophysical profile and obstetric Doppler examination findings were not conclusive, mainly because of the absence of fetal mortality and morbidity in that series (14). However, there is very little information about whether changes of fetal cardiac Doppler parameters present in pregnancies complicated with ICP. The aim of this study was to evaluate whether some Doppler alterations exist at the examination of fetal cardiac and peripheral circulation in pregnancies complicated with ICP and to compare them with healthy pregnancies.

Material and Methods

This observational study was conducted with the approval of the Ethical Committee of Aegean Maternity and Teaching

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Hospital, and the procedures followed were in accordance with the Declaration of Helsinki of 1975 (revised in 2008). All study participants provided informed consent.

The study was conducted in the clinic of Aegean Maternity and Teaching Hospital between January 2013 and January 2014. During the study period, there were 4037 normal vaginal and 2987 cesarean section deliveries, and 94 pregnant women with ICP were admitted to our hospital. The criteria that were used for diagnosing ICP were raised levels of serum bile acids (total bile acid level was ≥10 μmol/L) and/or pruritus coinciding with liver dysfunction during the third trimester (29-40 weeks), and the absence of skin lesions, and resolution of these symptoms following delivery. Elevated levels of liver alanine transaminase (ALT) and aspartate transaminase (AST) were used to confirm the diagnosis. Liver transaminase results exceeding 40 IU/L were considered abnormal (15, 16). Abnormal liver function tests were followed-up with viral marker testing and liver ultrasonography. The presence of biliary obstruction or gallstones during liver ultrasound or acute infection with hepatitis A, B, or C precluded the diagnosis of obstetric cholestasis. A medical history including pruritus in a prior pregnancy, outcome of prior pregnancies, skin disorders, liver/gall-bladder disorders, and use of oral contraceptives was obtained. For both patients and control subjects, exclusion criteria consisted of known multiple gestation, systemic lupus erythematosus, age <18 and >40 years, and fetuses with a known cardiac anomaly or arrhythmia. Additional causes of liver dysfunction, including hemolysis, elevated liver enzymes and low platelets syndrome, preeclampsia, primary biliary cirrhosis, acute fatty liver, and progesterone or any other medications were considered as criteria for exclusion from the study. The presence of confounding characteristics including intrauterine growth retardation (fetal weight below 10th percentile) and oligohydramnios (amniotic fluid index <50) were also considered as criteria for exclusion.

Serum AST and ALT levels were measured using Roche methods on a Hitachi 917 Analyzer (Roche Diagnostics, Basel, Switzerland). Total levels of serum bile acids were analyzed with an enzymatic, colorimetric method (Enzabile, Biostat Diagnostic Systems, Stockport, UK).

Ursodeoxycholic acid (UDCA 2×300 mg daily) was provided to all patients when the diagnosis of ICP was confirmed. The daily dosage of UDCA was further increased up to 900 mg or to a maximum of 1.500 mg for patients with severe symptoms.

Twenty-two pregnant women with ICP were found to be in compliance with the criteria of the study period. For each case, two healthy pregnant controls were matched for maternal age and gestational age at ultrasound (±1 week). An a priori sample size calculation was performed with an α value of 0.05 and a β value of 0.20 based on the estimated umbilical artery systolic/diastolic (UA S/D) ratio of 2.64±0.49 between 34 and 37 gestational weeks. It was estimated that a total sample size of 20 pregnant women would be required to reveal a difference of 0.5 in the UA S/D ratio between the two groups. Therefore, we observed that the number of patients that we evaluated during the study period was sufficient for analysis.

Sonographic examinations

A color Doppler unit (Toshiba Aplio 500, Tokyo, Japan) with a 3.5-MHz convex probe was used to perform all ultrasonographic measurements. Gestational age was determined based on fetal measurements and the date of last menstruation. The presence of congenital heart abnormalities was excluded by the ultrasonographic evaluation of fetal cardiac anatomy.

The angle of the transducer beam relative to the direction of blood flow was maintained at <20° throughout Doppler ultrasonography, and the high-pass filter was set at 100 Hz. All cardiac parameters were evaluated over 3-5 consecutive cardiac cycles and were stored for off-line analysis; a single investigator (S.K.) completed all measurements. All measurements were obtained in the absence of uterine contractions, fetal breathing, or other fetal movements, and the mother was positioned in the left lateral recumbent position.

The Doppler measurement of UA was conducted at the umbilical cord midsection. Insonation of the middle cerebral artery (MCA) occurred via the occipital or temporal bone window identified by the circle of Willis on the axial section of the brain. Resistance index (RI), pulsatility index (PI), and S/D ratio were evaluated for both UA and MCA.

The isthmus aortic peak systolic velocity (IAo PSV) was measured from either the sagittal longitudinal aortic view or three vessel trachea view with an insonation angle <30°. The atrioventricular valves were imaged from the apical four-chamber view of the heart. Two diastolic peaks were used to characterize flow velocity at the tricuspid valve (TV) and mitral valve (MV), corresponding to active ventricular filling during atrial contraction (A-wave) and early ventricular filling (E-wave). The E/A ratio was calculated from the E-wave and A-wave peak velocities.

The pulmonary veins (PV) were visualized by color Doppler imaging, following the four-chamber cross-section imaging of the fetal heart and thoracic cavity. Sample volumes were placed above PV immediately dorsal to the entrance into the left atrium. The angle of the ultrasound beam relative to the direction of blood flow was maintained at <10°, and PI and peak velocity Index (PVI) were evaluated.

The study included patients admitted to the hospital with the diagnosis of ICP, and according to our hospital protocol, UDCA treatment was initiated to all patients. For this reason, Doppler sonographic assessment was performed on the ICP group after the administration of UDCA, and it was not possible to assess the effect of UDCA on Doppler parameters.

Fetal Doppler examination for cardiac circulation was conducted once, and the results were compared with those of the control group. Fetal Doppler examination for peripheral circulation was conducted weekly before 36 weeks and twice a week after that until delivery in the ICP group, and the results were compared with the reference range consistent with gestational age (17). Thus, 72 Doppler readings were taken from 22 patients with ICP at scheduled intervals during the study period.

Figure 1 represents a flow chart of the study design.

Statistical analysis

Depending on the distribution of the measured values, Student's t test (data normally distributed) or Mann-Whitney U-test (data

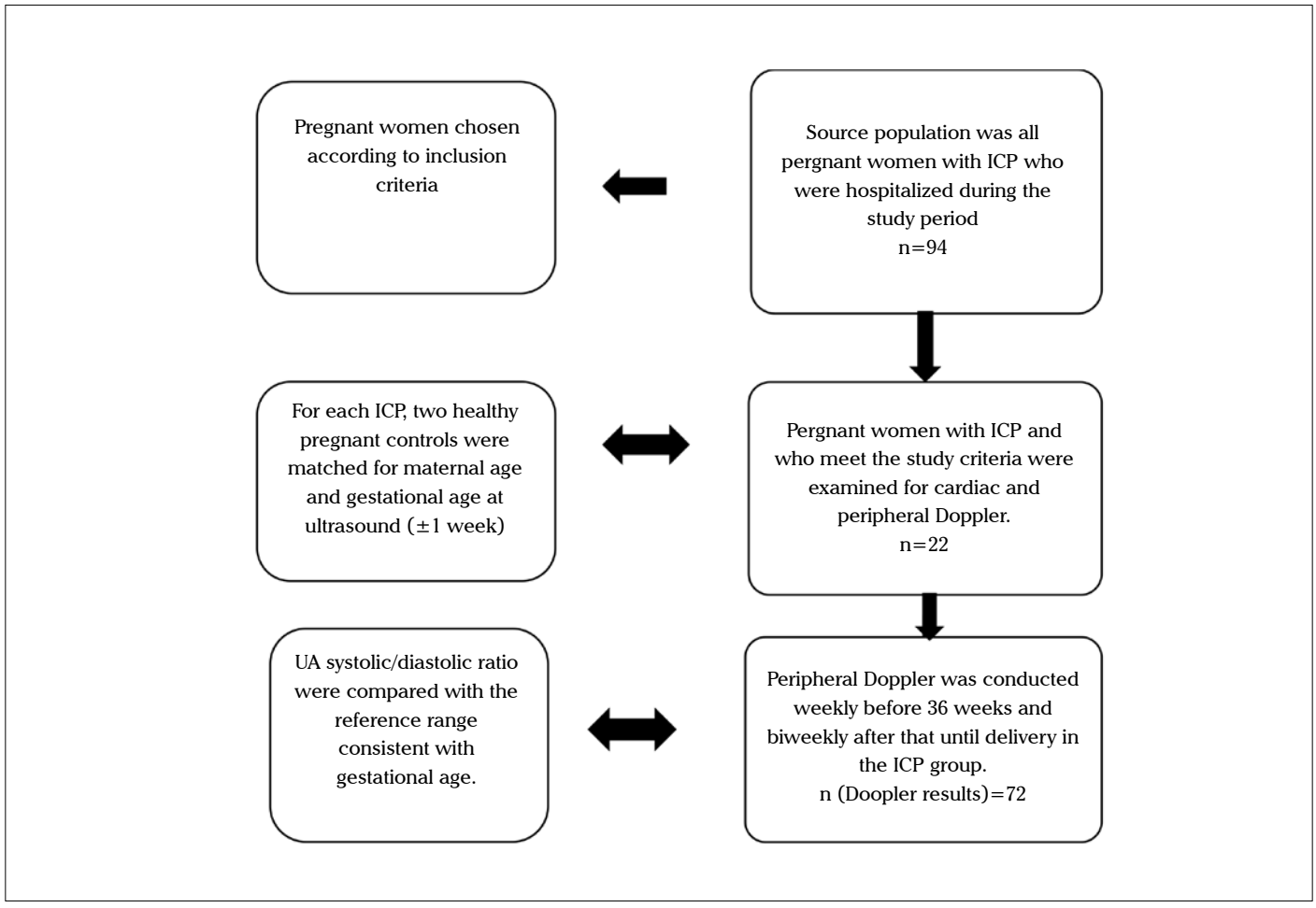

Figure 1. A flow chart of the study design
ICP: intrahepatic cholestasis of pregnancy; UA: umbilical artery

not normally distributed) were used to compare data between the fetuses with ICP mothers and normal control groups using MedCalc Version 9.3.1 (MedCalc Inc., Mariakerke, Belgium). Normal distribution of the continuous variables was assessed with the Kolmogorov-Smirnov test. $P<0.05$ was considered statistically significant.

Results

Totally, 66 pregnant women were included in this study; 22 pregnant women who had ICP comprised the ICP group and 44 women without ICP comprised the control group. The mean maternal age was 26.4±5.5 years and 27.6±4.8 years for the ICP group and control group, respectively. The median gestational age was 34.7 (29-40) weeks and 33.5 (31-38) weeks for the ICP group and control group, respectively. There were no significant differences in maternal age, gestational age, and gravida and parity between the two groups. The mean serum AST level at diagnosis was 138.90±97.6 IU/L (range 41-477IU/L); the mean serum ALT level was 154.62±104.2 IU/L (range 39-498 IU/L) in the study group. The demographic characteristics of both groups are shown in Table 1.

There was no statistically significant difference in the E/A ratio for each AV valve in the aorta and pulmonary artery peak systolic velocities and IAo PSV values between the study and control groups. Additionally, there were no significant differences in pulmonary vein PI and PVI values between the study and control groups. Doppler-derived fetal cardiac measurements are shown in Table 2.

There was no statistically significant difference in the UA and MCA Doppler S/D ratio, PI, and RI. Obstetric Doppler measurements are shown in Table 3.

When the findings were compared with the reference values of Doppler flow velocities of UA of a normal pregnant population, it was found that the S/D ratio readings were significantly above 2 SD before 35 weeks of gestation (Table 4).

No episode of fetal asphyxia or bradycardia was observed. The overall rate of meconium passage was 27.2% (6/22) in the ICP group ($p<0.01$). Spontaneous preterm birth was observed in 18.1% (4/22) of the ICP mothers. The mean gestational age was 39.1 weeks in the control group and 36.4 weeks in the ICP group ($p<0.01$). The mean birthweight was 3460.5 g in the control group and 2987.2 g in the ICP group ($p<0.01$). The cesarean delivery rate was 54.5% (12/22) in the ICP group. The median

Table 1. Characteristics of the study group

Clinical characteristics	Control group n=44	ICP group n=22	p
Age (years)	27.6±4.8	26.4±5.5	0.4
Parity	1.8±0.9	1.8±0.9	0.9
Gestational age at examination (weeks)	33.5±3.2	34.7±3.4	0.06
ALT (IU/L)	22.1±3.4	154.62±104.2	<0.01
AST (IU/L)	24.6±2.8	138.90±97.6	<0.01

Data are presented as mean±standard deviation. P<0.05 was considered statistically significant.
ICP: intrahepatic cholestasis of pregnancy; ALT: alanine aminotransferase; AST: aspartate aminotransferase

Table 2. Mean Doppler index values of Ao, Pa, Pv, tricuspid and mitral valves in ICP and healty pregnancies

Cardiac parameters	Control group n=44	ICP group n=22	p
Pa-PVI	76.2±11	82.5±13.1	0.09
Ao-PVI	88.7±14.1	90.4±12.3	0.51
Pv-PI	1.01±0.1	1.02±0.2	0.69
Pv-PVI	0.70±0.1	0.72±0.1	0.84
TV-E/A	0.75±0.1	0.74±0.1	0.94
MV-E/A	0.76±0.1	0.79±0.1	0.25
IAo-PSV	104.01±14.3	108.6±15.4	0.36

Data are presented as mean±standard deviation. P<0.05 was considered statistically significant.
ICP: intrahepatic cholestasis of pregnancy; Pa-PVI: pulmonary artery peak velocity index; Ao-PVI: aortic peak velocity index; Pv-PI: pulmonary vein pulsatility index; Pv-PVI: pulmonary vein peak velocity index; MV: mitral valve; TV: tricuspid valve; E/A: E- and A- wave peak velocity ratio; IAo-PSV: isthmus aortic peak systolic velocity

Table 3. Mean Doppler index values of umbilical and middle cerebral arteries in ICP and healthy pregnancies

Fetal Doppler parameters	Control group n=44	ICP group n=22	p
MCA-PI	1.77±0.4	2.56±4.3	0.48
MCA-RI	0.80±0.08	0.78±0.08	0.39
MCA-SD	6.1±2.9	5.4±2.4	0.35
UA-PI	0.89±0.14	0.92±0.17	0.40
UA-RI	0.59±0.06	0.60±0.07	0.31
UA-S/D	2.53±0.45	2.64±0.49	0.32

Data are presented as mean±standart deviation. P<0.05 was considered statistically significant.
ICP: intrahepatic cholestasis of pregnancy; MCA: middle cerebral artery; PI: pulsatility index; RI: resistance index; S/D: systole/diastole; UA: umbilical artery

Apgar score was 8 at 1 min and 9 at 5 min. None of the newborns had an Apgar score <7 at 5 min (Table 5).

Discussion

In this study, we examined fetal cardiac and systemic circulation using routine echocardiographic Doppler parameters which may add information regarding fetal circulatory dynamics in women who have ICP.

Bile acids and their toxic metabolic by products are implicated for fetal morbidity associated with ICP. In animal models, bile acids may exert toxic effects on the myometrium and placenta. Elevated serum taurocholate, a bile acid within the fetus, may contribute to fetal dysrhythmia and intrauterine mortality. Taurocholate may impair the propagation of cardiac conduction and disrupt synchronous contraction via the interruption of calcium dynamics of the cardiomyocytes and alter the function of the gap junctions (8, 9). In another experimental animal study, investigators evaluated the influence of tauro-conjugated cholic acid administration on in vitro cultures of adult and neonatal rat cardiomyocytes and reported that neonatal rat cardiomyoctes are more sensitive to adverse effects, including altered calcium dynamics, arrhythmias, and abnormal contraction, of bile acids relative to adult cardiomyocytes (18). These data are consistent with the observation that pregnant women with ICP do not have arrhythmia and cardiotoxic effects. It is not possible to investigate the effects of bile acids on the intact human fetal heart at a cellular level. However, it is postulated that if elevated bile acids are toxic on the fetal heart, there may be alterations in cardiac circulation and cardiac Doppler measurements.

In our study, we aimed to evaluate the fetal cardiac function using relatively simple Doppler measurements, which do not require special training and equipment. Based on this idea, we performed Doppler analysis to assess the diastolic function of the fetal heart using the E/A ratio of both mitral and tricuspid valves and pulmonary vein PI and PVI. Changes observed in pulmonary vein flow velocity indicate left atrial pressure dynamics occurring during the cardiac cycle (19). Peak flow velocities of the aorta and pulmonary artery in pulsed Doppler pattern were evaluated for the systolic function of the heart. Additionally, for investigating the balance between both ventricular outputs and differences in the impedance of both vascular systems, we performed aortic isthmus Doppler. We found no difference in the fetal cardiac and peripheral Doppler parameters between the two groups. A recent study evaluated fetal echocardiographic examinations of fetuses in pregnant women who have ICP (20). The researchers reported that the left ventricular longitudinal strain, systolic strain rate, and diastolic strain rate are significantly decreased in fetuses with severe cholestasis compared with those in control fetuses. Furthermore, there was a positive correlation between fetal myocardial deformation and maternal total bile acid levels.

Maternal prognosis is excellent in ICP, but there are significant risks for the fetus. We observed that both spontaneous and iatrogenic preterm labor, meconium-stained amniotic fluid, and neonatal unit admission ratio in the ICP group were significantly high than those in the control group. There are limited data regarding the association between obstetric Doppler and abnormal fetal outcome in women who had ICP. Guerra et al. (21) concluded that there are no significant changes in any of the blood flow velocity indices determined by Doppler blood flow analysis in patients with obstetric cholestasis. Zimmermann et al. (22) determined the Pourcelot ratio in affected pregnancies with obstetric cholestasis and found Doppler to be of little value

Table 4. Mean systolic/diastolic ratio of the umbilical artery in the ICP group for gestational week

Gestational week	Systolic/diastolic ratio in ICP group (mean±SD)	50th percentile	95th percentile	S/D ratio readings were above 2 SD (n, %)	p
33-34	3.52±1.1	2.52	3.68	3/7 (42.8)	0.01
34-35	3.26±0.9	2.46	3.58	9/25 (36)	0.04
35-36	2.71±0.7	2.39	3.49	4/28 (14.2)	0.09
36-37	2.69±0.9	2.34	3.41	1/12 (8.3)	0.6

In total, seventy-two Doppler results were evaluated. P<0.05 was considered statistically significant.
Data are presented as mean±standard deviation.
ICP: intrahepatic cholestasis of pregnancy; S/D: systole/diastole

Table 5. Perinatal outcomes of intrahepatic cholestasis of pregnancy (ICP) and healthy pregnancies

Perinatal outcomes of of ICP and healthy pregnancies	Control group n=44	ICP group n=22	p
Mean (±SD) gestational age at delivery (weeks)	39.1 (1.2)	36.4 (1.5)	<0.01
Preterm delivery (n, %)	4, 9%	8, 36.3%	<0.01
Spontaneous <37 weeks	1, 2.2%	4, 18.1%	<0.01
Iatrogenic <37 weeks	3, 6.8%	4, 18.1%	<0.01
Mode of delivery cesarean section (n, %)	18, 40.9%	12, 54.5%	0.05
Birthweight (g)	3460.5	2987.2	0.04
Stillbirth	-	-	-
5 min Apgar ≤7 (n, %)	-	-	-
Neonatal unit admission (n, %)	2, 4.5%	4, 18.1%	0.04
Meconium-stained amniotic fluid (n, %)	0	6, 27.2%	<0.01

P<0.05 was considered statistically significant.
ICP: intrahepatic cholestasis of pregnancy; SD: standard deviation

in studying the disease-specific risk of fetal compromise. Suri et al. (23) found that there are some alterations in UA Doppler parameters in pregnancies complicated by ICP compared with those in the normal range, but Doppler parameters do not correlate with the severity of disease and rates of preterm delivery or meconium-stained liquor. Doppler measurements of the fetal UA and MCA did not differ between the two groups in our study. S/D ratio readings in the ICP group were significantly above 2 SD before 35 weeks of gestation. Based on this data, it is claimed that the Doppler measurement of UA is useful in the monitoring of early onset intrahepatic cholestasis.

The present study has several important limitations. First, the study group was limited to a small group of women; future studies will require a broader and more diverse study pool. Second, the patients were evaluated for cardiac circulation only once, and serial measurements may have revealed additional insights. Furthermore, all women who have ICP were treated with UDCA, which may modify the course of the disease.

In summary, sudden fetal death in women who have ICP is an important problem that remains poorly understood. Women who have obstetric cholestasis do not exhibit Doppler alterations in fetal cardiac or systemic circulation. Further prospective studies with larger series are needed for defining fetal cardiac function in women who have ICP.

Ethics Committee Approval: *Ethics committee approval was received for this study from the ethics committee of Aegean Maternity and Teaching Hospital.*

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

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References

1. Reyes H. The enigma of intrahepatic cholestasis of pregnancy: lessons from Chile. Hepatology 1982; 2: 87-96. [CrossRef]
2. Fisk NM, Storey GNB. Fetal outcome in obstetric cholestasis. Br J Obstet Gynaecol 1988; 95: 1137-43. [CrossRef]
3. Rioseco AJ, Ivankovic MB, Manzur A, Hamed F, Kato SR, Parer JT, Germain AM. Intrahepatic cholestasis of pregnancy: a retrospective case-control study of perinatal outcome. Am J Obstet Gynecol 1994; 170: 890-5. [CrossRef]
4. Lee RH, Incerpi MH, Miller DA, Pathak B, Goodwin TM. Sudden fetal death in intrahepatic cholestasis of pregnancy. Obstet Gynecol 2009; 113: 528-31. [CrossRef]
5. Laatikainen TJ, Tulenheimo A. Maternal serum bile acid levels and fetal distress in cholestasis of pregnancy. Int J Gynaecol Obstet 1984; 22: 91-4. [CrossRef]
6. Glantz A, Marschall HU, Mattsson LA. Intrahepatic cholestasis of pregnancy: Relationships between bile acid levels and fetal complication rates. Hepatology 2004; 40: 467-74. [CrossRef]
7. Lee RH, Kwok KM, Ingles S, Wilson ML, Mullin P, Incerpi M, et al. Pregnancy outcomes during an era of aggressive management for intrahepatic cholestasis of pregnancy. Am J Perinatol 2008; 25: 341-5. [CrossRef]

8. Williamson C, Gorelik J, Eaton BM, Lab M, de Swiet M, Korchev Y. The bile acid taurocholate impairs rat cardiomyocyte function: a proposed mechanism for intra-uterine fetal death in obstetric cholestasis. Clin Sci (Lond) 2001; 100: 363-9. [CrossRef]
9. Williamson C, Miragoli M, Sheikh Abdul Kadir S, Abu-Hayyeh S, Papacleovoulou G, Geenes V, Gorelik J. Bile acid signaling in fetal tissues: implications for intrahepatic cholestasis of pregnancy. Dig Dis 2011; 29: 58-61. [CrossRef]
10. Al Inizi S, Gupta R, Gale A. Fetal tachyarrhythmia with atrial flutter in obstetric cholestasis. Int J Gynaecol Obstet 2006; 93: 53-4. [CrossRef]
11. Zhang K, Wang Z. Clinical value of fetal monitoring in intrahepatic cholestasis of pregnancy. Zhonghua Fu Chan Ke Za Zhi 2000; 35: 23-5.
12. Alsulyman OM, Ouzounian JG, Ames-Castro M, Goodwin TM. Intrahepatic cholestasis of pregnancy: perinatal outcome associated with expectant management. Am J Obstet Gynecol 1996; 175: 957-60. [CrossRef]
13. Sheibani L, Uhrinak A, Lee RH, Fong A, Pathak B. Intrahepatic cholestasis of pregnancy: the effect of bile acids on fetal heart rate tracings. Obstet Gynecol 2014; 123: 78S-9S. [CrossRef]
14. Martinez E, Rodriguez N, Lisoni M, Cruzat L, Glasinovic J, Marinovic I.Usefulness of biophysical profile in intrahepatic cholestasis of pregnancy. Rev Chil Obstet Ginecol 1987; 52: 137-41.
15. Bacq Y, Sapey T, Brechot MC, Pierre F, Fignon A, Dubios F. Intrahepatic cholestasis of pregnancy: a French prospective study. Hepatology 1997; 26: 358-64. [CrossRef]
16. Heikkinen J, Maentausta O, Ylostalo P, Janne O. Changes in serum bileacid concentrations during normal pregnancy, in patients with intrahepatic cholestasis of pregnancy and in pregnant women with itching. Br J Obstet Gynaecol 1981; 88: 240-5. [CrossRef]
17. Acharya G, Wilsgaard T, Berntsen GK, Maltau JM, Kiserud T. Reference ranges for serial measurements of umbilical artery Doppler indices in the second half of pregnancy. Am J Obstet Gynecol 2005; 192: 937-44. [CrossRef]
18. Sheikh Abdul Kadir SH, Ali NN, Brito-Martins M, Abu-Hayyeh S, Moshkov AV, Williamson C, et al. Embryonic stem cell-derived cardiomyocytes as a model to study fetal arrhythmia related to maternal disease. J Mol Cell Med 2009; 13: 3730-41. [CrossRef]
19. Zielinsky P, Piccoli AL Jr, Teixeira L, Gus EI, Mânica JL, Satler F, et al. Pulmonary vein pulsatility in fetuses of diabetic mothers: prenatal Doppler echocardiographic study. Arq Bras Cardiol 2003; 81: 604-7, 600-3. Epub 2004 Jan 28.
20. Fan X, Zhou Q, Zeng S, Zhou J, Peng Q, Zhang M, Ding Y. Impaired fetal myocardial deformation in intrahepatic cholestasis of pregnancy. J Ultrasound Med 2014; 33: 1171-7. [CrossRef]
21. Guerra F, Guzman S, Campos G. Evaluation of maternal and fetal blood flow indices in intrahepatic cholestasis of pregnancy. Rev Chil Obstet Ginecol 1994; 59: 17-21.
22. Zimmermann P, Koskinen J, Vaalamo P, Ranata T. Doppler umbilical artery velocimetry in pregnancies complicated by intrahepatic cholestasis. J Perinat Med 1991; 19: 351-5. [CrossRef]
23. Suri V, Jain R, Aggarwal N, Chawla YK, Kohli KK. Usefulness of fetal monitoring in intrahepatic cholestasis of pregnancy: a prospective study. Arch Gynecol Obstet 2012; 286: 1419-24. [CrossRef]

Comparison of effects of nifedipine and ritodrine on maternal and fetal blood flow patterns in preterm labor

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Abstract

Objective: The aim of this study was to investigate and compare the effects of nifedipine and ritodrine treatment on fetomaternal blood flow parameters in women with preterm labor.

Material and Methods: Sixty women with gestational age between 24 and 36 weeks admitted to the obstetrics clinic for preterm labor were enrolled in this study. Patients were randomly assigned to receive either nifedipine (n=30) or ritodrine (n=30) treatment. Demographic features, clinic and laboratory parameters, fetal and maternal side effects, and Doppler ultrasound indices of the umbilical artery (UA), uterine arteries (UtA), and middle cerebral artery (MCA) before, 2 hours after, and 48 hours after the initiation of tocolytic treatments were compared between the two groups.

Results: In both the groups, early- and late-onset changes in the pulsatility index (PI) and other Doppler indices for UA, UtA, and MCA were similar. In addition, time elapsed till delivery, fetal mortality, and maternal morbidity in both the groups were not statistically significant ($p>0.05$). However, maternal side effects such as tachycardia was more frequent ($p<0.05$) in the ritodrine group. Besides, in the ritodrine group, anxiety was only minimally observed.

Conclusion: Nifedipine and ritodrine used as tocolytic agents did not significantly alter early- and late-onset changes in Doppler ultrasonography parameters in fetal and fetomaternal circulation. (J Turk Ger Gynecol Assoc 2015; 16: 80-5)

Keywords: Doppler ultrasonography, tocolysis, umbilical artery, uterine artery, middle cerebral artery

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Introduction

There has been good news about rates of preterm birth in the United States. According to a preliminary study between 2006 and 2011, it was determined that the rates have fallen down from 12.8% in 2006 to 11.7% in 2011. The largest drop has been particularly observed in late preterm rates (34-36 weeks) (1). However, of course, in underdeveloped and developing countries, the condition is different. Improvements in assisted reproductive technology have caused an increase in the incidence of preterm labor (2). Preterm births accounts for 6%-10% of all births and is an important cause of perinatal mortality and morbidity (3). Preterm birth accounts for approximately two-thirds of neonatal mortality. In particular, in underdeveloped and developing countries, it causes serious social and economic loses (4). Therefore, it is important to prevent or delay preterm births to improve the perinatal outcome. This shows the importance of maternal corticosteroids and tocolytic treatments. In modern obstetrics, tocolytics play an important role in permitting the transfer of a pregnant patient to a tertiary care center and delaying birth for at least 48 hours. Thus, we can optimize the beneficial effects of corticosteroids to facilitate fetal pulmonary maturation, thereby decreasing complications such as necrotizing enterocolitis, intracranial bleeding, and respiratory distress syndrome (5).

In clinical practice, various pharmacological agents that inhibit uterine contractions are used. Tocolytic agents such as calcium channel blockers (nifedipine), beta-mimetics (ritodrine), and indomethacin may be used in cases of preterm labor in which uterine contractions cannot be controlled by intravenous hydration. These tocolytics can be used alone or in combinations (6). In general, maternal effects and side effects profiles of all these agents are known. However, their possible adverse effects on the fetus remain relatively unknown. There have only been limited data on tocolytics and their possible impacts on fetal and fetomaternal circulation (7). In the present study, we mainly aimed to determine the clinical side effects of nifedipine and ritodrine, mostly used tocolytic agents, and to evaluate their effects on the uterine arteries (UtAs), umbilical artery (UA), and middle cerebral artery (MCA) blood flow and Doppler ultrasonography parameters. Our secondary objective was to investigate the side effects of drugs.

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Metarial and Methods

Sixty pregnant women, who applied to our clinic because of preterm labor and were aged between 18 and 44 years, were included. The subjects were enrolled after institutional ethic committee approval. Informed consent was obtained from all participants. The research was conducted in women who fulfilled the following admission criteria: pregnant with a single fetus of 24-36-week gestation; fetus with intact amniotic membranes; and experiencing two or more painful and persistent uterine contractions in 10 minutes, as established by tococardiography. These contractions could not be controlled after 2 hours of bed rest and resulted in changes in the cervix (at least 2 cm cervical dilatation and 75% ripening) (8, 9). In all cases, fetal heart rates were recorded by ultrasonography or tococardiography. All patients included in the present study were in the latent phase of labor. Patients having cervical dilatation greater than 5 cm and effacement of 80% were not included in the present study. In addition, pregnant women with a concomitant morbidity such as heart, lung, or thyroid disease; high blood pressure; diabetes or infectious disease; an obstetric morbidity (e.g., pre-eclampsia, premature rupture of membranes, polyhydramniosis, gestational diabetes mellitus, intrauterine growth restriction, chorioanmionitis, or acute fetal distress); multiple pregnancies; or fetal malformations and patients who could not tolerate treatments were excluded from the present study.

Demographic features and obstetric histories were recorded. Age, gravidity, parity, abortion, frequency of uterine contractions in 10 minutes, cervical dilatation, ripening parameters, and Bishop scores of patients were recorded. Fetal biometry and estimated fetal weight were evaluated via obstetric ultrasonography. Monitorization of uterine contractions and fetal cardiac activity were performed using a tococardiography device CMS 800G (Contec Medical System, China) or Wallach Sonicaid Team (Wallach Surgical devices, USA) for 20 minutes. Tocolysis was started when regular uterine contractions (5-7 contractions/20 minutes) were associated with cervical change. In patients whose gestational age was below 34 weeks, maternal corticosteroids were applied to facilitate fetal pulmonary maturation. Corticosteroid regimen included 12 mg betamethasone or betamethasone disodiumphosphate (Celestone Chronodose, Schering-Eczacıbası®, Lüleburgaz, Turkey) applied intramuscularly, repeated at 24-hour intervals. Doppler velocimetry measurements were performed 24 hours after corticosteroid administration.

In this investigation, patients with a diagnosis of preterm labor were randomized to receive either oral nifedipine (Nidilat®, Santafarma, İstanbul, Turkey) (n=30) or intravenous ritodrine (Prepar® Zentiva, İstanbul, Turkey) (n=30). Before and during tocolysis, the fetal heart rate, maternal blood pressure, maternal pulse rate were measured in 15-minute intervals in the loading dosage period and 4-hour intervals in the maintenance dosage period. Because we know that there is no consensus about the nifedipine regimen, the protocol used at our institution was carried out. Nifedipine was applied to patients in two dosage periods: loading and maintenance dosages. It consisted of an initial oral dose of 10 mg nifedipine and three doses repeated at 20-minute intervals for 1 hour, while the maintenance regimen consisted of 10 mg taken orally every 6 hours for further 24 hours (a total maximum dose of 60 mg). Nifedipine treatment was terminated after 48 hours in patients whose uterine contractions had stopped.

Ritodrine hydrochloride was applied intravenously (iv) as the tocolytic agent. The solution was prepared by titering 150 mg ritodrine hydrochloride in 500 mL 5% dextrose to obtain a concentration of 0.3 mg/mL. Infusion was started with a dose of 0.05 mg/minute (12 mL/hour), and it was increased to maximum 0.08 mg/minute (20 mL/hour) progressively.

Drug infusion was continued at the rate at which uterine contractions of patients had stopped and terminated 12 hours after this. Cases in which uterine contractions had stopped in 2 hours of the initial dosage of drugs, were accepted as successful and treatment was continued. In patients whose contractions were not controlled by nifedipine or ritodrine, other tocolytic regimen protocols were used. This occurred in seven patients in nifedipine and six in ritodrine groups.

Therefore, new patients were randomly included instead of these 13 patients.

Doppler measurements were performed by the same operator using an Aloka alfa-10 ultrasound device (Hitachi Aloka Medikal Ltd., Tokyo, Japan) with a 5-MHz transabdominal probe. Doppler measurements were recorded after the fetal biometric measurements were performed. All measurements were repeated three times, and the mean values were taken by the same operator to obtain the minimal error factor. Doppler indices were measured before and at the beginning, 2 hours (early period), and 48 hours (late period) of tocolysis. Because the contractions affect UtA Doppler indices, measurements before tocolysis were performed in periods between contractions with the patient positioned in a semi-Fowler position to avoid orthostatic hypotension. The systole/diastole (S/D) ratio, pulsatility index (PI), and resistance index (RI) of UA and UtA as well as peak systolic velocity (PSV) of MCA was measured. UA measurement was performed on the free loop of the cord, more than 4 cm apart from the placental and fetal insertion site, and the mean was taken. UtA measurement was performed on both the right and left side at the point medial to the iliac artery and at the isthmus level where UtAs could be observed. UA and UtA Doppler parameter measurements were performed after visualizing five heart cycles. Three different heart cycles were measured, and their means were taken. MCA measurements could be performed by visualizing Willis polygone with Color Doppler ultrasonography, and one of MCAs (only anterior or posterior) was used for the study. Scans of the vessels were obtained during fetal inactivity, during periods of apnea, and in the absence of uterine contractions.

In the present study, neonatal parameters of Apgar score after 1 and 5 minutes as well as birth and placental weights were measured and complications such as fetal respiratory distress syndrome, necrotizing enterocolitis, intracranial hemorrhage, and fetal infections were recorded.

An a priori sample size calculation was performed with an α of 0.05 and a β of 0.20 on the basis of an estimated cere-

broplacental ratio of 2.06±0.5 between 27 and 33 gestational weeks. It was estimated that a total sample size of 25 pregnant women would be required to reveal a difference of 0.5 in the cerebroplacental ratio before and after treatment. In total, 30 participants were included in each group for power of research. Statistical analyses were performed by employing the Statistical Package for Social Sciences software 13.0 for Windows package software (SPSS Inc., Chicago, IL, USA). The descriptive statistical method used in the present study was analysis of covariance (ANCOVA). Comparative analysis between groups was performed by Student's t test. Side effects of tocolytic agents were analyzed by chi-square test and Fischer's exact test wherever appropriate to determine significance. Results were evaluated in terms of the 95% confidence interval, and p value <0.05 was accepted as significant.

Results

Sixty pregnant patients with preterm labor were included. Demographic properties of patients in nifedipine and ritodrine groups were similar (Table 1). In patient evaluations, there was no statistical difference in laboratory results of groups examined before and 48 hours after tocolytic treatments (p>0.05). In the present study, effects of tocolytic drugs on time to delivery were evaluated. In both groups, time to delivery was 11 days. There was no statistical difference in time to delivery between nifedipine and ritodrine groups (p>0.05). Besides, arterial blood pressure of participants was measured at 48 hours of treatment, and there was no statistical difference between groups (p>0.05). Because both drugs may have effects on the vascular area by arterial blood pressure or uteroplacental blood flow, 1-minute and 5-minute Apgar scores, birth weights, and placental weights of participants between groups were compared. There was no statistical difference between groups (p>0.05). Clinical parameters of cases are also shown in Table 1.

In the study, 47 (84%) patients gave birth vaginally and 13 (26%) patients gave birth by the cesarean section. In eight patients in the nifedipine group and five in the ritodrine group gave birth by the cesarean section. Major indications of the cesarean section were anomalous presentation, previous cesarean section, cephalopelvic disproportion, and fetal distress.

In the present study, fetal complications after labor were evaluated in both the groups. There was no case of neonatal sepsis, necrotizing enterocolitis, grade 3/4 intraventriculer hemorrhage, respiratory distress syndrome, and perinatal death in the groups. However, two neonates in the ritodrine group and one in the nifedipine group had transient tachypnea.

Maternal complications in treatment groups are shown in Table 2. The most commonly observed side effect of ritodrine was tachycardia. It was observed in 73.3% of patients. Headache, nausea-vomiting, dyspnea, anxiety, and chest pain were the other side effects. In the nifedipine group, tachycardia was observed in 20% and headache was the other most common side effect (13.3%). Tachycardia and anxiety were more commonly observed in the ritodrine group (p<0.05).

In present study, blood flow patterns of nifedipine and ritodrine in UA, UtA, and MCA before, 2 hours after, and 48 hours after tocolysis were recorded. For both the drugs, the Doppler findings of different arteries with time were compared. Besides, in each drug, the changes in blood flow patterns with time were compared. In both the groups, early- and late-onset changes in Doppler indices for UA, UtA, and MCA were similar. In addition, there was no significant difference in Doppler indices with time after the application of each drug (p>0.05, Table 3).

Table 1. Demographic parameters and clinical characteristics of patients

	Nifedipine (n=30) (mean±SD)	Ritodrine (n=30) (mean±SD)	p
Age (years)	26.9±5.71	27.4±5.85	0.73
Gestational age (weeks)	32.9±2.02	32.4±2.09	0.35
Gravidity	1.86±1.16	2.23±1.04	0.20
Parity	1.76±0.93	2.03±1.06	0.30
Primiparity (%)	7 (%23.3)	10 (%33.3)	0.56
Time to delivery (days)	11.50±1.61	11.26±2.09	0.63
1-minute Apgar score	7.13±0.77	7.13±0.73	1.00
5-minute Apgar score	8.10±0.71	8.23±0.67	0.46
Birth weight (g)	1989±288	2000±293	0.89
Placental weight (g)	363±57	359±62	0.79
Mean arterial blood pressure (mmHg)	89.80±6.12	87.58±5.36	0.14
*Statistical Significance: p<0.05			

Table 2. Maternal complications in treatment groups

	Ritodrine (n=30) (n-%)	Nifedipine (n=30) (n-%)	p
Tachycardia	22 (73.3%)	6 (20%)	0.001
Emesis and vomiting	4 (13.3%)	1 (3.3%)	0.161
Anxiety	4 (13.3%)	-	0.03
Dyspnea	1 (3.3%)	-	0.31
Chest pain	1 (3.3%)	-	0.31
Pulmonary edema	-	-	>0.05
Headache	1 (3.3%)	4 (13.3%)	0.16
Skin rashes	-	1 (3.3%)	0.31
*Statistical significance: p<0.05			

Discussion

In the present study, it was determined that nifedipine and ritodrine used as tocolytic agents did not significantly alter early- and late-onset changes in Doppler ultrasonography parameters in fetal and fetomaternal circulation. Various pharmacological agents have been used for tocolysis in preterm labor. Although we know much about pharmacokinetics and pharmacodynamics of these drugs, there are limited data about their effects on fetal and fetomaternal circulation (10).

Table 3. Doppler measurements of UA, UtA, and MCA before, 2 and 48 hours after tocolytic treatments (ANCOVA)

	Ritodrine			Nifedipine				p		
UA	**0 hour**	**2 hours**	**48 hours**	**0 hour**	**2 hours**	**48 hours**	**SEM**	**D**	**T**	**DxT**
PI	1.01	0.92	0.93	1.00	0.96	0.97	0.03	0.49	0.25	0.74
RI	0.62	0.60	0.60	0.62	0.61	0.61	0.01	0.55	0.24	0.87
S/D	2.77	2.61	2.58	2.73	2.59	2.63	0.08	0.98	0.13	0.84
Right Ut A										
PI	0.84	0.80	0.87	0.81	0.84	0.80	0.04	0.62	0.96	0.45
RI	0.53	0.52	0.53	0.51	0.54	0.51	0.01	0.69	0.89	0.43
S/D	2.25	2.17	2.20	2.11	2.27	2.17	0.09	0.75	0.93	0.44
Left Ut A										
PI	0.86	0.84	0.86	0.83	0.82	0.83	0.05	0.52	0.95	0.99
RI	0.55	0.53	0.54	0.53	0.52	0.56	0.01	0.74	0.52	0.69
S/D	2.37	2.30	2.43	2.26	2.24	2.39	0.12	0.50	0.51	0.95
MCA										
PI	1.76	1.74	1.73	1.85	1.81	1.86	0.06	0.07	0.83	0.91
RI	0.83	0.80	0.81	0.84	0.83	0.82	0.01	0.05	0.14	0.76
S/D	6.05	6.08	6.20	6.72	6.610	6.25	0.40	0.22	0.91	0.72
PSV	42.90	44.64	44.02	42.90	43.13	44.01	0.50	0.22	0.05	0.22

UA: umblical artery; Right UtA: right uterine artery; Left UtA: left uterine artery; MCA: middle cerebral artery; PI: pulsatility index; RI: resistance index; S/D: systole/diastole ratio; PSV: peak systolic velocity; SEM: standard error; D: drug; T: time; DxT: drug–time relationship

Doppler ultrasonography is mostly used to evaluate blood flow. In recent perinatology practice, Doppler ultrasonography has been used to determine fetal well-being, particularly in intrauterine growth retardation and fetal anemia, and it plays an important role in planning the treatment of these conditions. In addition, it is known that Doppler ultrasonography is used to evaluate the effects of tocolytic drugs, which have side effects on the cardiovascular system, uteroplacental blood flow, and the fetal vascular system. UtA, UA, and MCA are most commonly studied arteries to evaluate fetal well-being (6).

There are some controversies about the tocolytic usage of nifedipine because there are limited data about potential harmful effects of the drug on uteroplacental perfusion and fetal oxygenation (11). It blocks calcium channels and inhibits smooth muscle contraction. Thus, it decreases uterine vascular resistance (12). It passes through the placenta. Therefore, this vasodilatation effect of the drug raises doubts about the potential effects on the fetal circulatory system (13). Studies about nifedipine on animals have led to contradictory results. In literature, there are limited numbers of studies about Doppler ultrasonography investigations on pregnant women receiving tocolytic treatments. Guclu et al. (14) designed a study involving 21 pregnant women receiving nifedipine as a tocolytic agent. In that study, no significant difference was found in Doppler ultrasonography measurements of UA and fetal MCAs before and 3 hours after treatment. In another study, no difference was found in Doppler measurement parameters (PI and RI) in UA before and 3 hours after drug application (15). In our study, we did not find any significant difference in Doppler ultrasonography parameters for UA, UtA, and MCA before and 2 hours (early) after nifedipine treatment. This result showed that the nifedipine loading dosage (30 mg) and maintenance dosage (10 mg) repeated in the 6-hour period (40 mg/day) in the early phase did not cause any unfavorable effects on uteroplacental blood flow and the fetal vascular system. In a study on late-term effects of nifedipine, the PI value of UA did not change but the PI value of UtA and MCA significantly decreased 24-48 hours after treatment (16). In that study, it was found that nifedipine caused distinctive redistribution in the fetal vascular system and changed the cerebral blood flow (7). In our study, we found no statistically significant difference between PI and other Doppler indices for UA, UtAs, and MCA at 48h (late phase) and before 2h (early phase) after treatment. This indicated that nifedipine did not cause any late harmful effect on the fetal vascular system, fetal cerebral system, and uteroplacental blood flow. Of course, this is a preliminary result and should be supported by comprehensive studies including a high number of cases.

The application of ritodrine, a beta-mimetic agent, has been certificated in the 1980s. Ritodrine and its conjugates pass through the placenta, incorporate into fetal circulation, and are therefore found in the same concentration in both fetal and maternal plasma compartments (17, 18). This indicates that ritodrine can directly affect fetal circulation. In the study of Gokay et al. (18), the utilization of ritodrine as a tocolytic agent caused an increase in the PI value of MCA but a decrease in the PI value of UA (18). In another study of Rasanen, ritodrine led to a decrease in the PI value of MCA but did not cause any variation in Doppler parameters of UA (19). Ritodrine applied to maternal circulation directly affects the perfusion pressure of the fetus, in proportion with the dosage (20). Therefore, discrepancies in Doppler

parameter findings of the two studies are probably because of the application of different dosages of the drug. Gokay et al. (18) used the dosage of 350 mcg/minute, while Rasanen applied 200 mcg/minute at the maximum level. These results indicated that the dosage of the drug may directly affect variations in Doppler parameters and fetomaternal blood flow. In our study, ritodrine infusion started at dosage of 50 mcg/minute and increased to the basal dose at which uterine contractions had stopped. The maximum dosage was 125 mcg/minute. There was no statistical difference in Doppler indices of UA and both UtA and MCA, before, 2 hours after (early period) and 48 hours after (late period) ritodrine treatment. These results indicated that the application of ritodrine as a tocolytic agent did not cause any variation in uteroplacental blood flow and the fetal vascular system before as well as in the early and late periods of treatment. The discrepancy in the results of our study compared with those of other studies was probably because of an increase in the dosage in a progressive and controlled manner. In addition, the maximum dosage used in our research was less than the dosages used different studies. In a study of Sayın, ritodrine application did not cause any change in Doppler parameters of UA and MCA in 48 hours of treatment in pregnant women at 26-32 gestation weeks. On the other hand, changes of Doppler parameters in UA and MCA were observed after 48 hours of treatment and in pregnant women at 32-36 gestation weeks (21). In another study, similar to this, Doppler parameters of UA and MCA changed 48 hours after ritodrine treatment (22). Although changes in Doppler parameters due to ritodrine application were mostly observed after 32 weeks of gestation, in our study, cases included were predominantly between 26-32 weeks of gestation. Therefore, these controversies about impacts of ritodrine can be explained by different gestational weeks of pregnant women included in different studies.

In the perspective of literature, this investigation pointed out that nifedipine was a safe drug and that this drug did not cause any variation in Doppler parameters, indicating unfavorable effects on fetal and fetomaternal circulation at standard dosages. However, randomized controlled studies including a large number of cases are required to evaluate the effects on high dosages. Ritodrine was shown to be a safe tocolytic agent in short-lasting applications (<48 hours) and in 26-32 weeks of gestation. However, we must be cautious, particularly in long-lasting administrations (>48 hours) after 32 weeks of gestation. Therefore, large randomized posology researches including a high number of cases with different gestational ages are required to demonstrate the impressions of drugs on fetal and fetomaternal circulation.

Finally, it is obligatory to emphasize the situation of betamethasone, which is important for fetopulmonary maturation and mostly used in combination with tocolytic agents in preterm labor, while discussing results of our study on effects of nifedipine and ritodrine on fetal and fetomaternal circulation. There are too many investigations and many different results on effects of betamethasone on Doppler indices of fetal and fetomaternal circulation. In animal models, it did not affect the maternal heart rate and blood pressure increased fetal blood pressure (23). It had mild effect on the fetal heart rate (24). Although in some investigations, it was found that it did not affect Doppler parameters of UA, UtA, and MCA, in some, a decrease in Doppler indices of UA and MCA (25, 26) and ductus venosus, particularly PI of MCA, was seen (27). Therefore, it is thought that variations in fetal and fetomaternal circulation in the late period (24-48 hours) of nifedipine and ritodrine in different studies are caused by a combined effect of tocolysis and betamethasone.

In conclusion, nifedipine and ritodrine used as tocolytic agents did not cause any early- and late-onset change in Doppler ultrasonography parameters of fetal and fetomaternal circulation. Because the efficiency and vascular side effects of both drugs were similar, the side effect profile, cost-effectiveness, clinical efficacy, and patient compliance to treatment must be important in selecting the tocolytic agent, and nifedipine seems to be more preferable in tocolytic treatment of preterm labor.

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References

1. Hamilton BE, Martin JA, Ventura SJ. Births: preliminary data for 2012. Natl Vital Stat Rep 2013; 62: 1-20.
2. Stoinic J, Radunovic N, Jeremic K, Kolica Bk, Mitroyic M, Tulic I. Perinatal outcome of singleton pregnancies following in vitro fertilization. Clin Exp Obstet Gynecol 2013; 40: 277-83.
3. Arias F, Rodriquez L, Rayne SC, Kraus FT. Maternal placental vasculopathy and infection: two distinct subgroups among patients with preterm labor and preterm ruptured membranes. Am J Obstet Gynecol 1993; 168: 585-91. [CrossRef]
4. Gilbert WM. The cost of preterm birth: the low cost versus high value of tocolysis. BJOG 2006; 113 (Suppl 3): 4-9. [CrossRef]
5. Spong CY. Prediction and prevention of recurrent spontaneouspreterm birth. Obstet Gynecol 2007; 110 (2 Pt 1): 405-15. [CrossRef]
6. Cararach V, Palacio M, Martínez S, Deulofeu P, Sánchez M, Cobo T, Coll O. Nifedipine versus ritodrine for suppression of preterm labor Comparison of their efficacy and secondary effects. Eur J Obstet Gynecol Reprod Biol 2006; 127: 204-8. [CrossRef]
7. Guclu S, Gol M, Saygılı U, Demir N, Sezer O, Baschat AA. Nifedine therapy for preterm labor:effects on placental, fetal cerebral and atrioventricular Doppler parameters in the first 48 hours. Ultrasound Obstet Gynecol 2006; 27: 403-8. [CrossRef]

8. Creasy RK. Preterm labor and delivery: Maternal fetal medicine 3. Edition. Philadelphia: W.B. Saunders Company; Ch 33. 1994: 494.
9. Guinn DA, Goepfert AR, Owen J, Brumfield C, Hauth JC. Management options in women with preterm uterine contractions. A randomized trial. Am J Obstet Gynecol 1997; 177: 814. [CrossRef]
10. Haram K, Mortensen JH, Wollen AL. Preterm delivery: an overwiew. Acta Obstet Gynecol Scand 2003; 82: 687-704. [CrossRef]
11. Glock JL, Morales WJ. Efficacy and safety of nifedipine versus magnesium sulfate in the management of preterm labor: a randomized study. Am J Obstet Gynecol 1993; 169: 960-4. [CrossRef]
12. Braunwald E. Mechanisms of action of calcium-channel-blocking agents. N Engl J Med 1982; 307: 1618-27. [CrossRef]
13. Magee LA, Schick B, Donnenfeld AE, Sage SR, Conover B, Cook L, McElhatton PR, et al. The safety of calcium channel blockers in human pregnancy: a prospective, multicenter cohort study. Am J Obstet Gynecol 1996; 174: 823-8. [CrossRef]
14. Guclu S, Gol M, Doğan E, Demir N, Baschat AA. The short term effect of nifedipine tocolysis on placental, fetal cerebral and atrioventricular Doppler waveforms. Ultrasound Obstet Gynecol 2004; 24: 761-5. [CrossRef]
15. Garcia-Velasco JA, Gonzalez A. A prospective, randomized trial of nifedipine vs. ritodrine in threatened preterm labor. Int J Gynecol Obstet 1998; 61: 239-44. [CrossRef]
16. Stan CM, Boulvain M, Pfister R, Hirsbrunner-Almagbaly P. Hydration for treatment of preterm labour. Cochrane Database Syst Rev 2013; 11: CD003096. [CrossRef]
17. Brashear WT, Kuhnert BR, Wei R. Maternal and neonatal urinary excretion of sulfate and glucuronide ritodrine conjugates. Clin Pharmacol Ther 1988; 44: 634-41. [CrossRef]
18. Gokay Z, Ozcan T, Copel JA. Changes in fetal hemodynamics with ritodrine tocolysis. Ultrasound Obstet Gynecol 2001; 18: 44-6. [CrossRef]
19. Rasanen J. The effects of Ritodrine infusion on fetal myocardial function and fetal hemodynamics. Acta Obstet Gynecol Scand 1990; 69: 487-92. [CrossRef]
20. Ohashi M, Asai M, Maeda K, Suzuki M, Noguchi M, Nakanishi M. Effect of ritodrine hydrochloride on fetal perfusion pressure in dually perfused human placenta. Nippon Sanka Fujinka Gakkai Zasshi 1995; 47: 237-42.
21. Sayin C, Arda S, Varol FG, Süt N. The effects of ritodrine and magnesium sulfate on maternal and fetal Doppler blood flow patterns in women with preterm labor. Eur J Obstet Gynecol Reprod Biol 2010; 152: 50-4. [CrossRef]
22. Kulak N, Türkücüoğlu I, Kafkaslı A. Tokolitik Tedavinin Umbilikal, Uterin ve Spiral Arter Doppler Bulgularına Etkisi. Perinatoloji Dergisi 2007; 15: 93-145.
23. Koenen SV, Mecenas CA, Smith GS, Jenkins S, Nathanielsz PW. Effects of maternal betamethasone administration on fetal and maternal blood pressure and heart rate in the baboon at 0.7 of gestation. Am J Obstet Gynecol 2002; 186: 812-7. [CrossRef]
24. Lunshof MS, Boer K, Wolf H, Koppen S, Velderman JK, Mulder EJ. Short-term (0–48 h) effects of maternal betamethasone administration on fetal heart rate and its variability. Pediatr Res 2005; 57: 545-9. [CrossRef]
25. Deren O, Karaer C, Onderoglu L, Yigit N, Durukan T, Bahado- Singh RO. The effect of steroids on the biophysical profile and Doppler indices of umbilical and middle cerebral arteries in healthy preterm fetuses. Eur J Obstet Gynecol Reprod Biol 2001; 99: 72-6. [CrossRef]
26. Chitrit Y, Caubel P, Herrero R, Schwinte AL, Guillaumin D, Boulanger MC. Effects of maternal dexamethasone administration on fetal Doppler flow velocity waveforms. BJOG 2000; 107: 501-7. [CrossRef]
27. Kahler C, Schleussner E, Moller A, Seewald HJ. Doppler measurements in fetoplacental vessels after maternal betamethasone administration. Fetal Diagn Ther 2004; 19: 52-7. [CrossRef]

Hyperprolactinemia has no effect on plasma ghrelin levels in patients with prolactinoma

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Abstract

Objective: Accumulating evidence suggests that prolactin is a modulator of body weight and composition and that it regulates some transporters in adipose tissue. It was demonstrated that hyperprolactinemia is associated with weight gain and obesity. Ghrelin is a novel hormone secreted from many organs including the pituitary gland. Ghrelin acts by regulating energy homeostasis and stimulating appetite. The aim of this study is to investigate whether ghrelin has a role in the case of weight gain in patients with prolactinoma.

Material and Methods: Forty-four patients with prolactinoma, both newly diagnosed and undergoing cabergoline treatment, were included in this study. Age- and sex-matched healthy subjects were included in the control group. Serum fasting glucose, insulin, lipid profile, and ghrelin levels were measured. Homeostasis model assessment of insulin resistance (HOMA-IR) was also calculated. Body mass index (BMI) and total fat ratio (%) of all the participants were assessed by bioelectrical impedance analysis using TBF-310GS™ (Tanita Corporation, Tokyo, Japan).

Results: Patients with prolactinoma demonstrated significantly higher serum levels of fasting insulin, triglyceride, and waist and hip circumference measurement. No significant difference was found between the fasting glucose, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and HOMA-IR levels. BMI was significantly higher in the patients with prolactinoma than that in the control group ($p<0.05$). Additionally, the total body fat percentage was higher in the patients with prolactinoma than that in the control group; however, the difference was not significant ($p>0.05$). Furthermore, there was no significant difference in terms of the ghrelin levels between these groups. There was a correlation with serum ghrelin and growth hormone levels ($p<0.02$, rho=0.489). However, no significant correlation was obtained between serum prolactin or ghrelin levels and body fat percentage.

Conclusion: According to the results of our study, ghrelin has no effect on weight gain in patients with prolactinoma. Further studies are needed to evaluate whether ghrelin affects the prevalence of obesity in patients with prolactinoma. (J Turk Ger Gynecol Assoc 2015; 16: 86-90)

Keywords: Hyperprolactinemia, ghrelin, weight gain

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Introduction

Accumulating evidence suggests that prolactin is a modulator of body weight and composition and that it regulates transporters and enzymes in the adipose tissue and islets. Kok et al. (1) reported that increased prolactin secretion was demonstrated by serial prolactin measurements over 24h in obese women compared with those in lean subjects and that a proportional prolactin release is seen with an increasing body mass index (BMI) and size of visceral fat mass. Several studies reported that hyperprolactinemia is associated with weight gain, obesity, and insulin resistance (1-7). However, the mechanism by which hyperprolactinemia may cause weight gain and obesity is not clear. Two of the main potential reported explanations are the disruption of the central nervous system dopaminergic tone and the stimulation of lipogenesis (8). However, whether prolactin is directly related to weight gain or the consequences of the central dopaminergic effect is not clear.

Ghrelin, which is known as the ligand of the growth hormone secretagogue receptor (GHS-R), is a circulating orexigenic and adipogenic brain–gut peptide. According to recent studies, ghrelin is produced from several organs, such as the intestine, kidney, placenta, pituitary gland, hypothalamus, lung, lymphatic tissue, thyroid gland, adrenal gland, and gonads (9, 10). Ghrelin regulates the function of the anterior pituitary gland by stimulating the growth hormone, adrenocorticotropin, and prolactin, and it also modulates the functions of the exocrine and endocrine pancreas (11). Its effect on the regulation of energy balance and appetite is through the signaling GHS-R in the brain. Interestingly, ghrelin is expressed in a variety of pituitary adenomas (12). Rotondo et al. (13) noted that the highest ghre-

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lin expression is found in growth hormone-producing adenomas exposed to long-acting somatostatin analogs. In their study, they found a lower ghrelin expression in Cushing's disease, untreated growth hormone adenomas, and dopamine agonist-treated prolactinomas. However, no significant immunoreactivity was found in untreated prolactinomas. In conditions of anorexia nervosa, bulimia nervosa, obesity, and polycystic ovary syndrome, prolactin and growth hormone are released as a response to exogenous ghrelin. Messini et al. (14) demonstrated that bromocriptine blocks the stimulating effect of ghrelin on prolactin release in healthy premenapousal women.

Ghrelin has been reported to cause over eating by stimulating appetite resulting in increased body weight. Decreased ghrelin levels are associated with insulin resistance and abdominal adiposity in type 2 diabetes mellitus. Low ghrelin levels are found in obesity, acromegaly, and hypothyroidism associated with Hashimoto's thyroiditis (15-18). There are inadequate data in literature about the relationship between ghrelin and prolactin levels. Additionally, there is no study about ghrelin levels in patients with prolactinoma. Hence, we decided to examine whether circulating ghrelin levels in prolactinoma patients, both newly diagnosed and undergoing therapy, differ from those in healthy subjects in the present study.

Material and Methods

Forty-four patients with prolactinoma, both newly diagnosed and undergoing cabergoline treatment, were included in this study. The diagnosis of prolactinoma was based on increased serum prolactin levels and was located by magnetic resonance imaging of the pituitary gland that indicated an adenoma. Patients with hyperprolactinemia caused by other reasons and hypopituitarism were excluded. None of the patients had any endocrinopathy except hyperprolactinemia. Thirty-six patients were women, and eight were men. Eleven patients had macroprolactinoma, and thirty-three had microprolactinoma. Thirty-two healthy volunteers, without any metabolic diseases, of similar age and gender served as the control group (p=0.6). Participants with a history of metabolic disease, endocrine obesity, and those who took any medical or herbal drug that could affect metabolic parameters were excluded from the study. Additionally, we excluded participants with a history of eating disorders and weight loss. The hospital ethics committee evaluated and approved the study, and all participants gave informed consent.

Serum fasting glucose, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride concentrations were evaluated using enzymatic commercial kits. Prolactin and insulin levels were evaluated by a chemiluminescence assay (Advia Centaur, Siemens Healthcare diagnostics, USA). Intra- and inter-assay variation coefficients were 4.6%, 3.2%, and 3.3% and 5.9%, 2.6%, and 4.8% for 14.68 mU/L, 45.72 mU/L, and 124.51 mU/L of insulin, respectively. The intra-assay variation coefficient was 2.3% and 2.8% for 10.2 ng/mL and and 60.4 ng/mL of prolactin, respectively, whereas the inter-assay variation coefficient was 2.0% and 3.4% for 10.2 ng/mL and and 60.4 ng/mL of prolactin, respectively. The normal limits of prolactin levels were 2.7–18.3 ng/mL.

Blood samples for ghrelin measurement levels were collected into the tubes containing EDTA. The blood was centrifuged at 1.600×g for 15 min; the plasma was separated and stored at -80°C until assessment of ghrelin. The measurements of ghrelin levels were performed in an EPOCH system (BioTek Instruments Inc., Winooski, USA) using the commercially available enzyme-linked immunosorbent assay kit (Phoenix Pharmaceuticals, California, USA) in accordance with the manufactures' instructions. The assay range of the ghrelin ELISA kit was 0–100 ng/mL. The blood samples of both groups were measured simultaneuosly for ghrelin levels.

Waist and hip diameter was measured. BMI and homeostasis model assessment of insulin resistance (HOMA-IR) were calculated (19). The total fat ratio (%) of all the participants was assessed by bioelectrical impedance analysis (BIA) using TBF-310GS™ (Tanita Corporation, Tokyo, Japan) and was recorded.

Descriptive data from the measurements obtained were presented as numbers and arithmetic mean±SD. Kolmogorov–Smirnov test was used to test the normality of distribution for numerical data. Student's t-test and chi-square test were used to compare the two groups. Association among the numerical data was detected by Pearson correlation analysis. Using multivariate multiple regression, backward elimination was used to determine the association between the ghrelin and numerical measurements. $P<0.05$ was considered statistically significant. PASW version 18, (SPSS, Chicago, IL, USA) software was used for the statistical calculations.

Results

Demographic characteristics and biochemical data of the patients and healthy subjects are summarized in Table 1. Nineteen patients were newly diagnosed, and 25 patients were undergoing cabergoline treatment (mean duration since diagnosis, 35 months; range, 6–192 months). Only two patients had a transnasal transsphenoidal operation for macroprolactinoma. Compared with the age- and gender-matched control subjects, the patients with prolactinoma demonstrated significantly higher serum levels of fasting insulin, HOMA-IR, triglyceride, and waist and hip circumference measurement. No significant difference was found between fasting glucose, HDL-cholesterol, and LDL-cholesterol levels (Table 1). In the results of TANITA analysis, the total body fat percentage was higher in patients with prolactinoma compared with that in the healthy subjects; however, the difference was not significant (34.9±7.6% vs 31.3±7.3%, p=0.131). Furthermore, there was no significant difference in terms of the ghrelin levels between the patients with prolactinoma both newly diagnosed and undergoing cabergoline treatment and the healthy subjects (Table 2). Thyroid-stimulating hormone levels were similar in the groups (p=0.182). Estrogen levels were compared in female participants and were found to be 81.6±66.5 pg/mL and 58.7±73.9 pg/mL in the controls and patients, respectively (p=0.39). Growth hormone and somatomedin-C levels were 0.5±1.1 pg/mL and 176.1±76.2 pg/mL, respectively in the patient group.

Table 1. Demographic characteristics and biochemical data for patients and control subjects

	Patients (n=44)	Controls (n=32)	p
Male/female	8/36	5/27	0.51
Age (years)	38.7±10.3	40.9±8.4	0.341
PRL (ng/mL)	88.9±110.8	8.7±3.8	0.000
BMI (kg/m^2)	30.7±5.8	26.9±3.9	0.011
WC (cm)	93.3±14.1	85.6±8.1	0.018
HC (cm)	101.4±12.9	83.4±8.8	0.012
FBG (mg/dL)	88.6±11.1	84.2±75.9	0.07
HDL-C (mg/dL)	50.2±9.7	53.2±19.9	0.476
LDL-C (mg/dL)	117.3±31.9	114.3±34.9	0.719
TG (mg/dL)	123.5±54.2	99.8±45.5	0.050
Fasting insulin (IU/mL)	12.3±7.3	8.4±3.4	0.013
HOMA-IR	2.9±2.0	1.6±0.6	0.004
TSH	2.08±0.9	1.8±0.9	0.182
BFP (%)	34.9±7.6	31.3±7.3	0.131

*Data are presented as mean±SD
PRL: prolactin; BMI: body mass index; WC: waist circumference; HC: hip circumference; FBG: fasting blood glucose; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triglyceride; HOMA-IR: homeostasis model assessment of insulin resistance; TSH: thyroid-stimulating hormone; BFP: body fat percentage

Table 2. Ghrelin levels in patients and controls

	Ghrelin (pg/mL)	p
Patients with remission (n=19)	24.4±15.5	
Patients with new diagnosis (n=25)	27.4±16.3	
Controls (n=32)	25.6±11.8	0.795

There was a positive correlation between serum ghrelin and growth hormone levels (p<0.02, rho=0.489) in the correlation analysis. However, no significant correlation was obtained between serum prolactin or ghrelin levels and body fat percentage. Furthermore, a negative correlation was only found between ghrelin and fasting blood glucose levels, and a positive correlation was only found between ghrelin and HOMA-IR levels in multiple regression analysis (p=0.036, p=0.037) (Figure 1, 2).

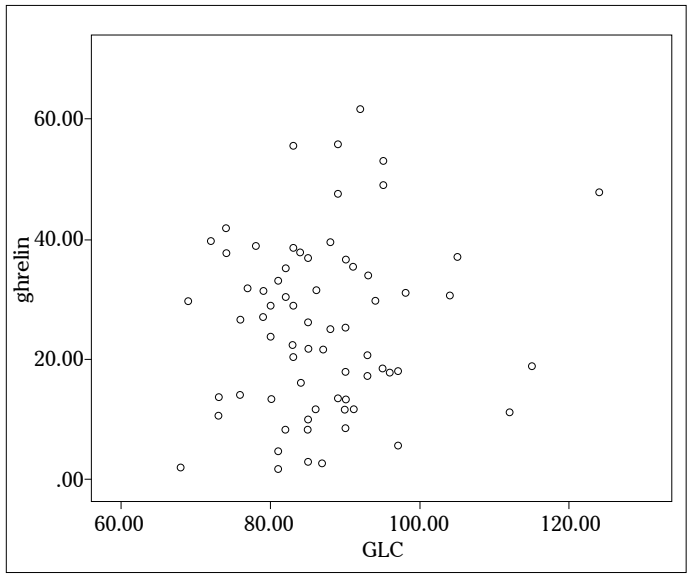

Figure 1. Relationship between levels of fasting serum ghrelin and glucose in patients with prolactinoma

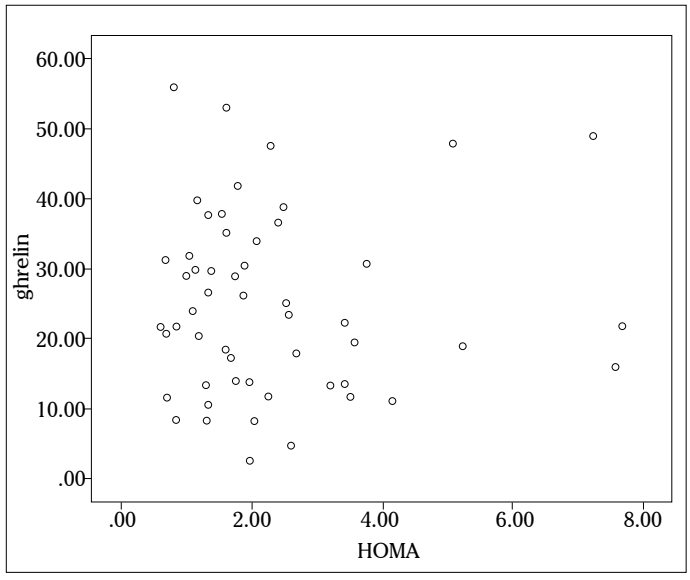

Figure 2. Relationship between levels of fasting serum ghrelin and HOMA-IR in patients with prolactinoma

Discussion

Ghrelin is a circulating peptide having many effects on both metabolism and neuroendocrine functions including weight control and growth. It was demonstrated that ghrelin stimulates prolactin secretion from the pituitary gland in women (20). However, the mechanism is not explained very well. In addition, ghrelin levels in patients with prolactinoma have not been investigated yet. Our data has demonstrated for the first time that fasting serum ghrelin levels had no relationship with prolactin in patients diagnosed with prolactinoma. These data suggest that ghrelin levels have no significant effect on weight gain and could not explain increased obesity prevalence in prolactinoma.

There are few studies conducted on the relation between prolactin and ghrelin levels. The stimulatory effect of ghrelin on prolactin secretion reflects the direct stimulation of somatomammotroph cells. In this study we found a positive correlation between serum ghrelin and growth hormone levels (p<0.02, rho=0.489) in the correlation analysis. Takaya et al. (21) demonstrated the stimulation of growth hormone, adrenocorticotropic hormone, cortisol, and prolactin after ghrelin injection. In another study, plasma total ghrelin values are found to be negatively correlated to IGF-I in patients with acromegaly (22). However, we found no significant correlation between serum prolactin and ghrelin levels. Furthermore, we evaluated the

relation between ghrelin and body fat percentage and found no significant correlation.

We evaluated ghrelin levels in two groups of the patients with prolactinoma; one group had active prolactinoma and the other had patients under remission with cabergoline treatment. We found higher ghrelin levels in newly diagnosed patients; however, the difference was not statistically significant. Messini et al. (14) investigated the effect of bromocriptine, which is a dopamine agonist similar to cabergoline on ghrelin-induced prolactin secretion in healthy premenopausal women. They demonstrated that bromocriptine block the stimulating effect of ghrelin on prolactin release (14). Thus, the insignificant lower levels of ghrelin in patients with remission may be related to the cabergoline effect of ghrelin on prolactin levels.

Ghrelin levels increase by fasting and decrease by food intake and overfeeding (23). Therefore, all samples were collected after eight hours of fasting. Conflicting results about the effect of gender on ghrelin levels were reported. To eliminate the possible effect of gender, we included participants with a similar ratio of both genders. Ghrelin reduces insulin secretion in humans. Tschöp et al. (24) found a negative correlation between plasma ghrelin and insulin concentrations. Lucidi et al. (25) reported a clear reduction in circulating ghrelin levels with an increase in insulin levels during both hypoglycemic and euglycemic clamp 5. In contrast, we did not observe any correlation between insulin and ghrelin levels. However, we found a negative correlation between ghrelin and fasting blood glucose levels and a positive correlation between ghrelin and HOMA-IR levels in multiple regression analysis.

Hyperprolactinemia is related to increased food intake and body weight in rats, and suppression of prolactin causes weight loss (26, 27). The mechanism of how hyperprolactinemia causes weight gain is not clear. Therefore, we investigated whether ghrelin was associated with increased food intake by stimulating appetite or other mechanisms and body weight. The participants in the present study had BMI ≥30 kg/m^2. They had significantly higher BMI than the controls; however, ghrelin levels were higher in the patients with prolactinoma. In contrast to our finding, Tschöp et al. (15) found circulating ghrelin levels in obese patients to be low. In patients with prolactinoma, it was found that the central dopaminergic tone is reduced because of the refractoriness of central dopaminergic neurons to prolactin, and it may contribute to weight gain in patients with prolactinoma (28). The central stimulation of dopamine receptors, either dopamine receptor 1 or dopamine receptors 2 and 3 simultaneously, leads to a significant decrease in ghrelin-induced food intake (29).

It could be argued that the level of ghrelin was evaluated without performing dynamic test. We accept this as a limitation of our study. Another limitation is the evaluation of only total ghrelin levels without separately evaluating the levels of full length ghrelin (acyl plus des-acyl) and des-acyl ghrelin as recommended by Liu et al. (30).

In conclusion, ghrelin has no effect on weight gain in patients diagnosed with prolactinoma. Plasma ghrelin may not directly reflect the ghrelin level in the pituitary gland. Further larger studies are needed to determine the relation between prolactin and ghrelin on obesity in patients with prolactinoma.

Ethics Committee Approval: *Ethics committee approval was received for this study from the ethics committee of Local Ethics Commitee, Dışkapı Teaching and Research Hospital.*

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References

1. Kok P, Roelfsema F, Frölich M, Meinders AE, Pijl H. Prolactin release is enhanced in proportion to excess visceral fat in obese women. J Clin Endocrinol Metab 2004; 89: 4445-9. [CrossRef]
2. Galluzzi F, Salti R, Stagi S, La Cauza F, Chiarelli F. Reversible weight gain and prolactin levels--long-term follow-up in childhood. J Pediatr Endocrinol Metab 2005; 18: 921-4. [CrossRef]
3. Creemers LB, Zelissen PM, van 't Verlaat JW, Koppeschaar HP. Prolactinoma and body weight: a retrospective study. Acta Endocrinol (Copenh) 1991; 125: 392-6. [CrossRef]
4. Greenman Y, Tordjman K, Stern N. Increased body weight associated with prolactin secreting pituitary adenomas: weight loss with normalization of prolactin levels. Clin Endocrinol (Oxf) 1998; 48: 547-53. [CrossRef]
5. Schmid C, Goede DL, Hauser RS, Brändle M. Increased prevalence of high Body Mass Index in patients presenting with pituitary tumours: severe obesity in patients with macroprolactinoma. Swiss Med Wkly 2006; 136: 254-8.
6. Inancli SS, Usluogullari A, Ustu Y, Caner S, Tam AA, Ersoy R, Cakir B. Effect of cabergoline on insulin sensitivity, inflammation, and carotid intima media thickness in patients with prolactinoma. Endocrine 2013; 44: 193-9. [CrossRef]
7. Arslan MS, Topaloglu O, Sahin M, Tutal E, Gungunes A, Cakir E, et al. Preclinical atherosclerosis in patients with prolactinoma. Endocr Pract 2014; 20: 447-51. [CrossRef]
8. Doknic M, Pekic S, Zarkovic M, Medic-Stojanoska M, Dieguez C, Casanueva F, Popovic V. Dopaminergic tone and obesity: an insight from prolactinomas treated with bromocriptine. Eur J Endocrinol 2002; 147: 77-84. [CrossRef]
9. Korbonits M, Kojima M, Kangawa K, Grossman AB. Presence of ghrelin in normal and adenomatous human pituitary. Endocrine 2001; 14: 101-4. [CrossRef]
10. Ueberberg B, Unger N, Saeger W, Mann K, Petersenn S. Expression of ghrelin and its receptor in human tissues. Horm Metab Res 2009; 41: 814-21. [CrossRef]
11. Lim CT, Kola B, Korbonits M, Grossman AB. Ghrelin's role as a major regulator of appetite and its other functions in neuroendocrinology. Prog Brain Res 2010; 182: 189-205. [CrossRef]

12. Leontiou CA, Franchi G, Korbonits M. Ghrelin in neuroendocrine organs and tumours. Pituitary 2007; 10: 213-25. [CrossRef]
13. Rotondo F, Cusimano M, Scheithauer BW, Rotondo A, Syro LV, Kovacs K. Ghrelin immunoexpression in pituitary adenomas. Pituitary 2011; 14: 318-22. [CrossRef]
14. Messini CI, Dafopoulos K, Chalvatzas N, Georgoulias P, Anifandis G, Messinis IE. Blockage of ghrelin-induced prolactin secretion in women by bromocriptine. Fertil Steril 2010; 94: 1478-81. [CrossRef]
15. Tschöp M, Weyer C, Tataranni PA, Devanarayan V, Ravussin E, Heiman ML. Circulating ghrelin levels are decreased in human obesity. Diabetes 2001; 50: 707-9. [CrossRef]
16. Katsuki A, Urakawa H, Gabazza EC, Murashima S, Nakatani K, Togashi K, et al. Circulating levels of active ghrelin is associated with abdominal adiposity, hyperinsulinemia and insulin resistance in patients with type 2 diabetes mellitus. Endocrinol 2004; 151: 573-7. [CrossRef]
17. Altinova AE, Toruner F, Karakoc A, Yetkin I, Ayvaz G, Cakir N, et al. Serum Ghrelin Levels in patients with Hashimoto's thyroiditis. Thyroid 2006; 16: 1259-64. [CrossRef]
18. Kawamata T, Inui A, Hosoda H, Kangawa K, Hori T. Perioperative plasma active and total ghrelin levels are reduced in acromegaly when compared with in nonfunctioning pituitary tumours even after normalization of serum GH. Clin Endocrinol (Oxf) 2007; 67: 140-4. [CrossRef]
19. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assesment: insulin resistance and beta-cell function from fasting blood glucoseand insuln concentrations in man. Diabetologia 1985; 28: 412-9. [CrossRef]
20. Broglio F, Benso A, Castiglioni C, Gottero C, Prodam F, Destefanis S, et al. The endocrine response to ghrelin as a function of gender in humans in young and elderly subjects. J Clin Endocrinol Metab 2003; 88: 1537-42. [CrossRef]
21. Takaya K, Ariyasu H, Kanamoto N, Iwakura H, Yoshimoto A, Harada M, et al. Ghrelin strongly stimulates growth hormone release in humans. J Clin Endocrinol Metab 2000; 85: 4908-11. [CrossRef]
22. Jarkovská Z, Rosická M, Marek J, Hána V, Weiss V, Justová V, et al. Plasma levels of total and active ghrelin in acromegaly and growth hormone deficiency. Physiol Res 2006; 55: 175-81.
23. Cummings DE, Schwartz MW. Genetics and pathophysiology of human obesity. Annu Rev Med 2003; 54: 453-71. [CrossRef]
24. Tschöp M, Weyer C, Tataranni PA, Devanarayan V, Ravussin E, Heiman ML. Circulating ghrelin levels are decreased in human obesity. Diabetes 2001; 50: 707-9. [CrossRef]
25. Lucidi P, Murdolo G, Di Loreto C, De Cicco A, Parlanti N, Fanelli C, et al. Ghrelin is not necessary for adequate hormonal counterregulation of insulin-induced hypoglycemia. Diabetes 2002; 51: 2911-4. [CrossRef]
26. Moore BJ, Gerardo-Gettens T, Horwitz BA, Stern JS. Hyperprolactinemia stimulates food intake in the female rat. Brain Res Bull 1986; 17: 563-9. [CrossRef]
27. Byatt JC, Staten NR, Salsgiver WJ, Kostelc JG, Collier RJ. Stimulation of food intake and weight gain in mature female rats by bovine prolactin and bovine growth hormone. Am J Physiol 1993; 264: E986-92.
28. Ben-Jonathan N, Hnasko R. Dopamine as a prolactin (PRL) inhibitor. Endocr Rev 2001; 22: 724-63. [CrossRef]
29. Romero-Picó A, Novelle MG, Folgueira C, López M, Nogueiras R, Diéguez C. Psychopharmacology (Berl). Central manipulation of dopamine receptors attenuates the orexigenic action of ghrelin. Psychopharmacology (Berl) 2013; 229: 275-83. [CrossRef]
30. Liu J, Prudom CE, Nass R, Pezzoli SS, Oliveri MC, Johnson ML, et al. Novel ghrelin assays provide evidence for independent regulation of ghrelin acylation and secretion in healthy young men. J Clin Endocrinol Metab 2008; 93: 1980-7. [CrossRef]

Mislocated extrauterine intrauterine devices: Diagnosis and surgical management

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Abstract

Objective: Presentation of the diagnostic and surgical treatment methods of our extrauterine intrauterine device (IUD) cases.

Material and Methods: We retrospectively evaluated the data of 21 extrauterine IUD cases at our clinic between 2008 and 2010. The symptoms, diagnostic methods, and surgical treatments were evaluated.

Results: A total of 14 copper and seven levonorgestrel (LNG) IUDs were used. IUD had been inserted during lactation in 71.4% of the patients. The reasons for presentation of patients were unintended pregnancy in 19.05%, pelvic pain in 19.05%, and pelvic pain with vaginal bleeding in 23.8%. IUD in two patients were located the retroperitoneal area. IUD string had not been visible during routine follow-up in 38.1% of the patients. Laparoscopy was performed in 14 patients and laparotomy was performed for dense adhesions in seven patients.

Conclusion: Extrauterine IUDs can present with various clinical symptoms. Ultrasonography and X-Ray are sufficient for the diagnosis. Surgical removal is needed to prevent possible complications, and the preferred surgical technique in appropriate patients is laparoscopy.

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Keywords: Extrauterine IUD, surgery, contraception

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Introduction

Intrauterine devices (IUDs) are highly effective reversible contraceptive devices commonly used throughout the world. Globally, they are the second most common contraceptive method (14%) following sterilization (21%) (1). They are also frequently used in Turkey (20.2%). The most common types are the copper-releasing IUD and the Levonorgestrel-releasing IUD (LNG-IUD) systems.

There are various complications with respect to IUD use (0.2-3.6/1000 applications), among which uterine perforation is a serious complication. Most uterine perforations are observed in IUD's inserted during lactation (2, 3). Other important complications are lower midline abdominal pain, organ perforation, strangulation, infection, and infertility. The adhesions that can gradually develop with intra-abdominal IUD's are the most important cause of additional morbidity (4). This complication has been reported both with LNG-IUDs (Mirena, Shering Plough, Germany) and copper IUDs (TCu-380A). Prevention and early diagnosis are the most important factors to avoid this complication. Therefore, it is necessary to see the IUD string immediately after insertion or in the first week with vaginal examination and to perform a check with ultrasonography in all patients. Surgical intervention is frequently required in uterine perforation.

We aim to present our clinical experience with the symptoms, diagnostic methods, and surgical treatment of extrauterine IUDs in this retrospective study.

Material and Methods

We retrospectively evaluated the patient charts of females with an extrauterine IUD and who had undergone laparotomy or laparoscopy at Adıyaman University Faculty of Medicine Training and Research Hospital, Department of Obstetrics and Gynecology between 2008 and 2014.

We first performed a search using the "IUD with no visible string at the cervical os" code (530.583) of the International Classification of Disease and Related Health Problems-10 (ICD-10) codes that have been adapted to Turkish. Following the evaluation of the data, the patients were divided into two groups as intrauterine and extrauterine IUDs. Patients who had an intrauterine IUD where no string was visible and that was removed with a simple vaginal procedure or hysteroscopy were excluded from the study. We found a total of 21 extrauterine IUD cases. Patient data were evaluated through review of the patient charts and the hospital system records. All patients underwent surgery after going through a similar evaluation process. A gynecological examination was performed first and IUD was evaluated with transvaginal ultra-

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Table 1. Demographic characteristics of patients

Patient	Age (years)	Gravity	Parity	BMI (kg/m²)	Number of CS	Previous IUD use	Time of total IUD use (months)	History of abdominal surgery
1	23	3	3	26.4	None	yes	24	no
2	25	3	3	23.6	1	no	0	no
3	28	4	3	27.8	None	yes	48	no
4	26	2	2	26.4	None	no	0	no
5	24	1	1	29.1	None	no	0	yes
6	34	5	5	28	1	no	0	no
7	38	7	4	26.1	None	no	0	no
8	36	5	4	26.5	3	no	0	no
9	34	3	3	25.9	None	no	0	no
10	31	4	4	24.9	2	yes	30	no
11	30	2	2	24.7	None	yes	48	yes
12	23	2	2	28.6	None	no	0	no
13	27	1	1	27	None	no	0	no
14	28	2	2	26.2	None	no	0	no
15	35	6	4	29	None	yes	48	no
16	30	4	4	26	None	no	0	no
17	26	3	3	31	None	no	0	no
18	32	8	6	27	None	yes	36	yes
19	36	5	4	28	None	yes	48	no
20	28	5	3	24	1	no	0	no
21	32	3	3	25.4	None	yes	36	no

BMI: Body mass index; IUD: Intrauterine device; CS: Caesarean section

sonography when the string could not be seen. Anteroposterior and lateral pelvic X-rays were obtained to support the diagnosis. None of the patients in the study underwent magnetic resonance imaging (MRI) or computed tomography (CT) scans. Patients who received a preliminary diagnosis of extrauterine IUD were prepared for laparoscopic surgery. Laparotomy with a Pfannenstiel incision was performed for patients who could not undergo laparoscopy. All surgical procedures were performed under general anesthesia.

The 21 patients detected within the defined period were evaluated. Age, obstetric history, extrauterine IUD type, time of application, time until diagnosis and surgical intervention, symptoms, and surgical route used were recorded. Informed written consent was obtained from all the women. This retrospective case-series study was exempt from ethical approval by the Adıyaman University Ethics commission. We did not conduct statistical analysis.

Results

Demographic data

The demographic data revealed a mean age of 29.4 years and a mean body mass index (BMI) value of 26.9 kg/m². Obstetric data revealed a mean gravida value of 3.6. The mean number of births by normal spontaneous vaginal delivery was 2.5, while the mean number of cesarean births was 0.4. An IUD had been used before the current one by 33.3% of the patients. The mean duration for which the previous IUD was used was 40.2 (24-48) months (Table 1).

IUD types and important time points regarding insertion

Table 2 presents the extrauterine IUD clinical data and usage characteristics of the patients. All mislocated extrauterine IUD applications had been performed in primary health care centers. Extrauterine IUDs consisted of seven LNG-IUDs and 14 copper IUDs (TCu-380A-IUD). The mean duration between IUD insertion and diagnosis was 8.1 months (3 days-24 months). The mean duration between the last pregnancy and IUD insertion was 14.7 (2-38) months. IUD had been inserted during lactation in 15 (71.4%) patients.

Symptoms and IUD localization

Symptoms at presentation were delayed menstruation in the four patients with an unintended pregnancy, pelvic pain in four, and pelvic pain with vaginal bleeding in five. In addition, the IUD strings of eight patients had not been visible during routine follow-up. Two of the patients with delayed menstruation had undergone pregnancy termination at private centers, while two

Table 2. Symptoms, the locations and treatment of IUD, type of IUDs and special time for IUD insertion

Patients no	Location of the IUD	Type of operation	Time from insertion to diagnosis	Time from pregnancy to insertion	Symptom(s)	Type of IUD
1	In the Douglas pouch	Laparoscopy	7 months	16 months	None	LNG-IUD
2	In the Douglas pouch	Laparoscopy	12 months	11 months	None	TCu 380 A-IUD
3	Near the uterine artery	Laparoscopy	6 months	8 months	None	TCu 380 A-IUD
4	Near the ovary	Laparotomy	3 months	4 months	Pelvic pain	TCu 380 A-IUD
5	In the Douglas pouch	Laparoscopy	18 months	2 months	None	TCu 380 A-IUD
6	In the Douglas pouch	Laparoscopy	24 months	8 months	None	TCu 380 A-IUD
7	In the Douglas pouch	Laparoscopy	12 months	16 months	Unintended pregnancy	TCu 380 A-IUD
8	Omentum	Laparotomy	10 months	24 months	Unintended pregnancy	LNG-IUD
9	Omentum	Laparotomy	6 months	38 months	Unintended pregnancy	LNG-IUD
10	Omentum	Laparotomy	4 days	36 months	Pain and bleeding	LNG-IUD
11	In the Douglas pouch	Laparoscopy	7 days	24 months	Pain and bleeding	LNG-IUD
12	In the Douglas pouch	Laparoscopy	3 days	10 months	Pelvic pain	TCu 380 A-IUD
13	In the Douglas pouch	Laparoscopy	5 days	8 months	Pain and bleeding	TCu 380 A-IUD
14	Retroperitoneum	Laparotomy	6 days	6 months	Pain and bleeding	TCu 380 A-IUD
15	In the Douglas pouch	Laparoscopy	3 days	22 months	Pelvic pain	LNG-IUD
16	Retroperitoneum	Laparotomy	24 months	18 months	Unintended pregnancy	TCu 380 A-IUD
17	Neary the ovary	Laparoscopy	7 months	12 months	None	TCu 380 A-IUD
18	In the Douglas pouch	Laparoscopy	13 months	2 months	None	TCu 380 A-IUD
19	Omentum	Laparotomy	8 months	36 months	None	LNG-IUD
20	Near the ovary	Laparoscopy	6 months	6 months	Pelvic pain	TCu 380 A-IUD
21	In the Douglas pouch	Laparoscopy	18 months	2 months	Pain and bleeding	TCu 380 A-IUD

LNG-IUD: Levonorgestrel intrauterine device; TCu 380 A-IUD: Copper- Intrauterine device; IUD: Intrauterine device

patients continued the pregnancy with an extrauterine IUD and had a normal spontaneous vaginal delivery. IUD was in the Douglas pouch and retroperitoneum in the patients who gave birth. IUD was surgically removed in the postpartum period in both patients. The retroperitoneal IUD was close to the right iliac artery bifurcation during the surgery. The surgery started as laparoscopy but was converted to laparotomy because of the IUD location and the dense adhesions.

The most common extrauterine IUD location was the Douglas pouch with 11 (52.3%) patients (Figure 1, 2). The rare location of the retroperitoneum was seen in two of our patients (Figure 3). Laparoscopic IUD removal was performed in a total of 14 (66.6%) patients. The most common reason to perform laparotomy was severe adhesions.

Table 2 presents the treatment method, IUD type, and localization. Sixteen patients were prepared for laparoscopy under general anesthesia. The surgery was converted to laparotomy because of dense adhesions in two patients. Laparotomy had been performed in five patients because of technical equipment failure. General surgery consultation was required for dense adhesions and abscess formation in two of the patients whose surgeries were converted to laparotomy. The patient with an abscess underwent abscess drainage, and there was no additional complication during follow-up. Both patients had a TCu-380A-IUD. There was no intraoperative complication.

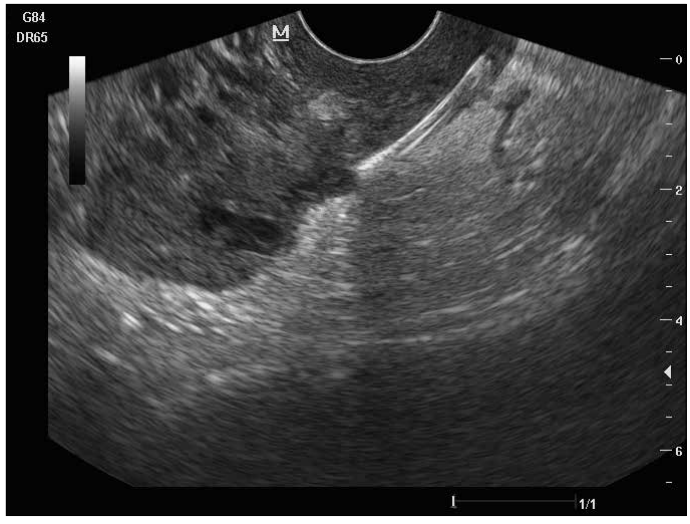

Figure 1. Ultrasonographic appearance of T-shaped IUD in Douglas pouch

Discussion

IUD use is a modern contraceptive use that is commonly employed throughout the world. The low cost, long duration of effectiveness, high efficacy, reversibility, lack of systemic side

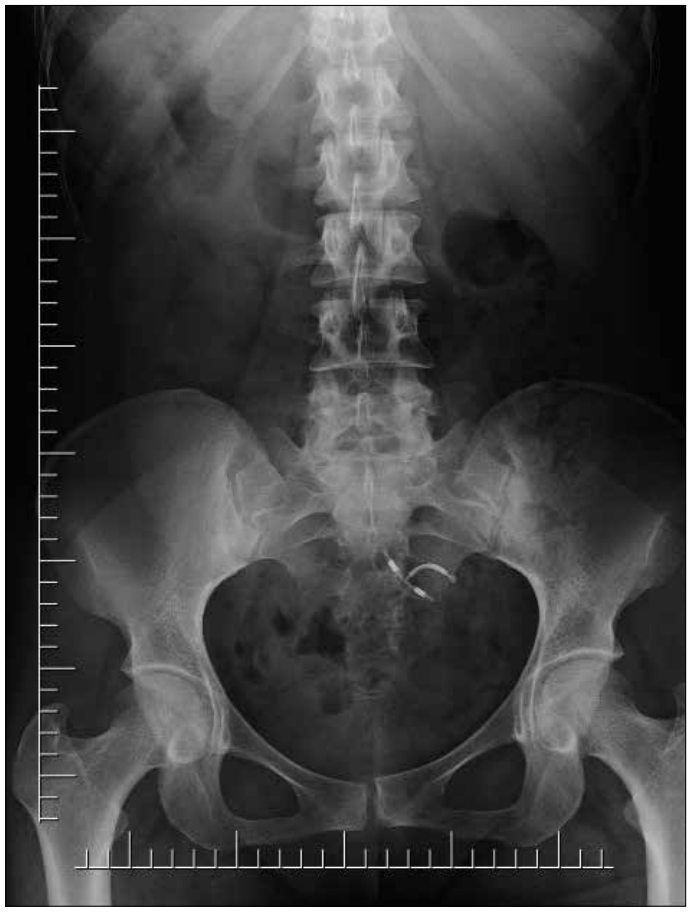

Figure 2. Anteroposterior abdominal X-ray demonstrating location of IUD (Coronal)

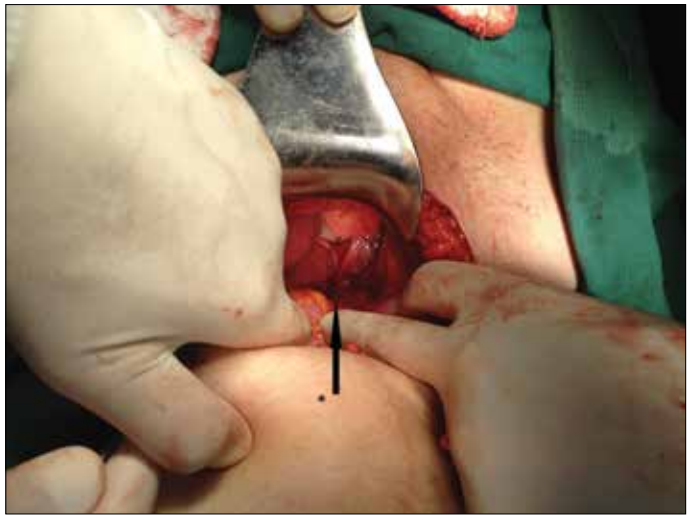

Figure 3. Intraoperative image of IUD (Laparotomy). The IUD string is intraperitoneal but the location of the IUD body is the retroperitoneal area

effects, and coitus-independent effectiveness have led to its widespread use. However, complications such as vaginal bleeding, abdominal pain, infection, uterus perforation, and migration to adjacent organs have been reported. Complications such as uterine perforation are rare but very well defined. Some risk factors for perforation with IUD use have been reported. The postpartum period, lactation period, uterus with undiagnosed pregnancy, congenital uterine abnormality, and excessive anteflexion or retroflexion are important risk factors. The most common association is uterus perforation with an IUD inserted during the lactation period where the risk increases 10-fold (5). Uterine perforation can cause vaginal bleeding and lower abdominal pain following insertion, but several cases have no symptoms for an extended period.

Several studies have reported a period of <1 year between IUD insertion and uterine perforation diagnosis; at least 80% of these patients have been found to be in the lactation period at the time of insertion (3, 6). Similarly, 71.4% of our patients had been in the lactation period during IUD insertion. However, the diagnosis can be delayed by months or even years with an intraperitoneal IUD. The main step in the diagnosis is suspecting an extrauterine IUD in patients where the IUD string is not seen at the cervical os during routine follow-ups or normal outpatient visits. Transvaginal ultrasonography is the best method for localization in case of suspicion. The location may be the Douglas pouch, inside the broad ligament, attached to the omentum, or the retroperitoneal area. Lateral and anteroposterior pelvic X-rays can also be obtained to support the diagnosis and for additional information on the location.

For the treatment of extrauterine IUDs, the World Health Organization recommends prompt surgical removal after diagnosis, independent of the localization and symptoms (7). Prompt decision with regard to surgery is important because adhesion formation becomes more marked and removal becomes more difficult with extrauterine IUDs as time passes. However, there are contrasting views with regard to asymptomatic patients (8). The most important complications of intra-abdominal IUDs are adhesions, intestinal obstruction, chronic pelvic pain, abscess development, and infertility (9, 10). Therefore, it is particularly important to remove IUDs in symptomatic patients. The preferred surgical route is laparoscopy because it is minimally invasive and can be used with a high success rate (11). Laparotomy should only be used in patients with significant adhesion or adjacent organ invasion.

IUDs are inserted by midwives and medical practitioners following a certification program in our country. Therefore, early follow-ups can be a problem. The lack of suspicion about perforation in the early stage can delay referrals to a gynecology specialist, and therefore the diagnosis. However, LNG-IUDs are generally inserted by obstetrics and gynecology specialists in our country. We found an extrauterine LNG-IUD in seven patients. This result indicates that the uterine perforation risk should be considered even when the insertion has been performed by a specialist.

Operator factors were not addressed in our study, and this is one of the limitations of our research. We did not have access to information regarding who performed IUD procedures; therefore, we could not address operator skill as a factor for uterine perforation and malposition of IUD.

The migration of IUD to adjacent structures following perforation has been reported with extrauterine IUDs in the literature.

Bladder and iliac vein migration is particularly noteworthy (12). Therefore, migration should be considered if IUD cannot be found (13-16). Retroperitoneal IUD migration is rare but important because of the adjacent vascular structures. Consultation of the relevant specialty may be intraoperatively acquired in such cases; we requested general surgery consultation because of diffuse intestinal adhesions for two cases and abscess formation at the sigmoid colon level for one case. Abscess drainage from the abdomen was performed for our patient with abscess formation. Most of the patients were diagnosed with an extrauterine IUD when the IUD string was not seen during routine follow-up and the patient was evaluated by ultrasonography and X-ray (17).

In conclusion, uterine perforation can present with symptoms such as lower abdominal pain and abnormal vaginal bleeding, with the IUD string not being seen during routine follow-up, or an unintended pregnancy. The combination of transvaginal ultrasound and anteroposterior/lateral X-ray is usually adequate for the diagnosis. It may be best for a specialist to perform the insertion in cases at risk such as those with a known uterine anomaly or excessive uterine anteflexion or retroflexion or patients in the lactation period. The early diagnosis of complications, such as uterine perforation, also requires the follow-up of the IUD location with postprocedure ultrasonography in several cases. In light of the data, we believe that all extrauterine IUD's should be surgically removed (preferably by laparoscopy) to prevent complications at later stages.

Ethics Committee Approval: *Ethics committee approval was received for this study from the ethics committee of Adıyaman University Faculty of Medicine Ethical Committee.*

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

Peer-review: *Externally peer-reviewed.*

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References

1. World Population Bureau. Family Planning Worldwide, 2008 Data Sheet. Available from: http://www.prb.org/pdf08/fpds08.pdf (29 January 2013, date last accessed)
2. Chi I, Feldblum PJ, Rogers SM. IUD-related uterine perforation: an epidemiologic analysis of a rare event using an international dataset. Contracept Deliv Syst 1984; 5: 123-30.
3. Caliskan E, Ozturk N, Dilbaz BO, Dilbaz S. Analysis of risk factors associated with uterine perforation by intrauterine devices. Eur J Contracept Reprod Health Care 2003; 8: 150-5. [CrossRef]
4. Adoni A, Ben Chetrit A. The management of intrauterine devices following uterine perforation. Contraception 1991; 43: 77-81. [CrossRef]
5. Heartwell SP, Schlesselman S. Risk of uterine perforation among users of intrauterine devices. Obstet Gynecol 1983; 61: 31-6.
6. Andersson K, Ryde-Blomqvist E, Lindell K, Odlind V, Milsom I. Perforations with intrauterine devices. Report from a Swedish survey. Contraception 1998; 57: 251-5. [CrossRef]
7. World Health Organization. Sexual and reproductive health. Available from: http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/en/index.html
8. Markovitch O, Klein Z, Gidoni Y, Holzinger M, Beyth Y. Extrauterine mislocated IUD: is surgical removal mandatory? Contraception 2002; 66: 105-8. [CrossRef]
9. Rao RP. Lost intrauterine devices and their localization. J Reprod Med 1978; 20: 195-9.
10. Ohana E, Sheiner E, Leron E, Mazor M. Appendix perforation by an intrauterine contraceptive device. Eur J Obstet Gynecol Reprod Biol 2000; 88: 129-31. [CrossRef]
11. Demir SC, Cetin MT, Ucunsak IF, Atay Y, Toksoz L, Kadayifici O. Removal of intra-abdominal intrauterine device by laparoscopy. Eur J Contracept Reprod Health Care 2002; 1: 20-3. [CrossRef]
12. Roy KK, Banerjee N, Sinha A. Laparoscopic removal of translocated retroperitoneal IUD. Int J Gynaecol Obstet 2000; 71: 241-3. [CrossRef]
13. Farouk K, Afridi Z, Farooq M, Qureshi I. Urological complications of ıntrauterine contraceptive device. Journal of Postgraduate Medical Institute 2007; 21: 260-5.
14. Yalcin V, Demirkesen O, Alici B, Onol B, Solok V. An unusual presentation of a foreign body in the urinary bladder: a migrant intrauterine device. Urol Int 1998; 61: 240-2. [CrossRef]
15. Demirci D, Ekmekcioglu O, Demirtas A, Gulmez I. Big bladder stones around an intravesical migrated intrauterine device. Int Urol Nephrol 2003; 35: 495-6. [CrossRef]
16. Kassab B, Audra P. The migrating intrauterine device. Case report and review of the literature. Contracept Fertil Sex 1999; 27: 696-700.
17. Ozgun MT, Batukan C, Serin IS, Ozcelik B, Basbug M, Dolanbay M. Surgical management of intra-abdominal mislocated intrauterine devices. Contraception 2007; 75: 96-100. [CrossRef]

Addition of gonadotropin releasing hormone agonist for luteal phase support in *in-vitro* fertilization: an analysis of 2739 cycles

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Abstract

Objective: Luteal phase is defective in in vitro fertilization (IVF) cycles, and many regimens were tried for the very best luteal phase support (LPS). Gonadotropin releasing hormone (GnRH) agonist use, which was administered as an adjunct to the luteal phase support in IVF cycles, was suggested to improve pregnancy outcome measures in certain randomized studies. We analyzed the effects of addition of GnRH agonist to standard progesterone luteal support on pregnancy outcome measures, particularly the live birth rates.

Material and Methods: This is a retrospective cohort study, including 2739 IVF cycles. Long GnRH agonist and antagonist stimulation IVF cycles with cleavage-stage embryo transfer were included. Cycles were divided into two groups: Group A included cycles with single-dose GnRH agonist plus progesterone LPS and Group B included progesterone only LPS. Live birth rates were the primary outcome measures of the analysis. Miscarriage rates and multiple pregnancy rates were the secondary outcome measures.

Results: Live birth rates were not statistically different in GnRH agonist plus progesterone (Group A) and progesterone only (Group B) groups in both the long agonist and antagonist stimulation arms (40.8%/41.2% and 32.8%/34.4%, $p<0.05$ respectively). Moreover, pregnancy rates, implantation rates, and miscarriage rates were found to be similar between groups. Multiple pregnancy rates in antagonist cycles were significantly higher in Group A than those in Group B (12.0% and 6.9%, respectively).

Conclusion: A beneficial effect of a single dose of GnRH agonist administration as a luteal phase supporting agent is yet to be determined because of the wide heterogeneity of data present in literature. Well-designed randomized clinical studies are required to clarify any effect of luteal GnRH agonist addition on pregnancy outcome measures with different doses, timing, and administration routes of GnRH agonists. (J Turk Ger Gynecol Assoc 2015; 16: 96-101)

Keywords: GnRH agonist, luteal phase support, in vitro fertilization (IVF), progesterone

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Introduction

In the current controlled ovarian hyperstimulation (COH) cycle management, gonadotrophin releasing hormone (GnRH) agonists or gonadotrophin releasing hormone antagonists are indispensable agents for the prevention of premature luteinization with acceptable live birth rates (1-3). However, supraphysiological steroid hormone levels together with the suppressed luteinizing hormone (LH) levels by both GnRH agonist and GnRH antagonist administration during COH cycles lead to a defect in the luteal phase, particularly in in vitro fertilization (IVF) cycles (3-8). Therefore, use of medication for luteal phase support (LPS) has been considered to be mandatory to ensure intact corpus luteum function and to avoid any decrease in implantation and pregnancy rates (7, 9). There is still controversy over the best LPS agent and protocol and its dose and duration as well as the time of initiation and cessation (10). Intravaginal or intramuscular progesterone application has become the routine practice to support luteal phase in COH cycles over the years either alone or in combination with estradiol (7, 11, 12). However, there is still a search to provide optimal luteal support for better pregnancy outcome rates in COH cycles.

In recent years, the beneficial effects of single or repeated doses of GnRH agonist for luteal phase support were considered in different studies. GnRH agonist luteal support was hypothesized to support luteal phase by various mechanisms. Augmentation of the corpus luteum function by increasing LH secretion by the pituitary cells, direct stimulation of endometrial local GnRH receptors, and potential direct stimulation effect of GnRH agonist on the embryo, which was evidenced by increased beta human chorionic gonadotropin (β-hCG)

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secretion were some of the proposed potential mechanisms of actions (13, 14).

The purpose of this study was to evaluate whether the addition of single-dose GnRH agonist to the progesterone for luteal support in IVF cycles improves the pregnancy outcome measures, particularly the live birth rates.

Material and Methods

Study design and study population

This study was a retrospective study conducted at Başkent University, Obstetrics and Gynecology Department Infertility and IVF Unit, from January 2006 to October 2013. Başkent University Institutional Review Board approved this study (project number: KA 12/57).

The inclusion criteria were as follows:

Couples undergoing IVF with their own gametes

Women below 40 years of age and follicle stimulating hormone (FSH) <10 IU

First two IVF cycles with long GnRH agonist or GnRH antagonist cycles with fresh embryo transfers

Couples having at least one grade 1 embryo available for transfer

Cleavage state embryo transfer [Day 3 embryo transfer after intracytoplasmic sperm injection (ICSI) IVF cycles with luteal phase support with intravaginal or intramuscular progesterone alone or in combination with triptorelin acetate (GnRH agonist)]

Ovarian stimulation and Assisted Reproductive Techniques (ART)

In the long GnRH agonist group, ovarian down-regulation was initiated with either daily 1 mg leuprolide acetate (Lucrin, Abbott GmbH) or 0.1 mg triptorelin (Decapeptyl, Ferring GmbH) that was commenced on Day 21 of the preceding menstrual bleeding. After ovarian suppression was achieved, the dose was reduced by half until the day of administering hCG. If there were no follicle cysts beyond 2 cm and the estradiol was <50 pg/mL, 150-300 IU gonadotropin stimulation with recombinant FSH (rFSH) (Puregon, MSD, the Netherlands) and rFSH (Gonal F, Merck Serono GmbH, Greece) or human menopausal gonadotropin (hMG) (Menogon, Ferring GmbH, Germany) was initiated with estradiol monitoring starting on the fifth day of stimulation. Ultrasound and blood estradiol and progesterone levels were continuously monitored until the day of ovulation induction with hCG, providing the criteria with three or more follicles that were of a diameter >17 mm.

In the GnRH antagonist group, gonadotropin stimulation with 150-300 IU of gonadotropins rFSH (Puregon, MSD GmbH), (Gonal F, Merck Serono GmbH) or hMG (Menogon, Ferring GmbH) was initiated on Day 3 of menstruation. Fixed GnRH antagonist protocol was performed by daily subcutaneously administering 0.25 mg ganirelix (Orgalutran, Organon, the Netherlands), which was commenced on the sixth day of stimulation. Blood progesterone and estradiol and progesterone levels were monitored until the day of ovulation induction by hCG. The criteria for ovulation induction were similar to the agonist stimulation cycles with three or more follicles >17 mm. Oocyte retrieval was performed 35-36 h after administering 10,000 IU hCG (Pregnyl, Organon Turkey) or 250 mg recombinant hCG (rhCG) (Ovitrelle, Merck Serono, Italy) under transvaginal ultrasonography guidance. The 17-gauge single-lumen needles were used for oocyte retrieval under sedation with propofol (propofol 1% Fresenius Kabi®). Routine ICSI was performed for every case after 2-2.5 h of incubation. Embryos were transferred at the cleavage stage, three days after ICSI.

Luteal phase support

Progesterone was the routine luteal support agent, and patients had luteal support either in the form of 90 mg intravaginal progesterone (Crinone 8% gel, Merck Serono GmbH) or 50 mg intramuscular progesterone (Progynex ampule, FARMACO GmbH). Progesterone support was commenced after the day of oocyte pick-up and continued until 10 completed weeks of pregnancy. In the GnRH agonist luteal support group, patients also received an additional single dose of 0.1 mg GnRH agonist namely, triptorelin (Decapeptyl Ferring GmbH) three days after the transfer (six days after ICSI). Pregnancy was defined as positive for hCG on detection of above 10 IU/mL, 12 days after the embryo transfer. Implantation rate was individually calculated for each woman as the number of gestational sac divided by the number of transferred embryos multiplied by 100. Presence of at least one gestational sac was defined as clinical pregnancy with fetal cardiac activity that was detectable by transvaginal ultrasound scans. Live birth rate was the birth of a viable fetus beyond 24 weeks of gestation.

Statistical analysis

Data, which were shown to evenly distribute, were expressed as means±SD. The baseline differences between the two groups were analyzed by independent t-test or one-way ANOVA test. The parameters with uneven distribution were expressed as median and minimum maximum values. The differences between the two groups were evaluated by Mann-Whitney U test. In contingency tables, the χ^2 test or the two-sided Fisher's exact test was performed. A value of $p<0.05$ was considered statistically significant. SPSS 20.0 for Windows was used for data analysis version 20.0 (SPSS Inc. IBM, Chicago, IL, USA).

Results

Among 9470 IVF cycles, a total of 2739 IVF cycles, which met the inclusion criteria, were included in the analysis (Figure 1). Baseline characteristics of the patients were presented in Table 1. The mean age of patients, body mass index (BMI), and Day 3 FSH levels and antral follicle count were similar between the groups. Cycle characteristics were listed in Table 2. Days of stimulation, retrieved oocytes and metaphase II oocytes numbers, estradiol levels, and endometrial thickness at the day of ovulation trigger were found to be similar. Grade 1 embryo number and the number of transferred embryos were found to be significantly high in progesterone only luteal support group in long agonist stimulation arm, and on the contrary, these values were found to be significantly low in the antagonist stimulation arm.

As we investigate the main outcome measures, live birth rates were not found to be statistically different in GnRH agonist

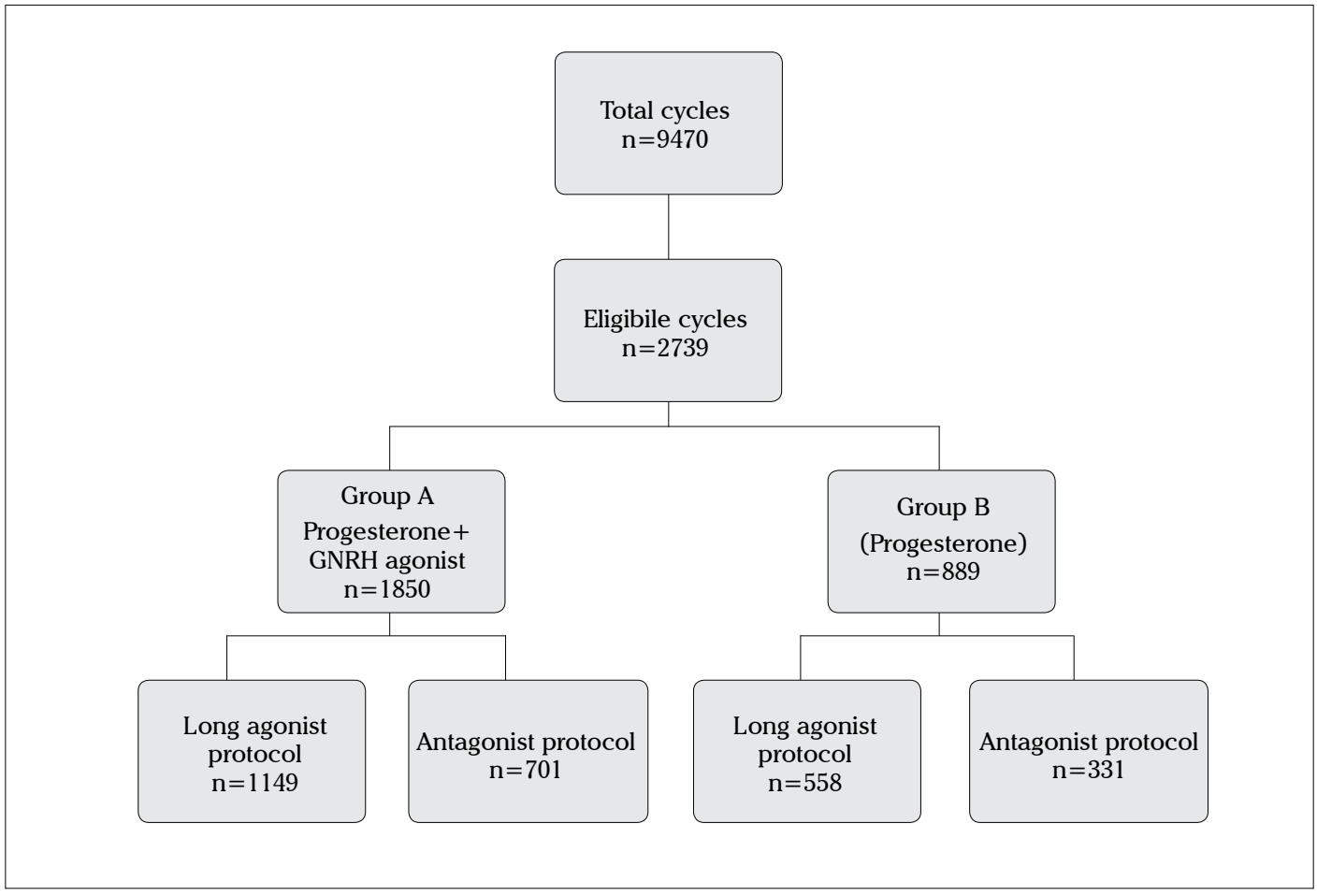

Figure 1. Flowchart of cycle distribution between groups

plus progesterone (Group A) and progesterone only group (Group B) in both the long agonist and antagonist stimulation arms (40.8%/41.2% and 32.8%/34.4%, respectively). Moreover, pregnancy, implantation, and miscarriage rates were found to be similar between the groups (Table 3). However, because the number of embryos transferred between groups was different, we stratified patients according to the number of embryos transferred. Live birth rates according to the number of transferred embryo were similar between the groups (Table 4). In contrast, stratification of live birth rates according to the number of transferred Grade I embryo (one, two, or three or more grade I embryo transfer) revealed similar results with no significant difference between the treatment groups (Table 5). Regression analysis demonstrated that age, antral follicle count, the number of metaphase II oocyte, the number of grade I embryo, and the transferred embryo significantly affected live birth rates. Luteal GnRH agonist addition showed no effect on regression analysis (p=0.48).

Discussion

The administration of GnRH agonist in the luteal phase was initially studied as a means of contraception with unsatisfactory results (15). It was observed that unintentional or accidental GnRH agonist administration in the luteal phase of IVF treatment cycles with pregnancies did not compromise the continuation of pregnancy but was observed to support implantation in initial reports (16-19). Although well-defined mechanisms by which GnRH agonist addition improves luteal support are lacking, presumptive effect at multiple levels were proposed. Direct release of LH by gonadotrophs was tested by Pirard et al. (20) and Tesarik et al. (14). Both Tesarik et al. (14) and Pirard et al. (20) found increased estradiol and progesterone levels during the luteal phase of GnRH agonist added cycles; however, the source and mechanisms of this increase were unclear. Furthermore, Tesarik et al. (21) reported increased hCG secretion in pregnancies with GnRH agonist luteal phase support. Authors also hypothesized a direct beneficial effect on implanting embryo (21), and increased levels of hCG in GnRH agonist luteal phase support pregnancies were observed (14). Moreover, authors suggested a direct stimulatory effect via GnRH receptors on the corpus luteum function (14).

Tesarik et al. (21) reported a pilot study in donation cycles, and Pirard et al. (13) in intrauterine insemination cycles investigated the role of GnRH agonist as a luteal support agent. The same authors Tesarik et al. (14) reported a randomized study in both the agonist and antagonist stimulated IVF-ICSI cycles with the addition of 0.1 mg triptorelin to luteal support with beneficial

Table 1. Patients' characteristics of the study group

		Group A	Group B	P value
Age	L agonist	30.72±4.47	30.42±4.51	0.19
	Antagonist	31.04±4.69	31.00±4.67	0.89
BMI	L agonist	25.34±4.18	25.46±3.92	0.79
	Antagonist	24.89±4.21	25.01±4.27	0.23
Duration of infertility (years)	L agonist	6.0 (0.6–22)	7.0 (1–22)	0.01
	Antagonist	5.0 (1–26)	4.5 (1–20)	0.02
Antral follicle count	L agonist	6.13±2.08	5.98±2.22	0.24
	Antagonist	5.06±2.27	5.14±2.28	0.14
Basal FSH	L agonist	5.89±1.79	5.94±1.99	0.62
	Antagonist	5.97±1.85	5.83±1.79	0.54

Group A: GnRH agonist+progesterone luteal support, Group B: Progesterone only luteal support.
Values=mean±2SD or Median (minimum–maximum).
BMI: body mass index; FSH: follicle stimulating hormone

Table 2. Cycle Characteristics of the study group

		Group A	Group B	p value
Days of stimulation	Long agonist	9.33±1.71	9.32±1.63	0.96
	Antagonist	8.73±2.02	8.67±2.10	0.64
Total dose of gonadotropins	Long agonist	2025 (300–7200)	2250 (725–7500)	0.001
	Antagonist	2062 (225–6800)	2025 (475–4650)	0.02
Retrieved oocyte per cycle	Long agonist	14 (1–49)	14 (2–38)	0.90
	Antagonist	10 (1–60)	11(1–39)	0.72
Metaphase II oocyte number	Long agonist	11(1–45)	12 (1–35)	0.58
	Antagonist	9 (1–56)	9 (1–37)	0.80
Estradiol on day of hCG	Long agonist	2223±1120	2162±1247	0.31
	Antagonist	1580±1044	1547±998	0.63
Grade I embryo number	Long agonist	2 (1–5)	2 (1–4)	0.003
	Antagonist	1 (1–5)	1 (1–5)	0.001
Number of transferred embryo	Long agonist	3 (1–6)	3 (1–5)	0.001
	Antagonist	2 (1–5)	1 (1–5)	0.001
Endometrial thickness on day of hCG	Long agonist	12.01±2.14	11.17±2.51	0.36
	Antagonist	11.72±2.29	10.64±2.15	0.39

Group A: GnRH agonist+progesterone luteal support, Group B: Progesterone only luteal support.
Values=mean±2SD or Median (minimum–maximum).
hCG: human chorionic gonadotrophin

effects on pregnancy outcomes. Pirard et al. (20) studied different doses of intranasal buserelin in intrauterine insemination and IVF cycles (13, 20). Both of Pirard et al. (13, 20) studies were pilot studies with very small number of patients (24 and 23 patients in each); therefore, the pregnancy outcomes of the

Table 3. Comparison of pregnancy outcome measures

		Group A	Group B	p value
Pregnancy rate, n (%)	Long agonist	758 (66.0)	343 (61.5)	0.68
	Antagonist	377 (53.8)	179 (54.1)	0.92
Implantation rate, (%)	Long agonist	33 (0-100)	33 (0-100)	0.17
	Antagonist	33 (0-100)	33 (0-100)	0.45
Miscarriage rate, n (%)	Long agonist	193 (16.8)	61 (10.9)	0.001
	Antagonist	85 (12.1)	48 (14.5)	0.28
Multiple pregnancy rate, n (%)	Long agonist	279 (24.3)	137 (24.6)	0.90
	Antagonist	84 (12.0)	23 (6.9)	0.01
Live birth rate, n (%)	Long agonist	469 (40.8)	230 (41.2)	0.87
	Antagonist	230 (32.8)	114 (34.4)	0.60

Group A: GnRH agonist+progesterone luteal support, Group B: Progesterone only luteal support.
Values=mean±2SD or Median (minimum-maximum).

effect of GnRH addition to LPS agents were not possible to generalize. In the year 2009, Isik et al. (22) reported a study in which patients were blindly randomized to the addition of single-dose 0.5 mg leuprolide acetate or hCG plus progesterone groups (22). Implantation rate and live birth rates were reported to be significantly improved by GnRH agonist addition (26.5% vs. 9.3% and 35.1% vs. 16.3%, respectively).

There are a considerable number of studies reporting against the improvement of pregnancy outcomes with GnRH analog addition to luteal phase support. One of the largest reported randomized trials with placebo control was published by Ata et al. (6) that included 570 patients in long agonist IVF stimulation cycles. The effect of the addition of a single dose of 0.1 mg triptorellin injection was not found to be superior over standard uniform intravaginal progesterone luteal phase support treatment (6). In the year 2010, the same authors investigated the role of GnRH agonist addition in the antagonist stimulated IVF cycles with the same study design demonstrating no beneficial effects of GnRH agonist addition on pregnancy outcomes (23). Isikoglu et al. (24) investigated the role of luteal GnRH analog in a different manner by extension of GnRHa administration until 12 days after embryo transfer in long agonist IVF-ICSI cycles. Authors did not report any significant improvement of implantation, clinical pregnancy, and live birth rates after randomization of 180 patients (24). Most recently, Yıldız et al. (25) in their randomized study failed to demonstrate significant improvement of pregnancy outcomes by single or double dose of GnRH agonist addition to progesterone and estradiol luteal support (25).

There are two meta-analyses focusing on GnRH agonist addition to LPS (26, 27). Oliveira et al. (26) included five and Kyrou et al. (27) included six randomized studies, four of which were common to both meta-analyses (Tesarik 2006, Ata 2008, Isik 2009, Razieh 2009). While Oliveira et al. (26) concluded that GnRH agonist addition increased implantation rates, clinical pregnancy rates were found to be increased only in antagonist cycles. In the more recent meta-analysis by Kyrou et al. (27), LPS with GnRH agonist was shown to significantly increase

Table 4. Live Birth Rates according to the number of transferred embryo

Number of transferred embryo		Group A	Group B	p value
1 embryo, n (%)	Long agonist	56 (31.6)	18 (28.1)	0.60
	Antagonist	92 (33.6)	60 (32.1)	0.73
2 embryos, n (%)	Long agonist	63 (36.2)	18 (31.0)	0.47
	Antagonist	67 (30.2)	46 (36.5)	0.22
3 or more embryos, n (%)	Long agonist	350 (43.9)	194 (44.5)	0.84
	Antagonist	71 (34.6)	8 (44.4)	0.40

Group A: GnRH agonist+progesterone luteal support, Group B: Progesterone only luteal support.

Table 5. Live Birth Rates according to the transfer of number of grade 1 embryo

Number of grade I embryo		Group A	Group B	p value
1 Grade I embryo, n (%)	Long agonist	208 (37.1)	86 (35.8)	0.75
	Antagonist	162 (32.0)	88 (32.4)	0.94
2 Grade I embryos, n (%)	Long agonist	141 (41.2)	70 (44.9)	0.49
	Antagonist	49 (35.3)	20 (39.2)	0.61
3 or more grade I embryos, n (%)	Long agonist	120 (48.8)	74 (45.7)	0.54
	Antagonist	19 (44.7)	6 (56.8)	0.16

Group A: GnRH agonist+progesterone luteal support, Group B: Progesterone only luteal support.

live birth rate (27). However, heterogeneity of data were prominent because of different agents used for luteal phase support, including various combinations of progesterone, estradiol, and hCG, among the studies [Tesarik et al. (14): vaginal micronized progesterone+r-hCG (single dose)+estradiol valerate; Ata et al. (6): Vaginal progesterone gel; Isik et al. (22): vaginal micronized progesterone+single-dose hCG; Isikoglu et al. (24): intramuscular progesterone; Razieh et al. (29): intravaginal progesterone; Fuji et al. (30): dydrogesterone+hCG) (6, 14, 22, 28-30). Therefore, luteal phase support regimens were not uniform.

Furthermore, in the meta-analysis and in different randomized studies, different doses, types and application route, and repeated doses of GnRHa were used, which would most probably cause considerable amount of heterogeneity of data and concerns of data interpretation [Fuji et al. (30): Buserelin 14 days after egg retrieval; Tesarik et al. (14): single-dose triptorelin; Ata et al. (6): 0.1 mg single-dose triptorelin; Isik et al. (22): single-dose 0.5 mg leuprolid; Isikoglu et al. (24): GnRHa 14 days after egg retrieval; Razieh et al. (29); single-dose 0.1 mg triptorelin; Yıldız et al. (25): single or double doses of 1 mg leuprolid].

All the aforementioned heterogeneities preclude drawing firm conclusions for the beneficial effects of GnRH agonist on reproductive outcome. Although our data was retrospective, uniform dose and route of administration of GnRH agonist and uniform luteal support combination with progesterone made comparison of the groups more reliable. Because the number of transferred embryos and Grade I embryo numbers were different between the groups, we performed subgroup analysis (Table 4, 5). By these analyses, we aimed to alleviate the confounding heterogeneity between the groups with respect to the number of both transferred embryos and Grade I embryos. After stratification of cycles, we ended up with the same conclusion of absence of beneficial effects of luteal GnRH agonist addition to progesterone in IVF cycles with respect to pregnancy outcome measures (Table 4, 5).

Another remarkable result was the significantly increased multiple pregnancy rates in antagonist cycles with GnRH agonist addition. However, this result was not observed in long agonist cycles with GnRH agonist arm in our study (Table 3). Increase in multiple pregnancies was observed in the studies of Tesarik et al. (14), Isik et al. (22), Yıldız et al. (25). It can be speculated that GnRH agonist addition may increase multiple pregnancy rates either by direct effect on embryo implantation via GnRH receptors present on the endometrium or by the receptors present on the embryo. However, any effect of this kind awaits verification in further studies with selective single embryo transfer cycles.

After initial clinical randomized trials with beneficial effects, we used GnRH agonist as a luteal adjunct in long agonist and antagonist stimulation IVF cycles relatively liberally in our IVF clinic. Absence of anticipated increase in live birth rates led us to cease routine GnRH agonist addition to progesterone in our clinic. Therefore, we reached the highest numbers of GnRH agonist administered cycles. Although retrospective in nature, this study constitutes the largest study on the effect of GnRH agonist addition to luteal support in IVF cycles. Predetermined fixed dose of GnRH agonist administration and standard luteal phase support with progesterone strengthen our data for more uniform analysis. However, there are limitations to our analysis: retrospective nature and uncontrollable patient and cycle characteristics preclude drawing firm conclusions. Although we tried to eliminate many confounding variables with strict inclusion criteria, there are still some other factors such as longevity of study with different culture mediums and different infertility reasons that may affect pregnancy outcome measures.

Although there are considerable studies on literature, beneficial effects on pregnancy outcome measures were highly blurred by the lack of uniform administration of GnRH agonist in regard to effective dose, administration period, and absence of ideal combination with which GnRH agonist combines with other luteal phase supporting agent or agents (i.e., progesterone, estradiol, hCG).

In conclusion, our study failed to demonstrate any benefit of addition of single 0.1 mg dose of luteal GnRH analog (triptorelin) to the routine luteal phase support with progesterone in IVF cycles on live birth rates. The mechanisms of actions and the ideal dose, administration route, and time interval of GnRH agonist administration in the luteal phase support remain largely undetermined. Presumptive beneficial effect, if any, may only be uncovered after carefully designed preclinical studies and well-designed randomized clinical studies with different dose regimens and administration routes. In the light of current literature and our findings, routine administration of single-dose GnRH agonist as a beneficial luteal phase adjunct in IVF cycles

cannot be recommended until after future randomized studies prove the beneficial effects.

Ethics Committee Approval: *Ethics committee approval was received for this study from the ethics committee of Başkent University (project number: KA 12/57).*

Informed Consent: *N/A*

Peer-review: *Externally peer-reviewed.*

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References

1. DiLuigi AJ, Nulsen JC. Effects of gonadotropin-releasing hormone agonists and antagonists on luteal function. Curr Opin Obstet Gynecol 2007; 19: 258-65. [CrossRef]
2. Macklon NS, Fauser BC. Impact of ovarian hyperstimulation on the luteal phase. J Reprod Fertil Suppl 2000; 55: 101-8.
3. Kolibianakis EM, Albano C, Kahn J, Camus M, Tournaye H, Van Steirteghem AC, Devroey P. Exposure to high levels of luteinizing hormone and estradiol in the early follicular phase of gonadotropin-releasing hormone antagonist cycles is associated with a reduced chance of pregnancy. Fertil Steril 2003; 79: 873-80. [CrossRef]
4. Tavaniotou A, Smitz J, Bourgain C, Devroey P. Ovulation induction disrupts luteal phase function. Ann N Y Acad Sci 2001; 943: 55-63. [CrossRef]
5. Tavaniotou A, Albano C, Smitz J, Devroey P. Impact of ovarian stimulation on corpus luteum function and embryonic implantation. J Reprod Immunol 2002; 55: 123-30. [CrossRef]
6. Ata B, Yakin K, Balaban B, Urman B. GnRH agonist protocol administration in the luteal phase in ICSI-ET cycles stimulated with the long GnRH agonist protocol: a randomized, controlled double blind study. Hum Reprod 2008; 23: 668-73. [CrossRef]
7. Pritts EA, Atwood AK. Luteal phase support in infertility treatment: a meta-analysis of the randomized trials. Hum Reprod 2002; 17: 2287-99. [CrossRef]
8. Fauser BC, Devroey P. Reproductive biology and IVF: ovarian stimulation and luteal phase consequences. Trends Endocrinol Metab 2003; 14: 236-42. [CrossRef]
9. Munoz E, Taboas E, Portela S, Aguilar J, Fernandez I, Munoz L, Bosch E. Treatment of luteal phase defects in assisted reproduction. Curr Drug Targets 2013; 14: 832-42. [CrossRef]
10. Aboulghar M. Luteal support in reproduction: when, what and how? Curr Opin Obstet Gynecol 2009; 21: 279-84. [CrossRef]
11. Hubayter ZR, Muasher SJ. Luteal supplementation in in vitro fertilization: more questions than answers. Fertil Steril 2008; 89: 749-58. [CrossRef]
12. van der Linden M, Buckingham K, Farquhar C, Kremer JA, Metwally M. Luteal phase support for assisted reproduction cycles. Cochrane Database Syst Rev 2011; CD009154.
13. Pirard C, Donnez J, Loumaye E. GnRH agonist as luteal phase support in assisted reproduction technique cycles: results of a pilot study. Hum Reprod 2006; 21: 1894-900. [CrossRef]
14. Tesarik J, Hazout A, Mendoza-Tesarik R, Mendoza N, Mendoza C. Beneficial effect of luteal-phase GnRH agonist administration on embryo implantation after ICSI in both GnRH agonist- and antagonist-treated ovarian stimulation cycles. Hum Reprod 2006; 21: 2572-9. [CrossRef]
15. Skarin G, Nillius SJ, Wide L. Failure to induce early abortion by huge doses of a superactive LRH agonist in women. Contraception 1982; 26: 457-63. [CrossRef]
16. Gartner B, Moreno C, Marinaro A, Remohi J, Simon C, Pellicer A. Accidental exposure to daily long-acting gonadotrophin-releasing hormone analogue administration and pregnancy in an in-vitro fertilization cycle. Hum Reprod 1997; 12: 2557-9. [CrossRef]
17. Kol S, Lightman A, Hillensjo T, Devroey P, Fauser B, Tarlatzis B, et al. High doses of gonadotrophin-releasing hormone antagonist in in-vitro fertilization cycles do not adversely affect the outcome of subsequent freeze-thaw cycles. Hum Reprod 1999; 14: 2242-4. [CrossRef]
18. Golan A, Ron-el R, Herman A, Weinraub Z, Soffer Y, Caspi E. Fetal outcome following inadvertant administration of long-acting DTRP6 GnRH microcapsules during pregnancy: a case report. Hum Reprod 1990; 5: 123-4.
19. Elefant E, Biour B, Blumberg-Tick J, Roux C, Thomas F. Administration of a gonadotropin-releasing hormone agonist during pregnancy: follow-up of 28 pregnancies exposed to triptoreline. Fertil Steril 1995; 63: 1111-3.
20. Pirard C, Donnez J, Loumaye E. GnRH agonist as novel luteal support: results of a randomized, parallel group, feasibility study using intranasal administration of buserelin. Hum Reprod 2005; 20: 1798-804. [CrossRef]
21. Tesarik J, Hazout A, Mendoza C. Enhancement of embryo developmental potential by a single administration of GnRH agonist at the time of implantation. Hum Reprod 2004; 19: 1176-80. [CrossRef]
22. Isik AZ, Caglar GS, Sozen E, Akarsu C, Tuncay G, Ozbicer T, Vicdan K. Single-dose GnRH agonist administration in the luteal phase of GnRH antagonist cycles: a prospective randomized study. Reprod Biomed Online 2009; 19: 472-7. [CrossRef]
23. Ata B, Urman B. Single dose GnRH agonist administration in the luteal phase of assisted reproduction cycles: is the effect dependent on the type of GnRH analogue used for pituitary suppression? Reprod Biomed Online 2010; 20: 165-6; author reply 7. [CrossRef]
24. Isikoglu M, Ozgur K, Oehninger S. Extension of GnRH agonist through the luteal phase to improve the outcome of intracytoplasmic sperm injection. J Reprod Med 2007; 52: 639-44.
25. Yıldız GA, Şükür YE, Ateş C, Aytaç R. The addition of gonadotrophin releasing hormone agonist to routine luteal phase support in intracytoplasmic sperm injection and embryo transfer cycles: a randomized clinical trial. Eur J Obstet Gynecol Reprod Biol 2014; 182: 66-70. [CrossRef]
26. Oliveira JB, Baruffi R, Petersen CG, Mauri AL, Cavagna M, Franco JG Jr. Administration of single-dose GnRH agonist in the luteal phase in ICSI cycles: a meta-analysis. Reprod Biol Endocrinol 2010; 8: 107. [CrossRef]
27. Kyrou D, Kolibianakis EM, Fatemi HM, Tarlatzi TB, Devroey P, Tarlatzis BC. Increased live birth rates with GnRH agonist addition for luteal support in ICSI/IVF cycles: a systematic review and meta-analysis. Hum Reprod Update 2011; 17: 734-40. [CrossRef]
28. Isikoglu M, Ozgur K, Oehninger S. Extension of GnRH agonist through the luteal phase to improve the outcome of intracytoplasmic sperm injection. J Reprod Med 2007; 52: 639-44.
29. Razieh DF, Maryam AR, Nasim T. Beneficial effect of luteal-phase gonadotropin-releasing hormone agonist administration on implantation rate after intracytoplasmic sperm injection. Taiwan J Obstet Gynecol 2009; 48: 245-8. [CrossRef]
30. Fujii S, Sato S, Fukui A, Kimura H, Kasai G, Saito Y. Continuous administration of gonadotrophin-releasing hormone agonist during the luteal phase in IVF. Hum Reprod 2001; 16: 1671-5. [CrossRef]

Bilateral sacrospinous fixation without hysterectomy: 18-month follow-up

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Abstract

Objective: The aim of this study was to evaluate the results of bilateral sacrospinous fixation (SSF), which was performed with surgical mesh interposition and bilateral vaginal repair.

Material and Methods: Twenty-two patients underwent SSF between 2010 and 2012, and the results were evaluated retrospectively. The results at preoperative and postoperative 6th, 12th, and 18th months of the pelvic organ prolapse quantification system (POP-Q) and the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire-12 (PISQ-12) were compared using Friedman and Wilcoxon Signed Ranks tests. Values of $p<0.05$ and <0.01 were considered statistically significant.

Results: According to the POP-Q, significant healing was observed on all vaginal vault points ($p=0.001$), and no prolapse was observed until the 18-month follow-up stage. There were also prominent patients who felt satisfactory with respect to their sexual life according to PISQ-12 ($p=0.001$).

Conclusion: This technique appears to provide an adequate clinical resolution, and it may be the primary surgical option for women with pelvic organ prolapse. (J Turk Ger Gynecol Assoc 2015; 16: 102-6)

Keywords: Pelvic organ prolapse, surgical mesh, vaginal vault

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Introduction

Pelvic organ prolapse (POP) is a common condition in women; the incidence increases during the post-menopausal period (1, 2). In POP, the bladder, uterus, and bowel can bulge into the vagina (3). Although this is not a life-threatening condition, it causes urinary and anal incontinence, pelvic discomfort, and discomfort during sexual intercourse, which negatively affects the quality of life (3).

The spontaneous recovery of POP is not possible. Treatment includes surgical and nonsurgical options. Surgery is an effective treatment. Nonsurgical treatment options (including behavioral therapy with pelvic floor muscle training and pessaries) are preferred for poor surgical candidates (4, 5). The goal of surgery is to increase the quality of life, restore the anatomy and functional status, and prevent the development of recurrent prolapse. Physicians must consider potential complications, de novo symptoms that may arise after anatomy is restored, and ultimately choose a procedure that is most appropriate for an individual patient (6). Apical support is the most important point for successful surgery (7, 8). Abdominal sacrocolpopexy (ASC) and vaginal sacrospinous fixation (SSF) offer a long-term efficiency of 78%-100% and 73%-97%, respectively, in providing apical support (9). The advantage of SSF is that it does not require laparotomy and general anesthesia, the procedure is cost-effective, and early discharge is possible (10, 11).

In the present study, bilateral SSF with surgical mesh (Prolen®; Ethicon, Norderstedt, Germany) was applied to 22 patients with POP of stages 2-4, and the results were compared by retrospective examination of the outcomes at the preoperative stage and at 18 months postoperatively.

Material and Methods

A total of 22 women with POP of stages 2-4 underwent bilateral SSF with surgical mesh (Prolen®; Ethicon, Norderstedt, Germany) interposition and concurrent bilateral vaginal repair, with transobturator tape (TOT) procedure if urinary incontinence was present, in Batman State Hospital department of Obstetrics and Gynecology between 02.2011 and 08.2012. There is no urodynamics unit in this clinic. Hence, we evaluated all the patients by using the stress test before and after reduction of the prolapsed part. The inclusion criteria were grade 2 or more symptomatic apical prolapse. Women with prolapse and indications of hysterectomy were excluded. Patients who cannot receive general or regional anesthesia were also excluded. All patients were informed about the surgical procedure and the consent form was signed. None of the patients underwent hysterectomy. In the preoperative period, all patients were examined according to the pelvic organ prolapse quantification system (POP-Q), and Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire-12

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(PISQ-12) forms were completed. In addition, all patients were evaluated with Pap smear, and transvaginal ultrasonography was performed to evaluate endometrial thickness in postmenopausal patients. The operation time and the intraoperative and postoperative complications were recorded. All patients were re-examined according to the POP-Q system, and PISQ-12 forms were completed at 6, 12, and 18 months postoperatively (12). Treatment failure was defined as the presence of more than stage 1 prolapse. All surgeries were conducted under spinal anesthesia by a single surgeon experienced in pelvic floor surgery. Foley catheter was removed 6h after surgery. Postvoiding residual volume was evaluated by the Foley catheter, and PVR of less than 50 ml is considered to constitute adequate bladder emptying (13). Postvoidal residual volume was evaluated only in patients with stress urinary incontinence. All patients were discharged from the hospital on postoperative day 2. There was no necessary approval of the local ethic community because of the retrospective design of the study.

The procedure was initiated with saline infusion from the posterior vaginal wall towards the ischial spine under the mucosa. After the initial midline incision was made on the posterior vaginal wall, digital blunt dissection of the coccygeus muscle was performed to access the sacrospinous ligament. The adipose tissue overlying the coccygeus muscle was removed to completely expose the sacrospinous ligament. A polypropylene suture (Prolen®; Ethicon, Norderstedt, Germany) (no:1) was bilaterally placed on the sacrospinous ligament. The tips of the 5×1.5 cm polypropylene mesh (Prolen®; Ethicon, Norderstedt, Germany) were suspended over this suture. The mid-point of the mesh was attached to the mid-section of the posterior surface of the cervix with three stitches using polypropylene no:1 sutures (Prolen®; Ethicon, Norderstedt, Germany) (Figure 1). Then, saline was infused laterally under the anterior vaginal wall. After midline incision, the dissection was extended laterally and the fascia of the obturator internus muscle was identified. The endopelvic fascia underlying the bladder was exposed, and midline fascial defects were repaired primarily using polypropylene no:0 sutures (Prolen®; Ethicon, Norderstedt, Germany). Four or five stitches were bilaterally placed on the obturator internus fascia using polypropylene no:1 sutures (Prolen®; Ethicon, Norderstedt, Germany). The other tip of the suture was placed on the opposing intact endopelvic fascia. The posterior edge of the endopelvic fascia was sutured with two or three nonabsorbable sutures (Prolen®; Ethicon, Norderstedt, Germany). Paravaginal support was completed after the placement of the sutures. Then, bilateral SSL sutures were placed while controlling the mesh tension with a finger placed in the rectum. The posterior vaginal wall was closed and the perineal body was elevated. All patients were administered vaginal estrogen therapy for 1 month postoperatively.

Statistical analysis

The statistical analyses were performed using the Number Cruncher Statistical System (NCSS) 2007 and the Power Analysis and Sample Size 2008 statistical software (PASS Inc., Utah, USA). The Friedman test was used to compare preoperative and postoperative POP-Q examination findings and PISQ-12 results, and the Wilcoxon Signed Ranks test was used in the analysis of PISQ-12 results in the postoperative period. The level of statistical significance was set at $p<0.01$ and $p<0.05$. The post-hoc power analysis was performed with the study data using the G*Power (Version 3.1.7) program.

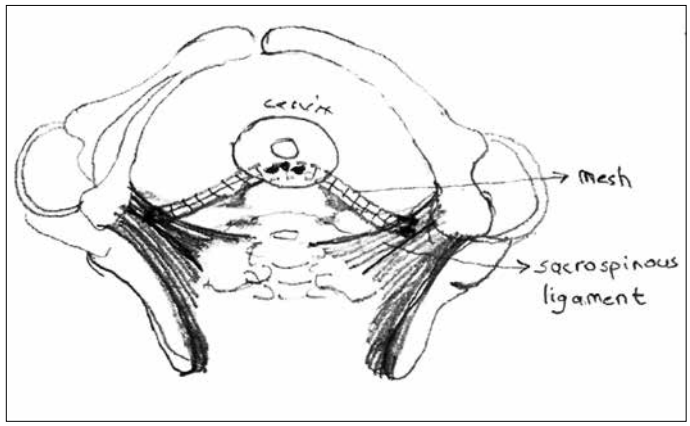

Figure 1. Surgery scheme

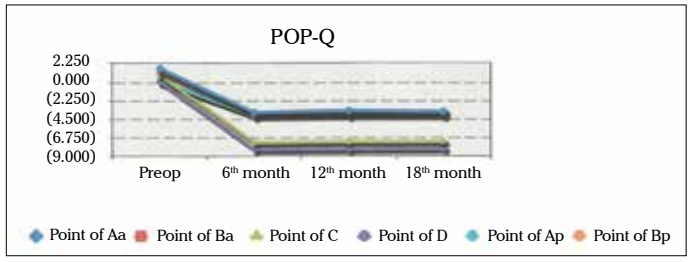

Figure 2. Changes in POP-Q examination
POP-Q: pelvic organ prolapse quantification system

Table 1. Classification of the patients according to disease status

		n	%
Complaint	Palpable mass	10	45.5
	Multiple complaints*	12	54.5
Prolapse Stage	Stage 2	3	13.6
	Stage 3	12	54.6
	Stage 4	7	31.8
SUI	No	19	86.4
	Yes	3	13.6
	Range	Mean (SD)	
Age (years)	24–70	38.8±13.9	
Parity	2–9	5.6±2.27	

*Palpable mass+difficulty in defecation+painful sexual intercourse; discomfort
SUI: Stress urinary incontinence; SD: standard deviation

Results

The age of the patients was between 24 and 70 years with the mean of 38.8±13.9 years. Complaints, stages of prolapse, and presence of stress urinary incontinence are presented in Table 1. All patients underwent bilateral SSF with surgical mesh (Prolen®; Ethicon, Norderstedt, Germany) interposition and bilateral paravaginal support, and three of the patients (13.6%) also

Table 2. The comparison of the prolapsed points before the operation and at 6, 12, and 18 months postoperatively

n=22	Preoperative Mean±SD	6 Months Mean±SD	12 Months Mean±SD	18 Months Mean±SD	[a]p
Aa Point	1.69±0.62	-3.68±0.43	-3.46±0.89	-3.58±0.41	0.001*
Ba Point	1.25±2.23	-3.85±0.41	-3.74±0.59	-3.85±0.39	0.001*
C Point	0.85±3.03	-7.35±0.41	-7.27±0.38	-7.26±0.36	0.001*
D Point	0.07±2.79	-8.20±0.31	-8.16±0.36	-8.13±0.37	0.001*
Ap Point	0.22±1.49	-4.10±1.09	-3.86±0.37	-3.85±0.36	0.001*
Bp Point	0.05±2.34	-4.10±0.37	-4.07±0.34	-4.07±0.33	0.001*

[a]Friedman Test, *p<0.01
SD: standard deviation

Table 3. The evaluation of PISQ-12 pain level scores during sexual intercourse (Question 5) and avoiding sexual intercourse (Question 8)

		Median (Min-Max)	Mean±SD	[a]p
PISQ 12 (Question 8)	Preoperative	1 (1-3)	1.35±0.67	0.001*
	6 Months	5 (2-5)	4.65±0.74	
	12 Months	5 (4-5)	4.95±0.22	
	18 Months	5 (5-5)	5.00±0.00	
PISQ 12 (Question 5)	Preoperative	2 (1-3)	1.75±0.64	0.001*
	6 Months	4 (3-5)	3.90±0.55	
	12 Months	4 (2-5)	4.10±0.72	
	18 Months	5 (3-5)	4.65±0.59	

[a]Friedman Test *p<0.01
PISQ-12: Pelvic organ prolapse/urinary incontinence sexual questionnaire-12; SD: standard deviation

Table 4. The comparison of the cases with respect to PISQ-12 scores in the preoperative period and at 6, 12, and 18 months postoperatively

n=20		Min–Max	Median	Mean±SD	p
PISQ-12	Preoperative[ABC]	30/43	40.5	39.50±3.41	0.001*
	6 Months[Ade]	38/46	43.0	43.10±1.94	
	12 Months[Bdf]	41/46	43.0	43.55±1.57	
	18 Months[Cef]	41/46	43.0	42.95±1.15	

*Repeated Measures Test where p<0.01, Wilcoxon Signed Rank tests were used for the paired comparisons, and capital letters were used where p<0.01, p values were A: 0.001, B: 0.001, C: 0.001, d: 0.216, e: 0.748, f: 0.110
PISQ-12: Pelvic organ prolapse/urinary incontinence sexual questionnaire-12; SD: standard deviation

underwent the TOT procedure. The mean operation time was 43±10 min (min-max: 32-67). There was no excessive bleeding or injury to the neighboring organs. Only one patient (4.5%) did not pass a stool in the postoperative period. This patient was administered laxatives on the 2nd day, which failed to provide any relief. Therefore, the patient underwent a repeat surgery on postoperative day 5, during which the mesh was separated in half and two pieces were placed lateral to the midline. This relieved the rectal pressure while maintaining apical support.

The comparison of preoperative and postoperative POP-Q results at 6, 12, and 18 months revealed strong significant differences for points Aa, Ba, C, D, Ap, and Bp (p=0.001). According to the POP-Q system, the recovery of the apical point and vaginal wall is remarkable in the postoperative period (Table 2, Figure 2).

In comparison to preoperative values, the rate of painful sexual intercourse and avoiding sexual intercourse because of vaginal bulging were significantly lower at 6, 12, and 18 months postoperatively (p=0.001) (Table 3).

The evaluation of the total PISQ-12 scores revealed significant improvement in the symptoms of the patients compared to the preoperative scores (p=0.001). There was no significant difference between postoperative PISQ-12 scores at 6, 12, and 18 months (p>0.05) (Table 4).

If forces are between 99.6% and 100%, α=0.05 level in the POP-Q scale up the six points of the effect size of 0.80-4.90; with the study group consisted of 22 patients.

Discussion

This present study demonstrated that vaginal bilateral SSF with mesh established adequate pelvic support for genital organ prolapse until 18 months. If SSF is performed bilaterally, vaginal axis may be more close to the original anatomic position. This can satisfactorily improve the patients' sexual life.

Unilateral SSF has been recommended for the treatment of vaginal vault defects. Unilateral SSF appears satisfactory, with a low recurrence rate, but is associated with the anatomical distortion of the vagina and the rectum that may alter both sexuality and bowel function (11, 14). Furthermore, some authors hypothesize that the higher POP recurrence and dyspareunia rates after unilateral SSF may be due to a posterior deviation of the vaginal axis and a tensioned repair with surgeons using permanent sutures during a unilateral SSF (15, 16). Because of these reasons, some authors recommend bilateral SSF, and a few studies including small number of patients have focused on anatomical and functional results after bilateral SSF (17-21). David Montefiore et al. (17) reported that bilateral SSF using non-absorbable sutures increased optimal anatomical results (94.3% objective and 93% subjective cure) and quality of life. In another study, bilateral SSF has been performed with a synthetic mesh in 10 women. Anatomical results of these 10 women were compared with nulliparous women using magnetic resonance imaging (MRI). A study showed that MRI measurements

of the distance between the vaginal apex and bony pelvic landmarks and the ischial spines were similar to the measurements in nulliparous women with normal support (18). This study is important because their technique is similar to our technique. Unfortunately, we did not evaluate the anatomical results by MRI or other radiological methods; however, we believe that the results are similar. On the other hand, we evaluated patients using the POP-Q system and PISQ-12 form and observed significant improvement after surgery (p=0.001).

We did not perform hysterectomy because we believed that preserving the uterus was a factor that influenced the success of the technique. The uterus itself passively causes prolapse. Although hysterectomy does not increase the success rate of the procedure, patients who do not undergo hysterectomy have reduced blood loss, shorter operation time, and a lower rate of complications (22). According to Petros (23), the uterus is vital to the maintenance of pelvic floor structure and functions, and hysterectomy could pave the way for prolapse by decreasing the blood supply of the uterosacral and cardinal ligaments. Furthermore, the presence of the cervix is important for the continuity of the cervical ring; however, we believe that setting the distal point on the cervix instead of the vaginal mucosa may increase the efficiency of SSF. More sutures can be placed through more durable tissue in the cervix. If sutures are placed in the mucosa, there are higher chances of ruptures, and it is not possible to place multiple sutures. Therefore, none of the patients in the present study underwent hysterectomy and none developed recurrence during their follow-up period of 18 months (p=0.001).

The complications of SSF are rare. A review that evaluated 22 studies encompassing 1229 SSF operations reported life-threatening bleeding from the sacral or pudendal vascular structures in only three patients (0.2%) (11). However, dyspareunia can pose an important problem after vaginal surgery. The studies have reported a de novo dyspareunia rate of 3.2% after SSF (24). In a study by Hefni et al. (25), only two patients (1%) had de novo dyspareunia because of vaginal stenosis that developed in relation to perineorrhaphy. Similarly, Holley et al. (26) attributed dyspareunia to vaginal stenosis. In the present study, fixation of the mesh to the cervix instead of the vaginal mucosa and leaving the vaginal mucosa in place may have reduced the likelihood of dyspareunia. Local estrogen also may have contributed to this result. Two patients did not have sexual intercourse at all in the preoperative and postoperative period. The other patients reported significant improvement in Question 5 of the PISQ-12 form at 6, 12, and 18 months postoperatively compared to preoperative scores (p=0.001). Another complication with respect to mesh is exposure and erosion. Although there was no erosion or exposure in the present study, Halaska et al. (27) reported that these rates are 20.8% and 37.5%, respectively. They treated these complications by surgical resection and local estrogen therapy. Halaska et al. (27) also used local estrogen for all the patients who underwent vaginal bilateral SSF with mesh. We have concern regarding our patients' comprehension regarding vaginal hygiene. Hence, we used local estrogen until 1 month to contribute to mucosal healing.

The rate of de novo cystocele ranges from 5.8% to 21.3% after construction of apical support (28). Cystocele reportedly develops because of a shift in intra-abdominal pressure from the reinforced posterior compartment to the anterior compartment (29). Simultaneous reinforcement of the anterior compartment or total repair of the prolapse may reduce the development of de novo defects. Brubaker et al. (30) reported that Burch colposuspension performed simultaneously with ASC reduced the development of stress urinary incontinence (SUI). Similarly, Sivaslioglu et al. (31) added Burch colposuspension to ASC because of the same reasons. In the present study, all patients underwent bilateral paravaginal support and primary repair if a midline fascial defect was present, and none of the patients developed a defect during a follow-up period of 18 months.

The anal functions may be affected after SSF. The pudendal nerve may be injured, which negatively affects the functions of the anal sphincter. In one study, 14 out of 200 cases developed de novo anal incontinence (32). In a study conducted by Vierhout et al. (33), one patient with stage 2 prolapse who underwent mesh repair of the posterior wall developed functional obstruction; the mesh was loosened because the patient did not respond to laxatives. The author suggested that sclerosis developed by the mesh on the rectum blocked rectal movement. In the present study, the tension of the mesh was tested with rectal examination before placing the mesh sutures. Nonetheless, one patient who did not respond to laxatives developed functional obstruction. In this patient, the mesh was not totally removed but rather cut from the midline in half. The two edges of the mesh were placed more laterally to re-establish apical support. During the follow-up period, the patient did not experience a recurrence of constipation.

The anatomic restoration is profoundly important in pelvic reconstructive surgery. MRI studies showed that ASC produces a vaginal axis closer to the original anatomic position than SSF (34). One study compared the outcomes of SSF, ASC, and posterior intra-vaginal sling (PIVS) using MRI to evaluate the vaginal axis and reported that PIVS produced the best outcomes and SSF produced the worst outcomes (15). However, this study only evaluated sagittal images, and no data was obtained regarding the difference in lateral deviation between ASC and PIVS because of the absence of coronal images. However, one important study was conducted by Nicolau-Toulouse et al. (18) Their technique is same as our technique, except for the use of capio suture capture device. Bilateral sacrospinous fixation was conducted in 10 patients. After bilateral sacrospinous fixation, these 10 patients were compared with 11 nulliparous women by MRI in three-dimensional planes. The average distance between vaginal apex and ischial spine was similar in sagittal, coronal, and axial planes. The most important limitation of the present study was the lack of a control group comprising patients who underwent PIVS or ASC. Another limitation was less patients, which did not allow evaluation of the complications. Nevertheless, the study contained a sufficient number of cases to suggest the efficiency of the operation. The fact that all patients were operated on by the same surgeon is another strength of the present study.

The present study presents a modified technique in prolapse surgery. The SSF procedure can produce a vaginal axis that is closest to the original anatomic position if it is performed bilaterally with surgical mesh interposition. If the procedure is performed without hysterectomy, durable and multiple sutures can be placed on the distal point, which increases the efficiency of the operation. Considering the costs and complications of abdominal surgery, this method may be the primary surgical option for women with pelvic organ prolapse.

Ethics Committee Approval: *N/A*

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

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Concept - M.B.Ş.; Design - M.B.Ş.; Supervision - M.E.; Resource - M.B.Ş., Y.Ç.; Materials - M.B.Ş., Y.Ç.; Data Collection &/or Processing - Y.Ç.; M.B.Ş.; Analysis &/or Interpretation - H.G.; Literature Search - M.B.Ş.; H.G.; Writing - M.B.Ş.; Critical Reviews - M.E.*

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References

1. Swift S, Woodman P, O'Boyle A, Kahn M, Valley M, Bland D, et al. Pelvic Organ Support Study (POSST): the distribution, clinical definition, and epidemiologic condition of pelvic organ support defects. Am J Obstet Gynecol 2005; 192: 795-806. [CrossRef]
2. Nygaard I, Barber MD, Burgio KL, Kenton K, Meikle S, Schaffer J, et al. Prevalence of symptomatic pelvic floor disorders in US women. JAMA 2008; 300: 1311-6. [CrossRef]
3. Tseng LH, Chen I, Chang SD, Lee CL. Modern role of sacrospinous ligament fixation for pelvic organ prolapse surgery--a systemic review. Taiwan J Obstet Gynecol 2013; 52: 311-7. [CrossRef]
4. Ng CC, Han WH. Comparison of effectiveness of vaginal and abdominal routes in treating severe uterovaginal or vault prolapse. Singapore Med J 2004; 45: 475-81.
5. Tenfelde S, Tell D, Thomas TN, Kenton K. Quality of Life in Women Who Use Pessaries for Longer Than 12 Months. Female Pelvic Med Reconstr Surg 2014. [Epub ahead of print]
6. Klauschie JL, Cornella JL. Surgical treatment of vaginal vault prolapse: a historic summary and review of outcomes. Female Pelvic Med Reconstr Surg 2012; 18: 10-7. [CrossRef]
7. Shull BL. Pelvic organ prolapse: anterior, superior, and posterior vaginal segment defects. Am J Obstet Gynecol. 1999; 181: 6-11. [CrossRef]
8. Toozs-Hobson P, Boos K, Cardozo L. Management of vaginal vault prolapse. Br J Obstet Gynaecol 1998; 105: 13-7. [CrossRef]
9. Morgan DM, Rogers MA, Huebner M, Wei JT, Delancey JO. Heterogeneity in anatomic outcome of sacrospinous ligament fixation for prolapse: a systematic review. Obstet Gynecol 2007; 109: 1424-33. [CrossRef]
10. Holley RL, Varner RE, Gleason BP, Apffel LA, Scott S. Recurrent pelvic support defects after sacrospinous ligament fixation for vaginal vault prolapse. J Am Coll Surg 1995; 180: 444-8.
11. Sze EH, Karram MM. Transvaginal repair of vault prolapse: a review. Obstet Gynecol 1997; 89: 466-75. [CrossRef]
12. Cam C, Sakalli M, Ay P, Cam M, Karateke A. Validation of the short forms of the incontinence impact questionnaire (IIQ-7) and the urogenital distress inventory (UDI-6) in a Turkish population. Neurourology and Urodynamics 2007; 26: 129-133. [CrossRef]
13. Tseng LH, Liang CC, Chang YL, Lee SJ, Lloyd LK, Chen CK. Postvoid residual urine in women with stress incontinence. Neurourol Urodyn 2008; 27: 48-51. [CrossRef]
14. David-Montefiore E, Garbin O, Hummel M, Nisand I. Sacro-spinous ligament fixation peri operative complications in 195 cases: visual approach versus digital approach of the sacro-spinous ligament. Eur J Obstet Gynecol Reprod Biol 2004; 116: 71-8. [CrossRef]
15. Rane A, Lim YN, Whithey J, Muller R. Magnetic resonance imaging findings following three different vaginal vault prolapse repair procedures: a randomized repair study. Aust N Z J Obstet Gynaecol 2004; 44: 135-9. [CrossRef]
16. Sze EHM, Meranus N, Kohli JR, Miklos JR, Karram MM. Vaginal configuration on MRI after abdominal sacrocolpopexy and sacrospinous ligament suspension. Int Urogynecol J Pelvic Floor Dysfunct 2001; 12: 375-80. [CrossRef]
17. David-Montefiore E, Barranger E, Dubernard G, Nizard V, Antoine JM, Daraï E. Functional results and quality-of-life after bilateral sacrospinous ligament fixation for genital prolapse. Eur J Obstet Gynecol Reprod Biol 2007; 132: 209-13. [CrossRef]
18. Nicolau-Toulouse V, Tiwari P, Lee T, Cundiff GW, Geoffrion R. Does bilateral sacrospinous fixation with synthetic mesh recreate nulliparous pelvic anatomy? An MRI evaluation. Female Pelvic Med Reconstr Surg 2014; 20: 222-7. [CrossRef]
19. Febrbraro W, Beucher G, Von Theobald P, Hamel P, Barjot P, Heisert M, Levy G. Feasibility of blateral sacrospinous ligament suspension with a stapler. Prospective studies with the 34 first cases. J Gynecol Obstet Biol Reprod 1996; 26: 815-21.
20. Pohl JF, Frattarelli JL. Bilateral transvaginal sacrospinous colpopexy: preliminary experience. Am J Obstet Gynecol 1997; 177: 1356-61. [CrossRef]
21. Shetty SD, Kirkemo AK. Bilateral bone anchor vaginal vault suspension: an initial report of a new technique. Tech Urol 1997; 3: 1-5.
22. Hefni M, El-Toucky T. Uterine prolapse in young women. Best Pract Res Clin Obstet Gynaecol 2011; 25: 157-65. [CrossRef]
23. Petros P. Influence of hysterctomy on pelvic floor disfunction. Lancet 2000; 356: 1275. [CrossRef]
24. Aigmueller T, Riss P, Dungl A, Bauer H. Long-term follow-up after vaginal sacrospinous fixation: patient satisfaction, anatomical results and quality of life. Int Urogynecol J Pelvic Floor Dysfunct 2008; 19: 965-9. [CrossRef]
25. Hefni MA, El-Toukhy TA. Long-term outcome of vaginal sacrospinous colpopexy for marked uterovaginal and vault prolapse. Eur J Obstet Gynecol Reprod Biol 2006; 127: 257-63. [CrossRef]
26. Holley RL, Varner RE, Gleason BP, Apffel LA, Scott S. Sexual function after sacrospinous ligament fixation for vaginal vault prolapse. J Reprod Med 1996; 41: 355-8.
27. Halaska M, Maxova K, Sottner O, Svabik K, Mlcoch M, Kolarik D, et al. A multicenter, randomized, prospective, controlled study comparing sacrospinous fixation and transvaginal mesh in the treatment of posthysterectomy vaginal vault prolapse. Am J Obstet Gynecol 2012; 207: 301.e1-7. [CrossRef]
28. Petri E, Ashok K. Sacrospinous vaginal fixation--current status. Acta Obstet Gynecol Scand 2011; 90: 429-36. [CrossRef]
29. Cosma S, Preti M, Mitidieri M, Petruzzelli P, Possavino F, Menato G. Posterior intravaginal slingplasty: efficacy and complications in a continuous series of 118 cases. Int Urogynecol J 2011; 22: 611-9. [CrossRef]
30. Brubaker L, Nygaard I, Richter HE, Visco A, Weber AM, Cundiff GW, et al. Two-year outcomes after sacrocolpopexy with and without burch to prevent stress urinary incontinence. Obstet Gynecol 2008; 112: 49-55. [CrossRef]
31. Sivaslioglu AA, Ilhan TT, Aydogmus S, Uzun M, Dolen I. The comparison of the anatomical and symptomatic outcomes of sacrocolpopexy and posterior intravaginal slingoplasty. Int Urogynecol J 2011; 22: 1363-8. [CrossRef]
32. Lovatsis D, Drutz HP. Safety and efficacy of sacrospinous vault suspension. Int Urogynecol J Pelvic Floor Dysfunct 2002; 13: 308-13. [CrossRef]
33. Vierhout ME, Withagen MI, Fütterer JJ. Rectal obstruction after a vaginal posterior compartment polypropylene mesh fixed to the sacrospinous ligaments. Int Urogynecol J 2011; 22: 1035-7. [CrossRef]
34. Sze EH, Meranus J, Kohli N, Miklos JR, Karram MM. Vaginal configuration on MRI after abdominal sacrocolpopexy and sacrospinous ligament suspension. Int Urogynecol J Pelvic Floor Dysfunct 2001; 12: 375-9; discussion 379-80. [CrossRef]

PARP inhibitors and more

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Abstract

Polyadenosine diphosphate (ADP) ribose polymerase (PARP) lends a panoramic view to the inner mystery of protection of integrity of deoxyribonucleic acid (DNA) in a cell genome. They are a balancing part of an even more dynamic equilibrium of normalcy against daily assaults. PARP finds its companion candidates in other tumor suppressors, with the most prominent and glaring one being breast cancer (BRCA) 1 and 2. The strength of both is split by PARP inhibitors, inculcating the synthetic lethality of tumor cell, which is now in the market for ovarian cancer treatment. There are many reasons for the resistance of such inhibitors, which are now becoming clinically important. These are seen along with other damage repair approaches. (J Turk Ger Gynecol Assoc 2015; 16: 107-10)

Keywords: PARP inhibitors, BRCA, olaparib, synthetic lethality, ovarian cancer

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Introduction

The history of polyadenosine diphosphate (ADP) ribose polymerase (PARP) invention is fascinating. Japanese did equally well when a French group (1) discovered in an experiment of kidney cortical nuclei that more phosphate is absorbed from nicotine adenine dinucleotide (NAD). This gives rise to branched poly's of ADP ribose, which not only could anchor on the single stand defects of DNA but could also bring the other players of single strand repair to the field. X-ray repair cross-complementing protein 1 (XRCC1) and other proteins are such players. The initiation of repair is a little confusing activity of the protein enzyme PARPs, which has its 17 types working mainly through types 1 and 2. Inflammation, chemical, and radiation injury are the least known about that activity. They have the onus to manage about ten thousand single strand breaks (SSB's) of a mixed etiology per day. In the presence of inhibitors, PARP cannot prevent stand breaks, instead SSB's pile up at fork to cause double strand breaks (DSB). This DSB is historically managed by breast cancer (BRCA) 1 in female breasts and in male breasts, particularly with tumor suppressor twin BRCA 2. They repair DSB, but being mutated congregates huge load of unrepaired DSB causing "synthetic lethality" of cancer cell. (2-4). These inhibitors will even be tried now in related tumors with BRCAness (5). BRCAness is a behavior of certain tumors, such as some non BRCA ovarian cancer and triple negative breast cancer. "BRCAness" traits in some sporadic cancers are similar to either BRCA1- or BRCA2-mutation carriers. They have 396 well appearances reciprocating those of BRCA negatives.

In the pharmaceutical industry, the invention of PARP inhibitor (PARPi) and eventual availability in the market of first molecule of its kind, such as olaparib, becomes possible only after very stringent clinical trial. Then, there will be a question of resistance, which could be as high as more than seventy percent in refractory group (6). We will take a look at the progress of the subject in following few paragraphs.

Olaparib

A new era begun in targeted therapy horizon when on 19th December last year, a first-in-class PARP inhibitor drug olaparib was approved in the United States for the treatment of advanced ovarian cancer patients with BRCA mutations who have had three or more lines of chemotherapy. It may be noted that in the early part of 2014, Oncologic Drugs Advisory Committee (ODAC) of the US Food and Drug Administration (FDA) voted against the approval of olaparib. This is not very surprising because the trial that the company placed before the committee was a placebo-controlled trial in 136 patients with platinum-sensitive ovarian cancer (7). Olaparib as a maintenance therapy in relapsed ovarian cancer did not fare well. Clinical Trials.gov, number NCT00753545. Hence, the committee defeated the proposal by an 11 to 2 vote.

On the basis of data from the same placebo-controlled trial in 136 patients with platinum-sensitive ovarian cancer, a second interim analysis (8) of overall survival and a retrospective, preplanned analysis of data by *BRCA* mutation status company found support of the hypothesis that patients with platinum-sensitive recurrent serous ovarian cancer with a BRCA mutation have the greatest likelihood of benefiting

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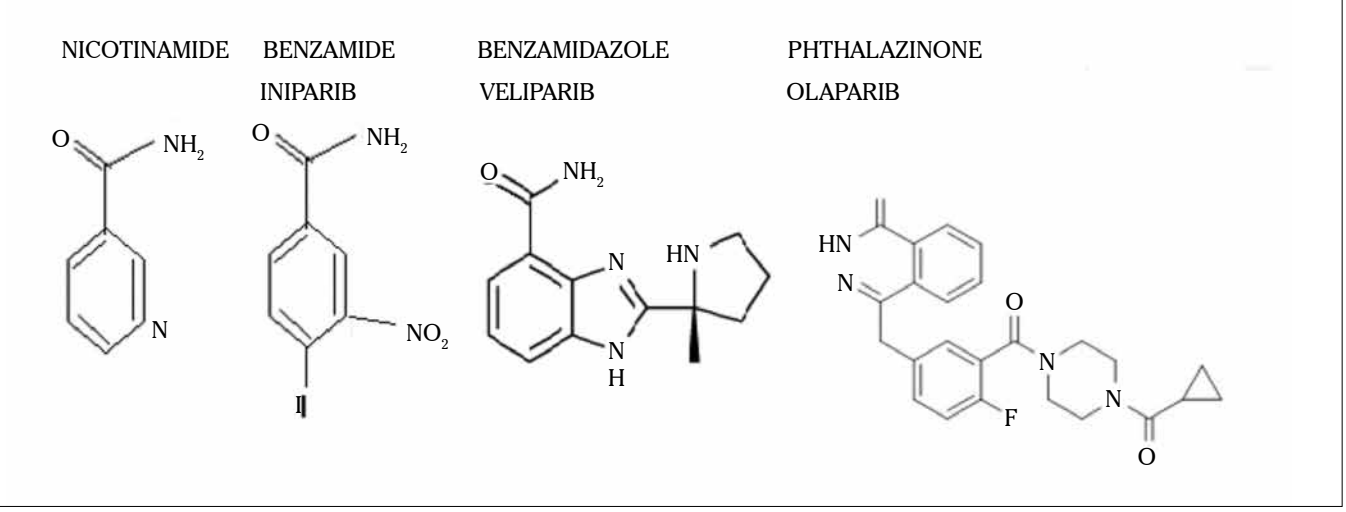

Figure 1. Different PARP inhibitors

from olaparib treatment (8). It is rather astonishing that FDA gave this compound an accelerated approval in December 19th, 2014 after an expedited review process over the same trial on the basis of second interim analysis.

On the other hand, a diagnostic company announced approval from the U.S. FDA on the same day for their BRACAnalysis CDx diagnostic kit to be used as the only companion diagnostic in conjunction with olaparib. BRACAnalysis CDx is this company's first FDA-approved companion diagnostic for use with a novel PARP inhibitor. It is a highly accurate molecular companion diagnostic test that identifies deleterious or suspected deleterious mutations in BRCA1 and BRCA2 genes using DNA obtained from a blood sample. Olaparib was approved for a similar indication in the European Union just only a day earlier than done by USFDA after a recommendation for approval obtained in October from the European Medicines Agency.

Breast cancer, which is associated with lesser percentage of such mutation (10% against 15%), is reasonably in the pipeline as a trial of this cancer is in phase III and is under way (NCT00516724, NCT01445418)

Nicotinamide, iniparib, and other PARPi

However, if we see nicotinamide as a primary inhibitor, different basic small molecules and molecules with appropriate scaffold (Figure 1) have come up as inhibitors of this PARP. Phthalazinone scaffolding has given rise to olaparib. With others in phase II, small molecule iniparib's tragic attempt and failure as PARPi teaches us a good lesson worthy of describing. It has since become a poster child in how not to develop a drug and also shows how a review article may play a crucial role in development of a drug. The preclinical experiments are still very challenging and it is proved by the fact that this small molecule, which is an 3 iodo 4 nitro derivative of benzamide, is a nicotinamide derivative. Although it had other mechanism for being apoptotic to cancer cells, it has no particular PARP inhibitory property.

Fojo et al. (9) the National Cancer Institute suggested in a commentary that the clinical trial design, which allowed the placebo arm to cross over and receive iniparib after their disease had progressed, may have biased the overall survival data in favor of iniparib. The drug's failure would not have been so dramatic had it not also slowed the pace of research. It led whole PARPi chapter to disrepute so that people would give up doing PARP as a whole. This subject's uniqueness of targeting a weakness rather than strength had been the center of controversy and confusion. Thus, further development up to olaparib is believed to be a paradigm shift to a later easy phase of rapid development. We may delve now to a chartable clinical picture in the context this article aims for.

Resistance

They already tested no less than 89 patients in a retrospective review of patients with BRCA1/2 mutation carrier ovarian cancer (PBMCOC) who received chemotherapy following disease progression on olaparib, administered at 200 mg twice daily for 1 month or more (10). An increased platinum-to-platinum interval was associated with an increased OS and likelihood of response following post-olaparib platinum. Heavily pretreated PBMCOC that are PARPi resistant retain the potential to respond to subsequent chemotherapy, including platinum-based agents. There are currently no other preclinical or clinical data to support this hypothesis; further work is certainly warranted in this regard. Therefore, what it leads to is a thorough search for inhibitor resistance pathways. They are described below following an order where postulates with more proofs needed are placed in last.

Decreasing intracellular availability of PARPi

Established molecule, P-glycoprotein 1 (P-gp), has a great importance in this subject. This acts by decreasing the intracellular availability of PARPi. The P-gp belongs to the ABC transporter family, which is inhibited by ADP ribose, a product of catalytic activity of PARP-1 (11). While Rottenberg et al. (12) elucidated its poly ADP dependence, P-gp inhibitors prevent the decrease of PARPi in human colorectal carcinoma cell line (HCT116) (13). This is made even robust with an available bio-

marker. The monitoring of poly ADP ribosylation and radiation sensitive gene (Rad51) foci formation as surrogate markers for PARP activity and homologous recombination (HR), respectively, supported their candidacy for biomarkers of PARP-1i responses. The multidrug efflux transporters, ATP-binding cassette sub-family G member 2 (ABCG2) (human breast cancer resistance protein (BCRP)) and ATP-binding cassette sub-family G member 1 ABCB1 (P-gp, multi drug resistance 1 (MDR1)), affected the oral availability and brain penetration of PARPi. Transport could be inhibited by the small-molecule ABCB1 and ABCG2 inhibitors zosuquidar and indole-3-propanoic acid 1.1-dimethylethyl ester (Ko143) (14).

Increased homologous recombination (HR) capacity pathways

53BP1 (also called TP53BP1) is a chromatin-associated factor that promotes immunoglobulin class switching and DNA DSB repair by non-homologous end joining. Assessment of 53BP1 is among candidate predictive biomarkers inducing Ataxia telangiectasia mutated (ATM)-mediated HR. Loss of 53BP1 allowed a partial ATM-dependent HR repair making these cells resistant to PARPi (15). Here, secondary mutations in BRCA2 is associated with clinical resistance to a PARPi (16).

Other postulated pathways among increased HR capacity are overexpression of BRCA via downregulation of a microRNA (miR-182) or PARP-1, increased activity of RAD51, and altered non-homologous end joining (NHEJ) capacity with a decrease in NHEJ capacity could increase their resistance to PARPi, as shown in BRCA 2-deficient cells by inhibition or downregulation of Ku80, a protein encoded by the XRCC5 gene, Artemis, or DNA-dependent protein kinase (DNA-PK) (17).

Reverse mutation of BRCA

Except above two, there is a third prominent and more "counting" routes for such possible inhibitions. It is a reverse mutation of BRCA prompting power for repair once again. For BRCA2, reverse mutation was in part due to the intragenic deletion of the c.6174delT mutation and restoration of the open reading frame (18-20) and for BRCA1, it is hypomorphic mutation (21).

Decreased levels or activity of PARP-1

Decreased levels or activity of PARP-1 is another one at hand though it is difficult at this moment to rationalize the link between cytoplasmic PARP-1 and resistance to PARPi.

Manipulation of other damage repair pathways

Whereas breakthrough researches in sub-pathaway battery of PARP inhibitor resistance may prove to be lucrative addendum to this PARP theory, even more basic should be other damage repair pathways manipulation, which may give rise to elementary vis-à-vis synergistic sister pathways predicted to be acting with many chemotherapeutic cocktail. We may like to summarize those effectively. A few established links, which have roots in alternate damage saving power are:

Tumor suppressor gene phosphatase and tensin homolog (PTEN) has links with many cancers, including 25%–40% of glioblastomas sensitive to PARP inhibitors with implication in prostate, colorectal, and endometrial cancers, which also have this dysfunction in DNA repair pathways (18). Locating DNA mismatch repair gene MSH mutation in tumors like hereditary non-polyposis colon cancer could be a key predictor of methotrexate sensitivity of the tumor. O^6-methylguanine–DNA methyltransferase (MGMT) repairs chemical DNA Its mutation in acute myeloid leukemia makes the cancer responsive to temozolomide.

Checkpoint proteins hold the cell replication cycle to protect DNA. Their defects such as p53 and Chk1 and Chk2 have been linked to cancer. Drugs targeted at checkpoint proteins with radiation can kill the cell by damage build ups of synthetic lethality. A small molecule inhibitor of checkpoint kinases (Chks) with potential chemosensitizing activity is tried by one pharma company in combination with gemcitabine in patients with solid tumors in phase I trial with no results shown yet (22). Jung-Min Lee of NCI on behalf of another company has a promising trial on another such inhibitor LY260636, which is already in phase II (23). With BRCA1/2 mutation associated breast or ovarian cancer, non-high risk triple negative breast cancer, and high grade serous ovarian cancer, another phase I study is ongoing after completing a phase 1 study in participants with advanced Cancer (24). We are very hopeful about this study.

Enzyme regulators of Chk1 and Chk2, the ATM kinase and another effector kinase, ATR (ataxia-telangiectasia and Rad3-related) are also targeted. In response to DNA damage, they initiate a cascade leading to DNA repair. In a preclinical study, ATM inhibitors KU-60019 radiosensitize GIC-driven tumors with low expression of TP53 and high expression of PI3K (22).

Members of the cyclin-dependent kinase (CDK) family stop the cell cycle for repair. They could be targeted by one Indian company who developed CDK1–CDK4 inhibitor called P276-00. In multiple early trials, it is used in combination with chemotherapy drugs to treat advanced malignant melanoma, pancreatic cancer, multiple myeloma, and head and neck cancer. There are no results of these phase II trial with Professor Peter Hersey of New Castle University in one melanoma trial. However, other members of the CDK family playing key roles in normal cell-specific CDK1 and CDK4 inhibitor are a requirement.

Conclusion

Clinical research is basically uncertain. Theory and practice may not coincide. Specificity is not always elicited in preclinical studies. Use of defects specific to cancer cell is not always harmless as it does not become apparent until trials have begun. Testing drug cocktails is a tough task, particularly with DNA damage repair inhibited synthetic lethality. While this is only a beginning of a whole new era of targeting weakness, there will be long perilous path for traversing till one may expect for some panacea.

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References

1. Chambon P, Weill JD, Mandel P. Nicotinamide mononucleotide activation of new DNA-dependent polyadenylic acid synthesizing nuclear enzyme. Biochem Biophys Res Commun 1963; 11: 39-43. [CrossRef]
2. Dobzhansky T. Genetics of natural populations. Xiii. Recombination and variability in populations of Drosophila pseudoobscura. Genetics 1946; 31: 269-90.
3. Bryant HE, Schultz N, Thomas HD, Parker KM, Flower D, Lopez E, et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature 2005; 434: 913-7. [CrossRef]
4. Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 2005; 434: 917-21. [CrossRef]
5. Turner N, Tutt A, Ashworth A. Hallmarks of 'BRCAness' in sporadic cancers. Nat Rev Cancer 2004; 4: 814-9. [CrossRef]
6. Kaufman B, Shapira-Frommer R, Schmutzler RK, Audeh MW, Friedlander M, Balma-a J, et al. Olaparib monotherapy in patients with advancedcancer and a germline BRCA1/2 mutation. J Clin Oncol 2015; 33: 244-50. [CrossRef]
7. Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med 2012; 366: 1382-92. [CrossRef]
8. Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomized phase 2 trial. Lancet Oncology 2014; 15: 852-61. [CrossRef]
9. Fojo, T, Amiri-Kordestani L, Bates, SE. Potential pitfalls of crossover and thoughts on iniparib in triple-negative breast cancer. J Natl Cancer Inst 2011; 103: 1738-40. [CrossRef]
10. Ang JE, Gourley C, Powell CB, High H, Shapira-Frommer R, Castonguay V, et al. Efficacy of chemotherapy in BRCA1/2 mutation carrier ovarian cancer in the setting of PARP inhibitor resistance: a multi-institutional study. Clin Cancer Res 2013; 19: 5485-93. [CrossRef]
11. Dumitriu IE, Voll RE, Kolowos W, Gaipl US, Heyder P, Kalden JR, Herrmann M. UV irradiation inhibits ABC transporters via generation of ADP-ribose by concerted action of poly(ADP-ribose) polymerase-1 and glycohydrolase. Cell Death Differ 2004; 11: 314-20. [CrossRef]
12. Rottenberg S, Jaspers JE, Kersbergen A, van der Burg E, Nygren AO, Zander SA, et al. High sensitivity of BRCA1-deficient mammary tumors to the PARP inhibitorAZD2281 alone and in combination with platinum drugs. Proc Natl Acad Sci U S A 2008; 105: 17079-84. [CrossRef]
13. Oplustilova L, Wolanin K, Mistrik M, Korinkova G, Simkova D, Bouchal J, et al. Evaluation of candidate biomar ers to predict cancer cell sensitivity or resistance to PARP-1 inhibitor treatment. Cell Cycle 2012; 11: 3837-50. [CrossRef]
14. Durmus S, Sparidans RW, van Esch A, Wagenaar E, Beijnen JH, Schinkel AH. Breast Cancer Resistance Protein (BCRP/ABCG2) and P-glycoprotein (P-GP/ABCB1) Restrict Oral Availability and Brain Accumulation of the PARP Inhibitor Rucaparib (AG-014699). Pharm Res 2015; 32: 37-46. [CrossRef]
15. Cao L, Xu X, Bunting SF, Liu J, Wang RH, Cao LL, et al. A elective requirement for 53BP1in the biological response to genomic instability induced by Brca1deficiency. Mol Cell 2009; 35: 534-41. [CrossRef]
16. Barber LJ, Sandhu S, Chen L, Campbell J, Kozarewa I, Fenwick K, et al. Secondary mutations in BRCA2 associated with clinical resistance to a PARP inhibitor. J Pathol 2013; 229: 422-9. [CrossRef]
17. Patel AG, Sarkaria JN, Kaufmann SH. Non-homologous end joining drives poly(ADP-ribose) polymerase (PARP) inhibitor lethality in homol- ogous recombination-deficient cells. Proc Natl Acad Sci U S A 2011; 108: 3406-11. [CrossRef]
18. Ashworth A. A synthetic lethal therapeutic approach: poly(ADP) ribose polymerase inhibitors for the treatment of cancers deficient in DNAdouble-strand break repair. J Clin Oncol 2008; 26: 3785-90. [CrossRef]
19. Edwards SL, Brough R, Lord CJ, Natrajan R, Vatcheva R, Levine DA, et al. Resistance to therapy caused by intragenic deletion in BRCA2. Nature 2008; 451: 1111-5. [CrossRef]
20. Sakai W, Swisher EM, Karlan BY, Agarwal MK, Higgins J, Friedman C, et al. Secondary mutations as a mechanism of cisplatin resistance in BRCA2- mutated cancers. Nature 2008; 451: 1116-20. [CrossRef]
21. Drost R, Bouwman P, Rottenberg S, Boon U, Schut E, Klarenbeek S, et al. BRCA1RING function is essential for tumor suppression but dispensable for therapy resistance. Cancer Cell 2011; 20: 797-809. [CrossRef]
22. Available from: http://clinicaltrials.gov/show/NCT00413686.
23. Available from: https://clinicaltrials.gov/show/NCT02203513
24. Available from: https://clinicaltrials.gov/show/NCT01115790
25. Vecchio D, Daga A, Carra E, Marubbi D, Baio G, Neumaier CE, et al. Predictability, efficacy and safety of radiosensitization of Glioblastoma initiating cells by the ATM inhibitor KU-60019. Int J Cancer 2014; 135: 479-91. [CrossRef]

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Impact of obesity on infertility in women

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Abstract

The prevalence of obesity and overweight are increasing and have become an epidemic worldwide. Obesity has detrimental influences on all systems, including reproductive health. The prevalence of obesity in infertile women is high, and it is well known that there is an association between obesity and infertility. The relationship between obesity and reproductive functions is still being explored. Overweight women have a higher incidence of menstrual dysfunction and anovulation. Overweight and obese women are at a high risk for reproductive health. The risk of subfecundity and infertility, conception rates, miscarriage rates, and pregnancy complications are increased in these women. They have poor reproductive outcomes in natural as well as assisted conception. These poor reproductive outcomes include assisted reproduction such as ovulation induction, *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI), and ovum donation cycles. Weight loss has beneficial effects on the reproductive outcomes in these patients. (J Turk Ger Gynecol Assoc 2015; 16: 111-7)

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Introduction

Obesity, which is an important health issue, is a common problem among women of reproductive age. Obesity and overweight involves an abnormal and excessive fat accumulation that negatively affects the health of the body. According to the World Health Organization (WHO), if the body mass index (BMI) equals to or is greater than 25 kg/m^2, it is considered overweight, whereas if the BMI equals to or is greater than 30 kg/m^2, it is considered obesity (1).

Obesity brings out many problems such as social, psychological, demographic, and health problems. It is related to increased health risks such as diabetes mellitus, hypertension, coronary heart disease, and osteoarthritis and is linked to various malignancies, particularly endometrium, breast, and colon cancers. Obesity also plays a significant role in reproductive disorders, particularly in women. It is associated with anovulation, menstrual disorders, infertility, difficulties in assisted reproduction, miscarriage, and adverse pregnancy outcomes.

In obese women, gonadotropin secretion is affected because of the increased peripheral aromatization of androgens to estrogens. The insulin resistance and hyperinsulinemia in obese women leads to hyperandrogenemia. The sex hormone-binding globulin (SHBG), growth hormone (GH), and insulin-like growth factor binding proteins (IGFBP) are decreased and leptin levels are increased. Thus, the neuroregulation of the hypothalamic-pituitary-gonadal (HPG) axis deteriorates (2). These alterations may explain impaired ovulatory function and so reproductive health.

Because of lower implantation and pregnancy rates, higher miscarriage rates, and increased maternal and fetal complications during pregnancy, obese women have a lower chance to give birth to a healthy newborn (3-6). In this review, the effects of obesity on fertility and effective management of infertility in obese and overweight women is summarized.

Epidemiology of obesity

The prevalence of obesity is increasing significantly worldwide. The International Obesity Task Force reported that 1,1 billion adults are overweight. They also reported that 312 million of them are obese (7). Approximately 3,4 million adults die each year because of health problems associated with obesity and being overweight. Of these, 44% of the problems are related to diabetes, 23% to ischemic heart disease, and between 7% and 41% to some malignancies associated with overweight and obesity (7). The prevelence of obesity has increased in developed countries because of a change in lifestyle, including reduced physical activity, changes in nutrition style, and an increased calorie intake (8). However, some other factors such as endocrine disorders, hormonal disorders, psychological disorders, and use of some drugs such as steroids and antidepressants may lead to obesity (9). The World Health Organization reported that 60% of women are overweight (≥25 kg/m^2) in the United States and most European countries and 30% of these are obese (≥30 kg/m^2) and 6% of these are morbidly obese (≥35 kg/m^2) (1, 7, 8).

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Obesity and reproductive functions

The relationship between obesity and reproductive functions has been known for many years (10, 11) and it is still being explored (12). The negative effects of obesity on reproductive consequence are well known. However, it is difficult to describe the mechanism of how obesity affects the reproductive system because it is complex and multifactorial. Several mechanisms are involved in the relationship of fertility and obesity. The insulin resistance and leptin levels are increased and hyperandrogenemia occurs in obese women. Similarly, anovulation, changes in adipokine levels and the HPG axis, and steroidogenesis in obese women affects the reproductive system (13-15).

Because of reduced pregnancy rates, increased miscarriage rates, and increased pregnancy complications, live birth rates decrease in obese women in both natural and assisted conceptions. Obesity may impair reproductive functions by affecting both the ovaries and endometrium (15). The HPG axis deteriorates because of changes in hormonal and some substrate levels. The levels of luteinizing hormone (LH), androstenedione, estrone, insulin, triglycerides, and very low density lipoprotein are increased and high density lipoprotein levels are decreased in obese women. Because of these changes, the HPG axis deteriorates and different gynecological effects occur (2).

Adipose tissue and adipokines

White adipose tissue is a multifunctional organ and it stores energy. It is also an important endocrine organ that regulates energy homeostasis and metabolism by secreting adipokines. These adipokines have important roles in the regulation of a number of physiological processes such as reproduction, immune response, and glucose and lipid metabolism. Adipokines are cytokines predominantly secreted by adipocytes. Some of these adipokines are leptin, adiponectin, resistin, visfatin, omentin, and ghrelin. Adipokines are signaling molecules (hormones), and abnormalities in adipokines can cause inflammation and abnormal cell signaling and thus can lead to deterioration in cell metabolism and function (12). It is well established that an excess or deficiency of white adipose tissue results in sexual maturation disorders, pubertal disorders, and fertility disorders (16). It is well known that stored energy is necessary for the normal function of the reproductive system, including pubertal development, production of reproductive hormones and gametes, and maintenance of pregnancy and lactation. Although adipose tissue is necessary for reproductive function and normal development, the excessive adipose tissue causes some reproductive disturbances.

Excess adipose tissue in women aggravates polycsytic ovarian syndrome (PCOS), and anovulation and may cause hypothalamic hypogonadism (17). In PCOS patients, it has been shown that adipokines such as tumor necrosis factor-alfa (TNF-α) is increased and some “beneficial adipokines” such as adiponectin is decreased because of dysfunction in the adipose tissue. Abnormal levels of adipokines have been shown to be associated with insulin resistance and type 2 diabetes mellitus (18).

The studies demonstrated that as the BMI increases, leptin levels increase both in blood and follicular fluid (19, 20). Thus, obesity is associated with high leptin levels in serum and follicular fluid. Leptin has a stimulatory effect on the HPG axis by providing a signal to initiate the reproductive maturation of the hypothalamus. In a mouse model, after increasing the dietary fat intake in both male and female DBA/2J strain mice, insulin resistance and glucose intolerance developed; however, only the female rats had a dietary-induced obesity and hyperleptinemia, thereby causing a 60% decrease in the spontaneous pregnancy rate (21). Normal ovulatory response and pregnancy rates in these rats after exogenous gonadotropin stimulation indicate a central effect related to increased leptin levels. Leptin inhibits insulin-induced ovarian steroidogenesis by acting on the theca and granulosa cell receptors. Leptin also inhibits its LH-stimulated estradiol production by the granulosa cells. The other effect of leptin on reproductive functions is the regulation of early embryo cleavage and development. This may explain the poor reproductive outcomes in obese women (22).

Adiponectin is the most common circulating protein synthesized by adipose tissue. In obese women, unlike the other adipose tissue hormones, adiponectin levels decrease (19, 20) and increase with weight loss. Adiponectin stimulates glucose uptake in the liver and muscle and decreases hepatic gluconeogenesis. As a result, insulin sensitivity is impaired. Adiponectin also affects lipid synthesis, energy homeostasis, vasodilatation, and atherogenic activity (23, 24). Thus, adiponectin decreases triglyceride accumulation and improves insulin sensitivity. In the absence of adiponectin in obese women, plasma insulin levels increase. Consequently, high levels of insulin lead to hyperandrogenemia.

The mechanism of other adipokines on reproductive functions such as resistin and ghrelin has not been fully understood. Resistin is a protein secreted by the adipose tissue. Steppan et al. (25) showed that after a 48 h fasting period in mice, resistin levels decreased and increased after re-feeding. They studied serum resistin levels in mice that caused obesity and insulin resistance on a high-fat diet. In obese mice, resistin caused insulin resistance and resistin antibody injection increased insulin sensitivity. As a result of increased resistin levels in obesity, insulin resistance occurs and this leads to decreased insulin sensitivity.

Another adipokine, visfatin, is secreted from several cell types and tissues, including adipose tissue and adipocytes, bone marrow, lymphocytes, muscle, liver, trophoblast, and fetal membranes (26). The association between visfatin and obesity and insulin action is not fully understood. It has been reported that visfatin shows insulin-mimetic effects, increases glucose uptake in adipocytes and muscle cells, and decreases glucose release from hepatocytes (26).

Chemerin is another adipokine that affects the adipocyte and glucose metabolism. It has been shown that chemerin levels increase during the metabolic syndrome; therefore, it is associated with obesity, metabolic syndrome, and type 2 diabetes mellitus (27). Chemerin also can impair follicle stimulating hormone (FSH)-induced follicular steroidogenesis and thus can play a role in the pathogenesis of PCOS (28).

Adipose tissue also affects follicular development by the inhibition of gonadotropin secretion through the conversion of andro-

Table 1. The effects of the adipokines on reproduction

Adipokines	Serum levels in obesity	Effects on reproduction in obesity
Leptin	Increases (leptin resistance occurred in obesity)	Inhibits insulin induced ovarian steroidogenesis
		Inhibits LH*-stimulated estradiol production by the granulosa cells
Adiponectin	Decreases	Plasma insulin levels increase
Resistin	Increases	Causes insulin resistance
Visfatin	Increases	Increased insulin sensitivity
Omentin	Decreases	Increased insulin sensitivity
Chemerin	Increases	Negatively regulates FSH§-induced follicular steroidogenesis

*luteinizing hormone
§follicle stimulating hormone
FSH: follicle stimulating hormone; LH: luteinizing hormone

gens to estrogens in the adipose tissue. Therefore, almost all of the adipokines seem to have their effects on reproduction by causing insulin resistance (Table 1).

Obesity, hyperandrogenemia, and PCOS

Obesity may not be the only factor that causes hyperandogenemia and anovulation because some obese women are fertile and do not have hyperandrogenism. Hyperinsulinemia and insulin resistance are the underlying causes that lead to obesity, accompanied by hyperandrogenemia, and alterations in steroidogenesis. It has been experimentally shown that insulin has various effects on steroidogenesis. It stimulates ovarian estrogen, androgen, and progesterone production in vitro. Some of these effects occur at physiological concentrations but sometimes may reach higher concentrations. Insulin stimulates androgen production in the theca cells (29, 30).

Another mechanism leading to hyperandrogenemia is hyperinsulinemia via insulin-like growth factor-1 (IGF-1). IGF-1 is secreted by human ovarian tissue, and its receptors are located in the ovary. Insulin can bind IGF-1 receptors as well as its own receptor. Insulin also decreases the production of the IGFBP-1 in liver and makes IGF-1 more effective. Androgen production increases from theca interstitial and stromal cells by the action of IGF-1 (31). Insulin decreases SHBG production from the liver; as a result, serum androgen levels increase in obese women (32).

PCOS is also a metabolic disorder characterized by hyperandrogenemia. Formerly, PCOS was known only to be in a hyperandrogenic state, which can lead to infertility. However, current data shows that PCOS is related to an increased risk of metabolic disorders such as insulin resistance (IR), hyperinsulinism (HI), impaired glucose intolerance, and obesity (33). In women with PCOS, weight loss decreases the androgen levels and improves insulin resistance (34).

Hyperinsulinaemia and hyperandrogenaemia changes the ovarian function in both obese and non-obese women. However, the mechanism of how hyperandrogenemia and/or hyperinsulinemia cause anovulation has not been fully understood.

Anovulation and menstrual disturbances

The mechanism of anovulation in obesity remains unclear. Insulin resistance and hyperandrogenemia significantly increased in obese women, particularly who have central obesity. Hyperandrogenemia due to hyperinsulenemia leads to granulosa cell apoptosis, and this may have an effect on ovarian functions. It is demonstrated that estrogen production in granulosa cells is stimulated by insulin (35).

The effect of FSH on estradiol and progesterone production increases by insulin. This is demonstrated in women with PCOS and insulin resistance. Thus, the estrogen level increases in the developing follicle. FSH enhances the excessive androgen substrate, leading to relatively improper estrogen levels in the developing follicle. Insulin also enhances steroidogenesis by augmenting the effect of LH on granulosa cells. LH stimulates steroidogenesis and inhibits further mitosis and final differentiation of granulosa cells in the preovulatory follicle (36). The effect of LH on granulosa cells is amplified in PCOS patients by the presence of hyperinsulinemia.

As a result of the enhanced steroidogenesis due to insulin and its interaction with LH, the unfavorable milieu causes cessation of the follicle growth. Thus, premature luteinization and follicular arrest develops and leads to menstrual cycle disorders and obesity-induced oligo-anovulation (37).

The increased estrogen due to peripheral convesion disturbs the HPG axis. In conclusion, both the excess estrogen and excess androgens play a role in the anovulation encountered in these patients.

Obesity and miscarriage

The association between obesity and miscarriage has been reported in a number of studies, both in the general population (38) as well as in women undergoing assisted reproductive techniques (ART) (39, 40). A remarkable number of these studies show an increase in the prevalence of miscarriage in case of obesity (38, 41-43); however, there are studies that found no association between these two issues (40, 44). The link between obesity and miscarriage has been reported in both natural and assisted conceptions. Bellver et al. (43) found a rise in the incidence of spontaneous miscarriage with increasing BMI in patients who had been treated by various ART, including embryo transfer using donor oocytes. The risk of miscarriage was found to be 38.1% in obese women, whereas this rate was 13.3% in patients with a normal BMI. In another study, the data

from 1644 obese women were matched with 3288 controls with normal BMI. Metwally et al. (45) found a higher risk of early, late, and recurrent miscarriage in the obese group.

Although several studies have shown the association between obesity and higher miscarriage rates, there is no consensus about the mechanism that causes this in obese women. It is possible that obesity may affect the embryo or the endometrium or both (45).

One of the proposed mechanisms is the endometrial damage induced by obesity that affects the implantation process more than fertilization and early pregnancy development. In fact, embryo chromosomopathy, the most frequent cause of first trimester miscarriage, does not seem to be increased in women with excess weight (46).

Some endocrine disorders such as PCOS, hypothyroidism, and insulin resistance are more common in overweight women and it is known that the rates of miscarriage are increased in these disorders. Although PCOS is closely associated with obesity, it appears that obesity may also cause miscarriages alone. In a study, Landres et al. (47) found increased euploid miscarriages in obese women regardless of the listed disorders.

In conclusion, alterations in endocrine milieu, embryo quality, or uterine receptivity may contribute to the increased miscarriages (48).

Obesity and infertility

Infertility is the lack of pregnancy despite regular unprotected sexual intercourse after a year or therapeutic donor insemination in women less than 35 years of age and after 6 months in women 35 years and older (49). It is one of the most frequent disorders of the reproductive system in developing countries. Although many obese multiparous women are able to get pregnant despite their obesity, there is an increased prevalence of infertility in obese women. Vahrati and Smith have found that a larger portion of women who are seeking medical help to get pregnant are obese (50). The studies demonstrated that the duration required to achieve a spontaneous pregnancy rate is increased and pregnancy rates are decreased in obese women, including regular ovulatory obese women (51, 52). In several studies, it is found that the risk of infertility is threefold higher in obese women than in non-obese women (53) and their fertility seems to be impaired in both natural and assisted conception cycles (54, 55). It has been shown that the probability of pregnancy is reduced by 5% per unit of BMI exceeding 29 kg/m^2 (56). The association between obesity and lower fertility rate has been shown in several studies, and it has been shown that obesity in early adulthood alters the reproductive functions. The risk of menstrual problems and infertility increased in these women (57). Obesity causes infertility through various pathways, including impaired ovarian follicular development, qualitative and quantitative development of the oocyte, fertilization, embryo development, and implantation (58). The interaction between obesity and fecundity is not fully understood. It seems that the exact cause of infertility is long standing anovulation due to hyperandrogenism.

Grodstein et al. (59) revealed that anovulatory infertility was higher in overweight and obese patients whose BMI was found to be greater than 26.9 kg/m^2. Obesity affects the HPG axis by increased free estrogen levels due to increased conversion of androgens to estrogens in adipose tissue. Increased estrogen causes a decrease in GnRH by negative feedback. Thus, the affected HPG axis causes irregular or anovulatory cycles. Overweight and obese women have a higher incidence of menstrual dysfunction and anovulation. Rogers and Mitchell (10) found that menstrual disturbances were fourfold more common in obese women. Hartz et al. (11) found this incidence to be 3.1 times higher in obese women. Several studies have shown the association between anovulatory infertility and obesity (60-63).

As mentioned above, anovulation is also a result of the effects of hyperinsulinemia, insulin resistance, and hyperandrogenism on steroidogenesis and the ovary. Another situation associated with anovulation and obesity is PCOS. Up to 35%–60% of patients with PCOS are obese, and menstrual disturbances, anovulation, and infertility are more common in these obese PCOS patients than in non-obese PCOS patients (64). Hyperinsulinemia and insulin resistance have been detected in a large number of patients with PCOS with or without of obesity. However, in some studies, a reduced fecundity was reported in overweight and obese women with regular menses (65). These findings suggest that either anovulation continues despite the regular menses, or a combination of possible adverse effects of increased androgens on the endometrium and developing oocytes and adverse effects of increased levels of circulating leptin on the granulosa and theca cells give rise to infertility.

As a conclusion, the negative effect of obesity on infertility, particularly in the presence of anovulation, is clearly shown in several studies.

Obesity and assisted conception

Because of the obesity epidemic worldwide and its association with infertility, a large number of overweight and obese women are treated using ART. However, poor reproductive outcomes are encountered in ART, such as natural conception, and this is particularly related with central adiposity and PCOS.

Rittenberg et al. (65) found that women who are overweight or obese have a poorer outcome following in vitro fertilization (IVF) treatment than women within normal weight ranges. Metwally et al. (66) demonstrated that there is an association between obesity and poor embryo quality in women below 35 years of age, and young obese women have a less chance of cryopreserved embryos and need a higher dose of gonadotropins. However, Bellver et al. (67) reported an impaired IVF outcome without a poor embryo quality in obese women. They also similarly found that obese women who are undergoing ovarian stimulation in ART programmes require higher doses and a longer period of gonadotropin treatment (65).

Obese infertile women who undergo ART face some difficulties during the treatment. Several studies have shown that the ovarian response to controlled ovarian stimulation in obese women undergoing IVF is low. The other adverse outcomes of ovarian stimulation in obese women are reduced oocyte retrieval, poor quality of oocyte and embryo, decreased intrafollicular human chorionic gonadotrophins concentration, decreased peak estradiol levels, decreased number of mature oocytes, decreased

incidence of embryo transfer, and decreased number of transferred embryos (68).
The endometrium may also be affected by obesity. Bellver et al. (15) also investigated the potential role of the endometrium for the development of infertility in obesity in ovum donation cycles. Oocytes from healthy, young, non-obese donors are given to recipients with different BMIs. They found that the pregnancy rates per cycle initiated was significantly lower in obese women than in normal weight women (15). Recent meta-analysis have investigated the effects of obesity on the chance of obtaining a pregnancy or a live birth following ART treatment (65, 69, 70). Rittenberg et al. (65) analyzed 33 reports consisting of 47.967 treatment cycles, and they found that women who were overweight or obese had significantly decreased clinical pregnancy and live birth rates and significantly higher miscarriage rates than women with a normal BMI. Maheshwari et al. (69) analyzed 37 studies, and they found decreased pregnancy and increased miscarriage rates, similar to that by Rittenberg (65), and they found that high doses of gonadotrophins is required in IVF cycles in overweight and obese women. However, why obese women required higher doses of gonadotropin remain unclear. Koning et al. (70) analyzed 27 studies. They found an odds ratio (OR) of 0.90 for the association between overweight and live birth, thus showing a 10% reduction in the success rates of IVF in overweight women. The effect of obesity on medication requirements has been reported in several studies. Souter et al. (71) found that BMI was negatively associated with the estradiol level produced per preovulatory follicle, resulting in lower estradiol levels with increasing BMI. Some of these studies demonstrated that obesity is related with elevated gonadotropin requirements, lack of follicular development, and reduction in the number of oocytes (72-75). Gonadotropin resistance may be induced by leptin because it is known that the increased concentration of leptin in serum and follicular fluid of obese women decreases estradiol secretion from granulosa cells and may regulate human ovarian steroidogenesis. In high concentrations, leptin acts as an inhibitory gonadotropin (76). The need to increase gonadotropin concentrations is also associated with differences in the absorption, distribution, and clearance rate of the administered gonadotropins by the excessive adipose tissue (71). Akpınar et al. (77) reported an increase in the total gonadotropin consumption and a decrease in the number of retrieved oocytes with an increased body mass index. However, they found an implantation and clinical pregnancy rate in obese and overweight women, similar to normal weight women following intracytoplasmic sperm injection.
In conclusion, recent studies and meta-analyses have shown that the obesity has adverse effects on assisted reproductive technology, including ovulation induction and IVF/ICSI treatments. Obesity reduces the pregnancy rates, live birth rates, and increases the miscarriage rates in treatment cycles.

Obesity and treatment in infertility

It is difficult to treat anovulatory infertility in obese women because, as mentioned above, the obese women have a lower chance of conception following ART as they require a higher dosage of gonadotropin, respond poorly to ovarian stimulation, and have a higher risk of miscarriage.
Weight loss among overweight and obese women has been shown to improve reproductive outcomes, including fertility. Clark et al. (63) found that even a small weight loss in anovulatory obese infertile women resulted in improvements in ovulation, pregnancy rate, and pregnancy outcome.

Weight loss should be primarily offered to the anovulatory overweight and obese women. However, the effect of weight loss in overweight and obese women with regular menstrual cycles is still unclear. It is important to determine which patients will benefit from weight loss and the interval between the weight loss and the initiation of an ART programme. However, if weight loss will continue for a long time, the patient can enter into a catabolic phase of fertility because advanced age is one of the most deteriorating factors in infertility.
Furthermore, most overweight and obese women have a partner that is also overweight or obese, and overweight men also have been shown to be a risk factor for a prolonged time to achieve pregnancy (78). It is shown in a study that weight loss of these men significantly increased total sperm count and percentage of sperm with normal morphology (79).

Conclusion

Overweight and obese patients should be informed about the importance of pre-pregnancy weight reduction and should be encouraged to lose weight before the treatment to reduce the poor obstetrical outcomes due to obesity.
Although weight loss is the gold standard of treatment in women with a high BMI, ART treatment should not be delayed too much because of increasing age. Many fertility centers have a protocol to initiate ART treatment; however, there are no evidence-based guidelines regarding fertility treatment in overweight and obese infertile women.
The association between high BMI and adverse fertility outcome is known clearly. There are several proposed mechanisms to explain how obesity may lead to infertility; however, the exact pathophysiology is not clearly understood.

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References

1. World Health Organization. Preventing and managing the global epidemic. Report of the World Health Organization on obesity. Geneva: World Health Organization, 1997.

2. Parihar M. Obesity and infertility. Reviews in Gynecological Practice 2003; 3: 120-6. [CrossRef]
3. Fedorcsa´ck P, Storeng R, Dale PO, Tanbo T, Abyholm T. Obesity is associated with early pregnancy loss after IVF or ICSI. Acta Obstet Gynecol Scand 2000; 79: 43-8. [CrossRef]
4. Raatikainen K, Heiskanen N, Heinonen S. Transition from overweight to obesity worsens pregnancy outcome in a BMI dependant manner. Obesity 2006; 14: 165-71. [CrossRef]
5. Callaway LK, Prins JB, Chang AM, McIntyre HD. The prevalence and impact of overweight and obesity in an Australian Obstetric population. Med J Aust 2006; 184: 56-9.
6. Watkins ML, Rasmussen SA, Honein MA, Botto LD, Moore CA. Maternal obesity and risk for birth defects. Pediatrics 2003; 111: 1152-8.
7. Haslam DW, James WP. Obesity. Lancet 2005; 366: 1197-209. [CrossRef]
8. Norman RJ, Noakes M, Wu R, Davies MJ, Moran L, Wang JX. Improving reproductive performance in overweight/obese women with effective weight management. Hum Reprod Update 2004; 10: 267-80. [CrossRef]
9. Pratt LA, Brody DJ. Depression and obesity in the U.S. adult household population, 2005-2010. NCHS Data BrieF 2014; 167: 1-8.
10. Rogers J, Mitchell GW. The relation of obesity to menstrual disturbances. N Engl J Med 1952; 247: 53-6. [CrossRef]
11. Hartz AJ, Barboriak PN, Wong A, Katayama KP, Rimm AA. The association of obesity with infertility and related menstrual abnormalities in women. Int J Obes Rel Metab Dis 1979; 3: 57-77.
12. Jungheim ES, Travieso JL, Carson KR, Moley KH. Obesity and reproductive functions. Obstet Gynecol Clin North Am 2012; 39: 479-93. [CrossRef]
13. Pasquali R, Pelusi C, Genghini S, Cacciari M, Gambineri A. Obesity and reproductive disorders in women. Hum Reprod Update 2003; 4: 359-72. [CrossRef]
14. Linne Y. Effects of obesity on women's reproduction and complications during pregnancy. Obes Rev 2004; 5: 137-43. [CrossRef]
15. Bellver J, Melo MA, Bosch E, Serra V, Remohi J, Pellicer A. Obesity and poor reproductive outcome: the potential role of the endometrium. Fertil Steril 2007; 88: 446-51. [CrossRef]
16. Mircea CN, Lujan ME, Pierson RA. Metabolic fuel and clinical implications for female reproduction. J Obstet Gynaecol Can 2007; 29: 887-902.
17. Tong Q, Xu Y. Central leptin regulation of obesity and fertility. Curr Obes Rep 2012; 1: 236-44. [CrossRef]
18. Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. J Clin Invest 2006; 116: 1784-92. [CrossRef]
19. Metwally M, Li TC, Ledger WL. The impact of obesity on female reproductive function. Obes Rev 2007; 8: 515-23. [CrossRef]
20. Gil-Campos M, Canete RR, Gil A. Adiponectin, the missing link in insulin resistance and obesity. Clin Nutr 2004; 23: 963-74. [CrossRef]
21. Tortoriello DV, McMinn J, Chua SC. Dietary-induced obesity and hypothalamic infertility in female DBA/2J mice. Endocrinology 2004; 145: 1238-47. [CrossRef]
22. Moschos S, Chan JL, Mantzoros CS. Leptin and reproduction: a review. Fertil Steril 2002; 77: 433-44. [CrossRef]
23. Kadowaki T, Yamauchi T. Adiponectin and adiponectin receptors. Endocr Rev 2005; 26: 439-51. [CrossRef]
24. Lee B, Shao J. Adiponectin and energy homeostasis. Rev Endocr Metab Disord 2014; 15: 149-56. [CrossRef]
25. Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, et al. The hormone resistin links obesity to diabetes. Nature 2001; 409: 307-12. [CrossRef]
26. Fukuhara A, Matsuda M, Nishizawa M, Segawa K, Tanaka M, Kishimoto K, et al. Visfatin: a protein secreted by visceral fat that mimics the effects of insulin. Science 2005; 307: 426-30. [CrossRef]
27. Bozaoglu K, Bolton K, McMillan J, Zimmet P, Jowett J, Collier G, et al. Chemerin is a novel adipokine associated with obesity and metabolic syndrome. Endocrinology 2007; 148: 4687-94. [CrossRef]
28. Chen X, Jia X, Qiao J, Guan Y, Kang J. Adipokines in reproductive function: a link between obesity and polycystic ovary syndrome. J Mol Endocrin 2013; 50: 21-37. [CrossRef]
29. Poretsky L, Grigorescu F, Seibel M, Moses AC, Flier JS. Distribution and characterization of insulin and insulin-like growth factor 1 receptors in normal human ovary. J Clin Endocrinol Metab 1985; 61: 728-34. [CrossRef]
30. Gilling-Smith C, Willis DS, Beard RW, Franks S. Hypersecretion of androstendione by isolated theca cells from polycystic ovaries. J Clin Endocrinol Metabol 1994; 79: 1158-65. [CrossRef]
31. Giudice LC. Insulin-like growth factors and ovarian follicular development. Endocrine Rev 1992;13: 641-69. [CrossRef]
32. Diamanti-Kandarakis E, Dunaif A. New perspectives in polycystic ovary syndrome. Trends Endocrinol Metab 1996; 7: 267-71. [CrossRef]
33. Cırık DA, Dilbaz B. What do we know about metabolic syndrome in adolescents with PCOS? J Turk Ger Gynecol Assoc 2014; 15: 49-55. [CrossRef]
34. Diamanti-Kandarakis E, Couli C, Tsianateli T, Bergiele A. Therapeutic effects of metformin on insulin resistance and hyperandrogenism in polycystic ovary syndrome. European J Endocrinol 1998; 138: 269-74. [CrossRef]
35. Willis D, Mason H, Gilling Smith C, Franks S. Modulation by insulin of follicle stimulating hormone and luteinizing hormone action in human granulosa cells from normal and polycystic ovaries. J Clin Endocrinol Metab 1998; 81: 302-9. [CrossRef]
36. Hillier SG. Current concepts of the roles of follicle stimulating hormone and luteinizing hormone in folliculogenesis. Hum Reprod 1994; 9: 188-91.
37. Franks S, Robinson S, Willis D. Nutrition, insulin and polycistic ovary syndrome. Rev Reprod 1996; 1: 47-53. [CrossRef]
38. Lashen H, Fear K, Sturdee DW. Obesity is associated with increased risk of first trimester and recurrent miscarriage: matched case-control study. Hum Reprod 2004; 19: 1644-6. [CrossRef]
39. Fedorcsak P, Dale PO, Storeng R, Ertzeid G, Bjercke S, Oldereid N, et al. Impact of overweight and underweight on assisted reproduction treatment. Hum Reprod 2004; 19: 2523-8. [CrossRef]
40. Lashen H, Ledger W, Bernal AL, Barlow D. Extremes of body mass do not adversely affect the outcome of superovulation and in-vitro fertilization. Hum Reprod 1999; 14: 712-5. [CrossRef]
41. Hamilton-Fairley D, Kiddy D, Watson H, Paterson C, Franks S. Association of moderate obesity with a poor pregnancy outcome in women with polycystic ovary syndrome treated with low dose gonadotrophin. Br J Obstet Gynaecol 1992; 99: 128-31. [CrossRef]
42. Bussen S, Sutterlin M, Steck T. Endocrine abnormalities during the follicular phase in women with recurrent spontaneous abortion. Hum Reprod 1999; 14: 18-20. [CrossRef]
43. Bellver J, Rossal LP, Bosch E, Zuniga A, Corona JT, Melendez F, et al. Obesity and the risk of spontaneous abortion after oocyte donation. Fertil Steril 2003; 79: 1136-40. [CrossRef]
44. Loveland JB, McClamrock HD, Malinow AM, Sharara FI. Increased body mass index has a deleterious effect on in vitro fertilization outcome. J Assist Reprod Genet 2001; 18: 382-6. [CrossRef]
45. Metwally M, Tuckerman EM, Laird SM, Ledger WL, Li TC. Impact of high body mass index on endometrial morphology and function in the peri-implantation period in women with recurrent miscarriage. Reprod Biomed Online 2007; 14: 328-34. [CrossRef]

46. Bellver J, Cruz F, MartínezMC, Ferro J, Ramírez JF, Pellicer A, Garrido N. Female overweight is not associated with a higher embryo euploidy rate in first trimester miscarriages karyotyped by hysteroembryoscopy. Fertil Steril 2011; 96: 931-3. [CrossRef]
47. Landres IV, Milki AA, Lathi BR. Karyotype of miscarriages in relation to maternal weight Hum Reprod 2010; 25: 1123-26. [CrossRef]
48. Luke B, Brown MB, Stern JE, Missmer SA, Fujimoto VY, Leach R, SART Writing Group. Female obesity adversely affects assisted reproductive technology (ART) pregnancy and live birth rates. Hum Reprod 2011; 26: 245-52. [CrossRef]
49. Practice Committee of American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss: a committee opinion. Fertili Steril 2013; 99: 63. [CrossRef]
50. Vahratian A, Smith YR. Should access to fertility-related services be conditional on body mass index? Hum Reprod 2009; 24: 1532-37. [CrossRef]
51. Gesink Law DC, Maclehose RF, Longnecker MP. Obesity and time to pregnancy. Hum Reprod 2007; 22: 414-20. [CrossRef]
52. Wise LA, Rothman KJ, Mikkelsen EM, Sørensen HT, Riis A, Hatch EE. An internet-based prospective study of body size and time-to-pregnancy. Hum Reprod 2010; 25: 253-64. [CrossRef]
53. Rich-Edwards JW, Goldman MB, Willet WC, Hunter DJ, Stamfer MJ, Colditz GA, et al. Adolescent body mass index and infertility caused by ovulation disorders. Am J Obstet Gynecol 1994; 171: 171-7. [CrossRef]
54. Zaadstra BM, Seidell JC, Van Noord PA, te Velde ER, Habbema JA, Vrieswijk B, Karbaat J. Fat and female fecundity: Prospective study of effect of body fat distribution on conception rates. BMJ 1993; 306: 484-7. [CrossRef]
55. Crosignani PG, Ragni G, Parazzini F, Wyssling H, Lombrosso G, Perotti L. Anthropometric indicators and response to gonadotrophin for ovulation induction. Hum Reprod 1994; 9: 420-3.
56. Van der Steeg JW, Steures P, Eijkemans MJ, Habbema JD, Hompes PG, Burggraaff JM, et al. Obesity affects spontaneous pregnancy chances in subfertile ovulatory women. Hum Reprod 2008; 23: 324-8. [CrossRef]
57. Lake JK, Power C, Cole TJ. Women's reproductive health: the role of body mass index in early and adult life. Int J Obes Relat Metab Disord 1997; 21: 432-38. [CrossRef]
58. Jungheim ES, Travieso JL, Hopeman MM. Weighing the impact of obesity on female reproductive function and fertility. Nutr Rev 2013; 71: 3-8. [CrossRef]
59. Grodstein F, Goldman MB, Cramer DW. Body mass index and ovulatory infertility. Epidemiology 1994;5: 247-50. [CrossRef]
60. Green BB, Weiss NS, Daling JR. Risk of ovulatory infertility in relation to body weight. Fertil Steril 1988; 50: 721-26.
61. Jensen TK, Scheike T, Keiding N, Schaumburg I, Grandjean P. Fecundability in relation to body mass and menstrual cycle patterns. Epidemiology 1999; 10: 422-8. [CrossRef]
62. Bolumar F, Olsen J, Rebagliato M, Saez-Lloret I, Bisanti L. Body mass index and delayed conception: a European Multicenter Study on Infertility and Subfecundity. Am J Epidemiol 2000; 151: 1072-9. [CrossRef]
63. Clark AM, Thornley B, Tomlinson L, Galletley C, Norman RJ. Weight loss in obese infertile women results in improvement in reproductive outcome for all forms of fertility treatment. Hum Reprod 1998; 13: 1502-5. [CrossRef]
64. Al-Azemi M, Omu FE, Omu AE. The effect of obesity on the outcome of infertility management in women with polycystic ovary syndrome. Arch Gynecol Obstet 2004; 270: 205-10. [CrossRef]
65. Rittenberg V, Seshadri S, Sunkara SK, Sobaleva S, Oteng-Ntim E, El-Toukhy T. Effect of body mass index on IVF treatment outcome: an updated systematic review and meta-analysis. Reprod Biomed Online 2011; 23: 421-39. [CrossRef]
66. Metwally M, Cutting R, Tipton A, Skull J, Ledger WL, Li TC. Effect of increased body mass index on oocyte and embryo quality in IVF patients. Reprod Biomed Online 2007; 15: 532-8. [CrossRef]
67. Bellver J, Ayllón Y, Ferrando M, Melo M, Goyri E, Pellicer A, et al. Female obesity impairs in vitro fertilization outcome without affecting embryo quality. Fertil Steril 2010; 93: 447-54. [CrossRef]
68. Norman RJ, Moran LJ. Weight, fertility and management approaches. In: Kruger TF, Van der Spuy Z, Kempers RD, editors. Advances in fertility studies and reproductive medicine. Capetown: Juta; 2007. p. 24-35.
69. Maheshwari A, Stofberg L, Bhattacharya S. Effect of overweight and obesity on assisted reproductive technology – a systematic review. Hum Reprod Update 2007; 13: 433-44. [CrossRef]
70. Koning AM, Mutsaerts MA, Kuchenbecker WK, Broekmans FJ, Land JA, Mol BW, Hoek A. Complications and outcome of assisted reproduction technologies in overweight and obese women. Hum Reprod 2012; 27: 457-67. [CrossRef]
71. Souter I, Baltagi LM, Kuleta D, Meeker JD, Petrozza JC. Women, weight, and fertility: The effect of body mass index on the outcome of superovulation/intrauterine insemination cycles. Fertil Steril 2011; 95: 1042-47. [CrossRef]
72. Fedorcsak P, Dale PO, Storeng R, Tanbo T, Abyholm T. The impact of obesity and insulin resistance on the outcome of IVF or ICSI in women with polycystic ovarian syndrome. Hum Reprod 2001; 16: 1086-91. [CrossRef]
73. Loh S, Wang JX, Matthews CD. The influence of body mass index, basal FSH and age on the response to gonadotrophin stimulation in non-polycystic ovarian syndrome patients. Hum Reprod 2002; 17: 1207-11. [CrossRef]
74. Mulders AG, Laven JS, Eijkemans MJ, Hughes EG, Fauser BC. Patient predictors for outcome of gonadotropin ovulation induction in women with normogonadotrophic anovulatory infertility: a meta-analysis. Hum Reprod Update 2004; 9: 429-49. [CrossRef]
75. Spandorfer SD, Kump L, Goldschlag D, Brodkin T, Davis OK, Rosenwaks Z. Obesity and in vitro fertilization: negative influences on outcome. J Reprod Med 2004; 49: 973-7.
76. Agarwal SK, Vogel K, Weitsman SR, Magoffin DA. Leptin antagonizes the insulin-like growth factor-I augmentation of steroidogenesis in granulosa and theca cells of the human ovary. J Clin Endocrinol Metab 1999; 84: 1072-6. [CrossRef]
77. Akpınar F, Demir B, Dilbaz S, Kaplanoğlu I, Dilbaz B. Obesity is not associated with the poor pregnancy outcome following intracytoplasmic sperm injection in women with polycystic ovary syndrome. J Turk Ger Gynecol Assoc 2014; 15: 144-8. [CrossRef]
78. Ramlau-Hansen CH, Thulstrup AM, Nohr EA, Bonde JP, Sørensen TI, Olsen J. Subfecundity in overweight and obese couples. Hum Reprod 2007; 22: 1634-7. [CrossRef]
79. Håkonsen LB, Thulstrup AM, Aggerholm AS, Olsen J, Bonde JP, Andersen CY, et al. Does weight loss improve semen quality and reproductive hormones? Results from a cohort of severely obese men. Reprod Health 2011; 8: 24. [CrossRef]

Prenatal diagnosis and management of a fetal neck mass

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Abstract

We report the case of a benign mesenchymal spindle-cell tumor located on fetal neck, diagnosed during prenatal ultrasound and magnetic resonance investigation. A 30-year-old woman (gravida 2, para 1) was referred to our perinatology unit for evaluation of a fetal neck mass that had been identified on ultrasonography at 29 weeks gestation. A right lateral neck mass was observed (size: 42×40 mm) that extended from the preauricular region to right clavicula. Fetal MRI revealed a solid heterogeneous mass arising from the right lateral neck and there was no invasion around tissue and no extension of the mass into the chest. At 37 weeks after birth, we observed that the mass was subcutaneous and there was no invasion to the surrounding tissue. The trachea was not compressed and there was no extension of the mass into the chest. Then, the neck mass was completely resected after birth without any complications. Histopathological examination of tumor was consistent with mesenchymal spindle-cell tumor. Immunohistochemical staining with CD34 and actin was positive; however, caldesmone, epithelial membrane antigen (EMA), and S-100 was negative. Fetal MRI performed during the pregnancy for investigation of fetal neck masses detected on ultrasound gives compatible results observed in the neonate after birth and maintains adequate findings for follow-up and planning of treatment. (J Turk Ger Gynecol Assoc 2015; 16: 118-20)

Keywords: Fetal neck mass, fetal magnetic resonance imaging, mesenchymal spindle-cell tumor

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Introduction

Congenital tumors are extremely uncommon in infants, particularly in the head and neck region (1). The most common fetal neck mass is cystic higroma; cervical teratoma is the most common the fetal neck tumor. Fetal neck masses are uncommon and may not be apparent during the second trimester ultrasonography (2). Differential diagnosis of fetal neck tumors is difficult to be detected by ultrasonography. Encephalomyelocele, lymphangioma/higroma, teratoma, sarcoma, haemangioma, neuroblastoma, and goiter should be included in the differential diagnosis of fetal neck masses (3). Prenatal diagnosis of fetal neck mass has improved the survival and morbidity of infants with giant neck masses (4). Prenatal ultrasonography and MRI may enhance the accuracy of antenatal diagnosis (location, extension, and intracranial spread) and help in the selection of patients who require treatment (5). In this case report, we present a solid heterogeneous mass arising from the right lateral neck with radiological, histological, and immunohistochemical findings.

Case Presentation

A 30 -year-old woman (gravida 2, para 1) was referred to our perinatology unit for the evaluation of a fetal neck mass that had been identified on ultrasonography at 29 weeks gestation. A right lateral neck mass (size: 42×40 mm) was observed, extending from the preauricular region to right clavicle. Generally, the mass had a solid component (Figure 1). We obtained consent for performing a fetal MRI from the family. The solid heterogeneous mass arising from the right lateral neck, without signs of invasion to surrounding tissues and no extension into the chest in three planes MRI images (Figure 2). At 37 weeks, C-section was performed due to the early membrane rupture. After parental consent was obtained for pictures, the macroscopic appearance of the newborn is shown in Figure 3. The Apgar scores were 8 and 9 at 1 and 5 min, respectively. The infant was a male who weighed 3150 g at birth. After birth, we obtained consent from the family for MRI in three planes, confirming the presence of a solid heterogeneous mass arising from the right lateral neck (Figure 4). The mass was subcutaneous and there was no invasion of surrounding tissues. The trachea was not compressed. There was no extension into the chest. Then, the neck mass was completely resected after the birth without complication. Histopathological examination of the tumor was consistent with mesenchymal spindle-cell tumor. Immunohistochemical staining with CD34 and actin was positive; however, caldesmone, epithelial membrane antigen (EMA), and S-100 were negative. Morphological examination confirmed the diagnosis of myofibroma or infantile hemangioperistoma.

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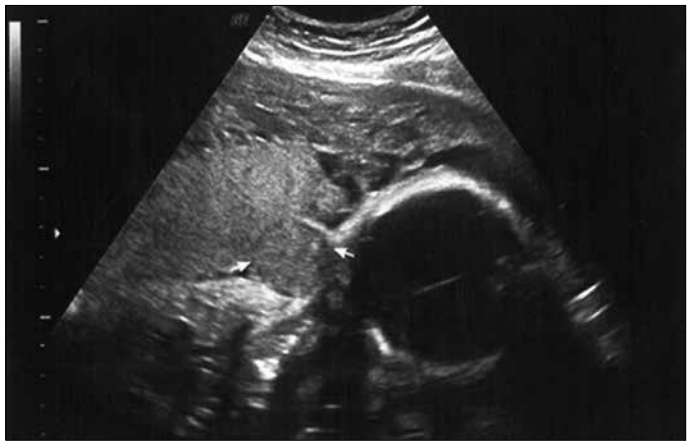

Figure 1. Sonographic image at 28 weeks and six days

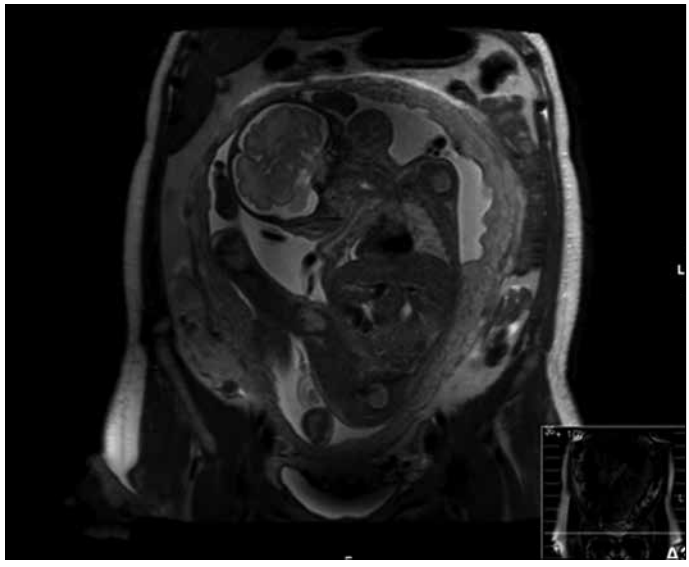

Figure 2. Fetal MRI image at 30 weeks and five days

Discussion

Congenital cervical tumors can be subdivided into anterior and posterior masses (2). In the anterior neck area, other masses can be caused by soft-tissue lesions, such as hamartomas, sarcomas, or goiter, and they may cause hyperextension of the neck (3). Large masses can have major fetal and perinatal effects due to the compression and distortion of surrounding cervical structures. Compression from a large lesion on the fetal esophagus and trachea can cause impaired fetal swallowing, polyhydramnios, and preterm labor in the prenatal period, and airway obstruction, hypoxia, and death after delivery (4, 6). After diagnosis, multidisciplinary prenatal management, including nondirective counseling, serial imaging, and planned delivery, was incorporated (6). Fetal ultrasonography helps to visualize the vascularity and consistency of the mass (solid or cystic) and can determine indirect signs of esophageal or tracheal obstruction. Fetal MRI enhances sensitivity in characterizing the extent of lesion infiltration and distorted anatomy of the neck structures. MRI is also useful in further delineating

Figure 3. Macroscopic appearance after the c-section

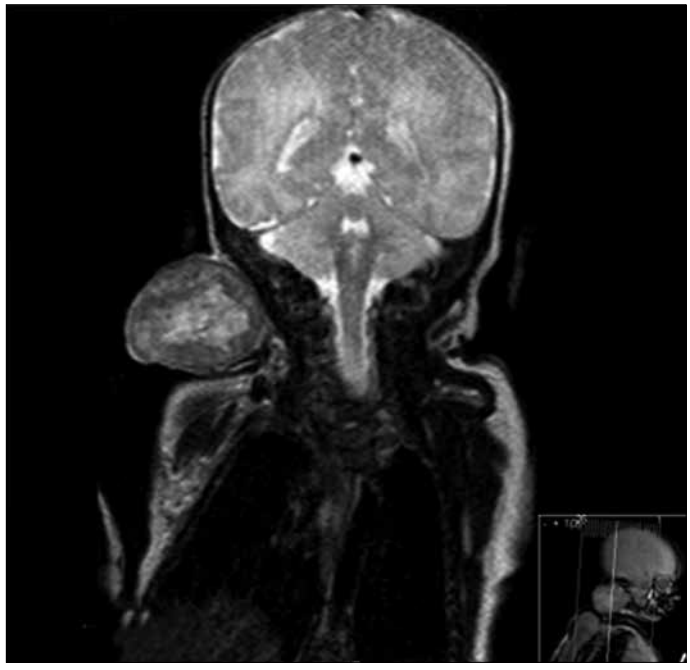

Figure 4. MRI image of infant after birth

lesions of neural and vascular origin (4). Antenatal fetal MRI and ultrasonography therefore it may be critical in identifying fetal neck masses that require ex utero intrapartum treatment (EXIT) procedure (5). Consequently, it is widely accepted that the cell of origin of all soft-tissue sarcomas is a primitive mesenchymal cell that can differentiate in many different directions. Fibromatoses, fibrosarcomas, neurofibrosarcomas, leiomyosarcomas, rhabdomyosarcomas, liposarcomas, angiosarcomas, mesotheliomas, and meningiomas are soft tissue sarcomas (7). Clinically, four common principles apply to spindle-cell sarcomas and soft-tissue sarcomas: the more superficial the location, the more likely the tumor is to be benign; if the tumor location is superficial, it is generally benign (deep tumors tend to be malignant); the larger the tumor, the more chances that it is malignant; and a rapidly growing tumor is generally more likely to be malignant. Benign tumors are relatively avascular, however most malignancies are hypervascular (7, 8). The most

common treatment of choice is excision; extensive excision or amputation should be performed when anatomically possible because spindle-cell sarcomas often infiltrate deep fascial planes that make it difficult to identify on gross examination of peripheral margins of the tumor. Those sarcomas have a greater potential for metastasis, and the time between recurrences is usually short. Generally, spindle-cell sarcomas do not respond well to radiotherapy; however, higher doses have been reported to control approximately 50% of them for up to a year. Surgical resection followed by radiation is also an option for local control. Chemotherapy for sarcomas has become a more acceptable treatment modality. The chemotherapeutic protocols involve the use of adriamycin often in combination with other agents, including cyclophosphamide, vincristine, dacarbazine, and methotrexate (8).

Ethics Commitee Approval: *Ethics committee approval was received for this study from the ethics committee of Local Instutional Ethics Committee.*

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

Author Contributions: *Concept - E.D.; Y.C.; Design - E.D.; Y.C.; Supervision - E.C.; Resource - Y.C.; Materials - Y.C.; Data Collection & /or Processing - Y.C.; Analysis & /or Interpretation - E.D.; Literature Search - Y.C.; Writing - E.D., Y.C.; Critical Reviews - E.C.*

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

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

References

1. Gupta A, Maddalozzo J, Win Htin T, Shah A, Chou PM. Spindle cell rhabdomyosarcoma of the tongue in an infant: a case report with emphasis on differential diagnosis of childhood spindle cell lesions. Pathol Res Pract 2004; 200: 537-43. [CrossRef]
2. Rauff S, Kien TE. Ultrasound diagnosis of fetal neck masses: a case series. Case Rep Obstet Gynecol 2013; 2013: 243590. [CrossRef]
3. Güzelmansur I, Aksoy HT, Hakverdi S, Seven M, Dilmen U, Dilmen G. Fetal cervical neuroblastoma: prenatal diagnosis. Case Rep Med 2011; 2011: 529749. [CrossRef]
4. Cass DL. Impact of prenatal diagnosis and therapy on neonatal surgery. Semin Fetal Neonatal Med 2011; 16: 130-8. [CrossRef]
5. Tonni G, De Felice C, Centini G, Ginanneschi C. Cervical and oral teratoma in the fetus: a systematic review of etiology, pathology, diagnosis, treatment and prognosis. Arch Gynecol Obstet 2010; 282: 355-61. [CrossRef]
6. Lazar DA, Cassady CI, Olutoye OO, Moise KJ Jr, Johnson A, Lee TC, Cass DL. Tracheoesophageal displacement index and predictors of airway obstruction for fetuses with neck masses. J Pediatr Surg 2012; 47: 46-50. [CrossRef]
7. Carew JF, Kraus DH. Clinical considerations for neoplasms of the neck. In: Fu Y-S, Wenig BM, Abemayor E, Wenig BL, editors. Head and Neck Pathology with Clinical Correlations. Philadelphia, PA: Churchill-Livingstone; 2001. p. 771-80.
8. Cynthia M. Kahn, Scott Line. Musculoskeletal system. The Merck Veterinary Manual, 10th Edition, 2010.

What is your diagnosis?

A 21-year-old patient presented during her first pregnancy at 34 weeks gestation. Her medical history was unremarkable, except that her husband was her cousin. During ultrasound evaluation of the fetus nothing remarkable except hyperechogenicity in the base of the heart was observed. This hyperechogenicity was observed both in the ascending aorta and main pulmonary artery (Figure 1a, b). Other fetal echocardiographic findings were normal, including cardiac position, situs, rhythm, size of the chambers, and main arteries. The toxoplasma, rubella, cytomegalovirus, herpes, syphilis (TORCH) panel was negative for recent infection. During her follow-up visit at 37 weeks gestation, new findings like hyperechogenicity in the abdominal aorta, inferior vena cava, and placenta were noted (Figure 2a, b). At 40 weeks gestation, she delivered a 3215 g male fetus with an APGAR score of 9/10 (1st and 5th minute) by C-section because of prolonged labor. His postnatal echocardiographic evaluation showed same findings.

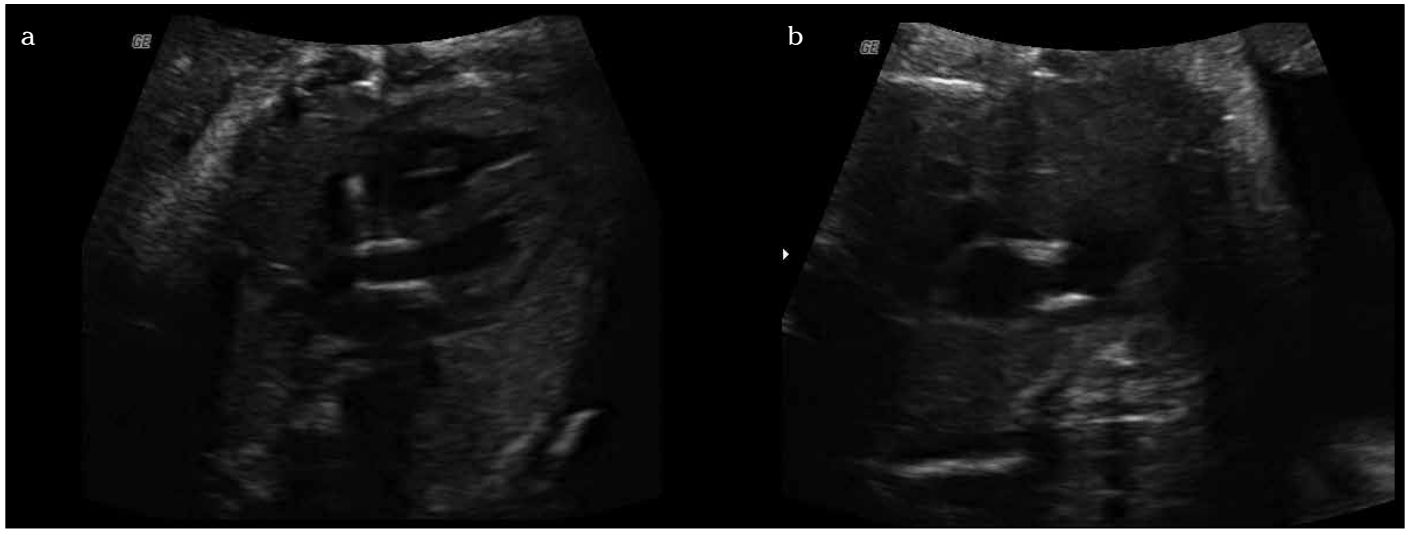

Figure 1. a, b. Hyperechogenicity in the great vessels. Aorta (a) main pulmonary artery (b)

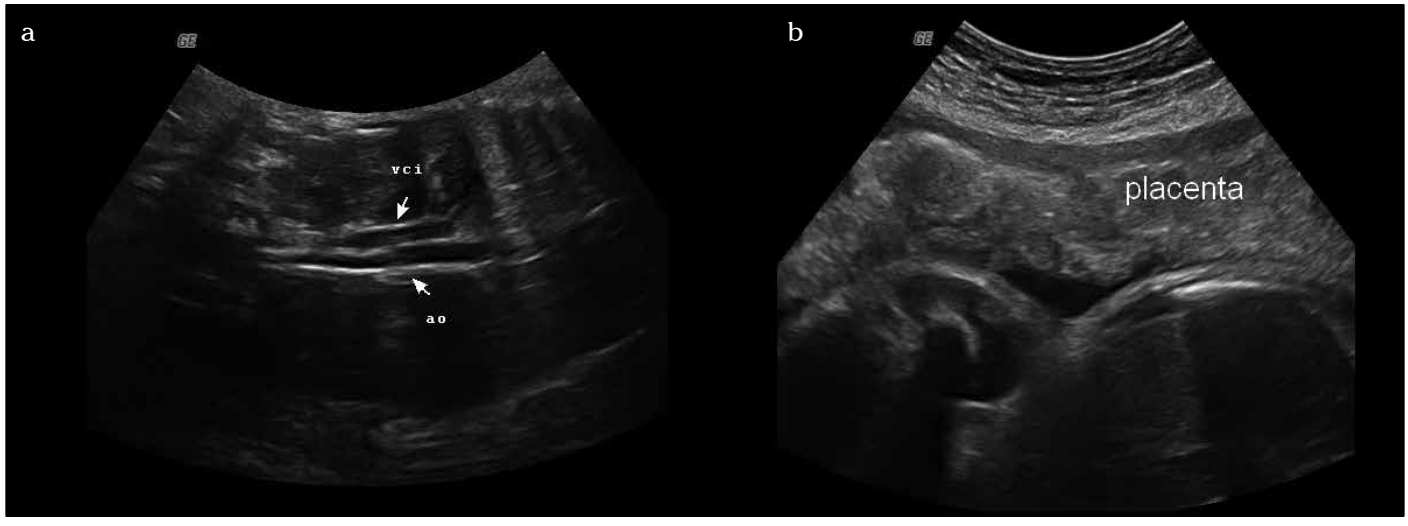

Figure 2. a, b. Hyperechogenicity in the vena cava inferior (vci) and abdominal aorta (ao) (a) hyperechogenic foci in the placenta (b)

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Answer

Postnatal echocardiography revealed patent ductus arteriosus as an additional finding. His abdominal ultrasound revealed diffuse vascular calcifications in the abdominal aorta and celiac trunk. Renal parenchymal calcifications were also noted. The patient was diagnosed with idiopathic infantile arterial calcification (IIAC). He was discharged from the hospital on postnatal 13th day. He was administered pamidronate, captopril, and furosemide for hypercalcemia and hypertension. Genetic analysis from peripheral blood of the infant revealed homozygote ectonucleotide pyrophosphate/ phosphodiesterase 1 (ENPP1) gene mutation (p.G738R [c.2212G>A]), which further confirmed the diagnosis. His parents were found to be heterozygote carriers of this mutation.

At the time of this report, the infant was eight months of age; hyperechogenicity in the abdominal aorta and renal parenchyma and patent ductus arteriosus were still persisting. He was still undergoing antihypertensive therapy.

IIAC, also known as generalized arterial calcification of infancy, is a very rare disease that was first reported in 1901 by Bryant and White. (1) Among nearly 200 cases reported until now, few have been prenatally diagnosed. It is inherited in an autosomal recessive pattern. It is characterized by disruption and calcification of the internal elastic lamina of the fetal arteries with calcium deposits, leading to fibrosis and occlusion of the arteries. (2) It is therefore almost always fatal. Fetuses with this disorder either develop cardiac failure and hydrops in utero or are born acutely ill with unstable cardiac functions. Among the survivors beyond the newborn period, few cases were reported to live until adulthood. (3) The gene responsible for this disease was found to be the ENPP1 gene, which is located on the long arm of sixth chromosome. This cell surface enzyme generates inorganic pyrophosphate (PPi), a solute that regulates cell differentiation and serves as an essential physiological inhibitor of calcification (4). Other genes that are also thought to be related to the disease are ATP-binding cassette, sub-family C member 6 (ABCC6), 5'-nucleotidase, ecto (NT5E) and solute carrier family 20, member 2 (SLC20A2). They all play a role in phosphate metabolism. Although bisphosphonates were used postnatally, no successful antenatal therapy with these drugs has been reported until now.

Main antenatal ultrasound findings are hyperechogenicity in great arteries (aorta, pulmonary artery), polyhydramniosis, and pericardial effusion. In advanced cases, cardiac failure and hydrops may develop (5).

The diagnosis of IIAC is clinically confirmed by ruling out other disorders associated with systemic calcium deposition, such as hyperparathyroidism, hypervitaminosis D, and metastatic calcification from renal disease (6). Most cases in literature base their postnatal definitive diagnosis on radiographical examinations, echocardiography, and autopsy. That's because, the demonstration of calcifications with these methods is not difficult. Genetic investigation for the mutation in ENPP1 in antenatally diagnosed cases is undertaken in very few cases together with ours (6-8). Either homozygote or combined heterozygote mutations can cause the disease (6).

Currently, there is no prenatal treatment for this disease. As the rates of prenatal diagnosis of this disease increase, studies regarding in utero treatment will ultimately increase. In order to increase prenatal detection rates, clinicians should be careful regarding the echogenicity of the great vessels during antenatal ultrasound evaluation. Determining the mutation will also provide first degree relatives of the parents to be tested and counseled for this lethal disease.

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References

1. Bryant JH, White WA. A case of calcification of the arteries and obliterative endarteritis associated with hydronephrosis in a child aged 6 months. Guys Hosp Rep 1901; 55: 17-28.
2. Rani H, Rao R, Rao U, Dinesh U, Ramamurthy B. Idiopathic infantile arterial calcification with thrombotic microangiopathy--a unique case. Fetal Pediatr Pathol 2010; 29: 413-8. [CrossRef]
3. van der Sluis IM, Boot AM, Vernooij M, Meradji M, Kroon AA. Idiopathic infantile arterial calcification: clinical presentation, therapy and long-term follow-up. Eur J Pediatr 2006; 165: 590-3. [CrossRef]
4. Kutty S, Cava JR, Frommelt MA. Idiopathic infantile arterial calcification: a case report of prenatal and postnatal echocardiographic diagnosis. Echocardiography 2009; 26: 862-4. [CrossRef]
5. Nagar AM, Hanchate V, Tandon A, Thakkar H, Chaubal NG. Antenatal detection of idiopathic arterial calcification with hydrops fetalis. J Ultrasound Med 2003; 22: 653-9.
6. Sawyer T, Stacey M, Mulreany M, Thompson M, Nitschke Y, Rutsch F, Mahnke CB. Generalized arterial calcification of infancy associated with meconium peritonitis: a case report and review of the literature. Am J Perinatol 2009; 26: 711-6. [CrossRef]
7. Ciana G, Trappan A, Bembi B, Benettoni A, Maso G, Zennaro F, et al. Generalized arterial calcification of infancy: two siblings with prolonged survival. Eur J Pediatr 2006; 165: 258-63. [CrossRef]
8. Reitter A, Fischer D, Buxmann H, Nitschke Y, Rutsch F, Mottok A, et al. Fetal hydrops, hyperechogenic arteries and pathological doppler findings at 29 weeks: prenatal presentation of generalized arterial calcification of infancy - a novel mutation in ENPP1. Fetal Diagn Ther 2009; 25: 264-8. [CrossRef]

Drug use and/or exposure in pregnancy: Presence of risk versus quantity of risk

To the Editor,

The case report by Karataş et al. (1), published in the fourth issue of the Journal of the Turkish German Gynecological Association in December 2014 was interesting. This report identified an infant with multiple cardiovascular malformations, whose mother was exposed to carbamazepine (CBZ) during pregnancy. This case report is well presented, and authors have provided a well-thought discussion. Nevertheless, I would like to mention some points relevant to the interpretation of human data in the field of teratology which may widen the readers' perspective regarding the management of drug exposure and/or use in pregnancy.

Case reports are very useful in terms of noticing rare and repeating patterns; however, they cannot provide any estimates regarding the absolute risk of malformations since they lack a denominator. The absolute risk is only available through the interpretation of epidemiological data from observational cohorts or case-control studies (2).

For a particular drug, being a teratogen or posing an unacceptable risk for use in pregnancy are two different concepts. A drug with established teratogenic effect may not always heighten the risk of teratogenicity to inacceptable levels, and CBZ is a good example for that. Although the risk for spina bifida may increase 2–10-fold after CBZ exposure, considering the prevalence of this malformation (1:1000), the absolute risk would still be small (0.2%-1% vs 0.1%) (3). A review of available epidemiological studies by the American Academy of Neurology and American Epilepsy Society subcommittees have shown that CBZ probably does not lead to a substantial increase in the risk of major congenital malformations and it is relatively safe in terms of major congenital malformations and neurodevelopmental outcomes when compared to other classical antiepileptic such as valproic acid (VPA) (4). A recent meta-analysis also suggests that CBZ is not associated with adverse neurodevelopmental outcomes in infants (5).

Therefore, in terms of absolute risk, CBZ has a relatively safe profile compared with other conventional antiepileptic drugs (AEDs), such as VPA, and still remains to be an option for the management of pregnant patients with epilepsy (5). When discussing the possible risks regarding drug use or exposure in pregnancy, the very first information that should be received by pregnant women is the rate for background risk of malformations (3%), which is present in every pregnancy regardless of an exposure (2). Afterwards, the available data regarding the drug, with considering possible confounders, should be discussed. Finally, an individual risk assessment and risk communication should be available to all pregnant women who may need drug treatment for their chronic diseases, not only in terms of the presence of risk but also in terms of the quantity of risk.

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References

1. Karataş Z, Karataş A, Özlü T, Goksugur SB, Varan B. Bicuspid aortic valve and severe aortic stenosis in a newborn exposed to carbamazapine during pregnancy. J Turk Ger Gynecol Assoc 2014; 15: 259-61. [CrossRef]
2. Koren G, Pastuszak A, Ito S. Drugs in pregnancy. N Engl J Med 1998; 338: 1128-37. [CrossRef]
3. Matlow J, Koren G. Is carbamazepine safe to take during pregnancy? Can Fam Physician 2012; 58:163-4.
4. Harden CL, Meador KJ, Pennell PB, Hauser WA, Gronseth GS, French JA et al. Practice parameter update: management issues for women with epilepsy—focus on pregnancy (an evidence based review): teratogenesis and perinatal outcomes. Epilepsia 2009; 50: 1237-46. [CrossRef]
5. Bromley R, Weston J, Adab N, Greenhalgh J, Sanniti A, McKay AJ, et al. Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child. Cochrane Database Syst Rev 2014; 10: CD010236. [CrossRef]

Author's Response

We thank the authors for their contribution to the paper. As we mentioned in the manuscript, carbamazepine is relatively safe in terms of major congenital malformations and neurodevelopmental outcomes when compared with other classical antiepileptic drugs (AEDs), such as valproic acid. Nevertheless, we again want to emphasize that the infants exposed to AEDs during pregnancy should be followed because the risk of congenital malformations may rarely occur. Furthermore, to prevent these risks, AEDs should be reduced to the lowest possible dose from the beginning of the preconception period and supplementation of folic acid should be considered.

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Prior vaginal delivery is a predictive factor affecting success in trial of labor after cesarean section

To the Editor,

I have read with great interest the article entitled "Maternal and obstetrical factors associated with a successful trial of vaginal birth after cesarean section" by Abdelazim et al. (1) that was published in the previous issue of the Journal of the Turkish German Gynecological Association. In this article, the authors brought to our attention the significance of distinct risk factors that could affect the outcome of a trial of labor after cesarean section (TOLAC). Although the report by Abdelazim and coworkers confirms findings from previous studies, I would like to include some considerations on the subject.

The objective of this study was to evaluate the risk factors associated with TOLAC, but the authors seem to overlook one important factor related to the results of this study. Previous history of vaginal delivery before cesarean section is not defined by the authors. The predictive role of prior vaginal delivery is strictly related to the outcomes of TOLAC and may require further clarification and discussion.

TOLAC is an important strategy to limit repeat cesarean sections and the complications related to the procedure. Although maternal morbidity in women with previous cesareans is higher when TOLAC fails, identifying the optimal patient who would attain maximum benefit is crucial. For this reason, determining risk factors before deciding whether the patient can undergo TOLAC or repeat cesarean section is important for the obstetrician. In the process of decision-making, it must be noted that patients with a prior vaginal delivery have higher rates of successful vaginal births after cesarean (VBAC) than patients without a prior vaginal birth (2).

Although evaluation of individual risks is important in determining who are appropriate candidates for TOLAC, the American College of Obstetricians and Gynecologists (ACOG) (3) defines prior vaginal birth and spontaneous labor as a strong predictor for TOLAC success. In view of this data, Grobman et al. (4) were the first to report the most utilized and validated model for predicting the probability of successful TOLAC. In this model, it is demonstrated that vaginal delivery and prior VBAC are the two characteristics that are useful for predicting successful TOLAC. These findings also have been repeatedly validated by multiple studies (5).

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References

1. Abdelazim IA, Elbiaa AA, Al-Kadi M, Yehia AH, Sami Nusair BM, Faza MA. Maternal and obstetrical factors associated with a successful trial of vaginal birth after cesarean section. J Turk Ger Gynecol Assoc 2014; 15: 245-9. [CrossRef]
2. Sentilhes L, Vayssière C, Beucher G, Deneux-Tharaux C, Deruelle P, Diemunsch P, et al. Delivery for women with a previous cesarean: guidelines for clinical practice from the French College of Gynecologists and Obstetricians (CNGOF). Eur J Obstet Gynecol Reprod Biol 2013; 170: 25-32. [CrossRef]
3. American College of Obstetricians and Gynecologists. ACOG Practice bulletin no. 115: Vaginal birth after previous cesarean delivery. Obstet Gynecol 2010; 116(2 Pt 1): 450-63.
4. Grobman WA, Lai Y, Landon MB, Spong CY, Leveno KJ, Rouse DJ, et al. Development of a nomogram for prediction of vaginal birth after cesarean delivery. Obstet Gynecol 2007; 109: 806-12. [CrossRef]
5. Tessmer-Tuck JA, El-Nashar SA, Racek AR, Lohse CM, Famuyide AO, Wick MJ. Predicting vaginal birth after cesarean section: a cohort study. Gynecol Obstet Invest 2014; 77: 121-6. [CrossRef]

Author's Response

I would like to thank the authors for their valuable comments on our study.

We entirely agree with the authors that previous vaginal delivery prior cesarean section influences the outcomes of trial of labor after cesarean section (TOLAC) and patients with previous vaginal delivery have higher rates of successful vaginal birth after cesarean section (VBAC), (1).

Also, American College of Obstetricians and Gynecologists defined prior vaginal birth and spontaneous labor as strong predictors for the success of TOLAC (2).

Women with one previous lower segment cesarean section for non-recurrent cause for cesarean section, without severe medical disorders, a singleton pregnancy with cephalic presentation, a clinically estimated fetal weight of ≤3.5 kg, an adequate pelvis and in spontaneous labor in the absence of maternal or fetal compromise, and who were willing to undergo the trial of a scar were included in Abdelazim et al's study (3). In addition,

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importance of spontaneous labor pains before TOLAC was mentioned in Raja and colleagues' study (4).

Item of previous vaginal birth was not included in Abdelazim et al. (3) study for two reasons: 1. Women with only one delivery by cesarean section without any prior vaginal birth were willing to be included in our study, and, 2. If there was no history of prior vaginal birth before TOLAC, a clinically estimated fetal weight of ≤3.5 kg and adequate maternal pelvis can replace prior vaginal birth.

Moreover, clinical estimation of the fetal weight and assessment of maternal pelvic capacity adds to the health provider's clinical experience.

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References

1. Sentilhes L, Vayssière C, Beucher G, Deneux-Tharaux C, Deruelle P, Diemunsch P, et al. Delivery for women with a previous cesarean: guidelines for clinical practice from the French College of Gynecologists and Obstetricians (CNGOF). Eur J Obstet Gynecol Reprod Biol 2013; 170: 25-32. [CrossRef]
2. American College of Obstetricians and Gynecologists. ACOG Practice bulletin no. 115: Vaginal birth after previous cesarean delivery. Obstet Gynecol 2010; 116(2 Pt 1): 450-63.
3. Abdelazim IA, Elbiaa AA, Al-Kadi M, Yehia AH, Sami Nusair BM, Faza MA. Maternal and obstetrical factors associated with a successful trial of vaginal birth after cesarean section. J Turk Ger Gynecol Assoc 2014; 15: 245-9. [CrossRef]
4. Raja JF, Bangash KT, Mahmud G. VBAC scoring: successful vaginal delivery in previous one caesarean section in induced labour. J Pak Med Assoc 2013; 63: 1147-51.

CONGRESS CALENDAR

INTERNATIONAL MEETINGS

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, Portugal 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
18-20 September, 2015	**NESA Days 2015** Berlin, Germany http://www.nesacademy.org
17-21 October, 2015	**ASRM Annual Meeting Baltimore** Maryland, United States http://www.asrmannualmeeting.org
07 November, 2015	**5th Stuttgarter Gynakologen-Herbsttag** Stuttgart, Germany

NATIONAL MEETINGS

15-18 September, 2015	**7th Annual Urogynecology Congress** İstanbul, Turkey http://www.urojinekoloji.org/
15-18 October, 2015	**15th National Congress of Perinatal Medicine** Muğla, Turkey www.perinatoloji2015.org
29 October-1 November, 2015	**5th Reproductuve Medicine & Surgery Congress** Antalya, Turkey http://www.utd2015.org/
29-31 October, 2015	**Turkey Maternal Fetal Medicine and Perinatology Association Ultrasonography Course** İstanbul, Turkey http://tmftp.org/
12-14 November, 2015	**12th Traditional Zekai Tahir Burak Days** Ankara, Turkey http://www.ztbgunleri2015.org/
11-15 May, 2016	**XI Turkish German Gynecologic Congress** Antalya, Turkey http://www.tajev2016.org

JTGGA CME/CPD CREDITING

Questions on the article titled *"Impact of obesity on infertility in women"* within the scope of CME/CPD

1. Which of the followings is wrong about adipokines?
   a) Adipokines are signaling molecules that have important roles in the regulation of reproduction, immune response, and glucose and lipid metabolism
   b) In PCOS patients, tumor necrosis factor-alpha (TNF-α) levels are increased and adiponectin levels are decreased
   c) Abnormal levels of adipokines are associated with insulin resistance and type 2 diabetes mellitus
   d) It has been shown that chemerin levels decrease in metabolic syndrome
   e) In obese women, adiponectin levels decrease and increase with weight loss

2. Which of the following adipokines decreases in obesity?
   a) Leptin
   b) Adiponectin
   c) Chemerin
   d) Resistin
   e) Visfatin

3. Which of the followings is not a risk factor for subfertility in overweight and obese women?
   a) Impaired ovarian follicular development because of obesity
   b) Long-standing anovulation because of hyperandrogenism
   c) Increased free estrogen levels because of increased conversion of androgens to estrogens in adipose tissue
   d) Effects of hyperinsulinemia, insulin resistance, and hyperandrogenism on steroidogenesis and ovary
   e) Decreased levels of insulin

4. What is the first step in the treatment of infertility in obese women?
   a) Starting ovulation induction with clomiphene citrate
   b) Starting intrauterine insemination as soon as possible
   c) Starting in vitro fertilization with higher dosage of gonadotropins
   d) Weight loss
   e) Laparoscopic drilling

5. Which of the followings is wrong about the effects of insulin in obese women?
   a) Insulin increases SHBG production from liver
   b) The effect of FSH on estradiol and progesterone production increases by insulin
   c) Insulin decreases the production of IGFBP-1 in liver
   d) Insulin levels are increased in obese women
   e) Insulin stimulates androgen production in the theca cells

6. Which of the followings is wrong in obese women?
   a) Insulin resistance and hyperandrogenemia are significantly increased in obese women, particularly in those with central obesity
   b) FSH enhances excessive production of the androgen substrate, leading to relatively improper estrogen levels in the developing follicle in obese women
   c) The duration required to achieve spontaneous pregnancy is increased and pregnancy rates are decreased in obese women, excluding those with regular ovulation
   d) Premature luteinization leads to menstrual cycle disorders and obesity-induced oligo-anovulation in obese women, particularly in those with PCOS
   e) It is possible that the increased miscarriage rates in obesity are due to the effects of obesity on the embryo or the endometrium, or both

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Türkçe Özler – Haziran 2015

Özgün Araştırma

J Turk Ger Gynecol Assoc 2015; 16: 64-67 DOI:10.5152/jtgga.2015.15235

Term gebelikte ultrason ile hesaplanan plasenta hacmi ve umblikal kord kanı hacminin korelasyonu

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Öz

Amaç: Term gebelikte ultrason ile ölçülen plasenta hacmi ve toplanan umblikal kord kanı (UKK) hacmi arasındaki korelasyonu araştırmak.

Materyal ve Metot: Maha Chakri Sirindhorn Tıp Merkezi doğumhanesinde tekil term gebeliği olan kadınlarda gözlemsel kesitsel bir çalışma yapıldı. Plasenta kalınlığı, yüksekliği ve genişliği 2 boyutlu (2D) ultrason kullanılarak ölçüldü ve volümetrik matematiksel model kullanılarak plasenta hacmi hesaplandı. Bebeğin doğumundan hemen sonra UKK toplandı ve hacmi ölçüldü. Daha sonra, doğum ağırlığı, plasenta ağırlığı ve gerçek plasenta hacmi analiz edildi. Pearson korelasyonu her iki değişken arasındaki korelasyonu belirlemek için kullanıldı.

Bulgular: Toplam 35 gebe kadın çalışma için uygun şartlara sahipti. Tahmini plasenta hacminin ve gerçek plasenta hacminin ortalama ve standart sapması sırasıyla 534±180 mL ve 575±118 mL idi. Medyan UKK hacmi 140 mL (98-220 mL aralığında) idi. UKK hacminin tahmini plasenta hacmi ile istatistiksel olarak anlamlı korelasyonu yoktu (korelasyon katsayısı 0,15; p=0,37). Bununla birlikte, UKK hacmi gerçek plasenta hacmi ile (korelasyon katsayısı 0,62; p<0,001) ve doğum ağırlığı ile (korelasyon katsayısı 0,38; p<0,02) anlamlı olarak koreleydi.

Sonuç: 2D ultrason ile tahmin edilen plasenta hacmi UKK hacmi ile anlamlı olarak korele değildi. Plasental görüntülemenin diğer tiplerini kullanarak tahmini plasenta hacmi ile UKK hacmi arasındaki korelasyonu tespit etmek için ileri çalışmalar gerekebilir.

Anahtar Kelimeler: Umblikal kord kanı hacmi, plasenta parametreleri, ultrason

Özgün Araştırma

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Labial Adezyon ve Bakteriüri

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Öz

Amaç: Bu çalışmanın amacı labial adezyonu olan 23 aylıktan küçük kızlarda klinik prezantasyonu, laboratuvar bulgularını ve tedaviye yanıtı değerlendirmektir.

Materyal ve Metot: 1998 ve 2013 arasında İran'ın kuzeydoğusunda Meşhed'de Dr Sheikh Çocuk Kliniğine sevk edilen, labial adezyon teşhisi konulmuş 23 aylıktan küçük tüm kızların kayıtları retrospektif olarak gözden geçirildi.

Bulgular: Gözden geçirme periyodu boyunca 63 hastaya labial adezyon teşhisi konuldu. Çoğu hastada fiziksel muayene sırasında veya işeme problemlerinin değerlendirilmesi sırasında doktorlar tarafından teşhis konuldu. Hastalar arasındaki en yaygın semptom işeme sırasında dizüri ve rahatsızlıktı. 21 (%33,3) hastada idrar yolu enfeksiyonu öyküsü vardı. 17 (%26,9) hastada steril piyüri vardı ve %69,8'i idrar örneklerinde bakteri varlığı gösterdi.

Sonuç: Doktorlar; idrar yolu enfeksiyonu belirtileri olmaksızın idrar tahlili steril piyüri veya koloni sayımı <105 olarak bakteri varlığı gösterebilen ergenlik öncesi kızlarla sıkça karşılaşabilmektedirler. Bu durumlarda, labial adezyondan her zaman şüphelenilmeli ve genital muayene yapılmalıdır.

Anahtar Kelimeler: Labial adezyon, bakteriüri, idrar yolu enfeksiyonu, topikal östrojen

Özgün Araştırma

J Turk Ger Gynecol Assoc 2015; 16: 70-73 DOI:10.5152/jtgga.2015.15009

Amerika Birleşik Devletleri'nde 2007 yılındaki Büyük Durgunluk ve doğumda erkek: kadın oranı

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Öz

Amaç: Erkek canlı doğumları yaklaşık %3 ile kadın canlı doğumlarını hafifçe aşmaktadır. Erkek doğumların toplam canlı doğumlara oranı konvansiyonel olarak E/K şeklinde gösterilmektedir. Birçok faktörün E/K'yi etkilediği gösterilmiştir, başlıca yoksulluk, toksinler ve stres E/K'yi düşürmektedir. Popülasyon stresi; deprem gibi doğal olaylardan ve kısa savaşlar, terörist saldırıları ve daralan ekonomiler gibi insan yapımı olaylardan meydana çıkabilir. Bu çalışma, Amerika Birleşik Devletleri'nde "Büyük Durgunluk" (2007) başlangıcının E/K'deki değişikliklerle ilişkili olup olmadığını belirlemek için yapılmıştır.

Materyal ve Metot: Ocak 2006 ila Aralık 2008 arası cinsiyete göre aylık canlı doğumlar yıllık olarak Amerika Birleşik Devletleri Hastalık Kontrol ve Önleme Merkezleri'nden temin edildi.

Bulgular: 2007'de 4316233 canlı doğum vardı (E/K: 0,51157; %95 güven aralığı: 0,51110-0,51205). E/K Ocak ve Haziran arasında yükseldi ve daha sonra Ağustos ve Aralık arasında hızla düştü. 2007'nin ikinci yarısında E/K istatistiksel olarak anlamlı düşüktü (p=0,007). Hazirandan Temmuza E/K'deki düşüş de anlamlıydı (p=0,02). Bu bulgular 2006 ve 2008 için birleştirilmiş verilerde tekrarlanmadı.

Sonuç: 2000'lerin ortalarında Amerika Birleşik Devletleri'ndeki konut patlaması yükselen konut fiyatları ve yoksul alıcılara verilen ucuz ipotekli krediler (mortgage) tarafından ateşlendi. Yükselen konut fiyatlarındaki duraksama Büyük Buhrandan bu yana en kötü mali krizi tetikleyerek, ödemede gecikmeler ve hacizlerle sonuçlandı. İlişkili stres ABD'de E/K'yi düşürmüş gibi görünmektedir.

Anahtar Kelimeler: Amerika Birleşik Devletleri, ekonomik durgunluk, doğum hızı/eğilimleri, infant, yenidoğan, cinsiyet oranı

Özgün Araştırma

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Gebelikte gelişen intrahepatik kolestazın fetal kardiak ve periferal dolaşıma etkisi

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Öz

Amaç: Çalışmanın amacı intrahepatik kolestaz gelişen gebelerde fetal kardiak ve periferal dolaşımın Doppler ultrason ile değerlendirilmesi ve sağlıklı gebeler ile karşılaştırılmasıdır.

Materyal ve Metot: Ocak 2013-Ocak 2014 tarihleri arasında Ege Doğumevi ve Eğitim Hastanesi'ne başvuran 22 kolestazlı ve 44 sağlıklı gebe değerlendirmeye alındı. Gebeler, fetal kardiak ve periferik Doppler ultrason ile değerlendirildi. Fetal kardiak dolaşımı değerlendirmek için Pulmoner Arter (Pa) veAorta (Ao) Pik velosite indeksi (PVI), Pulmoner Ven (Pv) PVI and Pulsatilite İndeksi (PI), Mitral Valv (MV) ve Trikuspid Valv (TV), E- ve A-dalgası pik velosite oranı (E/A) ve istmus Aorta (IAo) Pik Sistolik Velosite (PSV) ölçüldü. Periferik dolaşım ise, orta serebral arter (MCA) ve umbilikal arter (UA) PI, resistans indeksi (RI) ve sistol/diastol oranı (S/D) ile değerlendirildi.

Bulgular: TV E/A oranları (0.74±0.1 ve 0.75±0.1 (p=0.94)), MV E/A oranları (0.79±0.1 ve 0.76±0.1 (p=0.25), Ao pik velositeleri (90.4±12.3 ve 88.7±14.1 (p=0.51)), Pa pik velositeleri (82.5±13.1 ve 76.2±11 (p=0.09)) ve IAo pik velositeleri (108.6±15.4 ve 104.01±14.3 (p= 0.36)) olarak bulundu. UA ve MCA Doppler ölçümlerinin de (S/D, PI, RI) anlamlı fark göstermediği bulundu.

Sonuç: Kolestazlı gebelerin fetuslarında, periferik ve kardiak dolaşımın Doppler ultrason ile değerlendirilmesinde fark gözlenmemiştir.

Anahtar Kelimeler: Kolestaz, gebelik, fetal Doppler, kardiak dolaşım

Özgün Araştırma

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Nifedipin ve ritodrinin erken doğumda maternal ve fetal kan akımı paternleri üzerine etkilerinin karşılaştırılması

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Öz

Amaç: Bu çalışmanın amacı preterm doğum tehdidi olan hastalarda nifedipin ve ritodrinin yan etkilerini ve fetomaternal dolaşım üzerindeki etkilerini araştırmak ve karşılaştırmaktır.

Materyal ve Metot: Obstetri kliniğine erken doğum tehdidi tanısı ile başvuran, 24-36 gebelik haftaları arasındaki 60 hasta çalışmaya alındı. Hastaların random olarak seçilen 30'una nifedipin,30'una ritodrin tedavisi verildi.Demografik özellikler,klinik parametreler,hastaların laboratuar bulguları, fetal ve maternal yan etkileri karşılaştırıldı. Ayrıca, tedaviden önceki, tedaviden 2 saat ve 48 saat sonraki, umblikal arter (UA), her iki uterin arter (UtA) ve orta serebral arterdeki (OSA), Pulsatilite İndeksi (PI) ve diğer Doppler indeksleri araştırıldı.

Bulgular: Her iki grupta UA, UtA, OSA'de PI ve diğer Doppler indekslerindeki erken ve geç dönem değişimler istatistiksel olarak anlamı değil idi. Ayrıca,doğuma kadar geçen süre,fetal mortalite,maternal morbidite,her iki grupta istatistiksel olarak farklı değil idi.Fakat ritodrin grubunda taşikardi gibi maternal yan etkiler daha fazla gözlendi. ($p<0.05$) Ayrıca, anksiete ritodrin grubunda daha fazla oranda görülmesine rağmen fark istatiksel olarak anlamlı değildi.

Sonuç: Nifedipin ve ritodrin, fetal ve fetomaternal dolaşımdaki erken ve geç dönem Doppler ultrasonografi parametrelerindeki değişimleri etkilemez.

Anahtar Kelimeler: Doppler ultrasonografi, tokoliz, umblikal arter, uterin arter, orta serebral arter

Özgün Araştırma

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Prolatinomalı Hastalarda Hiperprolaktineminin Plazma Ghrelin Seviyelerine Etkisi Bulunmamaktadır

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Öz

Amaç: Giderek artan kanıtlar prolaktinin adipoz dokuda vücut kilosunu ve bileşimini düzenleyen taşıyıcıların modülatörü olduğu yönündedir. Hiperprolaktineminin kilo artışı ve obezite ile ilişkili olduğu gösterilmiştir. Ghrelin hipofiz bezini de içeren bir çok organdan salınan bir hormondur. Ghrelin etkisini enerji dengesini düzenleyerek ve iştahı uyararak göstermektedir. Bu çalışmanın amacı prolaktinomalı hastalarda kilo alımına ghrelin etkisi olup olmadığını araştırmaktır.

Materyal ve Metot: Yeni tanı ve kabergolin tedavisi altındaki toplam 44 hasta çalışma grubuna dahil edildi. Açlık kan şekeri, insulin, lipid profile, ghrelin (BioTek Instruments, Inc, USA) düzeyleri ölçüldü, insülin direnci (Homeostasis model assessment of insulin resistance, HOMA-IR) hesaplandı. Tüm olguların beden kitle indeksi (BMI) ve total yağ oranı (%) of all biyoelektriksel impedans analizi (BIA) (TBF-310GS™, Tanita Corporation, Tokyo, Japan) ile ölçüldü.

Bulgular: Prolaktinomalı hastaların açlık insülin, trigliserid, BMI, bel ve kalça çevresi ölçümleri kontrol grubuna göre anlamlı yüksek saptandı. Açlık glukoz, HDL-kolesterol, LDL-kolesterol ve HOMA-IR ölçümlerinde ise farklılık yoktu. Ayrıca total yağ oranı da hastalarda yüksek idi, ancak bu yükseklik anlamlı bulunmadı. Bunların dışında bakılan ghrelin seviyesinde de gruplar arasında anlamlı farklılık bulunmadı. Serum ghrelin ve büyüme hormonu arasında korelasyon gözlendi ($p<0.02$, $rho=0.489$). Ancak prolaktin ile ghrelin veya vücut yağ oranı arasında korelasyon saptanmadı.

Sonuç: Bizim çalışmamızın sonuçlarına göre ghrelin seviyesinin prolaktinomadaki kilo artışı üzerine etkisi yoktur. Ghrelin seviyesinin prolaktinomalı hastalarda obezite prevalansını etkileyip etkilemediğini değerlendirmek için ileri çalışmalar gerekmektedir.

Anahtar Kelimeler: Hiperprolaktinemi, ghrelin, kilo artışı

Özgün Araştırma

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Uterus dışı rahimiçi araç: Tanı ve Cerrahi Tedavisi

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Öz

Amaç: Uterus dışı rahimiçi araç (RİA) olan vakalarımızın tanısı ve cerrahi tedavisinin sunumu

Materyal ve Metot: Kliniğimizde 2008 ile 2010 tarihleri arasında gözlenen 21 RIA vakalarımızın retrospektif olarak değerlendirilmiştir. Şikayetleri, tanı metodları ve cerrahi tedavisi değerlendirilmiştir.

Bulgular: Toplam 14 bakırlı RİA ve 7 levonorgestrel (LNG) RİA saptandı. RAİ ların 71.4% si laktasyon döneminde uygulanmıştı. Hastaların 19.05% istenmeyen gebelik, 19.05% si pelvik ağrı ve 23.8% si pelvik ağrı ve vaginal kanama ile başvurdu. İki hastada RİA retroperitoneal alandaydı. Hastaların 38.1% inde RİA ipi rutin kontroller esnasında gözlenmemişti. 14 hastaya laparoskopi yapıldı. Laparotomi dens adezyon nedeni ile 7 hastaya uygulandı.

Sonuç: Uterus dışı RİA çeşitli klinik semptomlarla başvurabilir. Ultrasonografi ve X-Ray tanı için yeterlidir. Cerrahi olası komplikasyonların önlenmesi için gereklidir ve tercih edilen cerrahi yöntem laparoskopidir.

Anahtar Kelimeler: Uterus dışı rahimiçi araç, cerrahi, kontrasepsiyon

Özgün Araştırma

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İn vitro fertilizasyon sikluslarında luteal faz desteğine gonadotropin salgılatıcı hormon agonisti eklenmesi; 2739 siklus analizi

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Öz

Amaç: In Vitro Fertilizasyon (IVF) sikluslarında luteal faz defekti mevcuttur ve en iyi luteal faz desteği (LFD) sağlamak amacıyla birçok tedavi protokolü denenmiştir. Literatürde IVF sikluslarında Gonadotropin Salgılatıcı Hormon (GnRH) agonistlerinin luteal faz desteğini tamamlayıcı ajan olarak kullanımının yararlı olduğu öne sürülmüştür. Biz bu çalışmamızda IVF tedavisinde standart progesterone desteğine ek olarak tek doz GnRH agonist 0,1 mg subkütan enjeksiyon olarak eklenmesinin özellikle canlı doğum oranları olmak üzere gebelik sonuçları üzerine etkilerini analiz etmeyi amaçladık.

Materyal ve Metot: Bu çalışma 2739 IVF siklusunu içeren retrospektif bir kohort çalışmasıdır. IVF sikluslarında uzun GnRH agonist ve antagonist stimülasyon protokolleri dahil edilmiştir. Tedavi programındaki sikluslar ; tek doz luteal GnRH agonist ve progesteron alan Grup A (n=1850) hastalar ile yalnızca standart progesterone luteal desteği alan Grup B (n =889) hastalar olmak üzere 2 gruba ayrılmıştır. Çalışmanın primer sonucu canlı doğum oranlarıdır. Abortus ve çoğul gebelik oranları ise sekonder sonuçlardır.

Bulgular: GnRH agonist ve progesterone luteal faz desteği alan (Grup A) ve sadece progesterone alan (Grup B) arasında canlı doğum oranları açısından ; hem uzun agonist hem de antagonist stimülasyon kollarında istatistiki anlamlı farklılık gözlenmedi (sırasıyla 40,8%/41,2% ve 32,8%/34,4%,p<0,05). Gebelik oranları, implantasyon oranları ve abortus oranları her iki grupta benzer bulundu. Çoğul gebelik oranları ise antagonist sikluslarda , Grup A'da Grup B ye göre istatistiksel yüksek bulundu.(sırasıyla 12,0% ve 6,9%).

Sonuç: Luteal fazda destek tedavisi amacıyla GnRH agonistlerinin rutin luteal desteğe eklenmesi günümüz literatürü ışığında desteklenmektedir. Ancak kendi çalışmamızda luteal faza tek doz GnRH agonisti eklemenin gebelik sonuçları üzerine olumlu etkilerini gözlemlemedik. Ancak GnRH agonistlerinin luteal döneme eklenmesinin potansiyel faydasının ortaya konulabilmesi amacıyla farklı doz rejimleri ve uygulama periodları ile iyi tasarlanmış randomize klinik çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: GnRH agonist, luteal faz desteği, ivf, progesterone

Özgün Araştırma

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Histerektomi yapilmadan gerçekleştirilen bilateral sakrospinöz ligament fiksasyonu: 18 aylik takip

Mehmet Baki Şentürk[1], Hakan Güraslan[1], Yusuf Çakmak[2], Murat Ekin[1]

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Öz

Amaç: Bu çalışma cerrahi mesh lie bilateral yapılan sacrospinöz fiksasyon operasyonunun sonuçlarını değerlendirmeyi amaçlamaktadır.

Materyal ve Metot: 2010 ile 2012 yılları arasında opere edilen 22 hastanın sonuçları retrospektif olarak değerlendirildi. Operasyon öncesi ve operasyon sonrası 6., 12. ile 18. aylardaki sonuçlar Pelvic Organ Prolapse Quantification system (POP-Q) ve Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire-12 (PISQ-12) sıklası ile karşılaştırıldı. Karşılaştırma için Friedman and Wilcoxon Signed Ranks testleri kullanıldı. İstatistiksel olarak, p değeri 0.05 ve 001' den küçük olduğunda anlamlı kabul edildi.

Bulgular: POP-Q klasifikasyonuna göre vaginal duvarlar ve apical bölge prolapsusunda belirgin iyileşme gözlendi (p=0.001) ve 18 aylık takipler sonucunda prolapsus izlenmedi. Ayrıca PISQ-12 formuna göre hastalarda belirgin memnuniyet vardı (p=0.001).

Sonuç: Bu teknik ile yeterli klinik iyileşme sağlandığı görünmektedir ve pelvik organ prolapsus cerrahisinde ilk seçenek olabilir.

Anahtar Kelimeler: Pelvic Organ Prolapsusu, Cerrahi Mesh, Vaginal Duvarlar

Derleme

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PARP inhibitörleri ve dahası

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Öz

Poli adenozin difosfat (ADP) riboz polimeraz (PARP), hücre genomunda deoksiribonükleik asit (DNA) bütünlüğünün korunmasının içindeki gizeme panaromik bir görüş kazandırmaktadır. Günlük saldırılara karşı normal durumun daha dinamik dengelenmesi ile ilgili dengeleyici kısmıdırlar. PARP, en belirgini ve göze çarpanı meme kanseri (BRCA) 1 ve 2 olan diğer tümör baskılayıcılarının içinden eşlik eden adaylarını bulur. İkisinin gücü, over kanser tedavisi için artık piyasada olan PARP inhibitörlerince tümör hücresinin sentetik letalitesini sağlayarak bölünür. Böylesi inhibitörlerin direnci için artık klinik olarak önemli hale gelen birçok neden vardır. Bunlar diğer hasar onarım yaklaşımları ile birlikte görülmektedir.

Anahtar Kelimeler: PARP inhibitörleri, BRCA, olaparib, sentetik letalite, over kanseri

Derleme

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Kadınlarda Obezitenin İnfertilite Üzerine Etkisi

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Öz

Obezite ve şişmanlık prevalansı tüm dünyada gittikçe artmaktadır ve dünya çapında salgın haline gelmiş durumdadır. Obezitenin üreme sağlığı da dahil olmak üzere tüm sistemlerde olumsuz etkileri vardır. İnfertil kadınlarda obezite prevalansı yüksektir ve obezite ile infertilite arasındaki bağlantı iyi bilinmektedir. Obezite ve üreme fonksiyonları arasındaki ilişki bugün hala araştırılmaktadır. Aşırı kilolu kadınlarda adet düzensizliği ve anovulasyon yüksek bir orandadır. Aşırı kilolu ve obez kadınlar üreme sağlığı açısından yüksek risk altındadır. Subfertilite ve infertilite, gebelik oranları, düşük oranları ve gebelik komplikasyonları bu kadınlarda artmıştır. Bu kadınlarda doğal sikluslarda olduğu kadar yardımcı üreme sikluslarında da kötü reproduktif sonuçlar mevcuttur. Bu kötü reproduktif sonuçlar ovulasyon indüksiyonu, in vitro fertilizasyon / intrasitoplazmik sperm enjeksiyonu (IVF/ICSI) ve yumurta donörü sikluslarını da içeren yardımcı üreme tekniklerinde görülmektedir. Kilo verme bu hastalarda üreme sonuçları üzerinde olumlu etkilere sahiptir.

Anahtar Kelimeler: İnfertilite, adipoz doku, obezite

Olgu Sunumu

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Fetal boyun kitlesinin prenatal tanısı ve yönetimi

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Öz

Fetal boyun bölgesinde yer alan benign mezenşimal iğsi hücreli tümörün prenatal ultrasonografik ve MRI ile tanı konulmasını rapor ettik. 30 yaşındaki hasta (gravida 2, para 1) 29. gestasyonel haftada ultrasonografik incelemesinde fetusun boyun bölgesinde kitle tespit edilince perinatoloji ünitemize refere edildi. Fetusun sağ lateral boyun bölgesinde preauricular bölgeden sağ klavikulaya uzanan 42*40 mm boyutunda kitle izlendi. Fetal MRI görüntülerinde sağ lateral buyun bölgesinde çevre dokuya invaze olmayan ve göğüs boşluğuna uzanmayan solid heterojen kitle izlendi. 37. gestasyonel haftada, dğumdan sonra kitlenin sadece cilt altında olduğu ve çevre dokuya invaze olmadığı tespit edildi. Trakenin bası altında olmadığı ve kitlenin göğüs boşluğuna uzanmadığı anlaşıldı. Ardından kitle cerrahi olarak tamamen kompikasyonsuz bir şekilde rezeke edildi. Histopatolojik inceleme sonucunda kitleye mezenşimal iğsi hücreli tümör tanısı kondu. İmmünohistokimyasal boyama sonucunda CD34 ve kaldesmon pozitif, EMA ve S-100 negatif olarak değerlendirildi. Fetal MRI ve prenatal ultrasonografik inceleme ile fetal boyun kitlesi tanısı konulmuş olup, neonatal dönemdeki tedavi planı için yardımcı olmuştur.

Anahtar Kelimeler: Fetal boyun kitlesi, fetal MRI, mezenşimal iğsi hücreli tümör