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Dear Colleagues,

On February 6, 2023 the earthquake with a magnitude of 7.7 in Kahramanmaraş and the second earthquake with a magnitude of 7.4 that occurred in Elbistan approximately 9 hours after this earthquake, Turkey went into a deep sadness, life almost stopped. This earthquake storm, which affected Kahramanmaraş, Malatya, Adıyaman, Diyarbakır, Gaziantep, Hatay, Kilis, Osmaniye, Şanlıurfa and Adana, actually deeply upset all of country and broke our hearts. We wish our condolences to all our citizens who passed away and lost their relatives after this great disaster, also I would like to express my sincere blessings to all our people who were injured and had financial loss.

Nevertheless life goes on and science is an ongoing process and we need to act in realizing our scientific studies and activities once again.

The April issue of the Journal of Controversies Obstetrics & Gynecology and Pediatrics was published under these conditions. I would like to personally thank all of our colleagues and employees who contributed.

We are very happy and honored to be in front of you, our esteemed gynecologists and obstetricians, with the April issue of the brand new and richly scientific Journal of Controversies Obstetrics & Gynecology and Pediatrics, the second issue of 2023. In this issue, there are 4 original articles, 1 review and a letter to editor.

I wish to meet you all in the July issue of our magazine, more happier, more hopeful, believing in the light of science.

Best Regards,

Prof. Oya GÖKMEN, MD

Honorary Editor

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Original Article

DOI: 10.51271/JCOGP-0007

Exploring hysterosalpingography findings and pregnancy results among women applying to a tertiary referral hospital

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ABSTRACT

Aims: To find out the correlation between hysterosalpingography (HSG) pathologies and pregnancy results of infertility patients. Infertility is a complicated complaint prevalent among women of reproductive age with severe financial and social consequences. HSG, adopted for evaluating infertility, can be considered a secondary imaging technique in practice following ultrasound examination. The present study attempted to explore the HSG results of patients applying to our hospital with the complaint of infertility in the last two years and to compare these results with their pregnancy.

Methods: We retrospectively evaluated the HSG results of the patients applying to or referred to our hospital from an external center between 10.01.2018 and 30.08.2020 with the complaint of infertility.260 patients were included in the study. The patients were grouped by their primary and secondary infertility. We analyzed anomalies detected by HSG in two groups: uterine and tubal anomalies. Moreover, those becoming pregnant following HSG until June 2022 were grouped by reproductive techniques (spontaneous or assisted). Patients not having optimal imaging, with HSG reports obtained at an external center, and with insignificant results were excluded from the study.

Results: The patients' mean age was calculated to be 36 years (21-52 years). While 144 patients (55%) were diagnosed with primary infertility, 116 (45%) had a diagnosis with secondary infertility. There was no uterine or tubal anomaly in 157 patients undergoing HSG, but we discovered only a uterine defect in 28 of 103 patients and a tubal defect including at least one uterine and comorbid tuba in 44 patients. In 45 patients with a uterine anomaly, the most prevalent HSG findings were uterine filling defect (28 patients, 62.2%) and arcuate uterus (10 patients, 22.2%). We also discovered that 81 patients became pregnant at least once after HSG. While 50 of them got pregnant spontaneously, the remaining benefitted from assisted reproductive techniques. Our findings showed spontaneous pregnancy not to be associated with primary or secondary infertility (p=0.394; OR=0.765; 95% CI: 0.412-1.42). There was also no relationship between primary and secondary infertility and abnormal HSG findings (p=0.437; OR=0.820; 95% CI: 0.498-1.35). Finally, we concluded that abnormal HSG findings did not significantly contribute to the rate of spontaneous pregnancy (p=0.701; OR=1.13; 95% CI: 0.604-2.11).

Conclusion: We concluded that abnormal HSG findings did not contribute to the rates of spontaneous pregnancy.

Keywords: Infertility, hysterosalpingography , spontaneous pregnancy

INTRODUCTION

Fertility is defined as the clinical capacity of a woman of reproductive age to produce a pregnancy. Infertility, on the other hand, is a disorder characterized by the inability to have a clinical pregnancy following 12 months of regular and unprotected sexual intercourse, or the deterioration of the reproductive capacity of the individual or with their partner.[1] Therefore, it may be considered amultifaceted disorder with severe financial, psychological, and social consequences. The relevant research demonstrates that 10-15% of couples worldwide (49-72 million on average) struggle with infertility.[2–4] Whereas Turkey's infertility rate seems to be declined from15% to 8.1%, between 1993-2013.[5] Infertile women are often divided into two groups by means of previous pregnancy success: Primary and Secondary infertile women. Recent data have revealed that secondary infertility is the most prevalent form of female infertility worldwide, particularly in developing countries with high rates of unsafe abortions and inadequate postpartum maternity care.[6–8]

Ovulation disorders (27%), male factors (25%), and tubal/uterine factors (22%) are known to be the most common causes of infertility.[9] Evaluation of infertility basically includes evaluation of ovulation, female reproductive system anatomyand male-related factors. While the very first method applied to reveal male-related factors is sperm analysis, the evaluation of ovulation relies on ultrasound imaging of the ovaries examination and laboratory tests for Follicle Stimulating Hormone (FSH), estradiol, anti-mullerian hormone (AMH), thyroid stimulating hormone (TSH), prolactin (PRL), and androgens. Evaluation of pelvic anatomy is based on revealing tubal and uterine factors by radiological imaging techniques. Transvaginal ultrasonography (TVS) and hysterosalpingography (HSG) are two standard imaging techniques in practice due to their convenience and accessibility. TVS is known to be highly sensitive, specificand accurate in detecting uterine anomalies or polyps but limited in evaluating tubal abnormalities. A previous study reported the sensitivity and specificity of HSG in detecting tubal occlusions to be 65% and 83%, respectively.[10] HSG is capable of defining the condition of tubes, it also informs about the morphology of the uterus, its contours, the uterine cavity, and even the width of the cervical canal.[11] Uterine anomalies account for about 10% of female subfertility.[12] In the HSG technique, endometrial polyps, fibroids, or intrauterine adhesions may present with filling defects in the uterine cavity or irregular uterine contour. It was suggested that HSG has a therapeutic role in increasing subfertility.[13]

The present study aimed to explore the HSG results of the patients applied to our hospital with the complaint of infertility in the last two years and to evaluate the relationship between these results by the patients' infertility types and pregnancy outcomes following HSG.

METHODS

The study was carried out with the permission of İstanbul Medeniyet University Göztepe Training and Research Hospital Noninvasive Clinical Researches Ethics Committee (Date: 02/09/2020, Decision No: 2020-0572). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. All patients signed the free and informed consent form.

We retrospectively evaluated the HSG results of the patients applying to or referred to our hospital from an external center between 10.01.2018 and 30.08.2020 with the complaint of infertility. 260 patients were included in the study The patients were grouped by age, gravida, parity, previous ectopic pregnancy, previous tubal or uterine surgery, primary or secondary infertility, and causes of infertility (unexplained infertility, polycystic ovary syndrome, endometrioma, and male factor). Moreover, HSG results were grouped as tubal and uterine anomalies (arcuate uterus, uterus didelphys, filling defect in the cavity, hypoplastic uterus, uterine septum, etc.). We also grouped tubal anomalies by unilateral (right or left tubal occlusion) or bilateral tubal occlusions. 81 of 260 patients becoming pregnant following HSG until June 2022 were grouped by reproductive techniques (spontaneous or assisted).

Iohexol (a 50 ml water-soluble non-ionic radiopaque substance) had injected through the cervix during HSG. Then, the distribution of the radiopaque substance to the cervix, uterine cavity, and fallopian tubes and its passage from the tubes to the peritoneum had observed and recorded with the help of simultaneous radiographic imaging.

Patients who did not have optimal imaging reports, whose HSG reports were obtained at an external center and the ones with unclear results, patients with any endocrine abnormality, patients desiring IVF treatment in the following 6-12 months and whose partners had abnormality in semen parameters with TPMSS<1 million were excluded from the study.

Statistical Analyses

In statistical analyses, we considered a p-value < 0.05 to be significant. We used Chi-square test for correlation analysis.

RESULTS

Table 1 presents the patients' demographic characteristics. Accordingly, their mean age was calculated to be 36 years (21-52 years). While 144 patients (55%) were diagnosed with primary infertility, 116 (45%) had a diagnosis with secondary infertility. There was no uterine or tubal anomaly in 157 patients undergoing HSG, but we discovered only uterine defect in 28 of 103 patients with anomalies and a tubal defect including at least one uterine and comorbid tuba in 44 patients. We observed tubal defects in 75 patients (72.8%): 18 (17.4%) with bilateral and 57 with unilateral tubal defects. The right tubal filling defect was the most common in 52 patients. In 45 patients with a uterine anomaly, the most prevalent HSG findings were uterine filling defect (28 patients, 62.2%) and arcuate uterus (10 patients, 22.2%), followed by uterus didelphys in two patients, hypoplastic uterus in one patient, uterine septum in one patient, T-shaped uterus in one patient, bicornuate uterus in one patient, and concurrent transverse vaginal septum in one patient with filling defect in the cavity. We also discovered that 81 patients became pregnant at least once after HSG. While 50 of them got pregnant spontaneously, the remaining benefitted from assisted reproductive techniques. While 25 (17.3%) of 144 primary infertile patients had spontaneous pregnancy, it was discovered in 25 (21.5%) of 116 secondary infertile patients. As shown in **Table 2**, our findings showed spontaneous pregnancy not to be associated with primary or secondary infertility (p=0.394; OR=0.765; 95% CI: 0.412-1.42). Of 103 patients with abnormal HSG findings, 54 (52.4%) were primary infertile, and 49 (47.5%) were secondary infertile. There was also no relationship between primary and secondary infertility and abnormal HSG findings (p=0.437; OR=0.820; 95% CI: 0.498-1.35) (**Table 3**). Of 21 patients with an abnormal HSG findings who became pregnant spontaneously, 8 (38%) were found to be primary infertile and 13 (62%) to be secondary infertile. Finally, we concluded that abnormal HSG findings did not significantly contribute to the rate of spontaneous pregnancy (p=0.701; OR=1.13; 95% CI: 0.604-2.11) (**Table 4**)

Table 1. Patients' demographic characteristics

	n (%)
Age (years)	36 (21-52)
Feature of infertility	
Primary	144 (55%)
Secondary	116 (45%)
HSG result	
Normal	157 (60.3%)
Abnormal	103 (39.7%)
Uterine anomaly	45 (43.6%)
Filling defect	28 (62.2%)
Arcuate uterus	10 (22.2%)
Tubal anomaly	75 (72.8%)
Unilateral	57 (76%)
Bilateral	18 (24%)
Only uterine anomaly	28 (27.1%)
Uterine anomaly and at least one tubal anomaly	44 (42.7%)
Pregnancy following HSG	
No	179 (68.8%)
Yes	81 (31.2%)
Spontaneous pregnancy	50 (61.7%)
Pregnancy with assisted reproductive techniques	31 (38.3%)

HSG: Hysterosalpingography

Table 2. Spontaneous pregnancy following HSG - primary/secondary infertility relationship

Spontaneous pregnancy	Feature of infertility		Total	p-value p =0.394
	Secondary	Primary		
No	91 (43.3%)	119 (56.7%)	210 (100%)	
Yes	25 (50.0%)	25 (50.0%)	50 (100%)	
Total	116 (44.6%)	144 (55.4%)	260 (100%)	

HSG: Hysterosalpingography, (p=0.394; OR=0.765; 95% CI: 0.412-1.42)

Table 3. Abnormal HSG Findings- primary/secondary infertility relationship

Abnormal HSG Findings	Feature of infertility		Total	p-value p =0.437
	Secondary	Primary		
No	67 (42.7%)	90 (57.3%)	157 (100%)	
Yes	49 (47.6%)	54 (52.4%)	103 (100%)	
Total	116 (44.6%)	144 (55.4%)	260 (100%)	

HSG: Hysterosalpingography, (p=0.437; OR=0.820; 95% CI: 0.498-1.35)

Table 4. Abnormal HSG Findings- spontaneous pregnancy relationship

Abnormal HSG Findings	Spontaneous pregnancy		Total	p-value p =0.701
	No	Yes		
No	128 (81.5%)	29 (18.5%)	157 (100%)	
Yes	82 (79.6%)	21 (20.4%)	103 (100%)	
Total	210 (80.8%)	50 (19.2%)	260 (100%)	

HSG: Hysterosalpingography, (p=0.701; OR=1.13; 95% CI: 0.604-2.11)

DISCUSSION

Infertility rates vary by region across the world,[14] but recent years have witnessed a decrease in primary and secondary infertility rates in developed countries. Secondary infertility is considered the most prevalent form of female infertility worldwide.[15] Contrary to epidemiological research, the distribution of primary and secondary infertile patients in this study was found to be 52.4% and 47.6%, respectively.

HSG is a minimally invasive imaging frequently adopted in evaluating uterine cavity shape and size, uterine anomalies, and tubal pathologies in infertile women.[16] When compared to a similar study, although tubal pathologies were among the most common anomalies in HSG with 72%,[17] we discovered them to be higher in our primary infertile patients. Another study, including 120 infertile patients, concluded that the most common anomalies in HSG were related to tubal pathologies and that the patients had primary infertility the most.[18]

We discovered spontaneous pregnancy in 20.3% of patients with abnormal HSG findings, and among them, 62% were determined to be secondary infertile. In a meta-analysis comparing normal and abnormal findings in HSG and pregnancy rates, it was uttered that abnormal findings in HSG, except for bilateral tubal obstruction, were insufficient to determine the pregnancy prognosis.[19] Another study comparing laparoscopy and HSG in the diagnosis of tubal factors emphasized that HSG remains limited but diagnostic laparoscopy appears to be the gold standard diagnostic method in determining tubal occlusions and that false positive findings in HSG should not be ignored.[20]

Relying on the hypothesis that HSG has therapeutic effects as well as being a diagnostic tool, a Netherlands-based comprehensive prospective cohort study[13] calculated the probability of spontaneous pregnancy in the six-month period following HSG to be 15% and 21% for patients having HSG with the complaint of infertility with those not having HSG, respectively, promoting the hypothesis that HSG has possible therapeutic effects. However, more randomized controlled studies are needed on the subject since the patients were not randomized in the mentioned study. When it comes to our findings, we determined that abnormal findings in HSG did not change the rates of spontaneous pregnancy. The variability of the false positivity and negativity rates of HSG in diagnosing tubal pathologies, congenital anomalies, intra-abdominal adhesions, and uterine pathologies or the possible therapeutic effects of HSG may be associated with spontaneous pregnancies following HSG in patients with anomalies.

A study, investigating the pregnancy rates following HSG among 100 primary and secondary patients, found spontaneous pregnancy to be significantly associated with primary and secondary infertility,[21] which is not promoted by our findings.

The present study is not free of a few limitations. For example, the sample size was relatively small. Moreover, we took for granted the adequacy of HSG while evaluating abnormal HSG results. However, we did not utilize diagnostic laparoscopy or MRI to confirm tubal and uterine anomalies.

CONCLUSION

While secondary infertility is considered the most common form of female infertility worldwide, primary infertile patients constituted the majority of our patient group. Overlapping with the literature, the most common abnormal HSG finding was found to be a tubal pathology. We also concluded that abnormal HSG findings did not contribute to the rates of spontaneous pregnancy. Abnormal HSG findings, except for bilateral tubal obstruction, are deemed insufficient to determine pregnancy prognosis due to the high false positivity and negativity rates in HSG.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İstanbul Medeniyet University Goztepe Training and Research Hospital Noninvasive Clinical Researches Ethics Committee (Date: 02/09/2020, Decision No: 2020-0572).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Evaluation of the effects of raloxifene treatment on uterus in asymptomatic postmenoposal patients by transvaginal Doppler ultrasonography

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ABSTRACT

Aims: To evaluate the effects of raloxifene treatment on uterus in asymptomatic postmenopausal patients by Doppler transvaginal ultrasonography (TvUS).

Methods: Randomized controlled prospective study, 57 healthy postmenopausal asymptomatic patients, aged 45-60, who applied Okmeydanı Training and Research Hospital Obstetrics and Gynecology Outpatient Clinic between 2003-2004. Four patients were excluded from the study because they did not apply the treatment regularly. All of the patients were in natural menopause. They had not received any hormone replacement therapy before. Their body mass index (BMI) was below 30 kg/m² and had no systemic diseases. The patients were divided into two groups as those who received raloxifene (n: 27) and those who did not (n: 26). Raloxifene was given 60 mg/day for 6 months. In all patients enrolled in the study, endometrial and uterine volume, pulsatility (PI) and resistance indices (RI) were evaluated by TvUS Doppler. Endometrial biopsies (EB) were obtained with pipelle at 0 and 6 months.

Results: There was no significant difference in terms of age, height, weight and BMI ($p<0.05$). Parity, menopause time and endometrial thickness were similar ($p<0.05$). EB results were similar ($p<0.05$). Uterine volumes at month 0 and 6 were similar ($p<0.05$). PI and RI were found to be similar in the right and left arteries at baseline ($p<0.05$). While PI and RI on the right side were similar at 6 months, left uterine artery PI was found to be significantly higher in the treated group. Left uterine artery RI was similar.

Conclusion: Raloxifene treatment neither did stimulate the endometrium, nor increased the uterine volume or uterine blood flow. It did not have any stimulating effect on the uterine tissue.

Keywords: Menopause, raloxifene, transvaginal Doppler ultrasonography, uterus

INTRODUCTION

The World Health Organization (WHO) defines menopause as a permanent termination of menstruation as a result of loss of ovarian activity.[1] The menopause period is one of the stages of a woman's life and prolongation of the average life expectancy has extended it.[2]

The average age of onset of menopause in industrialized countries is in the 50s, although it is several years earlier in developing countries.[4,5] The mean age of menopause is reported as 52 in Western countries, 51 in the United States, and 47 in our country.[6,7]

The estimated life expectancy for women in Turkey is 81.2 years according to the 2022 data from the Turkish Statistical Institute (TUIK). In light of the provided data, if it is assumed that women will live approximately 81 years, one-third of their life which is approximately 27 years, will be spent in the postmenopausal period and may encounter health problems associated with this period.[5,8] This clearly demonstrates the importance of further studies on symptoms related to this period. Due to the increased risk of age-related diseases and cancer for women in this period, it seems essential to raise awareness about healthy living and preventive health services benefits. Many organs and systems undergo changes in the postmenopausal period. Early postmenopausal changes include; vasomotor symptoms (hot flashes on the face, neck, and chest, sweating, palpitations, insomnia) but later more serious changes such as bone mass loss, osteoporosis, increased risk of fracture, cardiovascular system changes and urogenital system atrophies are observed.[9]

Due to diminished ovarian function in postmenopausal women, bone turnover accelerates, bone mass decreases hence the risk of fracture increases. Hormone replacement therapy (HRT) may cause some undesirable effects as well as various beneficial effects. It prevents hip and spine fractures but some authors suggest it may pose increase therisk of coronary heart disease, venous thromboembolism, stroke, and breast cancer.[10] Selective estrogen receptor modulators (SERMs) have been developed as an alternative to HRT to increase bone mass. These molecules exert selective estrogen agonistic or antagonistic effects on the tissue. While an agonistic effect is observed on the skeletal system, serum lipid metabolism, and coagulation factors, an antagonistic effect is observed in breast and uterus tissue.[11]

Raloxifene, a tamoxifen analogue, belonging to the benzothiophene group of the SERM family, has a pronounced tissue-specific effect. It has been shown to prevent bone loss and reduce serum cholesterol levels without stimulating the endometrium.[12,13] Raloxifene, a non-steroidal benzothiophene, has been shown to inhibit estrogen receptor-dependent dimethyl benzantracene-induced mammary tumor growth in rats and reduce the occurrence of nitrosomethylurea-induced mammary tumors.[14] In the skeletal system it inhibits the osteoclastic differentiation process by binding to the Receptor activator of nuclear factor kappa-B ligand (RANKL), and stimulates the production of osteoprotegerin, which helps osteoclastic apoptosis by osteoblasts, resulting in an antiresorptive effect.[15] In addition, raloxifene has been reported to reduce the risk of spinal fractures in postmenopausal women.[16]

In the uterus and breast, raloxifene binds to the estrogen receptor and acts as an estrogen antagonist by competing with estrogen. The complex formed after the binding of raloxifene to the estrogen receptor does not induce transcriptional activity in these tissues. Thus, raloxifene effectively inhibits the induction of classical estrogen-response-element (ERE) containing genes, such as the progesterone receptor in the uterus, by competition for the estrogen receptor.[11]

Transvaginal Doppler ultrasound (TvUS) has been used for so many years for endometrial thickness measurement to assess risk for malignancy in the postmenopausal period. Interpretation of the uterine artery resistance index (RI) measurement together with endometrial thickness using color Doppler TVUS in the assessment of malignancy helps in the differentiation of malignant histopathology, especially at the first examination.

This study aimed to evaluate the effects of raloxifene treatment on the uterus with Doppler TVUS in asymptomatic postmenopausal patients.

METHODS

This study is a product of the first author's specialization in gynecology and obstetrics thesis numbered 1175860 and titled "Evaluation of the effects of raloxifene treatment on the uterus in asymptomatic postmenopausal patients by transvaginal doppler ultrasonography."

Okmeydanı Training and Research Hospital granted ethical approval to this prospective randomized controlled study (Date: 2002/5 Decision No: 797388). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki

This study evaluated 57 healthy postmenopausal asymptomatic patients aged 45-60 years who applied to Okmeydanı Training and Research Hospital Gynecology and Obstetrics Outpatient Clinic between December 2003 and February 2004. 28 patients who did not want to receive treatment were included in the control group, 29 patients who agreed to receive treatment were included in the study group that received raloxifene 60 mg/day. Two patients in the control group started to receive hormone replacement therapy after their menopausal complaints predominated hence were excluded from the study. Two patients in the raloxifene group were excluded from the study because they delayed their follow-up. Finally, a total of 53 patients were included in the analysis, 26 patients in the control group and 27 patients in the raloxifene treatment group.

The inclusion criteria for the study sample were: 1) Being in natural menopause, 2) The last menstrual period is at least 1 year ago, 3) FSH > 30 IU/L and Estradiol <20pg/mL, 4) Absence of severe menopausal vasomotor complaints, 5) No HRT until at least 6 months before the start of the study, 6) Body mass index (BMI) below 30 kg/m², 7) No complaint of vaginal bleeding of unknown cause, 8) Absence of endometrial/adnexal pathology and fibroids larger than 3 cm, 9) Absence of systemic disease, 10) Absence of deep vein thrombosis and any other thromboembolic disease,11) Absence of alcohol and smoking. Healthy asymptomatic postmenopausal patients of whom met these criteria were enrolled in this prospective controlled study with a 6-month follow-up period.

All patients' information were recorded and physical examinations were performed before inclusion in the study. Patients whose bone densitometry values showed osteoporosis were included in the raloxifene study group. Those found with abnormalities in other examinations were excluded from the study.

Endometrial and uterine volume were evaluated using Doppler TVUS and endometrial biopsies were performed at 0 and 6 months on all patients included in the study. PI and RI indices were measured with Doppler TvUS.

Evaluation of currents in Doppler was made with qualitative, quantitative, and semi-quantitative measurements. Qualitative measurements were evaluated by the presence of a current, the direction of the flow and the characteristics of the current. Quantitative measurements included flow rate and volume. The flow volume (cm^3/sn) was formulated by multiplying the mean velocity (cm/sn) and the cross-sectional area of the vessel (cm^2). Semi-quantitative measurements included peak systolic/diastolic ratio (SD), pulsatility index, also defined as impedance index, and RI.[17-19]

$$\text{Pulsatility Index (PI)} = \frac{\text{Peak systolic velocity} - \text{End diastolic velocity}}{\text{Average velocity}}$$

$$\text{Resistance Index (RI)} = \frac{\text{Peak systolic velocity} - \text{End diastolic velocity}}{\text{Peak systolic velocity}}$$

Endometrial biopsies were obtained with a Pipelle following ultrasonographical evaluation. All biopsy specimens were evaluated by the same specialist pathologist. Samples were classified according to Blaustein's morphological criteria. They were histologically divided into four categories: normal benign postmenopausal endometrium, benign stimulator postmenopausal endometrium, benign abnormal postmenopausal endometrium, and premalignant-malignant endometrial changes.

Endometrial double-layer thickness, uterus size, volume, and Doppler measurements were made by a specialist radiologist using a 2003 model ACUSON 128 XP 30 ART Color Doppler US system and a 5MHz endovaginal probe. Considering that prolonged manipulation of the uterus may activate the pelvic circulation and affect the results of the Doppler evaluation, Doppler analysis was performed first during the Doppler TvUS. The ascending branches of the uterine artery were detected at the level of the right and left uterine isthmus using equal pressure at an angle of approximately 0 degrees using a sample volume of 2 mm by means of color flow Doppler. Next, PI and RI were measured.

In the second part of the TvUS examination, uterine dimensions, endometrial thickness and echogenicity and adnexa were evaluated. All findings were recorded. Uterine volume was measured in the longitudinal (DI), anteroposterior (D2), and transverse (D3) planes of the uterus dimensions and was calculated by applying the DI *D2*D3*0.52 formula.

Statistical Analysis

SPSS for windows 10.0 statistical package program was used to evaluate the data. Student's T test, Mann Whitney U test, Chi-Square test and Paired T tests were used for comparisons. $p<0.05$ was considered significant.

RESULTS

The mean age at control group was 50.6±3,04 years and treatment group was 50±3,06 years. There was no statistically significant difference in terms of mean age ($p>0.05$). There was no statistically significant difference between the groups in terms of average height and weight ($p>0.05$).

There was no statistically significant difference between the groups in terms of mean body mass index (BMI), parity number, menopause time and endometrial thickness ($p>0.05$).

Endometrial biopsy results are presented in **Table 1**. There was no statistically significant difference in endometrial biopsy results between the groups ($p>0.05$).

Table 1. Endometrial biopsy results

Endometrial biopsy	Control group		Treatment group		Chi-quare	p value
	n	%	n	%		
Atrophic	9	34.6	9	33.3	4,19	0,24
Inactive	9	34.6	4	14.8		
Superficial epithelium	2	7.7	6	22.2		
Weak Proliferative	6	23.1	8	29.6		

In **Table 2**, comparisons of uterus volumes between the groups at 0 and 6 months are presented. There was no statistically significant difference between the groups in the mean of baseline and 6th month uterus volume ($p>0.05$).

Table 2. Comparisons of uterus volumes between groups at 0 and 6 months

Uterus volume	Control group	Treatment group	P value
	Mean±SD	Mean±SD	
Baseline	48.96±10.44	52.07±17.64	0.44
6th months	48.46±10.18	50.67±16.89	0.56

In **Table 3**, right and left uterine artery PI and RI indices were compared in both groups. There was no statistically significant difference between the groups in terms of baseline right PI and right RI values ($p>0.05$). There was no statistically significant difference between the groups in terms of baseline left PI and left RI values ($p>0.05$).

Table 3. Initial right and left uterine artery PI and RI indices of both groups

Baseline	Control group	Treatment group	P
	Mean±SD	Mean±SD	
Right			
PI	2.17±0.34	2.33±0.69	0.28
RI	0.83±0.04	0.84±0.05	0.66
Left			
PI	2.28±0.38	2.57±0.74	0.08
RI	0.85±0.05	0.85±0.05	0.94

Right PI value is given in **Figure 1**, left PI value in **Figure 2**, right RI value in **Figure 3**, left RI value in **Figure 4**.

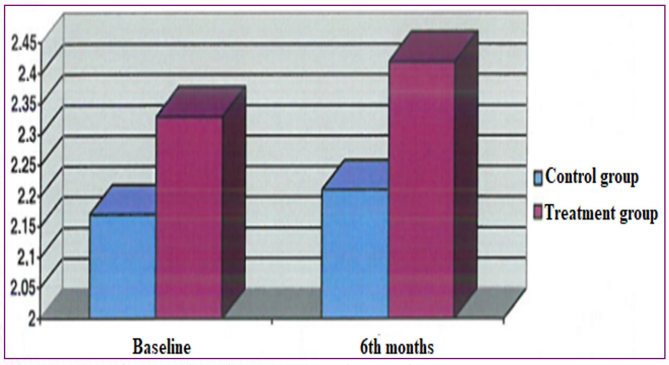

Figure 1. Right PI values by groups and periods

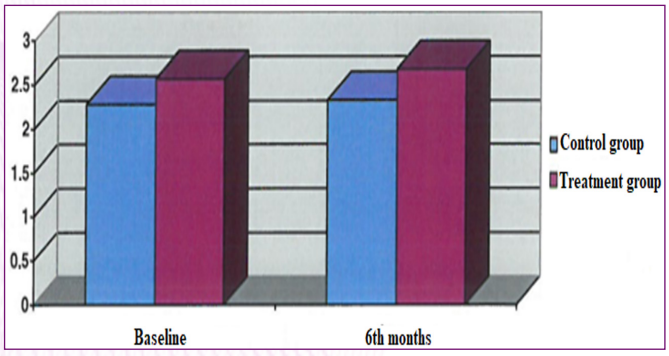

Figure 2. Left PI values by groups and periods

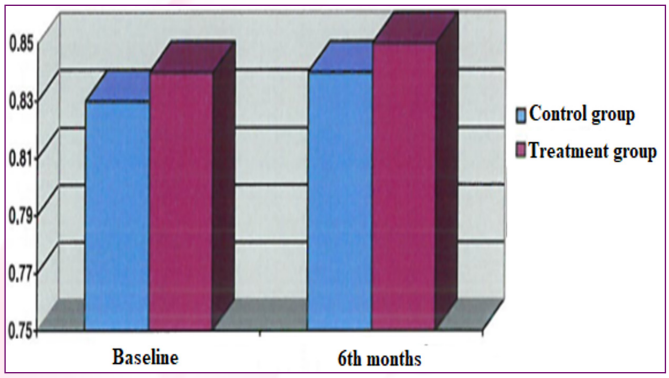

Figure 3. Right RI values by groups and periods

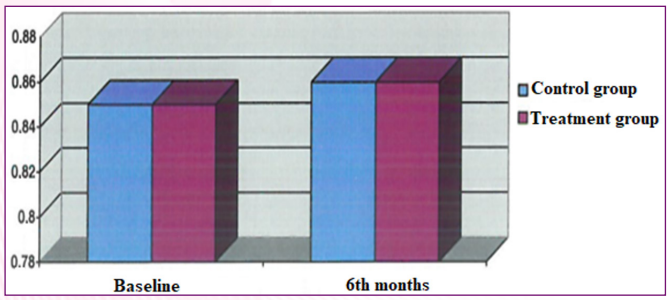

Figure 4. Left RI values by groups and periods

In **Table 4**, the PI and RI levels at 6 months of the right and left uterine arteries of both groups are presented. There was no statistically significant difference between the groups in terms of right PI and right RI values at 6 months (p>0.05). Left PI value at 6 months was significantly higher in the treatment group compared to the control group (p<0.05). There was no statistically significant difference between the groups in terms of RI values at 6 months (p>0.05).

Table 4. Right and left uterine artery PI and RI indices at 6th months of both groups.

6th months	Control group	Treatment group	p
	Mean±SD	Mean ±SD	
Right			
PI	2.21±0.33	2.42±0.65	0.15
RI	0.84±0.04	0.85±0.04	0.41
Left			
PI	2.33±0.38	2.68±0.69	0.02
RI	0.86±0.05	0.86±0.04	0.61

Table 5 shows the comparison of the baseline and 6th month uterine volume and Doppler results of the control group. There was no significant change in uterine volume in the control group (p>0.05). At 6 months, the right PI and RI values were significantly higher than at baseline (p<0.05 and p<0.001). At 6 months, left PI and RI values were significantly higher than at baseline (p<0.05 and p<0.001).

Table 5. Comparison of the baseline and 6th month uterine volume and Doppler results of the control group

Control group	Baseline	6th months	p
	Mean±SD	Mean±SD	
Uterus volumes	48.96±10.44	48.46±10.1	0.178
Right PI	2.17±0.34	2.21±0.33	<0.001
Right RI	0.83±0.04	0.84±0.04	<0.033
Left PI	2.28±0.38	2.33±0.38	<0.001
Left RI	0.85±0.05	0.86±0.04	<0.033

Table 6. Comparison of the uterine volume and Doppler results of the treatment group at baseline and 6 months is presented. There was a significant decrease in uterine volume in the treatment group (p<0.001). At 6 months, the right PI and RI values were significantly higher than at baseline (p<0.05 and p<0.001). At 6 months, left PI and RI values were significantly higher than at baseline (p<0.05 and p<0.001).

Table 6. Comparison of the baseline and 6th month uterine volume and Doppler results of the treatment group

Treatment group	Baseline	6 months	p
	Mean±SD	Mean±SD	
Uterus volumes	52.07±17.64	50.67±16.89	0,000
Right PI	2.33±0.69	2.42±0.65	<0.008
Right RI	0.84±0.05	0.85±0.04	0.028
Left PI	2.57±0.74	2.68±0.69	0.000
Left RI	0.85±0.05	0.86±0.04	0.012

DISCUSSION

In this 6-month prospective randomized controlled study, the effects of raloxifene on the uterus were evaluated by endometrial pipelle biopsy, TvUS, and Doppler TvUS. The results obtained after 6 months of treatment were not different from the control group. These results supported other studies claiming that raloxifene had no stimulatory effect on the uterus.[20]

Numerous studies have shown that raloxifene, a SERM, has no stimulatory effect on the breast. In our study, after 6 months of treatment, the uterine volume of the patients decreased, and PI and RI evels increased. At the end of 6 months, the right PI levels between the treatment group and the control group were clinically insignificant. As a result, Doppler indices in both groups showed changes suggesting atrophy.

In order to demonstrate the estrogen antagonistic effects of raloxifene in the uterus, healthy asymptomatic women who were by endometrial biopsy histologically diagnosed with benign postmenopausal endometrium at baseline, participated in the study. Thus, the stimulating effect of raloxifene on the endometrium could be easily detected.

Numerous studies have been conducted to determine the normal TvUS pattern of the endometrium in postmenopausal women. Although it is recommended to accept the cut-off value of the endometrium as 8 mm or above in postmenopausal asymptomatic women , it has been reported that the risk of endometrial disease is minimal when the endometrial thickness is less than 4 mm.[21,22]

In our study, the results of endometrial assessment with transvaginal ultrasonography after 6 months of raloxifene treatment did not differ from those before treatment. The Multiple Outcomes of Raloxifene Evaluation (MORE) study, which was a randomized double-blind placebo-controlled study, conducted at 180 centers in 25 countries between November 1994 and September 1999 supported the hypothesis that raloxifene did not increase the risk of endometrial hyperplasia or cancer.[23]

Post-treatment uterine volume did not differ significantly from baseline levels. These results were consistent with the results from previous studies by Azevedo et al.[24] and

Goldstein et al.[25] Goldstein et al., reported that the use of raloxifene did not affect the uterine volume, but there was a 22% increase in uterine volume in the estrogen-treated group.[25] Another study showed that when tamoxifen, a SERM drug with an estrogen agonistic effect on the uterus unlike raloxifene, was used, endometrial thickness and uterine volume increased.[26]

The cardiovascular effects of raloxifene are reported to be similar to those of estrogen.[27] The results of the MORE study showed that raloxifene did not have a cardiovascular risk, but significantly reduced the risk in the group at high risk of cardiovascular disease.[28] Another aim of our study was to show that besides its known cardioprotective effects, raloxifene does not increase blood flow in the uterine arteries and does not change Doppler indices, as it is a tissue-selective drug.

The onset of hypoestrogenism with menopause reduces the amount of blood going to the pelvic organs. This causes atrophy of the vaginal mucosa and lower urinary tract and a decrease in the volumes of the uterus and ovaries. High RI and PI levels detected in uterine artery Doppler analyses performed at this stage of women's life indicate high vascular resistance.[29] Although there is muchliterature on the vascular effects of estrogen, there is limited information on the vascular effects of raloxifene specifically, which is a second-generation SERM. Most information on SERMs is about the effects of tamoxifen on uterine perfusion.[30]

There are limited studies in which uterine perfusion was evaluated by Doppler ultrasonography during raloxifene treatment. A study by Post et al.[31] reported that postmenopausal women using 60 mg/d raloxifene did not show a significant difference in post-treatment PI values compared to the placebo group. In our study, there was no significant difference in Doppler indices after treatment compared to pretreatment. However, in the study by Post et al.[31], it was observed that PI values decreased significantly when 150 mg/d raloxifene was used. In the study conducted by Fugere et al.[32], it was shown that the use of raloxifene at a dose of 150 mg/d for at least 1 year did not affect uterine volume, endometrial thickness, and endometrial biopsy results. The conclusion reached in the study by Post et al.[31] was that high-dose raloxifene treatment reduces impedance in the uterine arteries and may therefore provide a cardioprotective effect at this dose. However, it is highly controversial whether uterine arteries can be a suitable model for investigating cardioprotectivity or not.

In our study, it was concluded that the 6-month raloxifene treatment administered at a dose of 60 mg/d did not stimulate the endometrium and did not increase the uterine volume and uterine blood flow. Our results supported the hypothesis that raloxifene has no estrogen agonistic effect on uterine endometrial tissue.

CONCLUSION

In the postmenopausal period, the most important factor responsible for the decrease in compliance with HRT, which is widely used all over the world to reduce the systemic effects of aging, is the patient's fear of cancer. The effects of estrogen-progesterone-containing combined preparations on the breast and cardiovascular system are controversial. There are studies suggesting that the progesterone component overshadows the beneficial effects of estrogen in these systems. For these reasons, new therapies alternative to HRT, are being trialed. In light of this information, Raloxifene, although not capable of soothing the vasomotor symptoms, can still replace HRT for its reknown benefits on bone mineral density, in a selected group of patiens when conventional HRT is contrindicated.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Okmeydanı Training and Research Education and Research Hospital granted ethical approval to this prospective cross-sectional study (Date: 2002/5, Decision No: 797388).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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The role of umbilical artery Doppler analysis in estimating perinatal morbidity and mortality in hypertensive pregnancy

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ABSTRACT

Aims: Uteroplacental (uterine artery systolic/diastolic (S/D) ratio) and fetal circulation changes (umbilical artery pulsatility Index (PI) value) can be evaluated non-invasively by using Doppler ultrasonography spectral analysis. The present study aimed to demonstrate how Doppler ultrasonography should be combined with classical well-being tests to detect perinatal morbidity and mortality in hypertensive pregnancy.

Methods: This prospective research was carried out with 88 pregnant women diagnosed with high-risk pregnancy and hypertension between April 1992 and May 1994. A non-stress test (NST) was performed in all cases, and fetal distress was evaluated by a biophysical profile (BP) and/or a contraction stress test (CST) subsequent to a non-reactive NST. Following the diagnosis of hypertension, longitudinal maternal (uterine artery) and fetal (umbilical artery) Doppler analyses were initiated at 7–10-day intervals. In the study, the Acuson 128 XP 10 device (Research project No. 515/080555592 was funded by the İstanbul University Research Fund) and a 3.5-5 MHz curvilinear probe were used. No Doppler pathology was considered solely in the timing of delivery.

Results: There was no case of perinatal loss, antepartum and intrapartum fetal distress, neonatal asphyxia, and oligohydramnios in the group with normal uterine and umbilical artery Doppler analyses. There was one case with umbilical artery Doppler flow pathology only, which was delivered by preterm cesarean section with the diagnosis of antepartum fetal distress. Fetus diagnosed to have a fetal growth restriction (FGR) and the findings of fetal distress, FGR, and cesarean delivery were concordant with the literature. There was also increased perinatal mortality (9.1%) among patients with pathological uterine artery Doppler and normal umbilical artery Doppler group, but there was no case of oligohydramnios in this group and the rate of neonatal asphyxia (5.min Apgar score <7) was 21.7%. The antepartum loss was 27%, the neonatal loss was 23.8%, and perinatal mortality was 44.8% in the group with pathological uterine and umbilical artery Doppler findings, and this group had all cases of oligohydramnios.

Conclusion: Overall, it seems reasonable to identify any pathologies with Doppler ultrasonography in hypertensive pregnant women in the early pregnancy and to follow them up with classical fetal antepartum surveillance tests at appropriate intervals related to their umbilical artery Doppler pathologies.

Keywords: Doppler ultrasonography, pregnancy, hypertension

INTRODUCTION

Hypertensive disorders, bleeding, and infections are considered significant causes of maternal death and, for example, accounted for 12% of maternal deaths between 1980 and 1985 in the USA.[1] Hypertension may be the most prevalent medical complication in pregnancy and is encountered in roughly 5-10% of pregnancies. Maternal or perinatal mortality related to hypertension in pregnancy is mostly preventable. Despite the early onset of the physiopathological findings of the disorder, clinical findings may appear after the 20th week of gestation.

In hypertensive pregnancy, fetal well-being is classically evaluated with fetal kick count, non-stress (NST) and contraction stress (CST) tests, amniotic fluid assessment, ultrasonographic fetal biometry, and biophysical profile (BP). These methods usually warns us for the fetuses with hypoxia and/or acidosis. Doppler ultrasonography velocimetry is a non-invasive method to measure the changes in the maternal and fetal circulation. A qualitative method, waveform (velocity) analysis, is utilized while evaluating blood flow with Doppler ultrasonography.[2] Qualitative Doppler analyses are performed

based on systolic and diastolic flow velocities. Among these, the systolic/diastolic (S/D) ratio, pulsatility index (PI), and resistance index (RI) are adopted for Doppler flow analysis.[3-5]

Uterine arteries have a flow with a low diastolic component before pregnancy and they have a diastolic notch. The S/D ratio is lower than 2.6, and the notch should disappear after the 26th week of gestation. The opposite case may indicate that the mother and fetus are prone to undesirable outcomes.[6,7]

Umbilical circulation is completed at the 12th week of gestation.[6] Abdominal Doppler flow velocity assessments can be initiated in the 15th week since diastolic flow appears following this week. Depending on the formation of new vessels and the development of the autonomic system of the fetus, the deviations in the S/D ratio are higher until the 28-30th week of gestation. Changes in blood pressure occur as the fetus grows, and it is recommended to utilize a value of 3.0 as the cut-off S/D ratio limit for the umbilical artery following the 30th week.[6-8] In the literature, it was previously asserted that the outcomes of hypertensive pregnancies classified by Doppler findings would be better and that perinatal outcomes would mostly be related to umbilical artery Doppler findings.[9-12]

METHODS

This study was produced from the first author's specialization thesis in gynecology and obstetrics numbered 32785 and titled "The role of fetomaternal Doppler analysis in estimating perinatal morbidity and mortality in hypertensive pregnancy"

İstanbul University, İstanbul Faculty of Medicine Department of Obstetrics and Gynecology Academic Board granted ethical approval to this prospective cross-sectional study (Date: 01.04.1992, Thesis no: 32785). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki

We carried out this prospective study with 88 patients selected among hypertensive pregnancy cases followed up in the High-Risk Pregnancy Clinic or hospitalized in the wards between April 1992 and May 1994 in the İstanbul Faculty of Medicine, Department of Obstetrics and Gynecology, Division of Perinatology.

Patients with a systemic blood pressure of 140/90 mmHg and above after 20 weeks of gestation were described as cases with hypertensive pregnancy. Besides, the cases were evaluated as preeclampsia in the presence of (+) positive proteinuria qualitatively and 0.3 g/l or more proteinuria quantitatively in the 24-hour urine sample.

Immediately after the diagnosis, longitudinal maternal and fetal Doppler analyses were initiated at 7-10-day intervals. Doppler findings were presented for clinical use, but the Doppler pathologies was not considered solely in the timing of delivery. In the study, the Acuson 128 XP 10 device (Research project No. 515/080555592 was funded by the İstanbul University Research Fund) and a 3.5-5 MHz curvilinear probe were used. We then evaluated presence of diastolic notch in uterine arteries and uterine artery S/D ratios. The findings were considered pathological in cases with a mean S/D ratio of 2.6 and above in the uterine arteries and/or the presence of a diastolic notch.

Umbilical artery Doppler findings were evaluated using mean±2SD values by gestational week offered by Nicholaides et al. (1994, FMF, unpublished data); the presence of absent end-diastolic and reversed flows were visually evaluated. The Doppler filter was kept to a minimum in the absence of end-diastolic flow.

With the help of uterine artery and umbilical artery Doppler findings, we sought perinatal mortality and timing, antepartum and intrapartum fetal distress and neonatal asphyxia rate, oligohydramnios, neonatal growth restriction (NGR), preterm birth, NST non-reactivity (in the whole group and above 30 weeks), low BP score (< 8), CST positivity, cesarean delivery rate and cesarean section for fetal distress rate, newborn intensive care rate and duration, delivery gestational week and weight, maternal mean arterial blood pressure, and presence of preeclampsia.

Statistical Analysis

We performed an independent samples t-test and Fisher's exact test to compare the Doppler findings and the mentioned parameters between the groups.

RESULTS

As shown in **Table 1**, we sought the relationship between the mentioned parameters and PI values in umbilical artery Doppler findings - categorized as normal (< +2 SD) and pathological (> +2 SD) - and compared them with the results of the antepartum fetal assessment tests.

Table 1: Comparison of Maternal and Fetal Outcomes Between the Groups with Normal and Pathological Umbilical Artery PI Values

	Normal Umbilical Artery PI Value		Pathological Umbilical Artery PI Value		
	(n=51)	(%)	(n=37)	(%)	
Antepartum fetal loss	1/51	1.9%	8/37	21.6%	*
Neonatal loss	2/50	4%	7/29	24.1%	*
Perinatal mortality	3/51	5.8%	15/37	40.5%	**
Intrapartum and antepartum fetal distress	12/51	23.5%	28/37	75.7%	**
Neonatal asphyxia	5/50	10%	4/29	13.8%	ǿ
Oligohydramnios	0/51	-	9/37	24.3%	**
Neonatal Growth Retardation	10/50	20%	8/29	62.1%	**
Preeclampsia	36/51	70.6%	33/37	89.2%	*
Preterm birth	28/50	56%	26/29	89.6%	*
NST non-reactivity rate	12/51	23.5%	31/37	83.8%	**
NST non-reactivity rate at > 30th week	8/46	17.4%	20/25	80%	**
BP score < 8	4/15	26.7%	11/19	57.9%	ǿ
CST positivity rate	3/7	42.8%	8/11	72.7%	ǿ
Cesarean section (live births}	27/50	54%	25/29	86.2%	*
Cesarean section for fetal distress	8/50	16%	17/29	89.5%	**
Newborn intensive care rate	28/50	56%	27/29	93.1%	**
Newborn care duration (mean)	14.8±16.7 days		19.7±17.6 days		ǿ
Gestational week at delivery (mean)	35.9±3.5 weeks		32.6±3.2 weeks		**
Birth weight (mean)	2346.3±826.7 gr		1418.6±637.7 gr		**
Mean arterial blood pressure (mean)	121.1±13.7 mmHg		118.7±14.4 mmHg		ǿ

* p < 0.05, ** p < 0.001, ǿ: insignificant

The findings revealed significantly increased antepartum fetal loss, neonatal loss, perinatal mortality, and antepartum and intrapartum fetal distress in the cases with pathological umbilical artery Doppler results. Despite no patient with oligohydramnios in the group with normal umbilical artery Doppler indices, it was found to be significantly increased in the other group. There were significantly more subjects with neonatal GR, preeclampsia, and preterm delivery in the group with pathological umbilical artery Doppler findings. Moreover, NST non-reactivity in all gestational weeks and above 30 weeks, low BP score (< 8), CST positivity, cesarean section rate, and cesarean section for fetal distress were found to be significantly increased in the group with pathological umbilical artery Doppler pathological indices. Regarding neonatal care rate and duration, the increase in only the cases requiring neonatal care was significant in the group with pathological umbilical artery Doppler findings. The mean gestational week and birth weight were found to be 35.9±3.5 weeks and 2346.3±826.7 g, respectively, among the cases with normal umbilical artery Doppler findings. These values were discovered to be 32.6±3.2 weeks and 1418.6±637.7 g, respectively, in the cases with pathological umbilical artery Doppler indices. The differences between the groups by these parameters were significant.

After examining the cases in two groups (normal and pathological) by their umbilical artery Doppler PI values (>+2 SD and <+2 SD), those with pathological findings were further divided as absent end-diastolic flow and reverse end-diastolic flow in the umbilical artery, described as severe Doppler pathologies in the literature. Accordingly, among 37 patients with pathological umbilical artery Doppler findings (PI value > +2 SD), we separately evaluated 20 patients with a reduction in end-diastolic flow, 12 cases with absent end-diastolic flow, and 5 cases with a reverse end-diastolic flow.

The antepartum fetal loss was significantly higher in the cases with a reverse end-diastolic flow, while the neonatal loss rate was statistically significant among the patients with pathological PI with diminished end-diastolic flow group. The perinatal mortality was found to be 5.8% in umbilical PI normal hypertensive cases, 40% in those with diminished end-diastolic flow, 25% in the cases with an absent end-diastolic flow, and 80% in those with a reverse end-diastolic flow. Antepartum and intrapartum fetal distress was significantly increased in all subgroups of the pathological cases. In addition, oligohydramnios was significantly higher in the cases with absent end-diastolic flow and reverse end-diastolic flow groups.

The severity of the Doppler pathology significantly affected the number of patients with neonatal GR. The difference between pathological cases with an end-diastolic flow and those with a normal umbilical flow was significant for preeclampsia ($p < 0.05$). Besides, NST non-reactivity rate was discovered to be significantly increased in all cases with pathological umbilical artery Doppler findings. However, we could not conclude significant differences between the groups by low BP score and CST positivity.

The cases with normal and pathological Doppler findings significantly differed by cesarean section rate and cesarean section for fetal distress. For example, the mean rates of cesarean section and cesarean section for fetal distress were found to be 90% and 70% in the cases with an absent end-diastolic flow loss, respectively. These values became 100% and 50% in the cases with a reverse end-diastolic flow.

We found that the rate of newborns requiring neonatal intensive care and the mean duration of care increased by the severity of Doppler pathology. Besides, the mean gestational week at delivery and birth weight significantly decreased by Doppler pathology. However, we could not find a relationship between the mean arterial blood pressure and the degree of umbilical artery Doppler pathology.

Table 2: Perinatal Outcomes of the Cases with Normal Umbilical Artery Doppler PI Values and the Patients with pathological PI with a diastolic flow, absent end-diastolic Flow, and Reverse End-diastolic Flow.

	Normal Umbilical Artery PI		Pathologic Umbilical artery PI with a diastolic flow			Absent End-diastolic flow			Reverse end-diastolic flow		
	(n = 51)	(%)	(n = 20)	(%)		(n = 12)	(%)		(n = 5)	(%)	
Antepartum fetal loss	1/51	1.9%	3/20	15%	ǿ	2/12	16.6%	ǿ	3/5	60%	*
Neonatal loss	2/50	4%	5/17	29.4%	*	1/10	10%	ǿ	1/2	50%	ǿ
Perinatal mortality	3/51	5.8%	8/20	40%	*	3/12	25%	ǿ	4/5	80%	**
Intrapartum and antepartum fetal distress	12/51	23.5%	14/20	70%	**	10/12	83.3%	**	4/5	80%	*
Neonatal asphyxia	5/50	10%	4/17	20.5%	ǿ	0/10	-	ǿ	0/2	-	ǿ
Oligohydramnios	0/51	-	1/20	5%	ǿ	4/12	33.3%	**	3/5	60%	**
Neonatal Growth Retardation	10/50	20%	8/17	47.05%	*	6/10	60%	*	2/2	100%	*
Preeclampsia	36/51	70.5%	19/20	95%	*	10/12	83.3%	ǿ	4/5	80%	ǿ
Preterm birth	28/50	56%	14/17	82.3%	*	10/10	100%	*	5/5	100%	ǿ
NST non-reactivity rate	12/51	23.5%	15/20	75%	**	12/12	100%	**	4/5	80%	*
NST non-reactivity rate at > 30th week	8/46	17.3%	9/13	69.6%	**	9/9	100%	**	2/3	66.6%	ǿ
BP score < 8	4/15	26.6%	7/11	63.6%	ǿ	3/5	60%	ǿ	1/3	33.3%	ǿ
CST positivity rate	3/7	42.8%	4/6	66.6%	ǿ	3/4	75%	ǿ	1/1	100%	ǿ
Cesarean section (live births}	27/50	54%	14/17	82.3%	*	9/10	90%	*	2/2	100%	ǿ
Cesarean section for fetal distress	8/50	16%	9/17	52.9%	*	7/10	70%	*	1/2	50%	ǿ
Newborn care rate	28/50	56%	15/17	88.2%	*	10/10	100%	*	2/2	100%	ǿ
Newborn care duration (mean)	14.8±16.7 days		15.3±12.9 days		ǿ	24.7±19.7 days		ǿ	28.5±38.9 days		ǿ
Gestational week at delivery (mean)	35.9±3.5 weeks		32.9±3.7 weeks		*	32.6±3.7 weeks		*	31.2±1.4 weeks		*
Birth weight (mean)	2346.3±826.7 gr		1588±781.9 gr		**	1325 ±314.1 gr		**	966 ±244.5 gr		**
Mean arterial blood pressure (mean)	121.1±13.7 mmHg		121.4± 16.1 mmHg		ǿ	117.5±12.9 mmHg		ǿ	111±7.7mmHg		ǿ

* $p < 0.05$, ** $p < 0.001$, ǿ: insignificant

DISCUSSION

We observed that all of the perinatal mortality (25.8%) in hypertensive pregnancies were the cases with pathological uterine artery Doppler findings. While the mean birth weight and gestational week were significantly decreased, the prevalence of antepartum and intrapartum fetal distress was significantly increased in these cases. Accordingly, the rates of cesarean section for fetal distress, preterm delivery, and neonatal asphyxia were significantly increased. Moreover, we concluded significant increases in preeclampsia, NGR, and neonatal care among the cases with pathological uterine artery Doppler findings. Our findings overlap with those of Campbell[13] and Fleischer.[14]

While some authors utilized the S/D ratio, some others preferred the umbilical artery PI value in the evaluation of umbilical artery Doppler indices. We found that antepartum and neonatal mortality significantly increased in the cases with umbilical artery PI value > +2 SD by gestational week. Moreover, perinatal mortality was 40.5%, and the difference was significant. Berkowitz et al.[15] reported that poor perinatal outcomes become more prevalent with abnormal Umbilical artery Doppler findings. Similarly, it was previously reported that in the group of growth retarded fetuses Doppler velocimetry help us to early and accurately diagnose the ones who would develop antepartum fetal distress.[16] In different studies, it was documented that almost all FGR-leading mortality and almost all cases requiring neonatal care were in fetuses with abnormal Doppler findings.[17,18] These findings seem to support our results.

All of the oligohydramnios cases were in the group with pathological umbilical artery Doppler findings. A study on oligohydramnios cases due to uteroplacental perfusion disorder demonstrated an increase in renal artery Doppler indices and, therefore, decreased flow in fetuses with oligohydramnios, which was then attributed to reduced umbilical artery flow in fetuses with growth restriction.[19] In our study, the prevalence of oligohydramnios significantly increased as the umbilical artery flow decreased. Similarly, Reed et al.[20] reported the prevalence of oligohydramnios as 57% in cases with no or reversed end-diastolic flow.

The idea of fetal preeclampsia can be supported by the relationship between Trisomy and preeclampsia.[21] Despite pregnancy-induced hypertension and normal uterine artery Doppler findings in the mother, the fetus may have abnormal umbilical artery Doppler findings.[22] In our study, postpartum Trisomy[21] was diagnosed in one case among 17 patients with an end-diastolic flow loss or reversed end-diastolic flow (5.8%). The presence of an absent end-diastolic flow or a reverse flow and the prevalence of Trisomy (13, 18, or 21) were previously reported to be between 12.6% - 17%.[11,12,18,20,23] Suspicion of abnormal karyotype increases in the third trimester, particularly in the absence of a maternal hypertension clinic or in the presence of unexplained FGR.[17] In cases without an absent umbilical artery diastolic flow or with a reverse flow, emergency delivery should never be indicated, but instead, daily fetal cardiotocographic monitoring is recommended upon such a Doppler finding.[24]

CONCLUSION

No clinical data, including maternal blood pressure, can be helpful enough to assess the severity of the condition in hypertensive pregnancy cases. The desire to regulate the course of treatment and identify a protocol for fetal evaluation often brings problems such as redundant fetal evaluation tests and hospitalization. In modern obstetrics, identifying maternal and fetal hemodynamic changes in hypertensive pregnancy cases is ensured with the use of Doppler ultrasonography. Its routine clinical deployment also provides information about the existing pathology and the etiology of hypertension in pregnancy.

Doppler ultrasonography is a convenient-to-use, non-invasive, and fast method for selecting cases with hypertensive pregnancy into specific risk groups and determining the prevalence of fetal evaluation tests. Since the morbidity of cases with normal uterine and umbilical artery Doppler findings similiar with the general population, it is deemed appropriate to perform maternal and fetal evaluations at weekly intervals. On the other hand, abnormal umbilical artery Doppler findings allow for predicting placental blood flow and resistance in the placental vascular bed. A reduced, absent, or reversed end-diastolic flow enables the obstetrician to perform more frequent, even daily fetal follow-ups and wait for the appropriate fetal maturity, which would mitigate prematurity-related perinatal complications. In a nutshell, umbilical artery Doppler is a valuable method in the management of high-risk pregnancies and may contribute to fetal outcomes by helping decide on the time of delivery.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İstanbul University İstanbul Faculty of Medicine Department of Obstetrics and Gynecology Academic Board (Date: 01.04.1992, Thesis no: 32785).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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The effect of thyroid autoimmunity on early pregnancy serum β-hCG levels in spontaneous pregnancy

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ABSTRACT

Aims: To examine the association between thyroid autoimmunity (TAI) and early pregnancy serum beta human chorionic gonadotropin (β-hCG) levels in spontaneous pregnancy.

Methods: In this retrospective case-control study, women between the ages of 20 and 40 were included. The study subjects were 130 women euthyroid and healthy patients with spontaneous pregnancy. Subjects were divided into two groups: those with autoimmune thyroid disease (TAI group; n=60) and those without the disease (control group; n=70).

Results: The mean age and body mass index (BMI) of the subjects were 30.22±4.14 years and 24.51±2.04, respectively. The value of anti-thyroid peroxidase antibodies (TPO-Abs) and anti-thyroglobulin antibodies (TG-Abs) in the TAI group is three times twenty times more than the control, respectively. Results found no statistically significant association between TAI and control groups in regard to hemoglobin, alanine transaminase (ALT), aspartate transaminase (AST), thyroid-stimulating hormone (TSH), platelet (PLT), creatinine, free thyroxin (FT4), and blood urea nitrogen (BUN) ($p>0.05$). There was statistically significant difference between groups in terms of the serum β-hCG level ($p<0.05$).

Conclusion: In this study, the effects of TAI were significant on early-stage pregnancy serum β-hCG levels; therefore, thyroid levels should be considered, and proper treatment should be started early.

Keywords: Thyroid autoimmunity, β-hCG, pregnancy, miscarriage

INTRODUCTION

To establish and keep the pregnancy, the immune and endocrine systems should work harmoniously to preserve normal function while adjusting to new conditions.[1] Consequently, immune and endocrine disorders or combined forms could negatively affect the reproductive system.[2] Thyroid autoimmunity (TAI) is estimated to have a prevalence of 5% to 15% as the most prevalent autoimmune disorder among women of reproductive age.[3]

This is the first autoimmune disease discovered by a Japanese doctor, Hakaru Hashimoto, in 1912, and the condition was registered in his name.[4] This disease is characterized by anti-thyroglobulin antibodies (TG-Abs) and anti-thyroid peroxidase antibodies (TPO-Abs) with antibody-dependent cell-mediated cytotoxicity against human thyroid cells.[5,6] Increasing values of TG-Abs and TPO-Abs indicate Hashimoto's thyroiditis leading to hypothyroidism. The increasing stimulating TSHR-Abs cause hyperthyroidism as the hallmark of Graves' disease. Both conditions can be regarded as the opposite ends of TAI's endless diversity.[7] There is an increasing risk of developing subclinical and overt hypothyroidism among TAI women, which has been extensively known for its negative effect on fertility, spontaneous and in vitro fertilization (IVF) reached outcomes of pregnancy.[8-10]

However, increasing evidence shows that TAI may affect reproductive health independently of thyroid hormone levels.[11] According to the hypothesis, the thyroid autoantibodies may disturb the normal process of fertilization, implantation, folliculogenesis, and even embryo development after implantation through various immunological mechanisms, leading to adverse outcomes of a pregnancy conceived either via assisted reproductive technologies or spontaneously.[12,13]

One of the biomarkers of fetal viability is serial serum quantitative assessment of beta unit human chorionic

gonadotropin (β-hCG). To improve determination of embryonic viability, the combined ultrasonography and serial β-hCG measurements are used to ensure the appropriate performance of interventions, particularly in case of ectopic pregnancy.[14] About 20% of the cases causing miscarriage are associated with increasing serum β-hCG levels.[15]

The impact of Hashimoto's thyroiditis on β-hCG in spontaneous pregnancy is still not clear. This study aims to determine whether TAI affects the first β-hCG value in spontaneous pregnancies. Studies in the literature show that β-hCG values are affected by TAI in IVF pregnancies. 1,16 However, there is not enough research on the possible effects of TAI in spontaneous pregnancy.

METHODS

The Ethics Committee of Medipol University approved this retrospective case-control study. (Date: 26.10.2022, Decision No: 903). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

One hundred thirty women participated in this study between January 2018 and March 2022. Women between the ages of 20 and 40 were included in this study and 70 women have included control group, and 60 women with thyroid autoantibody positivity were included in the case group.

The exclusion criteria were as follows: 1) known chronic disease, 2) age>40, 3) body mass index (BMI)>30, 4) multiple pregnancies, 5) antibody positivity with thyroid stimulating hormone (TSH)> 2.5, 6) those who use drugs to lower TSH and 7) pregnancy with IVF.

The inclusion criteria were as follows: 1) 20-40 years old, 2)with a body mass index between 18 and 30, 3) women with spontaneous pregnancy, 4) TSH<2.5, 5) positive thyroid antibodies and 6) single pregnancies.

TPO-Abs,TG-Abs, free thyroxin(FT4), TSH were studied with ECLIA (electrochemiluminescence immunoassay) (Roche Diagnostics GmbH, D-68298 Mannheim). TSH was measured with an analytical sensitivity of 0.005 µIU/mL. The TG-Abs measurement range is 10–4000 IU/mL, and the TPO-Abs measurement range is 5–600 IU/mL. TG-Abs < 115 IU/mL, TPO-Abs < 35 IU/mL were accepted as negative. ELISA (BioVendor, Heidelberg, Germany) was used to measure serum TSH and T4 concentrations. the DIAPLUS kit (Toronto, Canada) protocol was followed to perform this hormone assay. The reference ranges of FT4 and TSH were 4.4-10.8 µg/dl and 0.39-5.95 µg/dl, respectively. a double - blind procedure was used to diminish the experimental bias.

Statistical Analysis

The Statistical Package for Social Sciences software (SPSS 22.0, Chicago, IL) was employed for statistical analyses. The Kolmogorov-Smirnov test was conducted to study the normality, and the parametric (Independent t-test) and the nonparametric (Mann-Whitney U test) tests were performed to study the difference between the two groups. Mean, median, minimum, maximum, and standard deviations (SD) were measured as descriptive statistics for each variable, including age, BMI, hemoglobin, platelet (PLT), alanine transaminase (ALT), aspartate transaminase (AST), blood urea nitrogen (BUN), creatinine, β-hCG, TG-Abs, TPO-Abs, FT4, and TSH. A value of $p<0.05$ was accepted as statistically significant. To calculate the sample size with the GPower 3.1 program, two independent means(two groups) was measured based on the Independent test, the power of 85%, effect size of 50%, and 0.05 type 1 error for at least 118 patients.[17]

RESULTS

This study included one hundred thirty age-matched (30.22±4.14) and BMI-matched (24.51±2.04) women. The majority of study participants smoke (54.6%). Nine (15%) women in the TAI group and 13 (17.1%) in the control group, a total of 22 women who participated in the study, had abortions. **Table 1** displays descriptive statistics of research parameters.

Table 1. Descriptive statistics of research parameters (n=130).

Research parameters	Median (range) mean ± SD
Maternal characteristics	
Age	31 (21-36) 30.22±4.14
BMI	25 (18.4-29.6) 24.51±2.04
Laboratory values	
Hemoglobin	12 (10.1-13) 11.64±0.66
PLT	253000 (140000-486000) 257553.85±72208.36
ALT	14 (8-51) 15.05±6.42
AST	15 (10-41) 16.52±5.75
BUN	16 (4.6-29) 17.37±4.88
Creatinine	0.71 (0.5-0.92) 0.71±0.11
β-hCG	119 (40-196) 114.66±42.41
TPO-Abs	27 (10-65) 34.01±19.15
Anti -TG	4 (1-90) 19±22.2
FT4	1 (0.31-1.62) 1.04±0.28
TSH	1.63 (0.63-2.46) 1.56±0.53

SD, Standard Deviation; BMI, body mass index; PLT, Platelet; ALT, alanine transaminase; AST, Aspartate transaminase; BUN, blood urea nitrogen; β-hCG, Beta human chorionic gonadotropin; TPO-Abs, Anti-thyroid peroxidase; TG-Abs, anti-thyroglobulin; FT4, Free thyroxin; TSH, thyroid-stimulating hormone.

Table 2 shows comparison of TAI group and control groups on the research parameters.

As stated in **Table 2**, a Mann-Whitney test did not find a statistically significant association between TAI and control groups in regard to Hemoglobin, ALT, AST, TSH, and BUN ($p>0.05$).

As stated in **Table 2**, an Independent test did not find a statistically significant association between TAI and control groups in regard to PLT, Creatinine and FT4 ($p>0.05$). The value of TPO-Abs in the TAI group is three times more than the control. The value of TG-Abs in the case group is twenty times more than the control.

The serum β-hCG level is the main parameters of this research. There was statistically significant difference between groups in terms of the serum β-hCG level ($p<0.05$). The serum β-hCG level of control group (125.31±39.6) was significantly higher than the TAI group (102.23±42.51).

Table 2. Comparison of TAI group and control groups

Study parameters	Thyroid autoantibody negative Control (n=70) Median (range) mean ± SD	Thyroid autoantibody positive Case (n=60) Median (range) mean ± SD	p-value
Hemoglobin	12 (10.1-13) 11.62±0.73	12 (10.4-13) 11.65±0.58	0.208*
PLT	249500 (153000-486000) 257985.71±67466.9	256000 (140000-455000) 257050±77951.62	0.942**
ALT	13.5 (8-51) 15.03±7.84	14 (10-27) 15.07±4.25	0.163*
AST	15 (10-38) 16.6±5.07	14 (10-41) 16.43±6.5	0.278*
BUN	20 (4.6-29) 17.4±5.2	15.7 (8.4-29) 17.33±4.52	0.864*
Creatinine	0.72 (0.5-0.92) 0.71±0.11	0.71 (0.52-0.9) 0.71±0.11	0.976**
β-hCG	133.5 (40-196) 125.31±39.6	101.5 (42-189) 102.23±42.51	0.002**
TPO-Abs	15 (10-38) 16.96±6	54 (45-65) 53.9±3.57	<0.001*
TG-Abs	2 (1-5) 2.44±1.09	34 (9-90) 38.33±19.25	<0.001*
FT4	0.99 (0.53-1.54) 1.04±0.28	1.02 (0.31-1.62) 1.04±0.29	0.939**
TSH	1.37 (0.63-2.46) 1.53±0.53	1.76 (0.65-2.41) 1.59±0.53	0.466*

SD, Standard Deviation; n, number of subjects; PLT, Platelet; ALT, alanine transaminase; AST, Aspartate transaminase; BUN, blood urea nitrogen; β-hCG, Beta human chorionic gonadotropin; TPO-Abs, Anti-thyroid peroxidase; TG-Abs, anti-thyroglobulin; FT4, Free thyroxin; TSH, thyroid-stimulating hormone. *Mann-Whitney U test. **Independent t-test

Figure 1 shows the difference between two groups (Thyroid autoantibody negative and Thyroid autoantibody positive) on β-hCG.

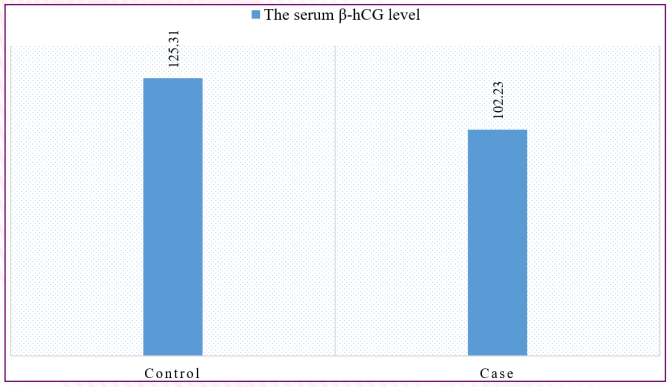

Figure 1. Comparison of case and control groups

DISCUSSION

This study showed that serum β-hCG levels are lower in patients with TAI in the early stage of spontaneous pregnancy. There was no significant statistical difference between the two groups of the TAI and controls in terms of other parameters. There is no study on serum β-hCG levels in patients with TAI in spontaneous pregnancy. This study investigated this case for the first time.

Thyroid hormone dysfunction is associated with a wide-ranging of reproductive system disorders from short luteal phases, premature delivery, miscarriage, failure to sustain a fertilized egg, menstrual irregularities, and infertility.[18] Since the 1950s, researchers have realized the impact of hypothyroidism on blood flow and cycle length in the menstrual cycle.[19] Oligomenorrhea or menorrhagia, infertility, and pregnancy loss indicate hypothyroidism, but these reproductive abnormalities have no well-known causes.[20] There are thyroid hormone receptors in oocytes of primordial, primary, endometrial stromal, and Ishikawa cells, secondary follicles, and human ovarian surface epithelium. TSH-stimulated granulosa cells significantly increased the concentration of cyclic adenosine monophosphate (cAMP) through activation based on the TSH receptor.[21] The thyroid hormone should be available in oocytes for maturation. Thyroid disorders are known as one of the causes of ovulation failure.[10]

TAI and thyroid hormonal dysfunction are associated with an increased risk of adverse pregnancy outcomes.[22] Moleti et al.[23] indicated that TAI poses a risk for preterm delivery and miscarriage. Huget Penner et al.[24] reported that maternal thyroid disease including maternal hypothyroxinemia, hyperthyroidism, hypothyroidism, thyroid autoantibodies, and hyperthyroidism increases the risk of these diseases in the fetus. Toloza et al.[25] reviewed the studies on the relationship between maternal thyroid function and pre-eclampsia. Thyroid disorders were associated with a higher risk of gestational hypertension and pre-eclampsia. Sitoris et al.[26] showed that TAI increased the risk of admission of the baby to the NICU, low birth weight, and preeclampsia. Busnelli et al.[27] reported that TAI increases the risk of miscarriage in women. The adverse effects of TAI on pregnancy outcomes in women have been reported in many studies. However, there is still controversy about the relationship between infertility and TAI.[1,29] Dosiou 28 reviewed recent studies in the field of infertility and thyroid. The thyroid affects women's reproductive system by affecting thyroidal stimulation from β-hCG.

The serum β-hCG level, or pregnancy hormone, is a type of glycoprotein with a lipid framework whose prominent role in pregnancy is to support the corpus luteum.[30] β-hCG is used in predicting, diagnosing, and treating some diseases and as an important prognostic marker showing early pregnancy outcomes.[31] Liu et al.[32] demonstrated higher levels of β-hCG as an essential mediator in the association of higher levels of β-hCG in early pregnancy with a lower risk of gestational diabetes mellitus. Korevaar et al.[33] reported that HCG treatment negatively affects TPO-Abs positivity of pregnancy thyroid response. The damaging effect of thyroid antibodies on the developing embryos or oocytes can cause adverse pregnancy outcomes.[27]

In the current study, lower levels of β-hCG were monitored in patients with TAI compared to the control group. This finding indicates a possible significant relationship between TAI and adverse pregnancy outcomes. Conducting a study with more participants is recommended to investigate this relationship more closely. Following the patient until delivery and examining the fetus's health can produce valuable findings. A decrease in

hCG is seen in ectopic pregnancies and premature labor. Clinicians should have a more detailed follow-up of hCG levels in women with TAI to avoid harmful effects on the fetus and the pregnancy process.

The main limitation of this study is the lack of follow-up on the condition of women in the study until the end of pregnancy. These women's conditions and the child's health after delivery will be investigated in future studies. In this way, the effect of thyroid autoimmunity in spontaneous pregnancy can be seen more accurately and clearly. It is recommended that more studies be conducted to evaluate the effectiveness of the serum β-hCG levels of TAI in spontaneous pregnancy, paying more attention to the genetic and demographic characteristics of women of reproductive age.

CONCLUSION

This study showed that the level of serum β-hCG in the early stages of spontaneous pregnancy is lower among women with TAI. This result can be used to predict the possibility of early pregnancy loss in pregnant women with TAI. Therefore, thyroid levels should be considered, and proper treatment should be started early.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Medipol University Ethics Committee (Date: 26.10.2022, Decision No: 903).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Review

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Menopausal period and homeopathy: a review

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ABSTRACT

Homeopathy, rather than suppressing existing disease symptoms; is a natural, side effect-free, safe, and inexpensive treatment method based on activating this natural healing power that has been impaired. In this method, which is based on the principle of similarity (like heals like), the person is evaluated individually and holistically. For example, not every woman is treated the same for the menopausal condition. Each woman is treated individually, considering all her symptoms. Therefore, instead of trying to eliminate the symptoms, the patient's treatment is targeted. Medicines used in homeopathic treatment are called remedies. Remedies include: plants, minerals, animal tissue and other sources that are all found in nature, 70% of which are obtained from plant sources. Today, there are around 8000 remedies that are available. Remedies are obtained by diluting these substances with water. Dilution process; it prevents side effects and increases the effect. By applying the shaking method, the power is increased. Remedial information; It is obtained as a result of studies called proving that are made by using healthy people. Animal experiments are not used. Within the scope of this review, it is aimed to give information about the remedies that can be used for homeopathic purposes in the menopausal period and the selection of the appropriate remedy.

Keywords: Homeopathy, materia medica, menopause, proving, repertory, remedy

INTRODUCTION

Homeopathy; is a term derived from the Greek words "similar" (homeos) and "pain" (pathos) and refers to the use of substances that act in the same way as the disease in order to stimulate the healing powers of the human body. The first to mention the term homeopathy; Hippocrates is considered the father of Medicine.[1] In his statement; Based on the principle of "equals are treated by their equals", it has sprouted the roots of homeopathy.

Homeopathy is a field that has been widely utilised since the end of the 18th century, but is very new for Turkey. For example, it is thought that 600 million people in India prefer homeopathy for medical support.[2] It has been the second accepted treatment method by the World Health Organization. According to the data from the World Health Organization, in 2008 $26 billion in China, $408 million in France, $346 million in Germany, $62 million in England, $7.3 million in Australia, and in 2007 $2.9 billion in the United States was spent on homeopathic remedies.[3]

In fact, although the history of homeopathy has existed since the beginning of medical history; German scientist Samuel Hahnemann (1755-1843) is accepted as the founder and developer of homeopathy.[4,5] Hahnemann first defined the use of quinine as a remedy in his studies. He used this plant, which is used for treatment in patients with fever symptoms, as a healthy person himself. He observed that the symptoms of malaria appeared.

Upon stopping taking the plant, the symptoms regressed. When he took the plant, they reappeared. Based on the experiences he gained from these early studies in the following years, he stated that the substances to be used for homeopathic purposes must be diluted.[5]

Over time, remedies such as poison ivy (Rhus toxicodendron), snake venom (Lachesis), table salt (Natrium muriaticum), head lice (Pediculus humanus capitis) were also used.[6] In the light of the information obtained from these studies, Hahnemann; concluded that "a substance that causes various effects (including harmful effects) when given to a healthy creature in large amounts creates a curative effect when given to a person with the same symptoms in an extremely small amount", and this situation is defined as the "law of similars" (similia similibus curanteur or like cures like).[7]

In fact, there are two more basic principles besides the principle of "like treats with like", which is one of the basic principles widely accepted in homeopathy. These can be considered as the principles of "life force" and "enhancement", "one remedy and minimum dose". The first of these, the principle of "life force", expresses a dynamic energy power that is present in every part of the body and that enables the mind, body and living thing to continue their duties in a healthy and normal way; The principle of "reinforcement",

on the other hand, states that although the amount of main substance that is within the homeopathic product decreases with each dilution, hence becoming more dynamic in terms of energy and thus becomes stronger. It has been defined as another principle that the patient should use one remedy at a time and at the minimum dose.[8]

Following Hahnemann, applications in the field of homeopathy quicklu became widespread; However in our country; Homeopathy has been officially first recognized with the "Regulation on Traditional and Complementary Medicine Practices" published in the Official Gazette dated 27.10.2014.[9]

There are many benefits of choosing homeopathic treatment during the menopausal period. With homeopathy, both healing is achieved and potential disease conditions that may await the person in the future are prevented. Every woman's menopause journey is different. For example, the constitution of two women with hot flashes can differ greatly. Hot flashes can be sudden, or they can be gradual. They may only occur at night, during the day, or at certain times of the day. Associated findings; palpitations, throbbing headaches, etc. it could be. The aim of homeopathic treatment is that the healing is permanent. Consequently: "Miasmatic Approach" is important in the choice of remedy. This can also be considered as structural cleaning. However, physical-spiritual traumas that intervene with the healing may result in the need for retreatment.

Before defining the remedies to be used for homeopathic purposes, a process defined as "proving" is performed. This process; The application of the remedies in healthy volunteers and the recording of all the data obtained after the application are followed. These records are added to the "materia medica" information or are also called "repertory".

The proving stage is followed by the dilution stage. This is the stage where the homeopathic substance to be used is diluted with solvents such as water, alcohol, aqueous alcohol. The dilutions here are performed logarithmically. Afterwards, a phase called "succussion" follows. This process is also known as shaking.[13-15]

SELECTING A SUITABLE REMEDY

Hahnemann; to find the most suitable remedy by comparing the symptoms of the known drugs that are most similar to all the symptoms of the natural patient; He stated that especially striking, unusual, strange, peculiar, characteristic signs and symptoms should be determined. Hence, the important thing here is; the detection of striking, rare and uniquely atypical symptoms. These symptoms are patient-specific symptoms; so, they are not disease-specific symptoms.

Since remedies are used against the patient (not against the disease) in homeopathic treatment; Detection of such symptoms is vital and valuable from a homeopathic point of view. As the table of effects of the remedy sought must be in accordance with these characteristic symptoms. General and vague findings such as loss of appetite, headache, weakness, sleep disturbance, feeling of discomfort; If they are not declared in detail, should not be taken into consideration. It is possible to encounter these general symptoms in almost every disease and every drug; therefore, it is more important to pay attention to uncommon, strange, distinctive (characteristic) signs rather than general symptoms, and the most appropriate remedy should be selected for these symptoms. Again, whether the problem has an acute or chronic course is one of the key points in determining the treatment process.[16,17]

This review will look at which remedy or remedies cover most or all the symptoms.

Belladonna: Immediacy and intensity are the main features of this remedy. This remedy may be helpful if the hot flashes are very sudden and intense. Sudden hot flashes accompanied with a red face, throbbing headache, dilated pupils, and followed by sweating. Uterine bleeding, vaginal discharge, nose bleeding, increase in temperature are among the other symptoms. Although the woman is emotionally stable, she may experience short bursts of anger during headaches or stressful situations. Migraine, sudden high blood pressure, craving for lemon or lemonade are other indications that require this remedy.[18-20]

Calcaria Carbonica: The individuals are overweight, pale, sluggish and feel cold. Excessive sweating, sweating at night especially in the head areas (despite the general coldness), weight gain during menopause are the symptoms that this remedy may help alleviate. Individuals that rquired this remedy are usually responsible and hardworking. They get tired quickly. Worsening with exercise (especially going up) and shortness of breath. They may have intense anxieties and fears. Overworking and stress can lead to temporary collapse. They have a feeling that they will lose their mind due to intense mental confusion and are afraid that others will notice it. There may suffer from cramps in their legs, stiffness in the joints, or vaginal bleeding. These inidividuals have a high craving for eggs and sweets.[18-20]

Cimicifuga: Hot flashes and heat on the top of the head will appear. Sadness, gloominess, volatile, very talkative, weak, feeling faint, palpitations, insomnia, joint and muscle pains are other important symptoms exhibited Cold and damp worsens their symptoms. Heat heals.[18]

Folliculinum: It is a very useful remedy during the menopause period. The individuals are restless, hyperactive, they feel worse with rest. There is a tendency to feel dizzy, faint. They exhibit hot flashes, profuse sweating, especially at night, bloating in the abdomen, vaginal bleeding, and vaginal dryness. Sweet cravings are high. Although they do not eat a lot, they gain weight easily. There is fatigue. They experience an identity crisis as if they have lost their will.[20]

Glonoinum: Throughout menopause; there are explosive pains in the head area with intense hot flashes and redness. These are accompanied by heart palpitation, irritability, mixed thoughts. The individual has confusion in finding direction. They get lost in places they know well. If they feel too hot or stay in the sun for prelonged periods of time, the symptoms can be aggravated and often they feel worsened after lying down. External pressure and sleeping in the dark are good for headaches.[18,20]

Graphites: During menopause, there is a tendency to gain weight, coldness, pallor, slow thinking, poor concentration. Hot flashes and night sweats are also common. Cracks in the skin with yellow infiltrates may appear. There may also be cracks and rashes behind the ear. Sweet foods tend to not be wanted by those in menopause. They can feel worse when feeling cold, hungry, and waking in the morning. Thick, hard, and deformed nails can be present. There is also a tendency to excessive calluses.[18-20]

Ignatia: It is useful for emotional ups and downs during menopause. The female is very sensitive, but tries to hide her feelings. She may appear cautious, defensive, grumpy, and hysterical. Nail-like headaches, sleep disturbances, frequent sighing, feeling of a lump in the throat, numbness, cramps, twitching, hair loss, hysterical cough, feeling of heaviness in the chest, sudden tears and bursts of laughter are strong symptoms. There is sweating localized on the face, especially on the upper lip. They are very uncomfortable with cigarette smoke. There is a sene of loss, separation, disappointment.[18-21]

Lachesis: Palpitations, intense hot flashes with a feeling of constriction, without sweating, are prominent features that appear. In the body; Varicose veins and red purplish color changes that occur easily due to trauma are common. There may be dark-colored vaginal bleeding that contains a clot. It is impossible for them to tolerate clothing that is tight in the neck and waist area. Irritability, depression, jealousy, talkativeness, sarcasm, pronounced skepticism are the mental-emotional manifestations. Fear of snakes is common. When the tongue is protruded, there is tremor. It gets worse when the individual lyes on the left side. In particular, there is difficulty in swallowing liquid foods. They have difficulty in swallowing their saliva and feel the need to spit frequently. They may wake up with a feeling of suffocation in their sleep. There is a feeling of being stuck, needing an emotional and physical exit. Their symptoms worsen as a result of suppression of sexuality. It is common in women who have lost their partner.[18,20,21]

Lilium Tigrinum: Anger, worry, haste, are common symptoms. It can be considered the most restless remedy. There is a conflict between a strong sexual drive and strong moral values. The individual feels chest tightness, weakness in the legs, and the feeling that the pelvic organs will fall out of the vagina, there feels the need to cross their legs.

Natrum Muriaticum: They are individuals who are introverted, hard-looking on the outside (soft when you get to know them), prefer to be alone, sensitive, easily hurt, and feel bad with consolation. They often feel deep grief. They may have deep trains of thought on past hurts and disappointments. Backaches and migraines can happen during their menopause. They feel relieved by profuse sweating. Meat, salt cravings and thirst are increased. There is dryness of the skin, eyes and joints. They have little tolerance for being in the sun. They may expeirence difficulty falling asleep.[18-21]

Oophorinum: It is a remedy obtained from the ovarian extract. It covers all menopausal symptoms. Vaginal bleeding, hot flashes, epileptic complaints, skin complaints such as psoriasis are common symptoms. It can be used in ovarian tumors. Its use after oophorectomy is also very beneficial.[20]

Pulsatilla: They inviduals who are shy, sensitive, gentle, and vary in physical and mental symptoms. A tendency to cry easily, a liking for attention, and comfort are the main symptoms they exhibit. If their demands for attention and love are not met, they can become jealous and irritable. They are very attached to their families and they are motherly. There have a lot of concerns with ageing. They dont feel thirsty. They feel worse in closed rooms and they improve outdoors. Fatty foods are bad for them. They are prone to gaining weight. They may have migratory joint pain. Cold application is good for these pains.[18-20]

Sanguinaria: Hot flushes, flushing on the face, an intense right-sided headache, burning on the soles of the hands and feet, and foul-smelling vaginal discharge are common. There may be a spice addiction. A cough that improves with belching, winding, or vomiting appears.[18,19]

Sepia: The individuals are prone to fatigue, fainting, and irritability. The slightest movement results in hot flashes accompanied excessive sweating. There may be excessive vaginal bleeding, vaginitis, and foul-smelling urine. There is indifference to family members (especially their spouse), and decreased interest in daily activities. Depression and the desire to be alone is present. There may be a feeling of weakness and sagging in the pelvic organs. Urinary incontinence, uterine prolapse may occur. They feel cold. Exercise, especially dancing helps alleviate their symptoms. Sexual reluctance is common.[18-21]

Staphysagria: Their personality is kind, sweet, gentle, and shy. However, they are filled with intensely suppressed emotions that cause emotional and physical ailments. There is a predisposition to frequent urinary tract infections. There may be urinary incontinence. Sleep during midday is not good for them. Sweet cravings are high. In menopause; they may experience depression or outbursts of anger that escalate to throwing objects. Skin symptoms such as easy tooth decay and psoriasis are common. There may be a history of childhood abuse or rape.[18-21]

Sulphur: They are friendly. Their face, head, hands, and feet are warm. Especially the soles of the feet feel very hot and exhibit a burning sensation. There are hot flashes and flushing, which wakes them up early in the morning causing them to remove their covers. They are very uncomfortable with the heat. They need constant cooling. There is a feeling of slight sweating, tiredness, fainting. There may have intense concerns regarding their health. They can be very theoretical, critical, selfish, lazy, and messy. They may dislike bathing. Their sweet and spice cravings can be intense. Their skin is dry and itchy. Skin symptoms may worsen with washing.[18-21]

Symphytum: It is a remedy used in periosteal and bone damages and facilitates bone union. Increases the hardness and durability of bone tissue. During old age, bone tissue turns into a more spongy and loose structure. It is prone to fracture due to the slightest trauma and falling. In fact, it is often thought the falls are due to the bone breaking spontaneously. It is also recommended to be used to prevent bone fractures.[18]

Schüssler Salts: They are 12 biochemical tissue salts developed by German Homeopath Dr. Wilhelm Heinrich Schüssler (1821-1898). According to Dr. Schüssler, the deterioration of health was due to an imbalance in the body's 12 essential tissue salts. Schüssler believed that these imbalances could be corrected with microdoses of each salt that are easily absorbed and prepared according to Homeopathic principles. Today, 12 basic salts, alone or in combination preparations, are widely used in the world. They have already taken their place in the medicine cabinets of families. The names of tissue salts and the tissues they affect are listed below:

1. Calcium Fluoride: Skin, connective tissue, tooth enamel, joints and bones.
2. Calcium Phosphate: All body tissues, especially teeth and bones.
3. Ferrum Phosphate: All parts of the body, especially red blood cells.
4. Kali Muriaticum (Potassium Chloride): All parts of the body, especially connective tissue.
5. Kali Phosphate (Potassium Phosphate): Brain and nerves, muscles, blood, body fluids.
6. Kali Sulphate (Potassium Sulphate): Skin, muscles.
7. Magnesium Phosphate: Muscles, blood cells, nerve tissue, bones, teeth
8. Natrum Muriaticum (Sodium Chloride): All body fluids and tissues.
9. Natrum Phosphate (Sodium Phosphate): Blood cells, muscles, nerve and brain cells, body fluids.
10. Natrum Sulphate (Sodium Sulphate): Extracellular fluid.
11. Silicea: Skin, hair, nails, muscles, nerves, glands, connective tissue.
12. Calcium Sulphate: Gallbladder and liver.

Schüssler salts can be defined as effective preparations of homeopathy on the physical plane. They can be utlised safely with remedies or alongside other drugs. They will be very beneficial to use during menopause. Although salts 2, 4, 6,7 are generally thought to be deficient in everyone, which tissue salt is needed is decided through facial analysis.[22]

Bach Flowers:. They are preparations that are made from flower essences, developed by British doctor, Dr. Edward Bach (1886-1936).

Dr. Bach argued that diseases are the result of the reflection of the deteriorated mental state on the human body. Each of the 38 flowers has a healing equivalent on a spiritual level. They can be defined as the effective preparations of homeopathy on the spiritual plane. They can be used safely with homeopathic remedies or other medicines.

CONCLUSION

Homeopathy indicates that the living organsim gets sick as a whole, therefore can be healed as a whole. In addition, it interprets the symptoms that we see as signs of illness as changes in the body's fight against the disease. In homeopathy, medicines are prepared by methods such as potentiation, but the effects of homeopathic medicines at the tissue level are not fully understood. Some researchers state that the effect of homeopathic substances can be explained based on the concept of quantum physics.

The tendency to homeopathic treatment methods is increasing due to the advantages of homeopathic treatment such as natural, side effects, cheap and non-addictive. Numerous scientific studies are available and ongoing for the mechanism of action and therapeutic evidence.

When the decision is made to undergo homeopathic treatment; a homeopathy doctor with a certificate of therapeutic competence should be chosen. After an evaluation process that takes an average of 60 minutes, the necessary remedy is determined. The patient is informed in detail about the application and what to pay attention to. Follow-ups should be carried out in in the period of time determined by the cooperation of the physician and patient.

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Letter to the Editor

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What do we know about kisspeptin?

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Dear Editor,

Kisspeptins are a group of peptide fragments that are expressed by the neurons of the hypothalamus mainly in the arcuate, dorsal-medial and antero ventricular, periventricular nuclei of the hypothalamus besides the amygdala.[1] Initially, Kisspeptin via its G protein-coupled receptor 54 (GPR54) was introduced to have an important role in cancer biology with its metastasis suppression effect. In light of recent research, Kisspeptin is found to have a major role in the neuroendocrine reproductive axis through the Kisspeptin 1 (KISS1) gene. The KISS1 gene that encodes Kisspeptin was first discovered in 1996 by researchers from the United States of America. Kisspeptinreceptors are also expressed by the same neurons. Kisspeptin has a pivotal role in reproduction through the hypothalamic-hypophysial axis while exerting an extra hypothalamic function on sexual and emotional behavior.

The peptide Kisspeptin is encoded by the KISS1 gene located on the long (q) arm of chromosome 1 at q32.[2] Kisspeptin and its GPR54 receptors (KISS 1R) in the hypothalamus, act as an important modulator of the pubertal and adult reproductive functions[3] mainly the central control of Gonadotrophin releasing hormone (GnRH) secretion, pubertal onset, sex differentiation in the brain, ovulation, implantation, placentation, and food consumption.[4]

The Kisspeptin precursor (pre-pro Kisspeptin), a protein of 145 amino acids, is converted into a protein of 54 amino acids (with a half-life of 28 minutes) and small peptide fragments of 14, 13, and 10 amino acids (isoforms). Two of these isoforms, Kisspeptin-10 and Kisspeptin-54, were administered peripherally exogenously to investigate clinical applications and were found to play a role in ovulation through GnRH secretion.[5] The KISS1 gene and its receptor (KISS1R) are also found in the placenta, Graff follicles, theca cells, and ovarian epithelium besides the hypothalamus. Moreover, their expression on luminal and glandular epithelial cells of the endometrium was shown.[6]

In an animal study, intracerebroventricular and peripheral administration active isoform of Kisspeptin; Kisspeptin-10 activated the hypothalamic-pituitary-gonadal axis potently most probably through the hypothalamic Luteinizing hormone-releasing hormone (LHRH) system and its effect was dose-dependent.[7] KiSS-1 and GPR54 are also present in human and marmoset ovaries and granulosa-lutein cells and also have a local role in the ovulation mechanism that is regulated by gonadotropins and COX-2: The addition of a Kisspeptin antagonist also inhibits oocyte maturation in porcine cumulus-oocyte complexes (COCs).[8,9] In particular, a significant association between low levels of Kisspeptin in serum and follicular fluid is related to unexplained infertility.[10,11] In a recent study serum Kisspeptin levels were reported to increase during ovarian hyperstimulation in in vitro fertilization (IVF) cycles however serum and follicular fluid Kisspeptin levels in pregnant and non-pregnant patients showed no significance.[12]

Kisspeptin came into the light to be used for oocyte maturation in IVF. Subcutaneous Kisspeptin-54 is proposed to be an alternative to HCG for oocyte triggering in GnRH antagonist cycles.[13] In addition, an improvement in oocyte maturation was noted after the administration of synthetic Kisspeptin due to the controlled increase in Luteinizing Hormone (LH) levels, especially in ovarian hyperstimulation syndrome (OHSS) patients.[14,15] In an animal study ovulation and fertilization were achieved in Kiss1-null mice after administration of gonadotropins that are known to have hypogonadotropic hypogonadism, however, the embryos failed to implant in the absence of Kisspeptin.[16] Jamil et al.[17] proposed to use Kisspeptinlevel on human chorionic gonadotropin (hCG) administration day as a predictor of intracytoplasmic sperm injection success.

Kisspeptin plasma levels increase 900-fold in the first trimester and 7,000-fold in the third trimester compared to non-pregnant women.[18] When Kisspeptin is measured after the 6th week of pregnancy, it has good diagnostic value with an AUC of 0.902 (0.866, 0.937) and even has a higher accuracy potential than hCG in distinguishing between abortion and viable intrauterine pregnancy.[18] However, it should be noted that the ideal measurement time for Kisspeptin released from the placenta is between 6 to 14 weeks.[19]

Mutation of the Kisspeptin receptors in the hypothalamus leads to the absence of pubertal development.[20] The most known cause of delayed puberty is structural delay and idiopathic hypogonadotropic hypogonadism. Measurement of serum gonadotropins (LH and follicle-stimulating hormone (FSH)), poststimulation gonadotropins, and inhibin B with GnRH or GnRH analogs can be used to predict the onset of puberty with a low sensitivity, specificity, or both.[21] GnRH responses to stimulation with Kisspeptin may be utilized as a promising test for predicting pubertal progression in children with pubertal tarda.[22]

The relationship between Kisspeptin signaling and food intake is remarkable.[23] The effect of Kisspeptin proopiomelanocort in neurons has been shown to regulate food intake by exerting an anorexigenic function through inhibition of orexigenic neuropeptide Y neurons.[24] In animal studies, all Kiss1 knockout mice exerted lower apatite than other mice, and gonadal estrogen levels were also reduced.[25] KISS1Rs, which regulate sexual and emotional behaviors and facilitate their interaction with the neuroendocrine reproductive axis, were also found to be involved in the regulation of appetite and food reward in the limbic brain system.[26] The effect of Kisspeptin on food-related olfactory processes has been reported.[27] Increased leptin levels in adipose tissue due to obesity impair Kisspeptin secretion and result in decreased GnRH pulsation and LH secretion.[28]

In summary, Kisspeptin can be used clinically either as a marker or as a pharmacological agent in treatment. Serum or plasma Kisspeptin level measurement needs accuracy with the use of the correct type of collection tubes, and time of collection, storage conditions, and processing times of samples as these factors may alter the results of Kisspeptin measurements. It can be used as a novel and promising method to induce oocyte maturation and increase pregnancy rates in IVF especially in patients at high risk of OHSS. In the future, it may be used as a therapeutic agent in the treatment of recurrent miscarriage and obesity. Kisspeptin has a promising future to be used as a biochemical marker for the diagnosis of puberty tarda and healthy pregnancy.

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