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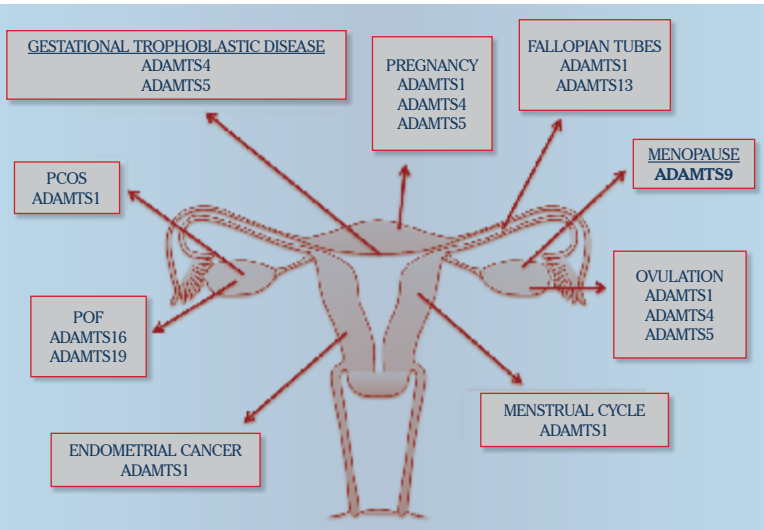


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# Contents

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# Editorial

Dear Colleagues,

Journal of the Turkish German Gynecological Association is the official, scientific and open access publication of the Turkish German Gynecological Education and Research Foundation. ***J Turk Ger Gynecol Assoc***, *which* publishes original studies on all aspects of gynecology, is now available in **PubMed Central**. Journal of the Turkish-German Gynecological Association is indexed in PubMed Central, EMBASE, Scopus, CINAHL, Gale/Cengage Learning, EBSCO, DOAJ, ProQuest and Index Copernicus.

It's been known preterm birth (PTB) is the major obstetric problem in developed and developing countries, accounting for the majority of neonatal mortality and morbidity. We got a paper that investigates the differences of serum G-CSF levels between subsequent spontaneous PTB and term-delivered healthy pregnant women. Granulocyte colony-stimulating factor is a hematopoietic cytokine that mediates the increase in leukocytes in pregnancy and may play a role in placentation.

It is my great pleasure to inform you that this issue is focused on maternal life threatening condition such as near miss and Posterior reversible encephalopathy syndrome (PRES). Posterior reversible encephalopathy syndrome is a clinical entity characterized by temporary neurological symptoms, including acute headache, altered mental status, vision loss, and coma. Among the etiological factors associated with PRES are such diseases as hypertensive encephalopathy, preeclampsia/eclampsia/HELLP syndrome, acute or chronic renal disease, thrombotic thrombocytopenic purpura etc. Pregnancy and the postpartum period often lead to this syndrome. In some cases, PRES can cause irreversible neurological deficits or death. For patients with severe radiological findings, early diagnosis and thiopental infusion, in addition to treatment with antihypertensive agents and magnesium sulfate, may lead to quicker and more effective recovery from clinical manifestations. We have another paper that investigates the "near miss"; which really deserves to be read.

There is another controversial paper from Egypt and Kuwait that try to detect the maternal and obstetrical factors associated with successful trial of vaginal birth among women with a previous cesarean delivery. They investigate 122 women who were eligible for a trial of labor after cesarean section (TOLAC) according to departmental protocol was included in this comparative prospective study. They said in carefully selected cases, TOLAC is safe and often successful. For more please review the article.

It is important that a mother ideally begins breastfeeding her newborn baby in the first hour after delivery. Cesarean section and primi-parity are important risk factors for late onset of breastfeeding. In one article the authors consider that the onset time of lactation is delayed in patients undergoing cesarean section with general anesthesia when compared with patients who undergo cesarean section with spinal and epidural anesthesia and with patients who undergo normal vaginal birth.

Playing a key role in the pathophysiology of many diseases, A Disintegrin-like and Metalloproteinase with Thrombospondin type-1 motif (ADAMTS) proteinases have been attracted more attention in obstetrics and gynecology. You will read a review is collecting previous studies about obstetrics and gynecology that are related to ADAMTS enzymes and discuss the subject in many aspects to give an idea to the investigators who are interested in the subject.

I would like to wish you a happy new year in 2015 and we are looking forward to receiving your valuable submissions.

Best regards,

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

# Comparison of serum granulocyte colony-stimulating factor levels between preterm and term births

*Çiğdem Kılıç, Mustafa Uğur, Bekir Serdar Ünlü, Yunus Yıldız, İshak Artar, Pervin Karlı, Kadriye Turgut*
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## Abstract

**Objective:** Preterm birth (PTB) is the major obstetric problem in developed countries, accounting for the majority of neonatal mortality and morbidity. Granulocyte colony-stimulating factor (G-CSF) is a hematopoietic cytokine that mediates the increase in leukocytes in pregnancy and may play a role in placentation. We aimed to investigate the differences of serum G-CSF levels between subsequent spontaneous PTB and term-delivered healthy pregnant women.

**Material and Methods:** Serum samples, collected from total of 600 singleton otherwise healthy pregnants at 24-28 weeks of gestation during a routine antenatal visit, were used to assess G-CSF levels; 40 of the total pregnants who delivered their infants spontaneously after preterm labor before 37 weeks of gestation were selected as the study group. Also, 120 pregnants were selected as a control group using a 1/3 ratio. Student's t-test, chi-square test, Mann-Whitney U-tests, and ROC curve analysis for prediction of PTB were used for the comparison of groups. $P<0.05$ was accepted as statistically significant.

**Results:** There was no significant difference in maternal serum G-CSF levels between the study and control groups ($p=0.28$) but maternal white blood cell (WBC) count was significantly different between them ($p=0.00$). In addition, G-CSF was insufficient in the prediction of PTB (AUC=0.419). In the preterm and term groups, no correlation was found between WBC and G-CSF ($p=0.165$ vs. $p=0.703$).

**Conclusion:** There were no differences in serum levels of G-CSF between term- and preterm-delivered pregnants. There was no predictive role for serum G-CSF in PTB. (J Turk Ger Gynecol Assoc 2014; 15: 208-11)

**Key words:** Preterm birth, granulocyte colony-stimulating factor, newborn infants

**Received:** 07 May, 2014 **Accepted:** 18 August, 2014

## Introduction

Preterm birth (PTB), or delivery before 37 weeks of gestation, is a major obstetric issue in developed countries, being responsible for most neonatal mortality and a considerable proportion of long-term neurological problems (1). Despite significant efforts to elucidate the molecular mechanisms that cause PTB, its etiology remains unclear (2). It has been proposed that there are certain proinflammatory mediators, including granulocyte colony-stimulating factor (G-CSF), that are involved in the mediation of events leading to PTB development (3-5). G-CSF is a hematopoietic cytokine affecting the proliferation, differentiation, and survival of neutrophil progenitors. G-CSF and its receptor (G-CSFR), which mediates its activity, are expressed at the maternal-fetal interface (6), G-CSF being produced by the placenta (7) and G-CSFR being present on trophoblast cells. G-CSF is believed to have an important role in pregnancy outcomes through the regulation of placentation (6).

Increased levels of G-CSF have been found in preterm infant serum in comparison with infants who are born at term (3). According to Seremak-Mrozikiewicz et al. (4), with a small number of cases, G-CSF levels in amniotic fluid were found not to differ between full-term and preterm pregnancies, although a relationship between maternal serum and amniotic fluid G-CSF levels and infection in utero was demonstrated. Plasma G-CSF level samples from 24 to 28 weeks of pregnancy were found to be a predictor of spontaneous PTB for deliveries earlier than 32 weeks of pregnancy (5). It is unclear whether increased G-CSF at 24-28 weeks is indicative of an acute influence or a cumulative influence of inflammation in the development of PTB or whether G-CSF makes a contribution as an indicator of disease progression. Another study (8) showed an association of PTB with high serum G-CSF levels at the beginning of the second trimester, implying that PTB may be the result of events starting early in pregnancy, if not before.

In this study, we planned to investigate differences in plasma granulocyte colony-stimulating factor between consecutive spontaneous preterm births and births that were delivered at term in healthy pregnant women, who were screened routinely at 24-28 weeks of gestation.

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## Material and Methods

This study was conducted between January 2011 and July 2011 in our perinatology clinic. Ethics approval was obtained from our institutional review board. Informed consent was given by all study participants. The study was designed as a prospective case-control study. PTB was defined as a delivery that occurs before the 37th week of gestation (9, 10). Inclusion criteria in the study group were singleton pregnancies with a diagnosis of preterm labor leading to preterm birth at or before 37 weeks of gestation. Women who had preterm premature membrane rupture (P-PROM), clinical signs of intrauterine infection (uterine tenderness, fetal or maternal tachycardia, maternal fever, etc.), or bacterial infection in the cervical/vaginal culture were not included in the study or control groups. Also, women who had a history of maternal cardiac disease, cervical incompetence, cervical cerclage or conization, fetal anomaly, or vaginal bleeding were excluded from the study and control groups.

A total of 600 singleton pregnant women were screened at 24-28 weeks of gestation and routinely followed up at the outpatient clinic until delivery. Demographic values of all pregnant women were recorded. Forty pregnant women delivered their infants spontaneously after preterm labor before 37 weeks of gestation. Also, 120 pregnant women were selected as a control group among these 560 women via a simple random sampling method, who delivered their infants after 37 weeks of gestation. All participants had 24-28-week plasma samples available for granulocyte colony-stimulating factor analysis.

For both groups, maternal blood samples were collected at 24-28 weeks of gestation during a routine prenatal screening program in the outpatient clinic. Venous blood samples from patients were collected into sterile, silicone-coated tubes, centrifuged, and stored at -70°C. Maternal serum G-CSF levels were measured with the G-CSF Human Enzyme-Linked Immunosorbent Assay (ELISA) kit (Novex®; Invitrogen, Los Angeles, USA).

The Statistical Package for the Social Sciences 14.0 (SPSS Inc.; Chicago, IL, USA) statistical package was used for the statistical analysis. Descriptive statistical methods (mean, standard deviation), as well as a comparison of quantitative data, Mann-Whitney U-test, chi-square test, and Student's t-test, were used for the determination of differences between the two groups. Statistically significant levels for the tests were set at a p value <0.05. Spearman's rank correlation coefficient rho was used for the correlation study.

## Results

The characteristics of 160 women and the comparison of the two groups are shown in Table 1. The difference of the mean age of the women between groups was not statistically significant (p=0.8). There were no significant differences in maternal serum G-CSF levels between groups (p=0.28).

Smoking status was different between cases of PTB and full-term pregnancies, but a statistically significant difference was not found (p=0.284).

ROC curve analysis was performed for the prediction of PTB, but unfortunately, the area under the curve was 0.419, and G-CSF was found to be insufficient for the prediction of PTB. Therefore, there was no need to calculate the sensitivity and specificity of this marker for PTB birth (Figure 1).

As expected, there was a significant difference between the study and control groups in the requirement for neonatal intensive care. We observed ratios of 47.5% versus 0% in the study and control groups, respectively (p=0.03).

In the preterm and term groups, no correlation was found between WBC and G-CSF (p=0.165 vs. p=0.703) (Table 2).

**Table 1. Characteristics of values in the overall population and comparison between the two**

| | Preterm (n=40) | Term (n=120) | p value |
|---|---|---|---|
| Age (years) | 27.7±5.9 | 27.4±4.8 | 0.821[a] |
| Height (cm) | 161.2±4.26 | 161.4±6.13 | 0.866[a] |
| Weight (kg) | 70.8±9.48 | 67.37±10.68 | 0.128[a] |
| Birth weight (gr) | 2065±883 | 3590±408 | 0.00[b]* |
| Birth week (weeks) | 32±3.98 | 39.5±1.38 | 0.00[b]* |
| G-CSF | 25.43±1.42 | 25.77±1.39 | 0.28[a] |
| WBC | 13.2±5.65 | 9.8±2.4 | 0.00[b]* |

[a]Independent-sample t-test, [b]Mann-Whitney U-test

Values as mean±standard deviation (SD) or median±interquartile range (IQR)

*Significant if p<0.05

G-CSF: granulocyte colony-stimulating factor; WBC: white blood cell

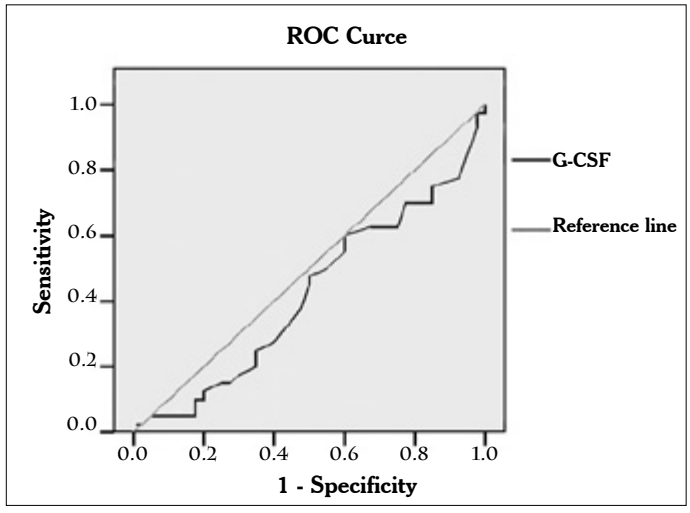


**Figure 1. ROC curve analysis for G-CSF**

**Table 2. Correlation in both groups for WBC and G-CSF**

| | rho | p |
|---|---|---|
| Preterm | 0.224 | 0.165 |
| Term | -0.62 | 0.703 |

Spearman's correlation coefficient used.

G-CSF: granulocyte colony-stimulating factor; WBC: white blood cell

## Discussion

Preterm labor still represents one of the major obstetric problems in developed countries and leads to poor results for the pregnancy and for the newborn's outcome. For reducing the proportion of preterm births and for their prediction, our efforts seem to be insufficient, even though, according to the literature, many studies on this topic have been conducted previously. G-CSF is a marker associated with inflammatory processes (11). Recent studies suggest that the majority of early spontaneous preterm births is associated with, and probably caused by, bacterial infection within the chorion-decidual interface (12). This infection causes an inflammatory response modulated by various cytokines, one of which is G-CSF (13), and elevated levels have also been observed in association with many other types of inflammatory processes.

We proposed to evaluate any differences in G-CSF levels between term- and preterm-delivered pregnant women. In the literature, some studies, such as Goldenberg et al., observed higher serum levels of G-CSF in early preterm-delivered patients (5), although other studies could not find any difference in serum levels of G-CSF between preterm- and term-delivered women (4). In our study, we observed no significant differences in serum levels of G-CSF at 24-28 weeks of pregnancy between term- and preterm-delivered women. It is well known that infection may cause an increase in maternal serum and amniotic fluid G-CSF values. In a literature search, the existence of G-CSF was described during clinically diagnosed intra-amniotic infection in amniotic fluid (14-17), and its relationship to labor was reported as either increased serum levels of G-CSF or no difference between term- and preterm-delivered patients (4, 5). In our study, any participant with any sign of infection was excluded in order to eliminate a bias in G-CSF levels. We considered an insufficiency in our study to be that G-CSF levels were evaluated only in maternal serum, not in amniotic fluid or in umbilical cord blood. It may have provided different results if a detailed examination of G-CSF levels was performed in body fluids, making it easier to determine any relationship between infection and serum G-CSF levels leading to preterm birth.

White blood cell count is increased in pregnancy (18). Leukocytosis, occurring during pregnancy, is due to the physiologic stress induced by the pregnant state (19). A normal WBC value for third trimester is between 5.6 to $16.9 \times 10^3/mm^3$ (20). In our study, white blood cell count was significantly higher in preterm-delivered women compared to term-delivered participants, although no significant correlation was found between the two parameters in either the term- or preterm-delivered groups, even though we excluded patients who had any sign of infection. These differences were not considered clinically significant, because it was in the normal range for the pregnancy state.

A weakness of our study was the limited number of subjects fulfilling the inclusion criteria.

In conclusion, we found no differences in serum levels of G-CSF between term- and preterm-delivered pregnant women. Previous studies on this issue in the literature are conflicting. All of the findings above suggest that a predictive role of serum G-CSF in PTB is questionable. Therefore, we consider that to reach a definitive conclusion, further studies should be performed to evaluate the conflicting results on the relationship between G-CSF levels and preterm and term labor.

***Ethics Committee Approval:*** *Ethics committee approval was received for this study from the Institutional Review Board.*

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

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

***Author Contributions:*** *Concept - Ç.K., M.U.; Design - Ç.K., M.U.; Supervision - M.U., B.S.Ü; Resource - Ç.K.; Materials - Ç.K., B.S.Ü.; Data Collection&/or Processing - Ç.K., İ.A., P.K.; Analysis&/or Interpretation - B.S.Ü., Y.Y.; Literature Search - P.K., K.T.; Writing - B.S.Ü., Y.Y.; Critical Reviews - M.U., İ.A., K.T.*

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# Changes in first trimester screening test parameters in pregnancies complicated by placenta previa and association with hyperemesis gravidarum

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## Abstract

**Objective:** To assess the possible changes in first trimester screening test parameters in pregnancies complicated with placenta previa and to determine whether there is an association between hyperemesis gravidarum and placenta previa.

**Material and Methods:** A total of 131 singleton spontaneously conceived pregnancies that were complicated by placenta previa and delivered between May 2006 and May 2013 were evaluated from birth charts. Ninety patients without placenta previa were selected amongst patients who delivered within the same period of time as the control group. Cases of low lying placenta (n=52) within the study group were assessed as a separate group. The rest of the cases was considered to be in a different group.

**Results:** Beta human chorionic gonadotropin (BhCG) multiples of medians (MoMs) and nuchal translucency (NT) MoMs were significantly higher in the placenta previa group in comparison with the low lying placenta and control groups. Apgar scores at both the 1st and 5th minutes were significantly lower in the placenta previa group. Hyperemesis gravidarum was found to be significantly more frequent in the placenta previa group.

**Conclusion:** The prevalence of hyperemesis gravidarum in the first trimester is higher in pregnancies complicated by placenta previa. Paying more attention to the development of placenta previa in the routine pregnancy follow-up of patients with hyperemesis gravidarum could be considered. (J Turk Ger Gynecol Assoc 2014; 15: 212-6)

**Key words:** Placenta previa, hyperemesis gravidarum, first trimester screening, BhCG, PAPP-A

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## Introduction

Placenta previa is a condition in which the placenta partially or completely obstructs the internal cervical os and is seen approximately 0.3%-0.5% of pregnancies (1). This condition leads obstetric complications, like antepartum second or third trimester bleeding, preterm delivery, and transient tachypnea of the newborn, and also increases the risk of peripartum hysterectomies (2). The pathogenesis of placenta previa remains an obscure issue. Advanced maternal age, multiparity, prior cesarean delivery, multiple pregnancies, prior spontaneous or induced abortions, maternal smoking, and drug abuse are factors that are known to increase the occurrence of placenta previa (3). Impaired placental blood supply in early pregnancy was proposed as an underlying cause by some authors (3). Although there are conflicting results in the literature, the vast majority of the studies does not demonstrate an association between placenta previa and markers of placental insufficiency in term pregnancies. However, placental insufficiency in early pregnancy could be compensated for as placenta previa develops. We aimed to investigate the changes in the first trimester in pregnancies later complicated by placenta previa. In this study, we compared cases of placenta previa and pregnancies with a normal placentation in terms of first trimester screening test parameters, fetal birth weight, and time of delivery and also history of hospitalization due to hyperemesis gravidarum in the first trimester.

## Material and Methods

This retrospective cohort study was conducted in the Department of Obstetrics and Gynecology of Ankara University in Ankara. The aforementioned hospital is a tertiary care setting in Turkey. Approval from the institutional board was obtained. Birth records between May 2006 and May 2013 were evaluated. Pregnancies conceived by assisted reproduction and cases with diabetes mellitus, chronic hypertension, and other co-morbidities were excluded from the study. From 8256 singleton births, 131 cases were found to have placenta previa in the third trimester. Ninety patients that gave birth in the selected period of time were established as the control group. Pregnancies with chromosomal abnormalities or

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neural tube defects were intended to be excluded from the study; however, neither of the situations was found amongst the randomly selected women. First trimester screening test parameters of these women were obtained. Placenta previa was classified as 4 types. The term "type 1 placenta previa (low lying placenta)" was used for women with a placental edge between 2-5 cm from internal cervical os. "Type 2 placenta previa (marginal placenta previa)" was described as a placental edge between 0-2 cm far from the internal cervical os. "Type 3 placenta previa (partial placenta previa)" was defined as a placenta partially covering the internal cervical os. "Type 4 placenta previa (complete placenta previa)" was described as a placenta fully covering the internal cervical os. Cases of placenta previa were diagnosed with trans-abdominal ultrasound, and the diagnosis was confirmed by trans-vaginal ultrasound. For the first trimester screening tests, plasma samples were collected following nuchal translucency (NT) measurements. Collected plasma samples were analyzed within 3 hours for beta human chorionic gonadotropin (BhCG) (Siemens 06601846 Immulite® Free Beta hCG Kit; Siemens Medical Solutions Diagnostics, London, United Kingdom) and pregnancy-associated plasma protein A (PAPP-A) (Siemens 06609553 Immulite® 2500 PAPP-A Kit; Siemens Medical Solutions Diagnostics, London, United Kingdom).

All cases with a low lying placenta had attempted spontaneous or induced vaginal deliveries. All cases that had type 2, type 3, or type 4 placenta previa had elective or emergent cesarean sections and were included in the placenta previa group. Cases with a low lying placenta were included in another study group, and 90 women without placenta previa were established as the control group. Categorical variables were expressed as number and percentages. Non-parametric data were compared by Kruskal-Wallis test. P values less than 0.05 were considered statistically significant. Significant differences obtained by Kruskal-Wallis test were further evaluated with post hoc analysis (IBM SPSS Statistics 20.0; IBM Corporation Software Group, New York, United States of America).

## Results

A total of 12,069 birth charts were retrospectively evaluated, and 8256 were found to be singleton spontaneously conceived pregnancies. Following exclusion of patients with co-morbidities, 131 cases were found to have placenta previa in the third trimester; 52 of them were found to be low lying placenta, 40 of them were type 2 placenta previa (marginal placenta previa), 2 of them were type 3 placenta previa (partial placenta previa), and 37 of them were diagnosed with type 4 placenta previa (complete placenta previa).

The mean maternal ages were significantly higher in the low lying placenta and placenta previa groups in comparison with controls (p=0.012 and p=0.003, respectively) (Table 1, 2). Mean gravidity, parity, and abortion numbers were significantly higher in the low lying placenta and placenta previa groups in comparison with the controls (Table 1, 2).

Mean PAPP-A levels were 1239.6 ng/mL, 1137.5 ng/mL, and 1619.3 ng/mL in the control group, low lying placenta group, and placenta previa groups, respectively (Table 3). There were no significant differences observed between groups (p=0.934). Mean BhCG levels were 86,892 IU/mL, 85,193 IU/mL, and 112,674 IU/mL in the control, low lying placenta, and placenta previa groups, respectively. Similarly, there were no significant differences observed between groups (p=0.151). PAPP-A MoM values were also similar between groups (p=0.604). BhCG MoM value was significantly higher in the placenta previa group in comparison with the low lying placenta group and control group (p=0.029 and p=0.011, respectively). There were no significant differences found between the low lying placenta group and control group in terms of BhCG MoMs (p=1). Although there were no significant differences found in NT measurements, NT MoM values were significantly higher in the placenta previa group in comparison with controls (p=0.020). Gestational ages at delivery were significantly lower in the placenta previa group in comparison with the control and low lying placenta groups (p<0.001 and p=0.017, respectively). No

**Table 1. Characteristics of the study population and neonatal outcomes**

| | Control group | Low lying placenta group | Placenta previa group | p values |
|---|---|---|---|---|
| Number of patients | 90 | 52 | 79 | |
| Maternal age (years) | 27.45±5.023 | 29.77±4.035 | 29.68±5.988 | 0.001 |
| Gravidity | 2.1±1.1 | 3.4±0.9 | 3.5±0.8 | <0.001 |
| Parity | 0.8±0.4 | 1.9±0.3 | 2.2±0.6 | <0.001 |
| Abortion history (number) | 0.6±0.4 | 1.3±0.8 | 1.8±0.5 | <0.001 |
| Maternal body weight[a] (kg) | 63.45±11.76 | 60.41±8.241 | 62.08±8.627 | 0.528 |
| Fetal birth weight (gr) | 3253.6±456.9 | 3127.6±684.7 | 3122.4±594.1 | 0.384 |
| Gestational age at delivery (weeks) | 39.3±1.06 | 38.3±2.83 | 37.9±1.85 | <0.001 |
| Apgar score at 1 minute | 8.5±1.06 | 7.87±1.92 | 7.92±1.04 | <0.001 |
| Apgar score at 5 minute | 9.6±0.66 | 8.98±1.96 | 9.16±0.77 | <0.001 |

Values are compared by Kruskal-Wallis test and are given as mean±standard deviations. P<0.05 is significant.

[a]Maternal weight in first trimester.

**Table 2. Post hoc analysis of Table 1 and Table 3**

| p values | Control group vs low lying placenta group | Low lying placenta group vs placenta previa group | Placenta previa group vs control group |
|---|---|---|---|
| Maternal age | 0.012 | 1 | 0.003 |
| Bhcg MoM | 1 | 0.029 | 0.011 |
| NT MoM | 1 | 0.152 | 0.020 |
| Gravidity (number) | 0.009 | 0.214 | <0.001 |
| Parity (number) | 0.012 | 0.068 | <0.001 |
| Abortion (number) | 0.002 | 0.096 | <0.001 |
| Gestational age at delivery | 0.213 | 0.017 | <0.001 |
| Apgar score at 1 minute | 0.021 | 0.414 | <0.001 |
| Apgar score at 5 minute | 0.029 | 0.880 | <0.001 |

p<0.05 is significant

NT: nuchal translucency; Bhcg: beta human chorionic gonadotropin; MoMs: multiples of medians

**Table 3. Comparison of first trimester screening test parameters of control group and study groups**

| First trimester screening test parameters | Control group (n=90) | Low lying placenta group (n=52) | Placenta previa group (n=79) | p values |
|---|---|---|---|---|
| PAPP-A (ng/mL) | 1239.6±791.6 | 1137.5±549.2 | 1619.3±4311.8 | 0.934 |
| PAPP-A MoM | 1.14±0.64 | 1.04±0.51 | 1.16±0.71 | 0.604 |
| Bhcg (IU/mL) | 86.892±47. 653 | 85.193±42.063 | 112.674±13.6793 | 0.151 |
| Bhcg MoM | 1.04±0.54 | 1.01±0.50 | 1.27±0.56 | 0.005 |
| NT (mm) | 1.35±0.35 | 1.4±0.39 | 1.48±0.48 | 0.150 |
| NT MoM | 1.1±0.28 | 1.13±0.29 | 1.26±0.42 | 0.019 |

Values are compared by Kruskal-Wallis test and are given as mean±standard deviations.

p<0.05 is significant

PAPP-A: pregnancy-associated protein A; Bhcg: beta human chorionic gonadotropin; NT: nuchal translucency; MoM: multiples of median

differences were observed between these two study groups and the control group in fetal birth weight (p=0.384) (Table 1). Both 1-minute and 5-minute Apgar scores were significantly lower in the low lying placenta and placenta previa groups in comparison with the control group (Table 1, 2). No significant differences were observed between the low lying placenta and placenta previa groups in terms of 1-minute and 5-minute Apgar scores (p=0.880).

Hospitalization due to hyperemesis gravidarum was observed in 3 cases within the control group (3.3%), 2 cases within the low lying placenta group (3.8%), and 8 cases within the placenta previa group (10.1%). The prevalence of hyperemesis gravidarum in the placenta previa group was significantly higher in comparison with the control and low lying placenta groups (p=0.029) (data not shown).

## Discussion

According to the results of this study, the prevalence of hyperemesis was significantly higher in the placenta previa group, which was also demonstrated to have significantly higher values of BhCG MoM.

Some previous studies demonstrated elevated mean BhCG levels in cases with hyperemesis gravidarum (4). Despite the presence of studies with controversial results, stimulation of the thyroid gland with BhCG seems to play a role in the development of this condition (4), and the higher levels of BhCG observed in cases with placenta previa might be the cause of the higher prevalence of hyperemesis in the placenta previa group.

BhCG is a glycoprotein, and its maternal serum levels are used to assess the risk of aneuploidies in the first and second trimesters. This glycoprotein is secreted from syncytiotrophoblasts that form the outer layer of chorionic villi in the human placenta (5). Previously, increased mean numbers of trophoblastic giant cells were demonstrated in deciduas and myometrial blood vessels of cases with placenta previa in comparison with normal placentas (6). This could explain the higher BhCG MoM values observed in the placenta previa group. Increased BhCG MoMs might be a consequence of an increased number of syncytiotrophoblasts in placenta previa cases, or better oxygenation might have resulted from increased fusion of cytotrophoblasts.

In considering the higher prevalence of hyperemesis in women with placenta previa, it could be suggested that a history of hyperemesis in a pregnancy might be predictive for the devel-

opment of placenta previa in the second and third trimester. Nevertheless, this issue should be clarified by specifically designed studies with larger populations prior to considering hyperemesis as a risk factor for later development of placenta previa. However, paying more attention to the development of placenta previa in the routine pregnancy follow-up of patients with hyperemesis gravidarum could be kept in mind.

The pathogenesis of placenta previa has not been fully understood yet. According to the trophotropic theory, the placenta migrates to better vascularized tissues. In normal pregnancies, the placenta grows towards the fundus, which can provide more blood. Distal portions of the placenta, close to the lower segment that has a relatively lower blood supply, regress or undergo atrophy. This process is known as "trophotropism." In accordance with the growing fetus, the uterus enlarges as the gestation progresses, and differential growth is observed at the lower uterine segment. These changes also increase the distance between the lower placental edge and cervix in normal pregnancies. Prior uterine damage or uterine scarring is known to be associated with the development of placenta previa. Defective vascularization of the endometrium due to scarring or atrophy caused by previous trauma, surgery, or infection may result in reduced differential growth of the lower uterine segment and less of an upward shift in placental location (7). The isthmic segment of the uterine artery's ascending branch has a wider diameter and a freer course than distal parts of blood vessels in placenta previa. It was previously suggested that a better blood supply and oxygenation might be provided in cases of placenta previa as a consequence of this condition (8). Factors, such as advanced maternal age, multiparity, prior cesarean delivery, multiple pregnancies, prior spontaneous or induced abortions, maternal smoking, and drug abuse, increase the occurrence of placenta previa (3). Utero-placental underperfusion due to atherosclerotic changes in uterine blood vessels was previously demonstrated in older women (9). The surface area of the placenta might be enlarging in these women to maintain sufficient blood supply, which may lead to encroachment of the placenta to the lower uterine segment. Similarly, uterine blood vessels localized at the prior placental attachment site might be deteriorated (10), and decreased utero-placental blood flow in early pregnancy owing to these changes in blood vessels in the prior placental attachment site might lead to the development of placenta previa in multiparous women. Moreover, scarring of the endo-myometrium in women with a history of cesarean delivery is thought to predispose them to the development of placenta previa, possibly due to decreased blood supply provided by the scarred portion of the endometrium (3). Therefore, it could be supposed that the development of placenta previa could be a measure against impaired placental blood supply in early pregnancies. The higher NT MoM values found in the placenta previa group could be a consequence of increased fetal cardiac workload due to subclinical placental dysfunction in early pregnancy. Although they were below the limit of statistical significance, NT MoM values were also higher in the low lying placenta group in comparison with controls. Lower levels of the increase in NT MoMs in the low lying placenta group in comparison with the placenta previa group could be associated with the mildness of the condition.

Although it should be primarily demonstrated by studies directly focusing on the status of supply maintenance of the early placenta, a period of impaired placental nutrition or blood supply in early pregnancy might induce the development of placenta previa as a compensatory mechanism, as mentioned above. However, placenta previa did not seem to be associated with findings of placental insufficiency in later periods of pregnancy (11). Therefore, if placenta previa is a compensatory mechanism against placental insufficiency in early pregnancy, it could be suggested that it usually succeeds.

There were no significant differences observed in fetal birth weights between the control and study groups in our study, and there are some studies with conflicting results about this aspect. Some of the studies indicate an increased incidence of fetal growth restriction in cases of placenta previa (12, 13), while others found no association after adjusting for confounding factors, like prematurity, preeclampsia, and smoking status (14, 15), and suggested that placenta previa was not associated with placental insufficiency, which also seems to be consistent with our results.

Atherosclerotic changes in uterine blood vessels of older women have shown to cause impairments in blood supply to the uterus and endometrium (9), and advanced maternal age was defined as a risk factor for placenta previa in previous studies (16). In our study, consistent with previous studies, maternal ages were significantly higher in the low lying placenta and placenta previa groups in comparison with controls.

Not surprisingly, mean gravidity, parity, and abortion rates were higher in the low lying placenta and placenta previa groups in comparison with controls. The association between multiparity, prior cesarean sections, prior abortion history, and placenta previa has already been demonstrated in previous studies (3).

Gestational ages at delivery were significantly lower in the placenta previa group in comparison with the low lying placenta and control groups. As we mentioned above, all cases in the placenta previa group were delivered by emergent or elective cesarean sections as soon as they reached sufficient fetal maturity. Contrarily, all cases with low lying placenta were attempted to be delivered by spontaneous or induced vaginal birth. This explains the difference in gestational ages at delivery between groups.

Both the 1- and 5-minute Apgar scores were lower in the low lying placenta and placenta previa groups in comparison with controls. This finding has been demonstrated in previous studies and is probably associated with possible adverse neonatal outcomes due to lower gestational age at delivery or maternal bleeding (13).

In conclusion, the prevalence of hyperemesis gravidarum in the first trimester seems to be increased in pregnancies that are complicated with placenta previa in the third trimester, and higher values of BhCG MoMs could be observed in these pregnancies in the first trimester aneuploidy screening tests.

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# An intensive care approach to posterior reversible encephalopathy syndrome (PRES): An analysis of 7 cases

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## Abstract

**Objective:** The aim of this study was to retrospectively evaluate the intensive care unit treatments applied to obstetrics patients with a diagnosis of posterior reversible encephalopathy syndrome (PRES).

**Material and Methods:** The cases of 7 pregnant patients who had been diagnosed with PRES between July 2011 and July 2013 were retrospectively reviewed. The patients' clinical data, brain magnetic resonance imaging (MRI) images before and after treatment, and neuropsychological tests were evaluated.

**Results:** Five out of 7 patients had eclampsia, 1 patient had severe preeclampsia, and 1 patient developed HELLP syndrome secondary to PRES. Calcium channel blockers and β-blockers were used as antihypertensive treatment. All patients were treated with parenteral magnesium sulfate. In addition, sodium thiopental was given to control sedation and convulsions in all patients except 1. The neurological and radiological findings of all cases treated in the intensive care unit improved.

**Conclusion:** Posterior reversible encephalopathy syndrome is a clinical condition with a multifactorial etiology and can result in different clinical findings. Radiological imaging techniques can be used for the diagnosis of PRES. Pregnancy and the postpartum period often lead to this syndrome. In some cases, PRES can cause irreversible neurological deficits or death. For patients with severe radiological findings, early diagnosis and thiopental infusion, in addition to treatment with antihypertensive agents and magnesium sulfate, may lead to quicker and more effective recovery from clinical manifestations. We suggest supplementation of standard treatment with early thiopental infusion. (J Turk Ger Gynecol Assoc 2014; 15: 217-21)

**Key words:** PRES, intensive care unit, obstetrics patient

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## Introduction

Posterior reversible encephalopathy syndrome (PRES) is a clinical entity characterized by temporary neurological symptoms, including acute headache, altered mental status, vision loss, and coma. Among the etiological factors associated with PRES are such diseases as hypertensive encephalopathy, preeclampsia/eclampsia/HELLP syndrome, immunosuppressive/cytotoxic drugs, acute or chronic renal disease, thrombotic thrombocytopenic purpura/hemolytic uremic syndrome, high-dose steroid therapy, liver failure/transplantation, endocrine dysfunction, hypercalcemia/hyperparathyroidism, bone marrow transplantation, massive blood transfusion/erythropoietin therapy, and porphyria (1, 2). Neuroimaging studies (MRI) in patients with PRES showed posterior cerebral edema (3-5). Following elimination of PRES-triggering factors and initiation of appropriate treatment, clinical and radiological findings usually resolve (6-8).

Most PRES cases occur concomitantly with acute or subacute neurological signs associated with convulsions. Usually, convulsions are initially local and then become generalized. Sometimes, seizures cause status epilepticus. In addition, changes in behavior and consciousness -ranging from somnolence and lethargy to stupor and coma- can occur. Moreover, various visual impairments, including hemianopsia, blurred vision, and cortical blindness, can be observed (1-4).

Patients with PRES are treated via provision of hemodynamic stability and hydration (intravenous crystalloid-colloids), maintenance of adequate arterial oxygen pressure, and improvement of electrolyte disturbances and coagulopathy (9). In patients with pulmonary aspiration, pulmonary edema, and hypoxemia, endotracheal intubation and mechanical ventilation are performed to maintain adequate oxygenation, while in those with impaired cardiac function, a central venous catheter may be required (10, 11). Although PRES is reversible when diagnosed and treated in a timely fashion, it can lead to neurological complications, including permanent brain damage and chronic epilepsy, when diagnosed at later stages (1, 2). Herein, we present 7 pregnant patients diagnosed with PRES, based on clinical and radiological findings, who were treated in our intensive care unit during a 2-year period. Patient

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records were retrospectively reviewed, and the medical treatment outcomes were evaluated in light of the literature.

## Material and Methods

The study protocol was approved by the ethics committee. The clinical records of 7 patients (aged 20-36 years) who were diagnosed with PRES and treated at the intensive care unit of Fırat University Medical School Hospital between July 2011 and July 2013 were retrospectively reviewed. The clinical diagnosis in all patients was made as previously described. Preeclampsia was diagnosed and classified according to American College of Obstetricians and Gynecologists (ACOG) criteria. Severe preeclampsia was defined as blood pressure ≥160/110 mm Hg, with either a urine dipstick showing 3+ or 4+ in a random urine sample or proteinuria ≥5.0 g during 24 h. Other evidence of severe disease included elevated serum creatinine, eclampsia, pulmonary edema, oliguria (<500 mL 24/h), fetal growth restriction, oligohydramnios, and symptoms indicative of significant end-organ involvement (headache, visual disturbance, and epigastric or right upper quadrant pain) (12). HELLP syndrome was defined based on the presence of hemolysis (serum LDH >600 IU/L, bilirubin >1.2 mg/dL, and the presence of schistocytes in peripheral blood), elevated liver enzymes (serum ALT and/or AST >70 IU/L), and thrombocytopenia (platelet count <100,000 $mm^{-3}$) after 20 weeks of gestation (13).

Cranial MRI (Signa Excite 1.5 T system (GE Healthcare, Milwaukee, WI, USA) using an 8-channel neuro-vascular head coil was performed in all patients after the onset of symptoms. Neuroimaging of the brain was performed via spin-echo T2-weighted (TR/TE/number of excitations =2880/126/2), spin-echo T1-weighted (460/14/2), and T2-FLAIR-weighted MRI (TR/TI/TE/number of excitations =8800/2000/126/2) in the axial, sagittal, and coronal planes with 5-mm slice thickness. In addition, cranial MRI and detailed neuropsychological test (EMG, EEG, NCV, VEP-BERA, and TCD) findings obtained 1 month post-treatment were evaluated in each patient.

## Results

The clinical and radiological findings are summarized in the Table 1. The mean age of the patients was 26.85±7.10 years

**Table 1. The clinical and radiologic findings and treatment in the PRES patients**

| Patients | Age (years) | G/P/A (n) | Clinical diagnosis | Gestational age (weeks) | Neurological symptoms | Status epilepticus | Location of T1-Hypo/ T2-Hyper intense abnormalities | ICU therapy | Time to remission (d) | Time to MV (d) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 21 | 1/0/0 | Eclampsia | 31 | Convulsions, Confusion, Headache Amlodipia | No | Bilateral Occipital | Thiopental, Esmolol, Magnesium | 4 | 1 |
| 2 | 20 | 1/0/0 | Eclampsia | 39 | Convulsions, Headache | Yes | Bilateral Occipital | Thiopental, Esmolol, Magnesium, Amlodipine | 4 | 2 |
| 3 | 33 | 4/3/0 | HELLP Syndrome | 26 | Convulsions, Headache | No | Left Basal Ganglia, Cerebellum | Thiopental, Esmolol, Magnesium, Amlodipine | 5 | 3 |
| 4 | 34 | 1/0/0 | Eclampsia | 36 | Convulsions, Headache | Yes | Bilateral Occipital Cerebellum | Thiopental, Esmolol, Magnesium, Amlodipine | 2 | 1 |
| 5 | 21 | 1/0/0 | Eclampsia | 31 | Convulsions, Headache | No | Bilateral Parieto-Occipital and Bilateral Basal Ganglia | Thiopental, Esmolol, Magnesium, Amlodipine | 4 | 2 |
| 6 | 23 | 2/1/0 | Severe Pre-eclampsia | 36 | Headache | No | Bilateral Occipital | Esmolol, Magnesium, Amlodipine | 2 | Ø |
| 7 | 36 | 3/0/2 | Eclampsia | 31 | Headache, Convulsions, Blurred Vision | Yes | Bilateral Cerebellar, Frontal, Parietal, Frontal, Occipital | Thiopental, Esmolol, Magnesium, Amlodipine | 15 | 10 |

PRES: posterior reversible encephalopathy syndrome; G: gravidity; P: parity; A: abortus; ICU: intensive care unit; MV: mechanical ventilation

(range: 20-36 years). The etiology of PRES was as follows: eclampsia: n=5 (72%); severe preeclampsia: n=1 (14%); and HELLP syndrome: n=1 (14%). Among the patients, hypertension (160-210/110-130 mm Hg), headache, and altered consciousness (ranging from confusion to coma) were observed. In all, 1 patient had blurred vision (14%) and 3 had status epilepticus (43%). Cranial MRI showed edema localized mainly to the posterior cerebral region. In addition, the cerebellum; basal ganglia; and frontal, parietal, and occipital lobes were affected to varying degrees (Figure 1).

Calcium channel blockers (amlodipine (Norvasc; Pfizer, İstanbul, Turkey) 10 mg/d, enteral) and β-blockers (esmolol (Brevibloc, Eczacıbaşı-Baxter, İstanbul, Turkey) 50-200 mg/kg/min, parenteral) were administered to treat hypertension. Parenteral magnesium sulfate (Osel Drug, İstanbul, Turkey) (4-6 g 20/min IV and 1-2 g/h infusion) was administered to all patients. Moreover, all patients but 1 (case 6) were treated with thiopental sodium (I.E. Ulagay, İstanbul, Turkey) (2-4 mg/kg bolus, followed by infusion of 3-5 mg/kg/h for 24-48 h) to control sedation and convulsions (Table 1). In total, 5 patients received mechanical ventilation support for 1-3 d, 1 patient required mechanical ventilation for 10 d (SIMV, f:12/min; FiO2: 40, TV: 7 mL/kg, PEEP: 5 cm H2O, I/E: 1/2), and 1 patient did not require mechanical ventilator support.

All patients but 1 improved neurologically 2-5 d after PRES was diagnosed. The patient who required mechanical ventilator support for 10 d regained consciousness on d 10; however, she had speech impairment that lasted 15 d and improved at the end of the first month. After discontinuing mechanical ventilation, all patients were given parenteral magnesium sulfate. The magnesium level in each patient was monitored and maintained in the therapeutic range (4.8-8.4 mEq/L), and deep tendon reflexes, respiratory rate, and urine output were observed hourly. Patients whose general condition improved were transferred to the obstetrics and gynecology clinic to continue their treatment. Cranial MRI findings 1 month later were normal (Figure 2). None of the patients had intracranial pathologies, such as fatal subarachnoid hemorrhage due to negative results. Long-term evaluation (>1 year) was possible in 3 of the patients, and neuropsychological dysfunction was not observed.

## Discussion

In the present study, the records of 7 pregnant women who were diagnosed with PRES, based on clinical and neuroimaging findings, and treated in the anesthesia intensive care unit of Fırat University Medical School Hospital between July 2011 and July 2013 were retrospectively reviewed. PRES was first described by Hinchey (1) as a sudden increase in blood pressure due to a defect in the autoregulation of posterior circulation that causes clinical symptoms, including headache, generalized seizures, visual disturbances, lethargy, confusion, stupor, changes in mental status, and focal neurological signs. The diagnosis of PRES is made based on clinical and radiological findings (1).

All patients in the present study were diagnosed with PRES based on clinical and radiological findings and had pregnancy-related preeclampsia and/or HELLP syndrome. In addition, all but 1 of the patients had generalized seizures, and 3 patients had status epilepticus. Moreover, 1 patient had blurred vision and speech impairment that lasted 15 d. One patient that was diagnosed with PRES based on radiological findings (hyperintensity in T2-weighted sequences of the bilateral occipital region) had only headache as a neurological symptom, whereas the other patients had widespread neurological symptoms.

Cranial CT can be used to diagnose hypodense lesions of posterior encephalopathy; however, MRI is the gold standard for diagnosing PRES (1-3). Currently, PRES is diagnosed

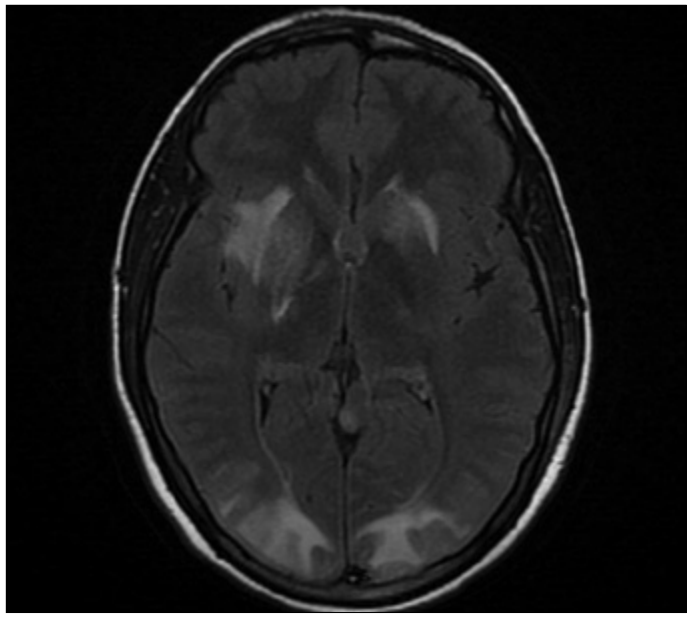

**Figure 1. T2-weighted cranial MRI sequences showing multiple, hyperintense areas bilaterally in the parietal-occipital regions and basal ganglia**

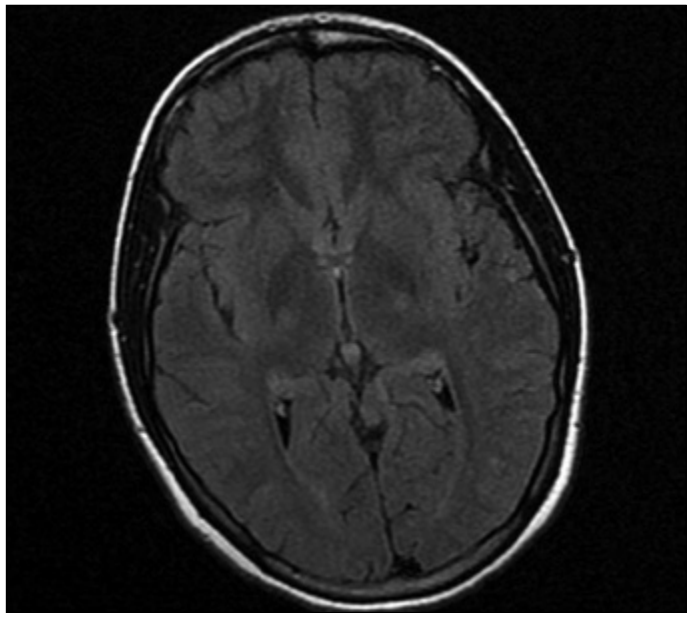

**Figure 2. MRI scan obtained 1 month post-treatment in patient 5**

more frequently than in the past due to the ubiquity of MRI. During the acute phase of PRES, hyperintensity is observed in T2-weighted MRI sequences, and iso-hypointensity is observed in T1-weighted sequences of gray and white matter. PRES primarily affects the parietal-occipital lobe; however, the cerebellar hemispheres, basal ganglion, frontal lobes, and brainstem are also frequently affected (1, 2, 14). Diffusion-weighted MRI is more sensitive to changes in the distribution of brain fluid, can detect edema in white matter during early-stage PRES, and is more reliable for differentiating between vasogenic edema and cytotoxic edema in PRES patients (3, 14). In patients with clinical symptoms suggestive of PRES, T2-weighted MRI sequences showed hyperintensity anomalies, especially in the occipital, parietal, and frontal lobes; cerebellum; and basal ganglia.

The pathogenesis of PRES is not fully understood, but it is likely to be associated with endothelial damage and disruption of cerebral autoregulation. Accordingly, edema that is reversible has been suggested to occur in PRES due to impaired autoregulation associated with hyperperfusion and blood-brain barrier disruption without infarction (15-18). When increased systemic blood pressure exceeds cerebral autoregulatory mechanisms, it increases the permeability of the blood-brain barrier, thereby causing extravasation of fluid and blood into the brain parenchyma (6, 19). Elevated blood pressure leads to focal dilation in cerebral blood vessels, exceeding the upper limit of autoregulation; consequently, both vasodilation and vasoconstriction develop in these regions (20, 21). Another theory of the development of PRES is that cerebral artery spasms, ischemia, and cytotoxic edema are caused by acute hypertension due to a decrease in cerebral blood flow (9).

With the appropriate treatment, most PRES patients completely recover within a few weeks (1). Delays in the diagnosis and treatment can negatively affect brain tissue, resulting in permanent neurological damage (5, 22-25). Sometimes, even with appropriate treatment, full recovery may not be achieved (26-28). In particular, ischemia can complicate the clinical picture, whether or not posterior encephalopathy with vasospasm and infarction are present (29). Full clinical remission was achieved in 2-5 d in 6 of the 7 presented patients, and MRI scans obtained 1 month later indicated that radiological remission was achieved in all patients. The intensive care process was delayed in 1 patient in the present study; she received mechanical ventilation support for 10 d, remission was delayed for up to 15 d, and her speech impairment persisted, even after she regained consciousness. This patient had the most common radiological involvement.

If elevated systemic blood pressure is left untreated, it can cause the development of or aggravation of cerebral edema. In such patients, mean arterial blood pressure should be maintained at 105-125 mm Hg. Nicardipine and labetalol are usually the first-choice drugs for the treatment of hypertension. Fenoldopam mesylate is a selective dopamine-1 agonist that can also prevent renal failure. Nitroglycerin is also frequently used in such patients but was reported to aggravate brain edema by causing vasodilation in the brain (30). Sodium nitroprusside, hydralazine, diazoxide, and nimodipine, which is reported to have neuroprotective effects, may also be useful for lowering blood pressure (31, 32). Esmolol (a β-1 selective adrenoceptor antagonist) was recently reported to potentially inhibit an increase in catecholamines and to have neuroprotective effects by causing changes in the immune system (33). In the present study, parenteral esmolol was administered in addition to an enteral calcium channel blocker (amlodipine) to all 7 PRES patients in order to maintain their mean arterial pressure at 110 mm Hg.

Magnesium sulfate, propofol, benzodiazepines, phenytoin, barbiturates, and fosphenytoin can be used to treat refractory status epilepticus in pregnant women. In addition to general systemic supportive care, magnesium sulfate is considered to be the mainstay of refractory status epilepticus treatment in pregnant women. Magnesium sulfate increases vasodilation, thus decreasing calcium-dependent vasoconstriction and increasing cerebral blood flow, which prevents ischemic attacks that cause coma (34, 35). Patients with refractory status epilepticus are usually treated with continuous infusion of midazolam, propofol, or barbiturates (36). In the present study, patients with generalized convulsions or status epilepticus were treated in the intensive care unit via endotracheal intubation, followed by thiopental infusion (2-4-mg/kg bolus followed by 3-5 mg/kg/h infusion for a period of 24-48 h) and mechanical ventilation support. The duration of mechanical ventilator support in the present study's patients was determined according to the severity of the clinical and radiological findings. In addition, after discontinuation of mechanical ventilation, patients were given a magnesium sulfate infusion (monitored to be in the therapeutic range of 4.8-8.4 mEq/L) for 1 d.

In conclusion, PRES is a clinical condition with a multifactorial etiology, is characterized by varying clinical symptoms, and is diagnosed via radiological imaging techniques. PRES can be diagnosed clinically and radiologically in cases of a sudden increase in blood pressure and consequent neurological conditions, such as headache, generalized seizures, visual disturbances, lethargy, confusion, stupor, and changes in mental status caused by the disruption of autoregulation of posterior circulation. We think that timely supplementation of thiopental infusion to antihypertensive and magnesium sulfate treatment can improve the clinical status faster and more efficiently in patients diagnosed with PRES who experience generalized seizures.

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# Maternal mortality and derivations from the WHO near-miss tool: An institutional experience over a decade in Southern India

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## Abstract

**Objective:** Preceding the use of World Health Organization (WHO) near-miss approach in our institute for the surveillance of *Severe Maternal Outcome (SMO)*, we pilot-tested the tool on maternal death cases that took place over the last 10 years in order to establish its feasibility and usefulness at the institutional level.

**Material and Methods:** This was a retrospective review of maternal deaths in Christian Medical College Vellore, India, over a decade. Cases were recorded and analyzed using the WHO near-miss tool. The International Classification of Diseases, 10th Revision was used to define and classify maternal mortality.

**Results:** There were 98,139 total births and 212 recorded maternal deaths. Direct causes of mortality constituted 46.96% of total maternal deaths, indirect causes constituted 51.40%, and unknown cases constituted 1.9%. *Nonobstetrical cause* (48.11%) is the single largest group. Infections (19.8%) other than puerperal sepsis remain an important group, with pulmonary tuberculosis, scrub typhus, and malaria being the leading ones. According to the WHO near-miss criteria, cardiovascular and respiratory dysfunctions are the most frequent organ dysfunctions. Incidence of coagulation dysfunction is seen highest in obstetrical hemorrhage (64%). All women who died had at least one organ dysfunction; 90.54% mothers had two- and 38.52% had four- or more organ involvement.

**Conclusion:** The *screening questions* of the WHO near-miss tool are particularly instrumental in obtaining a comprehensive assessment of the problem beyond the *International Classification of Diseases-Maternal Mortality* and establish the need for laboratory-based identification of organ dysfunctions and prompt availability of critical care facilities. The *process indicators*, on the other hand, inquire about the basic interventions that are more or less widely practiced and therefore give no added information at the institutional level.

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**Key words:** Maternal mortality, who near-miss tool, organ dysfunction

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## Introduction

A state's health status can largely be assessed by the incidence of its maternal mortality. The Millennium Development Goals (MDG) of the United Nations (1) had set the goal of 109/100,000 live births by 2015. In this regard, India and many of its most populous states have performed fairly under national government initiatives, like the *National Rural Health Mission (NRHM)*, *Janani Shishu Suraksha Yojana* (conditional cash transfer scheme*),* and *Accredited Social Health Activists* schemes (2). But, after the initial success, India may have to wait until 2023-2024 to attain the targeted maternal mortality ratio (MMR) if it fails to continue the linear declining tread achieved in 1997-2009 (3).

The study of "near-miss" and maternal death cases can provide useful insights into processes that can lead to maternal adverse outcomes (4). In 2007, the WHO established a technical working group to develop a standard definition and uniform identification criteria for maternal near-miss cases. The near-miss identification criteria thus developed target cases presenting with features of severe organ dysfunctions (5). It has been shown to yield useful and reliable data that can be used to improve the quality of care and monitor maternal health care interventions.

Preceding the use of the WHO near-miss approach in our institute for the surveillance of *severe maternal outcomes*, we pilot-tested the tool over the maternal death cases that took place over the last 10 years in order to establish its feasibility and usefulness at the institutional level.

## Material and Methods

This is a retrospective study based on data from the labor ward, intensive care unit, discharge summaries, and admis-

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sion records maintained by the medical records unit of Christian Medical College (CMC), Vellore, India. Situated in the southern India, CMC is a tertiary referral center and one of the oldest medical college hospitals in India. The hospital receives referrals mainly from the southern parts of the country. All mortality statistics in the concerned departments were compiled into an Epi Info database using the WHO near-miss tool (6) as the format. All maternal deaths following admission to the CMC from January 1, 2003 to December 31, 2012 were reviewed and analyzed. The CMC's maternal mortality audit team, in collaboration with the medical records unit, identified the maternal deaths. The case records with deficient information were used to calculate the MMR and the underlying cause of death only.
Identification and classification of *Maternal Death- Direct and Indirect,* along with further subdivisions (nine subgroups), were done according to WHO application of International Classification of Disease (ICD) to deaths during pregnancy, childbirth, and the puerperium: ICD-Maternal Mortality (ICD-MM) which is based upon the 10th revision of the ICD (ICD-10) (7).

**Data analysis**
Maternal mortality data were analyzed using Excel (Microsoft; Washington, USA) spreadsheet. Proportions and maternal mortality rates per 100,000 live births were calculated. Where more than one cause for death was recorded, only the first or the underlying cause (ICD-MM) of death was considered. Other secondary or tertiary causes of the obstetric death were noted if they satisfied the WHO near-miss criteria (6), which are further classified into *a) potentially life-threatening conditions, b) critical interventions,* and *c) organ dysfunction criteria.* Readers are advised to read through *the sample data collection form* in the WHO document (8) for maximum benefit from the discussion below.
Institutional ethical committee permission was sought and obtained for the study. The study was not funded. The authors declare that there is no conflict of interest.

## Result

There were 98,139 total births and 95,384 live births between 2003 and 2012. During this period, there were 28,788 cesarean deliveries and an average perinatal mortality rate of 35,391 per 1000 live births. There were 212 recorded maternal deaths during this period. The yearly maternal mortality ratio per 100,000 live births per year is shown in Table 1. The mean age at death was 24 years (standard deviation (SD) 4.4), mean parity was 1 (SD 0.97), and the mean period of gestation at delivery or death was 24 weeks (SD 8.15). The distribution of age, parity, period of gestation at death or birth, end of pregnancy mode, fetal outcome, and comorbidities is shown in Tables 2 and 3. Perinatal mortality was seen in 69% of cases.
*The direct causes* of mortality constituted 46.96% (99), *the indirect causes* constituted 51.40% (109), and *unknown cases* constituted 1.9% (4) (Table 4). It is interesting to note that the percentage distribution of the causes of maternal deaths did not change significantly over the decade, as depicted in Figure 1, where the causes have been shown against the three 40-month time periods. The killer trio *hemorrhage, puerperal sepsis, and hypertension* maintained their position as the leaders of death due to direct causes. These three together caused 37.1% of maternal deaths in our hospital over the last decade. Deaths related to abortions have shown a decline, and no such case was seen in the last 40-month period.
ICD-MM group VI "*Non-Obstetrical cause"* [48.11% (102/212)] is the single largest group, composed of numerous common and uncommon diseases. Rheumatic heart disease and fulminant liver disease were the most important medical conditions resulting in maternal death in this group. Infections [19.8% (42/212)] other than puerperal sepsis remain an important group, with pulmonary tuberculosis, scrub typhus, and malaria

**Table 1. Maternal mortality ratio from 2003 to 2012**

| Year | Total live births | Number of maternal deaths | Maternal mortality ratio (per 100,000 live births) |
|---|---|---|---|
| 2003 | 7758 | 29 | 374 |
| 2004 | 7938 | 17 | 214 |
| 2005 | 7625 | 18 | 236 |
| 2006 | 7753 | 25 | 322 |
| 2007 | 8629 | 18 | 208 |
| 2008 | 9316 | 15 | 161 |
| 2009 | 10,068 | 27 | 278 |
| 2010 | 11,115 | 22 | 198 |
| 2011 | 12,099 | 18 | 148 |
| 2012 | 13,084 | 26 | 198 |
| Total | 95,385 | 215 | 222 |

**Table 2. Maternal age, parity, and gestational age at delivery/death**

| | |
|---|---|
| **Maternal age** | 149 (100%) |
| 15-19 | 12 (8%) |
| 20-24 | 67 (45%) |
| 25-29 | 46 (31%) |
| 30-34 | 19 (13%) |
| 35-39 | 5 (3%) |
| **Parity** | 135 (100%) |
| 0 | 80 (59%) |
| 1 | 33 (24%) |
| 2 or more | 22 (16%) |
| **Gestational age at delivery or death** | 149 (100%) |
| 12 weeks or less | 9 (6%) |
| 13-28 weeks | 19 (13%) |
| 29-34 weeks | 28 (18%) |
| 35-41 weeks | 94 (68%) |

**Table 3. Mode of delivery, fetal outcome, and associated comorbidities**

| | |
|---|---|
| **Final mode of delivery** | 147 (100%) |
| Vaginal | 70 (48%) |
| Cesarean section | 47 (32%) |
| Abortion | 10 (7%) |
| Laparotomy for perforation | 3 (2%) |
| Discharged or died pregnant | 17 (12%) |
| **Fetal outcome** | 143 (100%) |
| Live birth | 43 (30%) |
| Stillborn | 84 (58%) |
| Early neonatal death | 16 (11%) |
| **Associated comorbidities** | 145 (100%) |
| Anemia | 77 (53%) |
| HIV positive | 4 (2.7%) |
| Prolonged labor | 5 (3.4%) |
| Previous LSCS | 8 (5.5%) |

LSCS: lower section caesarean section; HIV: human immunodeficiency virus

being the leading ones. There are clustered cases of maternal deaths due to H1N1 during an outbreak. Heat stroke caused 6 maternal deaths during the 10-year period. The higher percentage of maternal deaths due to medical conditions (Group 7 ICD-MM O98) was probably due to the presence of a large proportion of women with medical conditions in a tertiary referral hospital.

According to the WHO near-miss criteria, the organ dysfunctions encountered before the maternal death are shown in Figure 2. Cardiovascular and respiratory dysfunctions were the most frequently seen organ dysfunctions, either being an underlying cause or a later sequela. Among the six main primary causes, cardiovascular dysfunction was present in 53.73% (108/201) of cases and respiratory dysfunction was present in 60.19% (121/201). Coagulation dysfunction in the form of failure to form clots, massive transfusion of blood or red cells (≥5 units), and severe acute thrombocytopenia (<50,000 platelets/ml) was seen in a significant percentage (36.31%) of mothers who subsequently died, with the highest percentage in the mothers of group III *obstetrical hemorrhage* (64%). Uterine dysfunction, defined as hemorrhage or infection leading to hysterectomy, was seen in 32% of cases in group III *obstetrical hemorrhage*. Hysterectomy was also done in 7.15%, 3.8%, and 3.9% of cases in group I *pregnancy with abortive outcomes*, group II *hypertensive disorders,* and group VII *non-obstetric complications,*

**Table 4. Causes of maternal death according to International Classification of Diseases 10th Revision (ICD-10 & ICD-MM)**

| **Direct causes** | **99 (46.69%)** | **Indirect causes** | **113 (53.30%)** |
|---|---|---|---|
| *Group I. Pregnancy with abortive outcome* | *14 (6.6%)* | *Group VII. Non-obstetric complications* | *102 (48.11%)* |
| O00 Ectopic | 4 | O99 Other maternal diseases classifiable elsewhere | 67 |
| O01 Molar pregnancy | 3 | Cardiovascular causes | 28 |
| O03-O06 Septic abortion | 7 | Haematological causes | 6 |
| *Group II. Hypertensive disorders* | *26 (12.6%)* | Hepatic disorders | 24 |
| O15 Eclampsia | 12 | Neurological disorders | 4 |
| O14 Severe pre eclapsia & HELLP | 14 | Renal disorders | 2 |
| *Group III. Obstetrics hemorrhage* | *25 (11.8%)* | Respiratory disorders | 3 |
| O43 Placenta accreata | 1 | O98 Maternal infectious and parasitic diseases | 35 |
| O72 Post partum hemorrhage | 21 | *Group VIII. Unknown* | *4 (1.9%)* |
| O71 Ruptured uterus | 3 | *Group IX. Coincidental causes* | *7 (3.3%)* |
| *Group IV: Pregnancy related infections* | *27 (12.7%)* | Heatstroke | 6 |
| O41.1 Choriamnionitis | 1 | Road traffic accident | 1 |
| O86 Caesarean wound infection | 1 | | |
| O85 Puerperal sepsis | 25 | | |
| *Group IV. Other obstetric complications* | *3 (1.4%)* | | |
| O88 Amniotic fluid Embolism | 3 | | |
| *Group V. Unanticipated complication of management* | *4 (1.9%)* | | |
| O74 Complications of anesthesia during childbirth | 4 | | |

respectively. Neurological dysfunction was exceptionally high in group II *hypertensive disorder* (46.2%) and group IV *pregnancy-related infections* (25.9%) compared to other major ICD-MM groups (8.5% to 16%). All women who died had at least one organ dysfunction; 90.54% mothers had two- and 38.52% had four- or more organ involvement (Figure 3). WHO screening criteria other than *organ dysfunction* was not uniformly present in all maternal deaths. The *life-threatening conditions* and *critical* interventions, if used alone, would have missed 24% (36/150) and 8.6% (13/150) of cases, respectively (Figure 4).

Seventy-nine percent (26/33) of the deaths that took place within 12 hours of admission were women referred from outside. The average time *since delivery to death (days)* showed a declining trend, whereas the average duration of *hospital stay* showed a significant increasing trend over the decade (Figure 5).

## Discussion

To counter the stagnation in the decline of maternal mortality in many growing economies, like India, a pre-emptive approach to identify and treat maternal near-miss events seems prudent. In 2009, the WHO working group on maternal morbidity and mortality classifications (6) put forth the WHO near-miss criteria containing 25 severity markers, primarily laboratory-based, that were shown to be independently associated with poor maternal outcome. Cecatti et al. (9), in a prospective study of 673 cases of severe maternal morbidity, tested the performance of the WHO criteria against the SOFA score (10, 11), the gold standard for organ dysfunction identification in intensive care settings, and found it to be 100% sensitive and 70.4% specific for predicting maternal death cases. Sauza et al. (12), in their prospective study across 27 referral centers in a Latin American country, used a binary logistic regression model to describe the association between

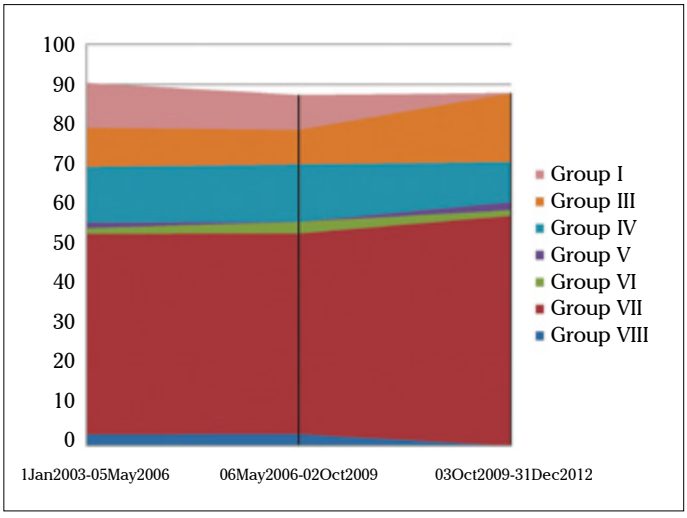


**Figure 1. Trends in maternal mortality cases (ICD-MM groups)**

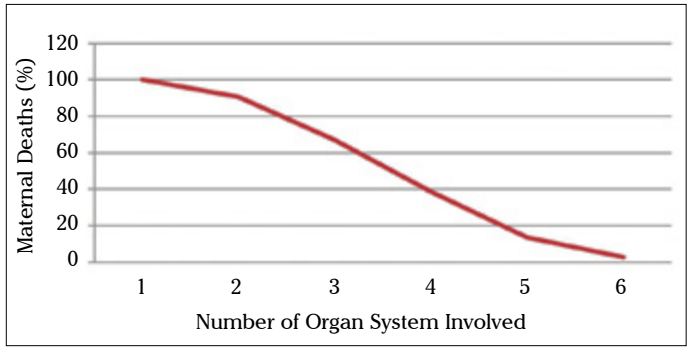


**Figure 3. Organ dysfunction(s) in maternal mortality (WHO Criteria)**

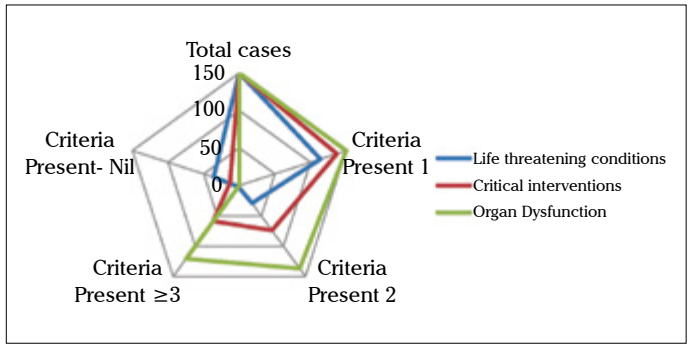


**Figure 4. WHO screening criteria in maternal mortality (Ability of different groups of screening criteria to identify mortality cases)**

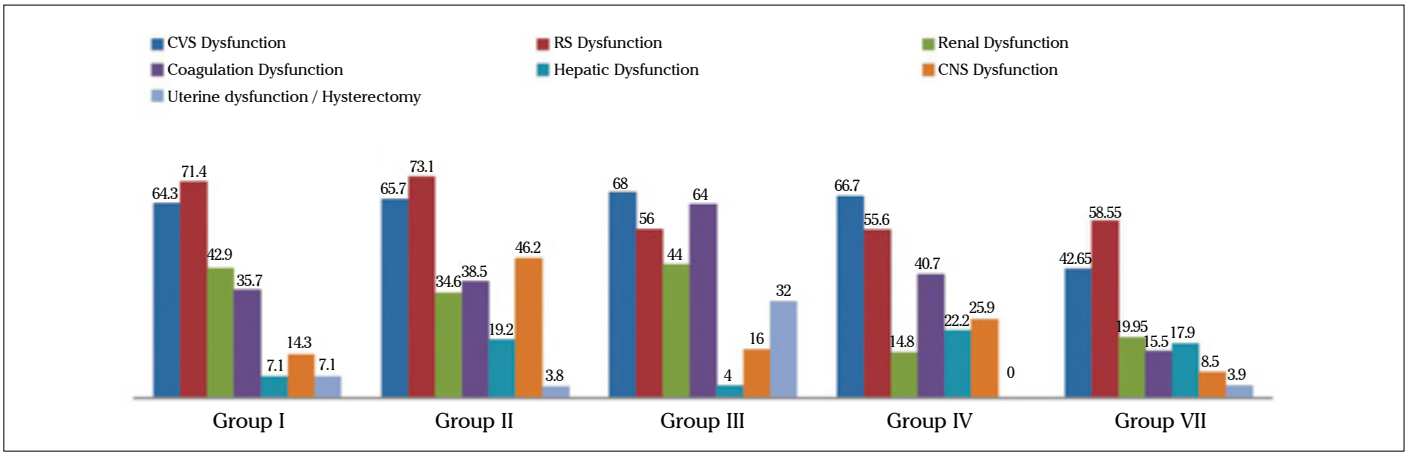


**Figure 2. Organ dysfunction (%) in major ICD-MM groups**

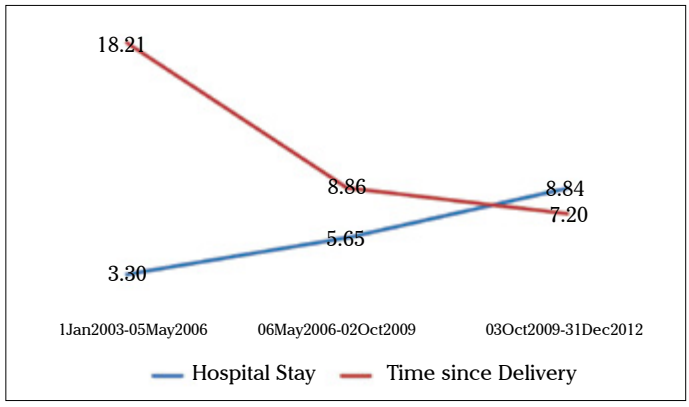


**Figure 5. Hospital stay vs time since delivery (Days)**

severe maternal outcome and WHO near-miss criteria. With a positive likelihood ratio of 106.8 (95% CI 99.56-114.6), the WHO near-miss criteria had a high association with maternal deaths. The presence of at least one organ dysfunction in every maternal mortality case in the present study seconds the findings of Sauza et al. (12). A maternal severity index model was also proposed by Sauza et al. (12) that predicted the probability of maternal death with complications of pregnancy. The WHO Multicountry Survey (WHOMCS) (13) on maternal and newborn health was conducted across 29 countries in Asia, Africa, and Latin America among 357 centers and showed that older, less educated, and higher-parity mothers with cesarean deliveries were more likely to have a severe maternal outcome (SMO). Perinatal outcome was dismal in SMO cases, with a 15 times higher perinatal mortality rate and a proportionate increase in preterm labor and neonatal intensive care unit admissions. Postpartum hemorrhage and hypertensive disorders of pregnancy were the most common obstetric complications. The incidence of sepsis and systemic infections was higher in comparison to puerperal endometritis, similar to the observations of the present study. Cardiovascular, respiratory, and coagulation dysfunctions were the most common organ dysfunctions, as also seen in the present study. Our study could further show that the spectrum of organ dysfunction across all major ICD-MM groups was similar, with very few exceptions, like higher coagulation disorder in the obstetric hemorrhage group and neurologic dysfunction in the hypertensive group. This dilutes the importance of classifying maternal deaths by the underlying cause and establishes the need for laboratory-based identification of organ dysfunction and prompt availability of critical care facilities. In spite of the high coverage of the indicated essential interventions (process indicators) across the health facilities, the WHOMCS showed unequal performance regarding maternal mortality. Furthermore, in the instances where the indicated essential interventions were missed in SMO cases (missed opportunities), the risk of death was not higher. This questions the relevance of the indicated essential interventions in reducing maternal mortality further beyond a limit. The WHOMCS included women in early puerperium up to 7 days postpartum and may have missed late puerperal cases of SMO, which by definition is up to 42 days.

The present study was limited by its retrospective design and the incomplete information in the medical records. Since this study was conducted with only mortality cases, the extrapolation of the findings to all pregnant women remains hypothetical. Nevertheless, in light of the previous works, this study gathers further support in favor of the use of the WHO maternal near-miss approach.

The WHO screening questions, composed of potentially life-threatening conditions, critical interventions, and organ dysfunction criteria, are particularly instrumental in obtaining a comprehensive assessment of the problem beyond the ICD-MM. The use of criteria on potentially life-threatening conditions alone, however, does not add information above what is already provided by the section on underlying cause of death/near-miss. The process indicators, especially the use of interventions, on the other hand, inquires about basic interventions, which are more or less widely practiced and therefore gives no added information.

The approach to improving maternal health is ideally through defining, quantifying, and taking measures to reduce severe maternal outcomes, which include both maternal near-miss and death. Provided that basic antenatal care and emergency obstetric care is available to the majority, further success will follow only a more aggressive approach in averting maternal mortality by identifying maternal near-miss and providing advanced life support to mothers with severe organ dysfunctions.

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***Informed Consent:*** *N/A.*

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

***Author contributions:*** *Concept - A.H., R.J.; Design - A.H., R.J.; Supervision - A.H., R.J., R.V.; Resource - A.H., R.V.; Materials - A.H., R.V.; Data Collection&/or Processing - A.H., R.J., R.V.; Analysis&/or Interpretation - A.H., R.J., R.V.; Literature Search - A.H., R.V.; Writing - A.H., R.J.; Critical Reviews - A.H., R.J.*

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# Effect of tamoxifen on ovarian reserve: A randomized controlled assessor-blind trial in a mouse model

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## Abstract

**Objective:** To determine whether tamoxifen (TMX) exposure causes a permanent decrease in ovarian reserve.

**Material and Methods:** A randomized controlled assessor-blind trial including 30 adult female inbred BALB/C mice. Fifteen mice in the TMX group were given a single 0.1-mg dose of TMX intraperitoneally. Fifteen mice in the control group were given a single dose of the vehicle at the same volume intraperitoneally. Two cycles later, blood samples were collected for determination of anti-Müllerian hormone (AMH) levels, and the mice were sacrificed. After gonadectomy, ovarian size was measured, and follicles were counted under light microscopy.

**Results:** Median serum AMH levels were 6.53 and 6.14 ng/ml in the control and TMX groups, respectively (p=0.03). Ovarian size was significantly decreased in the TMX group. While the number of primordial (9 vs 8), primary (6 vs 3), and secondary (4.5 vs 5) follicles were similar, there were significantly fewer preantral (11.5 vs 6, p<0.01) and antral (2 vs 1, p: 0.03) follicles, as well as corpora lutea (6 vs 3, p: 0.04), in the TMX group than in the control group. The number of atretic (2.5 vs 5, p: 0.048) follicles was increased in the TMX group.

**Conclusion:** Tamoxifen administration leads to arrested growth of gonadotropin-sensitive follicles, while insensitive follicles can remain unaffected. TMX is merely an endocrine disruptor, and it does not cause a decrease in primordial follicle pool. (J Turk Ger Gynecol Assoc 2014; 15: 228-32)

**Key words:** Tamoxifen, anti-Müllerian hormone, ovarian reserve, folliculogenesis, antral follicle count

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## Introduction

The incidence of premenopausal breast cancer is 15.1 per 100,000 woman-years for white women under 40 years of age (1). As such, it is the most common malignancy among women of reproductive age (1). While surgery is the mainstay of treatment, adjuvant chemotherapy significantly improves the survival of women with breast cancer. The 15-year survival rate of breast cancer patients under age 40 is increased by 6.1% if they receive chemotherapy (2).

However, chemotherapy can be gonadotoxic and impair the reproductive potential of women who survive the disease. The extent of gonadal damage inflicted by chemotherapy depends on several factors, including the age and pre-treatment ovarian reserve status of the patient, as well as the type, dose, and duration of the chemotherapy regimen.

Tamoxifen (TMX) is one of the commonly used agents for adjuvant chemotherapy following breast cancer. Compared to placebo, TMX results in a 13% and 15% reduction in the risk of recurrence and breast cancer mortality, respectively (3). While the gonadotoxicity of some chemotherapeutics, such as alkylating agents, is well established, there is limited information regarding whether TMX is harmful to the ovaries.

In the present study, we evaluated ovarian reserve, as assessed by serum anti-Müllerian hormone (AMH) levels and follicle counts, before and after TMX administration in a mouse model.

## Material and Methods

The study protocol was in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals and was approved by the Animal Care Committee of Uludağ University (no: 2012-04/08) (4).

### Animals and experimental protocol

Thirty 8-week-old female inbred BALB/C mice weighing 25-30 g were housed in ambient temperature of 20-24°C and humidity of 60%-70%. The lab had a 12-h light and dark cycle. Mice had access to chow and water *ad libitum*.

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The mice were randomly allocated to two groups. Fifteen mice in the TMX group were given a single 0.1-mg dose of TMX (100 μL TMX in vehicle consisting of 10% ethanol and 90% corn oil) with an intraperitoneal injection. Fifteen mice in the control group were given a single dose of the vehicle at the same volume intraperitoneally.

Mice were sacrificed by ether inhalation after two estrus cycles. Ovaries were removed and fixed in Bouin's solution for 3-4 hours and embedded in paraffin blocks. Blood samples were collected by intracardiac catheterization following anesthesia. Blood samples were immediately centrifuged at 3000 r/min for 30 minutes at room temperature, and the supernatant was collected for cryostorage at -20°C until analysis.

**Follicle counts**

Paraffin-embedded ovarian tissues were sectioned at 4-5 μm. The largest cross-section was used for Crossmann's triple staining in order to count the follicles in each developmental stage under light microscopy (5). The surface area of this section was measured in order to give a surrogate measure for ovarian size. A digital camera (Sony DSC-F717, Tokyo, Japan) attached to a Nikon 4S-2 Alphaphot light microscope (Nikon 4S-2 Alphaphot, Tokyo, Japan) and Scion-Image software (Scion Corporation, Boonsboro, Maryland, U.S.) were used for the measurements. The image analysis system was calibrated using a stage micrometer.

The follicles were categorized as follows: primordial, an oocyte surrounded by squamous pre-granulosa cells, of which not more than one is an enlarged granulosa cell; primary, a relatively larger oocyte surrounded by at least two or more cuboidal granulosa cells; secondary (transitional), an oocyte surrounded by two to three layers of cuboidal granulosa cells; pre-antral, an oocyte surrounded by more than three layers of granulosa cells with no apparent antrum; antral, an oocyte surrounded by multiple layers of granulosa cells with an antrum; and atretic, an oocyte with a pyknotic nucleus and vacuolated cytoplasm and detached granulosa cells also showing degenerative changes and floating freely in the antrum (Figure 1) (6).

**AMH measurements**

A mouse AMH kit (Hangzhou Eastbiopharm Co. Ltd.; Hangzhoui, China) was used to determine plasma AMH levels using the ELISA method. The analytical sensitivity of the kit was 0.05 ng/mL, and the boundaries of analysis were 0.1-40 ng/mL.

**Statistical analysis**

Continuous variables were defined with median and interquartile ranges. Mann-Whitney U-test was used for comparisons between the study groups. A two-sided p value $<0.05$ was considered statistically significant. Statistical Package for Social Sciences v20 (IBM; Armonk, N.Y., U.S.A.) was used for analyses.

## Results

While 25 mice survived during the study period, 5 mice in the control group were found dead in their cages 4 days after intraperitoneal injection. Upon laparotomy, there was no evidence of peritonitis or bowel perforation, and the cause of death remained unknown for these mice. They are not included in the comparative analysis.

**Area of ovarian section**

The largest cross-section of the ovaries was significantly smaller in TMX-exposed mice than in the controls (1.51, 1.09-1.84 $mm^2$ vs 2.12, 1.63-2.62 $mm^2$, respectively, p=0.01).

**Follicle counts**

Follicles of all stages were observed in ovarian sections of both the control and TMX groups (Figure 2).

While the numbers of primordial, primary, and secondary follicles were similar in the two groups, there were significantly fewer preantral and antral follicles and corpora lutea present in the TMX group than in the control group. The number of atretic follicles was increased in the TMX group. The follicle counts in both groups are presented in Table 1.

**Plasma levels of AMH**

Median serum AMH levels were 6.53 (5.71-7.47) and 6.14 (6.06-6.52) ng/mL in the control and TMX groups, respectively (p=0.03).

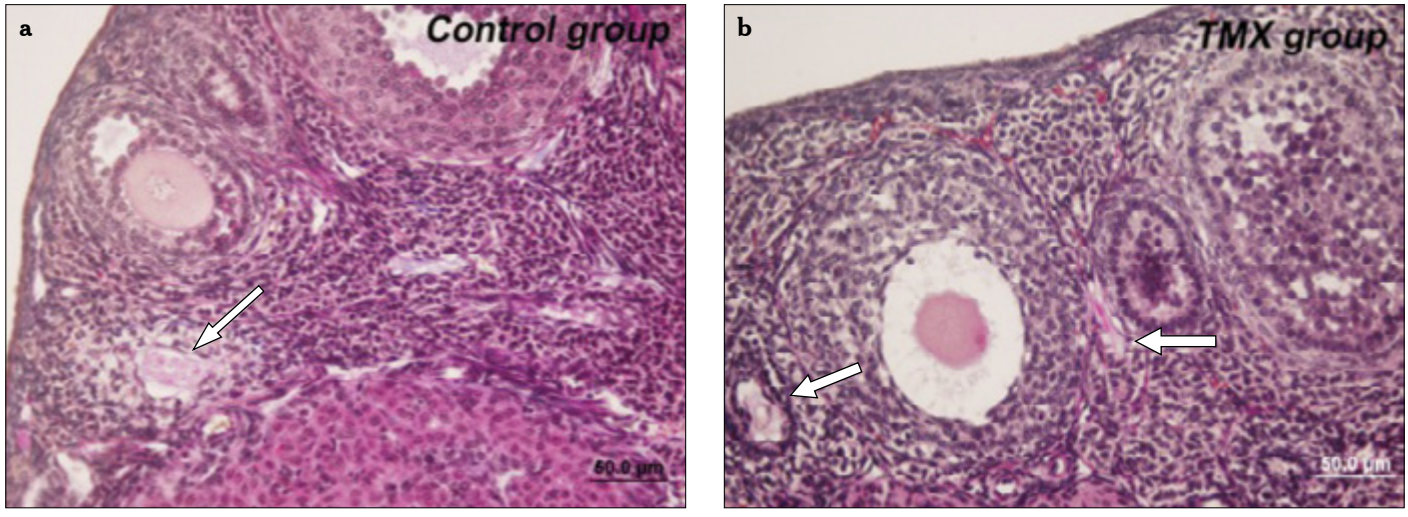


**Figure 1. a, b. Ovarian sections of control (a) and tamoxifen-exposed (b) mice show atretic follicles. Arrows indicate atretic follicles**

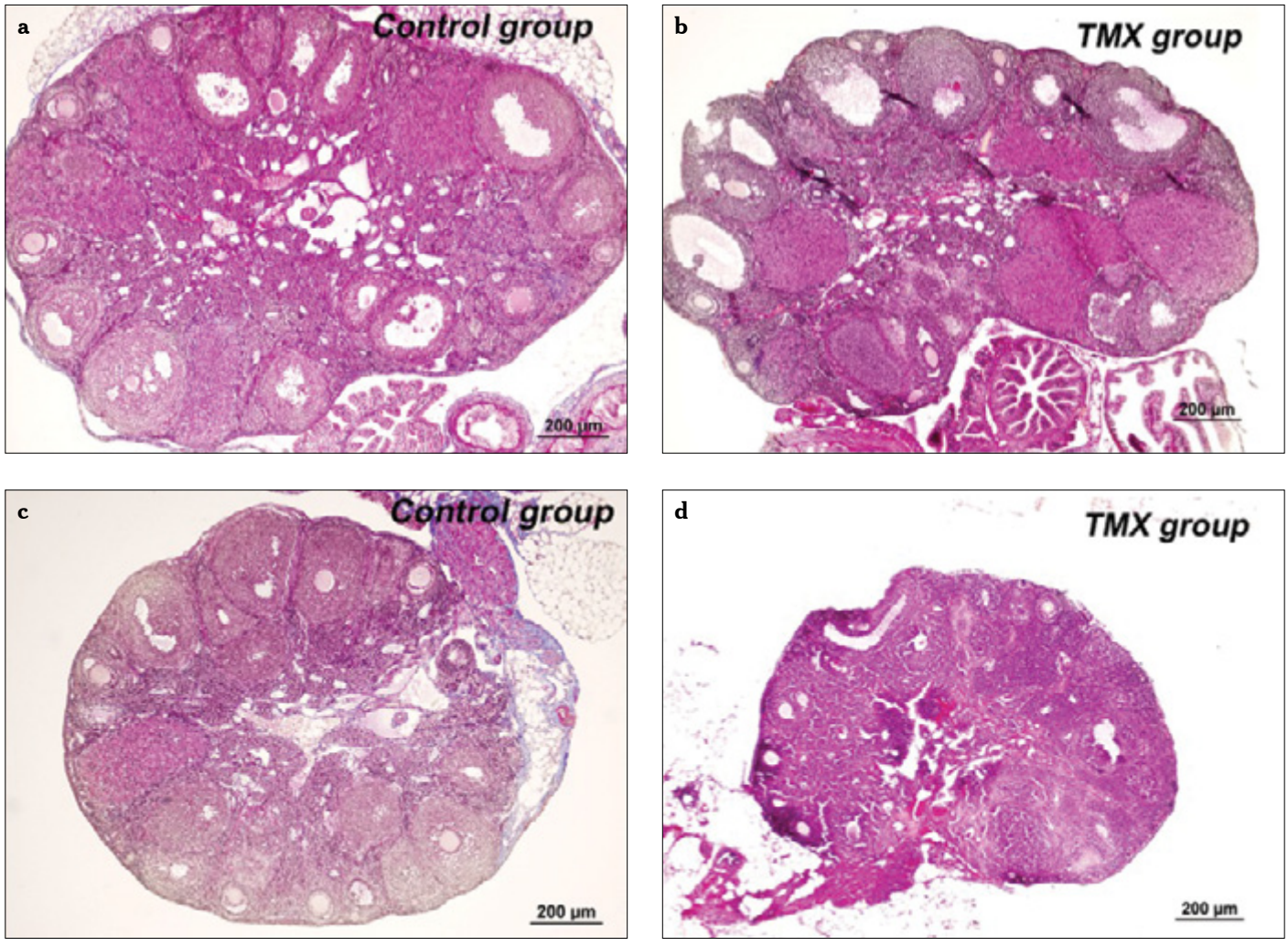


**Figure 2. a-d. Ovarian sections of control (a,c) and tamoxifen-exposed (b,d) mice show follicles in different stages of development. Ovarian size is reduced in tamoxifen-exposed mice**

**Table 1. Follicle counts in ovarian specimens from tamoxifen and control groups**

| Follicle type | Control (n=10) | Tamoxifen (n=15) | p value |
|---|---|---|---|
| Primordial | 9 (6-11) | 8 (6-13) | 0.89 |
| Primary | 6 (3-7) | 3 (3-5) | 0.26 |
| Secondary | 4.5 (2.8-7.8) | 5 (4-6) | 0.68 |
| Preantral | 11.5 (9-16.3) | 6 (4-9) | <0.01 |
| Antral | 2 (0.8-2) | 1 (1-1) | 0.03 |
| Corpora lutea | 6 (2-8) | 3 (1-5) | 0.04 |
| Atretic | 2.5 (1.5-4.5) | 5 (4-7) | 0.048 |

All values are median ($25^{th}$-$75^{th}$ percentile).

## Discussion

Our results indicate that TMX exposure is associated with decreased ovarian size and decreased numbers of pre-antral and antral follicles in ovarian sections. However, the numbers of primordial, primary, and secondary follicles were not affected. In addition, while the number of corpora lutea decreased, the number of atretic follicles increased following TMX exposure. Finally, TMX was also associated with a significant decrease in serum AMH levels, a finding that is in keeping with the observed decrease in pre-antral and antral follicle counts, the major source of circulating AMH.

Tamoxifen is a selective estrogen receptor modulator; however, its mechanism of action in different tissues is not clearly understood. Upon binding to nuclear estrogen receptors, TMX causes a conformational change of the dimeric receptor and interferes with its interactions with co-factors of estrogen receptor-mediated gene regulation. The type of estrogen receptor, such as ER-alpha or ER-beta, and variations in co-factors in different tissues and under different conditions are likely to play a role in the tissue-specific effects of TMX. While TMX blocks the effects of endogenous estrogen in breast tissue, it exerts estrogenic effects in the uterus, bone, and liver. It is thought to interfere with estrogen feedback at the hypothalamic and pituitary levels. However, there are limited data about the direct effects on the ovary and ovarian follicles.

The effects of TMX on various organ systems, the estrous cycle, and fertility potential were investigated in a number of rodent studies (7-11). In these studies, TMX was administered orally (7, 9-11) or subcutaneously (8) for 2 to 4 weeks. The daily TMX dose ranged between 0.03 and 5 mg/kg. TMX exposure led to anovulation in the majority of rats in all but one study assessing estrous cycles-70% of TMX-exposed rats were anovulatory in the study by Donath and Nishino (8, 9, 11).

Compared to controls, both absolute and relative ovarian weight was found to be significantly decreased following TMX exposure in all but one study (7-11). Similar to our findings, Matsuda et al. (7) and Tsujioka et al. (11) noted a decrease in the number and size of corpora lutea in TMX-treated groups. Tsujioka et al. (11) reported similar numbers of small- and medium-sized follicles in TMX-treated and control groups, which was consistent with our observations. In addition to follicle counts under light microscopy, Tsujioka et al. (11) conducted immunohistochemical staining with anti-proliferating cell nuclear antigen (PCNA) antibody in order to better identify resting primordial follicles. PCNA immune-stained sections confirmed the similar numbers of small- and medium-sized follicles in TMX and control groups. Unchanged numbers of small follicles, which represent gonadotropin-insensitive primordial and primary follicles, accompanied by decreased numbers of pre-antral and antral follicles, as well as decreased numbers of corpora lutea, were observations that were common to all of the studies mentioned above (7-11). This suggests that TMX per se is not harmful for resting primordial and gonadotropin-insensitive small follicles. However, the decreased numbers of pre-antral and antral follicles and corpora lutea, accompanied by increased numbers of atretic follicles, suggest that gonadotropin stimulation of further follicular growth and ovulation is impaired with prolonged TMX exposure. This is also supported by the observation of impaired estrous cycles in the studies by Donath (8) and Tsujioka (11). In the only study in which serum gonadotropin levels were assessed, basal levels of serum luteinizing hormone, androgens, and estradiol were found to be decreased in TMX-treated rats. Preovulatory surges of LH and follicle-stimulating hormone (FSH) were also suppressed in TMX-treated rats in the same study (8). In addition, the significantly decreased pituitary weight that was observed following TMX exposure in the studies by Matsuda et al. (7) and Tsujioka et al. (11) suggested decreased gonadotropin production following extended TMX exposure.

In addition to gonadotropin deprivation, local effects of TMX on follicular estrogen receptors can contribute to follicular atresia. Although the exact mechanisms are unknown, it is widely accepted that FSH action is augmented by estradiol (12). Estradiol maximizes FSH induction of antrum formation, aromatase expression, and activity and LH receptor expression and LH activity (12-20). Whether extended TMX exposure only decreases gonadotropin production or also interferes with the stimulation of granulosa cells by existing FSH remains to be determined, but the latter could have contributed to our observations.

Overall, TMX seems to decrease gonadotropin stimulation of pre-antral and antral follicles, leading to anovulation and follicular atresia. Decreased numbers of these large follicles can lead to decreased ovarian size/weight, as observed in the present and former studies. As pre-antral and early antral follicles produce AMH, the decreased serum AMH levels observed in our study are consistent with histological observations. However, the preserved numbers of primordial, primary, and secondary follicles suggest that the resting follicle pool is unaffected by extended TMX exposure. Therefore, despite impaired growth of gonadotropin-sensitive/-dependent pre-antral and antral follicles, it is reasonable to suggest that ovarian reserve, defined as the quantity of resting follicles, remains unaffected by TMX exposure. TMX seems to be solely an endocrine disruptor, and ovaries should be able to respond adequately to gonadotropin stimulation following restoration of hypothalamo-pituitary-ovarian feedback mechanisms.

***Ethics Committee Approval:*** *Ethics committee approval was received for this study from Animal Care Committee of Uludağ University.*

***Informed Consent:*** *N/A.*

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

***Author contributions:*** *Concept - K.Ö.; Design - K.Ö., A.T.A.; Supervision - K.Ö., B.Ata.; Resource - K.Ö., A.T.A.; Materials - A.T.A., B.Z. ; Data Collection&/or Processing - A.T.A., B.Z., S.P., B.Avcı.; Analysis&/or Interpretation - B.Ata, K.Ö., A.T.A.; Literature Search - B.Ata., A.T.A.; Writing - B.Ata., A.T.A.; Critical Reviews - K.Ö., B.Avcı., B.Z.*

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

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# Effects of different anesthesia protocols on lactation in the postpartum period

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## Abstract

**Objective:** Many factors can influence the secretion of breast milk. Cesarean section is a risk factor for late onset of breastfeeding.

**Material and Methods:** In our study, we compared the lactation process by mothers who underwent elective cesarean section under general anesthesia, spinal anesthesia, epidural anesthesia, and normal birth; 84 patients between 18-40 years of age with a risk of ASA I-II were included. Randomly patients were divided into four groups: group G (general anesthesia, n:21), group S (spinal anesthesia, n:21), group E (epidural anesthesia, n:21), and group V (vaginal birth, without anesthesia, n:21). Oxytocin and prolactin values of all patients before and after operation or birth were recorded. In addition the initiation time of lactation after delivery or cesarean section were recorded.

**Results:** In all groups, there were no significant differences among hormone levels in the prepartum period (p=0.350). Prolactin levels in group G (p=0.011) and oxytocin levels in group V (p=0.012) in the postpartum period were significantly higher than in the other groups. The start of lactation was significantly delayed in group G (p=0.003).

**Conclusion:** We consider that the onset time of lactation is delayed in patients undergoing cesarean section with general anesthesia when compared with patients who undergo cesarean section with spinal and epidural anesthesia and with patients who undergo normal vaginal birth. Because of the delay of awakening and recovery of cognitive functions in general anesthesia, communication between the mother and the newborn is delayed and so is the lactation. (J Turk Ger Gynecol Assoc 2014; 15: 233-8)

**Key words:** Anesthesia technique, lactation, normal birth

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## Introduction

Breast milk has many features reinforcing newborn development, and as a nutrient, it is superior to all artificial nutrients (1). Breastfeeding is given great value in the healthy development of a newborn (2). It is important that a mother ideally begins breastfeeding her newborn baby in the first hour after delivery. Cesarean section and primiparity are important risk factors for late onset of breastfeeding (3). Cesarean section is one of the most important operations in obstetrics, and its incidence is approximately 25% of all deliveries and is progressively increasing. General and regional anesthesia techniques are performed in the anesthetic management of cesarean sections (2).

Consulting the relevant literature, articles about the effects of epidural anesthesia on lactation are common, but there is no article about the effects of general, spinal, and epidural anesthesia techniques and normal vaginal birth on lactation. We designed this study to test our clinical observations about the difference in lactation between patients who underwent cesarean section and vaginal birth.

In our study, we aimed to compare the lactation process by mothers who underwent elective cesarean section under general anesthesia, spinal anesthesia, epidural anesthesia, and normal vaginal birth.

## Material and Methods

The study was approved by the Ethical Committee of Clinical Research from the University of Duzce, Faculty of Medicine (date: 04.08.2011, number: 2011/173). The study was supported by the Committee on Scientific Research Projects from the Düzce University (date: 05.12.2011, number: 2011/350). A total of 84 patients were included into the study, and 6 patients were excluded (Figure 1); 63 of them were underwent elective cesarean section, and 21 patients had a normal vaginal delivery in the Clinic of Gynecology and Obstetrics. All patients were between 18-40 years of age and had a risk of ASA I-II. Before the procedure, informed consent was obtained from all patients (ClinicalTrial.gov ID: NCT02016937).

Exclusion criteria were: non-elective cases, plural pregnancies, preterm pregnancies, fetal anomalies, retardation of fetal development, newborns with birth weight under 2500 grams, infants with a risk of aspiration of meconium or amnions, pathologies affecting acid-base balance, diabetes mellitus,

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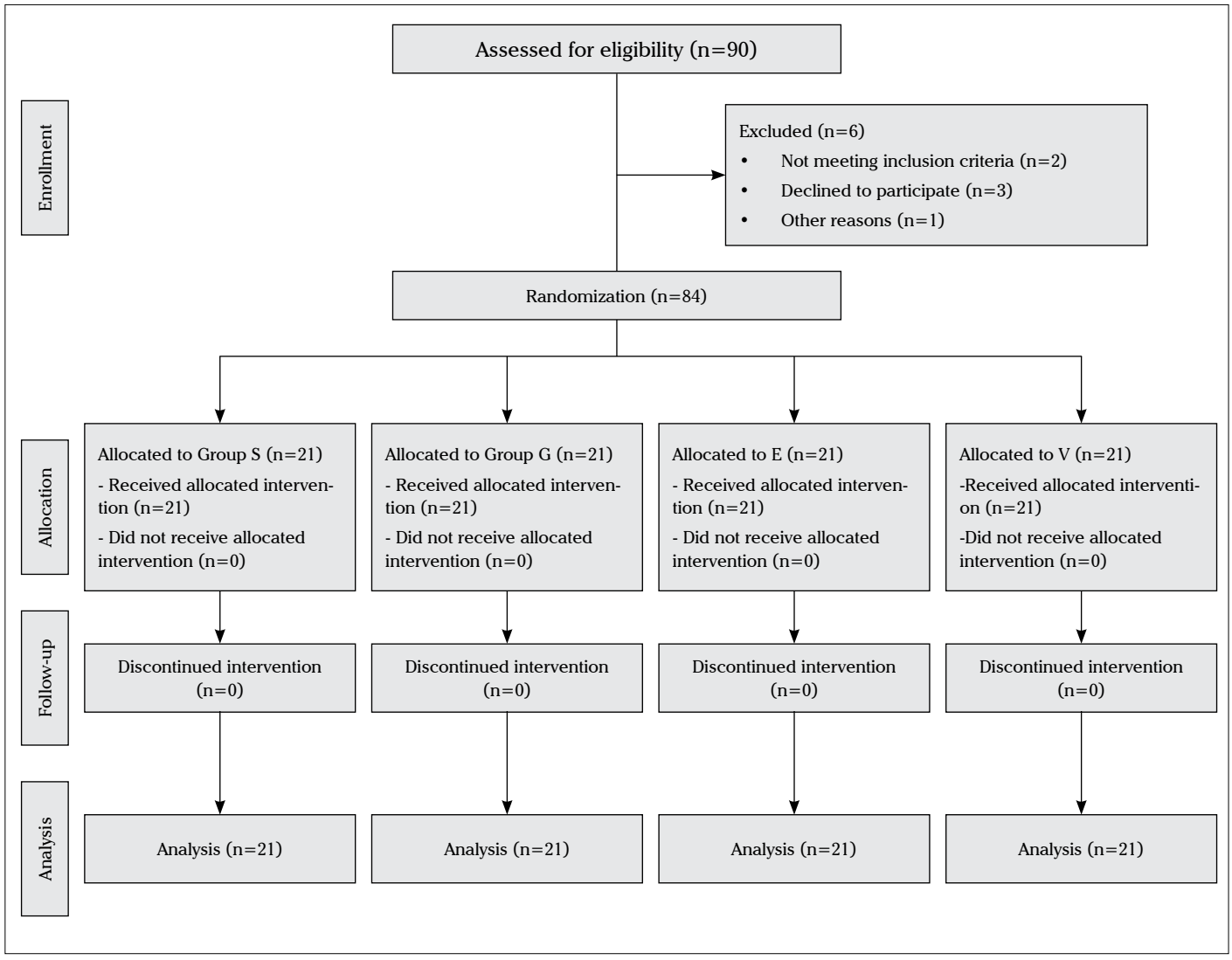


**Figure 1. Consolidated Standarts of Reporting Trials (CONSORT) flow diagram of the study**

hypertension, antepartum hemorrhage, asthma, COPD (chronic obstructive pulmonary disease), Rhesus incompatibility, obstetric complications (like congenital malformations), history of malignant hyperthermia, morbid obesity, opioid sensitivity, alcohol or drug addiction, diseases of the coronary arteries, congestive heart failure, serious anemia, history of liver or kidney diseases, hypovolemia, hypotension, systemic inflammatory response syndrome, sepsis, history of allergic reactions to drugs used in the study, and history of drugs affecting lactation. Patients were randomly divided into 4 groups: group G (general anesthesia for cesarean section, n=21), group S (spinal anesthesia for cesarean section, n=21), group E (epidural anesthesia for cesarean section, n=21), and group V (normal vaginal birth without anesthesia, n=21). A blood sample of 3 milliliters was taken from all patients 2.5 hours before the procedure, and oxytocin and prolactin levels in these blood samples were determined. No patient received premedication. Group G (general anesthesia for cesarean section) received preoxygenation with 100% oxygen for 3-5 minutes before intubation. In order to expose the fetus minimally to anesthetic agents, induction was performed after the disinfection and covering up of the surgical area. Induction was performed with propofol (2 mg/kg) and rocuronium (0.6 mg/kg). After the onset of neuromuscular block, patients were intubated with compression maneuver of the cricoid cartilage. Controlled ventilation was provided with a Datex Ohmeda S/5 Avance anesthesia machine with a tidal volume of 8-10 ml/kg and respiration frequency of 10-12/ min. Anesthesia was maintained with oxygen (50%), air (50%), and sevoflurane of 1 MAC. In the maintenance of anesthesia, rocuronium 0.15 mg/kg was administered when it was necessary. After delivery of the newborn, fentanyl 1-1.5 mcg/kg was administered. Patients in group S (spinal anesthesia for cesarean section) received 750-1000 ml of 0.9% NaCI solution (10-15 ml/kg) as infusion over 20-30 minutes. Under strict aseptic precautions, a 25 G Quincke spinal needle was introduced into the L3-L4 or L4-L5 intervertebral space in a midline approach in the sitting posture, and after confirmation of free flow of CSF, 10-11 mg of predetermined drug solution (hypertonic bupivacaine

0.5%) was injected. We let the operation begin when sensory and motor blockade was verified. Oxygen of 100% (3 L/min) was administered throughout the operation via nasal cannula. Patients in group E (epidural anesthesia for cesarean section) received 750-1000 ml of 0.9% NaCI solution (10-15 ml/kg) as infusion over 20-30 minutes. We conducted epidural anesthesia with an 18-gauge Tuohy needle at the L3-L4 or L4-L5 epidural space by midline approach in the sitting position. Then, 3-5 minutes after injection of 3 ml lidocaine as a test dose, when the patient had no sign of a subarachnoid injection, like prickling in the lower extremities, or of intravascular injection, like nausea, vomiting, tachycardia, and tinnitus, a 20-gauge epidural catheter was inserted to cephalic. We injected 10 ml of 0.5% bupivacaine via epidural catheter. The operations began when sensory and motor blockade was verified. Oxygen of 100% (3 L/min) was administered throughout the operation via nasal cannula.

Patients in all 3 groups were monitored in the operation room with a Datex-Ohmeda monitor, and the electrocardiogram (ECG), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), heart rate (HR), and peripheral oxygen saturation ($SPO_2$) were recorded. Ephedrine 5-10 mg and/or atropine 0.5 mg was administered when significant hypotension and bradycardia occurred. After delivery of the newborn, 30 IU of oxytocin in a 1000-cc solution of 0.9% NaCI was infused, and if the patient was not hypertensive, methylergonovine 0.2 mg was administered intramuscularly.

Patients in group V (spontaneous vaginal birth without anesthesia) were observed by gynecologists in the Clinic of Gynecology and Obstetrics during the delivery. They received no anesthesia. After delivery of the newborn, 30 IU of oxytocin in a 1000-cc solution of 0.9% NaCI was infused, and if the patient was not hypertensive, methylergonovine 0.2 mg was administered intramuscularly.

In all groups, blood samples were taken at the 24$^{th}$ hour after delivery, and oxytocin and prolactin levels were measured. Plasma of blood samples, taken pre- and post-partum, were stored at a temperature of -80°C. Prolactin levels were determined with the chemiluminescence immunoassay technique Cobas e 601 kit (Roche® Diagnostics, Mannheim, Germany) using a commercial kit (Roche®). Oxytocin levels were determined with a commercial ELISA kit (Cusabio Biotech CO. Ltd). All patients' onset times of lactation were recorded. Our primary outcome was lactation onset time. Our secondary outcome was blood prolactin and oxytocin levels.

### Statistical analysis

Data were analyzed using Statistical Packages for the Social Sciences (SPSS, ver. 18.0 for Windows; SPSS Inc. USA). Descriptive statistical methods (average value, standard deviation) were used for evaluation of the data. A power calculation ensured that 21 patients were recruited to provide 80% power for a 30% difference in the ratio of patients whose onset of lactation was within 24 hours after delivery either with or without anesthesia techniques at an alpha significance level of 0.05. We used the one-way ANOVA test for quantitative comparison of parameters with normal dispersion, because there were more than two groups, and Tukey test for the determination of the group that was causing the difference. We used independent-samples t-test for comparison of quantitative data and for comparison of parameters with normal dispersion between all groups. Repeated-measures ANOVA was used for comparison of parameters with normal dispersion in the same group, and Bonferroni test was used for determination of the difference-causing quantity. The results were assessed at a confidence interval of 95%. A p value $<0.05$ was considered to be statistically significant, and $p<0.01$ was highly significant.

## Results

Following approval from the institutional ethical committee, written informed consent from 84 patients was obtained. Mean age was 27.80 years, and mean weight was 75.42 kg, and there were no significant differences in age, weight, and duration of pregnancy between groups (Table 1). In all groups, there was a significant difference between APGAR scores in the 1st and 5th minutes ($p<0.001$). The data in Table 1 and the conditions that affected the time of lactation were similar in each group; so, they were not taken into consideration.

There was no significant difference in the prepartum period prolactin levels among all groups ($p=0.350$). In the postpartum period, prolactin levels were significantly higher in group G compared to the other groups ($p=0.011$). In group, E they were significantly lower in the postpartum period than in group V and group G ($p=0.026$). Additionally, in group S, prolactin levels were significantly lower in the postpartum period than in group V and group G ($p=0.015$) (Table 2). There was no significant difference in the prepartum period oxytocin levels among all groups ($p=0.138$). In group V, they were significantly higher in the postpartum period than in group G and group S ($p=0.012$). Eventually, postpartum period oxytocin levels in group E were significantly higher in than in group S ($p=0.039$) (Table 2). Lactation onset time was compared between groups with and without anesthesia. It was determined that the time of lactation was significantly delayed in the general anesthesia group. Between the other three groups, there was no significant difference in the lactation onset time. In the three groups that received anesthesia, the lactation started after the 24$^{th}$ hour in 13 of 63 patients (20.6%). In group V, the lactation started after the 24$^{th}$ hour in 2 of 21 patients (9.5%). When compared within groups, the lactation onset time was later than the 24$^{th}$ hour in

**Table 1. Demographic characteristics**

| | Group G | Group S | Group E | Group V | p value |
|---|---|---|---|---|---|
| Age | 28.4±7.0 | 28.1±4.2 | 26.9±5.1 | 27.6±5.5 | 0.71 |
| Weight (kg) | 74.1±11.4 | 77.7±14.9 | 74.5±6.2 | 73.1±9.2 | 0.56 |
| Gestation (week) | 38.3±1.2 | 38.5±1.3 | 38.4±1.1 | 38.6±1.1 | 0.88 |
| APGAR 1$^{st}$ min | 8.2±0.5 | 8.1±0.5 | 8.1±0.4 | 8.1±0.4 | 0.83 |
| APGAR 5$^{th}$ min | 10±0.2 | 10.0±0.0 | 10.0±0.0 | 10±0.2 | 0.83 |

Group G: general anesthesia group; Group S: spinal anesthesia group; GroupE: epidural anesthesia group; Group V: normal vaginal birth group

8 patients in group G (38%), 3 patients in group S (14.2%), and 2 patients in group E (9.5%) (Table 3).

## Discussion

In our study, it was determined that prolactin levels were highest in group G and that oxytocin levels were highest in group V (Table 2). The onset time of lactation was delayed in group G (Table 3).

In cesarean sections, general and regional anesthesia techniques may be performed. Recently, regional anesthesia has been preferred because of its advantages, such as enabling decreased transfer of general anesthetics to the newborn, convenience of controlling early and late onset postoperative pain, avoidance of stress response to surgical trauma, maintenance of consciousness, having no risk of aspiration, avoidance of respiratory depression of the newborn, and avoidance of atonic uterus. Additional advantages of regional anesthesia are that patients can see their baby right after birth and begin breastfeeding in a very short time (4). The most important disadvantages of regional anesthesia are allergic and toxic reactions to local anesthetics, inadequate analgesia, and increased practice time, and it may cause surgical difficulties, headache, lumbar pain, and hypotension. The advantages of general anesthesia are faster induction, less hypotension, less cardiovascular depression, and easier control of airway and respiration (5). In our clinic, we perform general, spinal, or epidural anesthesia according to the patient's demand, the presence of additional diseases, and urgency of the case.

There is no doubt that breastfeeding has a vital necessity for a newborn's health. Breastfeeding is affected by many factors, like the mother's feeding demands, regional traditions, the relationship between the mother and the newborn, education, social factors, type of delivery, and duration of delivery. Because of these factors, the type of anesthesia can play a role on onset time of breast feeding. In the literature, there is no study about the effects of different anesthesia techniques on the beginning time of lactation. So, we think that our study could enlighten future studies. The effects of different types of analgesics and the differentiation of systemic and neuroaxial anesthesia could not be determined. In a few studies, the side effects of epidural anesthesia on breastfeeding were compared between patients undergoing epidural anesthesia and patients without anesthesia, and no negative effect of epidural anesthesia was observed (6).

In one study from the literature, bupivacaine and fentanyl were used for epidural anesthesia, and another group received no anesthesia (7). The beginning time of lactation was determined. Similarly, Chang and Heaman (8) established two groups with and without epidural anesthesia, and no significant difference between the groups was determined in either study. In another study that was found, a significant difference in the lactation onset time was determined between cesarean section patients undergoing regional and general anesthesia, but there was no difference between the epidural anesthesia and no-anesthesia groups (9). In our results, no significant difference in the lactation onset time was determined between the epidural and spinal anesthesia and vaginal birth groups. However, in the general anesthesia group, lactation onset time was significantly delayed compared to other groups (p=0.003). The most significant difference was between the groups of general and spinal anesthesia (p=0.006). In the same study, onset of lactation was significantly later in the general anesthesia group (9). In all three studies, the groups of epidural anesthesia and no anesthesia were compared, and it was determined that the onset time of lactation was the latest in the epidural group (10-12). Especially, the breastfeeding rate in the first 4 hours was determined to be lower in mothers who delivered with epidural anesthesia (13). These newborns needed synthetic nutrients, and in addition, a lower

**Table 2. Comparison of hormone levels pre- and post-partum between groups. Oxytocin levels were defined as pg/mL, and prolactin levels were defined as ng/mL**

| | Group G | Group S | Group E | Group V | p value |
|---|---|---|---|---|---|
| $Prolactin_{pre}$ | 244.6±105.7 | 198.2±57.4 | 222.3±81.9 | 237.1±103.5 | 0.350 |
| $Prolactin_{post}$ | 363.7±120.9 | 270.4±100.4[a] | 264.0±108.2[b] | 300.8±87.5 | 0.015 |
| $Oxytocin_{pre}$ | 2.3±0.2 | 2.2±0.4 | 2.4±0.5 | 2.4±0.3 | 0.138 |
| $Oxytocin_{post}$ | 2.3±0.3 | 2.2±0.5 | 2.6±0.7[d] | 2.8±0.4[c] | 0.012 |

Group G: general anesthesia group; Group S: spinal anesthesia group; Group E: epidural anesthesia group; Group V: normal vaginal birth group; Pre: preoperative; post: postoperative

[a]group S significantly lower than group V and group G, [b]group E significantly lower than group V and group G, [c]group V significantly higher than group G and group S, [d]group E significantly higher than group S

**Table 3. Comparison of lactation onset time among groups**

| | Group G | Group S | Group E | Group V | p value |
|---|---|---|---|---|---|
| Lactation onset time (hour) | 25.0±22.9[a] | 10.8±10.2 | 11.8±8.8 | 10.9±9.7 | 0.003 |

[a]group G significantly higher than the other groups

Group G: general anesthesia group; Group S: spinal anesthesia group; Group E: epidural anesthesia group; Group V: normal vaginal birth group

proportion of them was breastfeeding only when discharged. In the literature, it was reported that epidural analgesia enhances postpartum analgesia and mental condition and that it has positive effects on breastfeeding (14). In our study, no significant difference was determined between the epidural anesthesia and vaginal birth groups in lactation onset time.

In one study, prolactin, estrogen, and ACTH levels before and after cesarean section were determined in 17 patients. Three different anesthetics were used before general and epidural anesthesia; 9 women could breastfeed, and when compared with the other patients, their prolactin levels were increased, and their ACTH and estrogen levels were decreased (15). There was no significant difference in hormone levels and lactation between anesthetic techniques. In our study, there was no significant difference in prepartum hormone levels, but we determined that postpartum prolactin levels were significantly higher in group G than in the other groups. So, the results of this study were not consistent with ours.

Prolactin levels and lactation onset times were compared between women undergoing epidural analgesia and women who had a vaginal birth without anesthesia (16). Prolactin levels in the epidural group were significantly lower, but there was no significant difference in lactation-relevant parameters. In addition, it was determined in this study that prolactin arrived at the peak level in the second hour and persisted at that peak level for 24 hours (16). In our study, prolactin levels were lower in the epidural anesthesia group than in the vaginal birth group but not statistically significantly (Table 2). We thought that the cause of the higher prolactin levels in the general anesthesia group than in the spinal anesthesia group could be the difference between the effects of the anesthetic agents used in both anesthesia techniques. As is known, many drugs can affect prolactin levels. These effects occur more often with systemic usage of drugs, and it could increase prolactin levels. Increasing oxytocin, prolactin, and beta-endorphin levels can affect the emotional state of the mother, the relationship between the mother and the newborn, and lactation (17). Oxytocin and prolactin increase the production and secretion of breast milk all throughout the breastfeeding period. Oxytocin plays an important role in the contraction of the uterus by vaginal birth. It was determined that oxytocin and prolactin levels increase significantly during lactation. Basic levels of hormones were determined to be especially high between the 4th day and 3rd or 4th month (18). In studies that included a limited number of patients and in which only oxytocin levels in normal delivering women were measured, it was determined that there was no relationship between oxytocin levels and lactation but that only multiparity had a positive correlation with oxytocin. In these two studies, no different anesthesia techniques were used, and only oxytocin levels were evaluated in normal delivering women (19-20). One of them evaluated oxytocin levels in patients undergoing cesarean section with spinal anesthesia and made a comparison between patients that had contractions and the ones who had no contractions (20). They determined no significant difference in oxytocin levels in blood serum, cerebrospinal fluid serum, and umbilical cord serum between both groups. In our study, no significant difference between prepartum oxytocin levels was determined, but there were differences in postpartum oxytocin levels among the four groups. Oxytocin levels were especially lower in the groups undergoing general and spinal anesthesia. In oxytocin levels compared between the epidural and normal birth groups, there was no significant difference, and the levels were significantly increased compared with the other two groups. It has to be taken into consideration that oxytocin is playing an important role in lactation and uterine contractions. Because of the similar effects of epidural anesthesia on hormone levels during normal birth, it is more rational to prefer epidural anesthesia (20). We determined that the most significant difference in prolactin levels was between groups G and S, and eventually, the most significant difference in lactation onset time was among groups G, S, and E. As a result of these considerations, spinal and epidural anesthesia may have advantages over general anesthesia.

We observed that lactation onset time is delayed in patients undergoing cesarean section with general anesthesia when compared with patients undergoing cesarean section with spinal and epidural anesthesia and normal birth. Because of the delay in awakening and in the recovery of cognitive functions in general anesthesia, communication between the mother and the newborn is delayed and so, too, is lactation. General anesthetic drugs may have an effect on brain stimulation of the breast milk secretion process and the onset of lactation.

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

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

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***Author contributions:*** *Concept - L.K., I.S.S., Y.D.; Design - L.K., Y.D.; Supervision - G.S., S.A.K.; Resource - Y.D.; Materials - L.K., I.K.; Data Collection&/or Processing - L.K., O.E.; Analysis&/or Interpretation - L.K., Y.D.; Literature Search - L.K., I.S.S.; Writing - I.S.S., Y.D.; Critical Reviews - I.S.Ş., Y.D., O.E.*

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# The effects of subchorionic hematoma on pregnancy outcome in patients with threatened abortion

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## Abstract

**Objective:** To assess the effects of ultrasonographically detected subchorionic hematomas on pregnancy outcomes in patients with vaginal bleeding within the first half of pregnancy.

**Material and Methods:** Patients diagnosed with threatened abortion due to painless vaginal bleeding and who were followed up in an inpatient service during the first vaginal bleeding between January 2009 and December 2010 were included in this retrospective cohort study. Patients were divided into two groups according to the presence of subchorionic hematoma. Miscarriage rates and pregnancy outcomes of ongoing pregnancies were compared between the groups.

**Results:** There were no statistically significant differences between the groups regarding demographic parameters, including age, parity, previous miscarriage history, and gestational age at first vaginal bleeding. While 13 of 44 pregnancies (29.5%) with subchorionic hematoma resulted in miscarriage, 25 of 198 pregnancies (12.6%) without subchorionic hematoma resulted in miscarriage (p=.010). The gestational age at miscarriage and the duration between first vaginal bleeding and miscarriage were similar between the groups. The outcome measures of ongoing pregnancies, such as gestational week at delivery, birth weight, and delivery route, were also similar between the groups.

**Conclusion:** Ultrasonographically detected subchorionic hematoma increases the risk of miscarriage in patients with vaginal bleeding and threatened abortion during the first 20 weeks of gestation. However, it does not affect the pregnancy outcome measures of ongoing pregnancies. (J Turk Ger Gynecol Assoc 2014; 15: 239-42)

**Key words:** Abortion, threatened, miscarriage, spontaneous, pregnancy outcome

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## Introduction

Vaginal bleeding is a frequent complication of pregnancy during the first trimester, with an incidence of 16%-25% (1). Intrauterine bleeding without cervical dilatation and tenderness during the early pregnancy period is defined as threatened abortion. Generally, it is not associated with pain and excessive bleeding. These bleedings result in maternal anxiety and may be associated with fetal/maternal adverse outcomes (2-4). One of the suggested mechanisms for threatened abortion is placental dysfunction, which can also cause several late complications, such as preeclampsia, preterm labor, preterm birth, placental abruption, placenta previa, intrauterine growth restriction, and perinatal mortality (2, 3). Similarly, insufficient angiogenesis is associated with early pregnancy losses, and maternal serum AFP and β-hCG are suggested to be used as markers of angiogenesis in the first trimester (5). Together with these markers, chronic inflammation of the decidua might also be the underlying cause of early pregnancy bleedings.

Intrauterine hemorrhages are commonly observed features on ultrasound examinations, especially among patients with clinically evident bleeding in early pregnancy, and the incidence has been reported to be 4%-22% (6). Subchorionic hematomas (SCHs) usually appear as hypoechoic or anechoic crescent-shaped areas on ultrasonography. Although the exact etiology is uncertain, they are believed to result from partial detachment of the chorionic membranes from the uterine wall (7). Uterine malformations, history of recurrent pregnancy loss, and infections are the possible predisposing factors (8-10). The clinical significance of SCH remains controversial (11-14). It is also not certain if these hemorrhages result in abortion. However, according to the results of a recent meta-analysis, the presence of SCH increases the risk of early or late pregnancy loss by 2-fold (15). It is suggested that the presence of SCH increases the risk of an adverse obs-

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tetric outcome, and fetal outcome is associated with the size of the hematoma, maternal age, and gestational age (16, 17).
The aim of the present retrospective cohort study was to assess the effects of ultrasonographically detected SCH on pregnancy outcomes in patients with vaginal bleeding within the first half of pregnancy.

## Material and Methods

In this retrospective cohort study, patients with threatened abortion (n=242) who were followed at a university-based perinatology clinic between January 2009 and December 2010 were recruited. The study was approved by the institutional review board of Ankara University School of Medicine. The inclusion criteria were hospitalization due to threatened abortion, singleton pregnancy, gestational age <20 weeks, and being followed up at our clinic until the end of the pregnancy. The exclusion criteria were a diagnosis of incipient abortion, no fetal cardiac activity, gestational age ≥20 weeks, multiple pregnancy, and recurrent pregnancy loss. The study group consisted of 44 patients with SCHs observed on ultrasonography, and the control group consisted of 198 patients without SCHs. All included patients were hospitalized for at least 3 days following the first vaginal bleeding episode. All patients were administered prophylactic progesterone treatment in oral (Progestan capsule; Koçak Farma, İstanbul, Turkey), vaginal (Crinone 8% gel; Serono, İstanbul, Turkey), or intramuscular (Proluton depot ampule; Schering Alman, İstanbul, Turkey) forms. Subsequent to discharge from the hospital, patients went on routine antenatal follow-up programs. The pregnancy outcomes were compared between the study and control groups. In patients whose pregnancies resulted in miscarriage, the gestational age at miscarriage and the duration between the first bleeding and miscarriage were compared. In patients whose pregnancies resulted in delivery, gestational age at labor, birth weight, preterm delivery, and cesarean section rates were compared between the groups.

### Statistical analysis

Statistical Package for the Social Sciences (SPSS) 15.0 for Windows (Chicago, IL, USA) was used for all statistical analyses. Shapiro-Wilk test was used to test the distribution of normality. According to the results, non-parametric tests were preferred. Continuous variables were compared with Kruskal-Wallis test. Categorical variables were compared with chi-square test or Fisher's exact test where appropriate. A p value of <.05 was considered statistically significant.

## Results

The incidence of SCH among patients with threatened abortion was 18.2% (44/242) for this population. The demographic variables of the study and control groups are presented in Table 1. The mean ages of the patients with and without SCH were 29.5±6.2 and 29.0±5.5 years, respectively (p=.624). The groups were comparable regarding previous parity and miscarriage histories (Table 1). Similarly, the groups were comparable regarding gestational age at the first vaginal bleeding (9.3±2.8 vs. 10.2±3.3 weeks, respectively; p=.085).
Table 2 summarizes the parameters of both groups regarding miscarriage; 13 of 44 pregnancies with SCH resulted in miscarriage (29.5%), while 25 of 198 pregnancies with SCH resulted in miscarriage (12.6%) (p=.010). The gestational age at miscarriage was similar between the study and control groups (10.8±3.6 vs. 10.9±4.8 weeks, respectively; p=.581). Similarly, there was no statistically significant difference between the study and control groups regarding duration between the first vaginal bleeding and miscarriage (16.4±23.8 vs. 9.0±7.5 days, respectively; p=.436).
Table 3 summarizes the pregnancy outcomes of 204 patients whose pregnancy resulted in delivery. The mean gestational ages at delivery were 37.4±4.1 weeks in 31 patients with SCH

**Table 1. Demographic parameters of the study and control groups**

| | SCH (+) n=44 | SCH (-) n=198 | p |
|---|---|---|---|
| Age (years) | 29.5±6.2 | 29.0±5.5 | .624 |
| Parity (n) | .5±.8 | .6±.8 | .581 |
| Previous miscarriage (n) | .5±.7 | .4±.8 | .657 |
| Gestational age at first vaginal bleeding (weeks) | 9.3±2.8 | 10.2±3.3 | .085 |
| SCH: subchorionic hematoma | | | |

**Table 2. Comparison of miscarriage and related parameters between study and control groups**

| | SCH (+) n=44 | SCH (-) n=198 | p |
|---|---|---|---|
| Miscarriage, n (%) | 13 (29.5) | 25 (12.6) | .010 |
| Within pregnancies resulting in miscarriage | n=13 | n=25 | |
| Gestational age at miscarriage (weeks) | 10.8±3.6 | 10.9±4.8 | .581 |
| Duration between first bleeding and miscarriage (days) | 16.4±23.8 | 9.0±7.5 | .436 |
| SCH: subchorionic hematoma | | | |

**Table 3. Comparison of pregnancy outcomes in patients whose pregnancy resulted in delivery**

| | SCH (+) n=44 | SCH (-) n=198 | p |
|---|---|---|---|
| Gestational age at delivery (weeks) | 37.4±4.1 | 37.4±3.6 | .962 |
| Preterm delivery, n (%) | 5 (16.1) | 44 (25.4) | .362 |
| Birth weight (kg) | 2958±810 | 3004±763 | .792 |
| Cesarean section, n (%) | 13 (41.9) | 80 (45.9) | .701 |
| SCH: subchorionic hematoma | | | |

and 37.4±3.6 weeks in 173 patients without SCH (p=.962). There was no statistically significant difference between the study and control groups regarding preterm birth rate (16.1% vs. 25.4%, respectively; p=.362). Similarly, the birth weights were comparable between the groups (2958±810 g vs. 3004±763 g, respectively; p=.792). The cesarean section rates were also similar between the study and control groups (41.9% vs. 45.9%, respectively; p=.701).

## Discussion

The results obtained from the present study revealed that the presence of SCH in patients with threatened abortion is an important factor for the continuation of pregnancy. The presence of SCH in patients with threatened abortion increases the risk of miscarriage. However, it does not affect the gestational age at miscarriage or the duration between the first bleeding and miscarriage. In patients whose pregnancies resulted in delivery, gestational age at labor, birth weight, preterm delivery, and cesarean section rates were not affected by the presence of SCH. Previously, several studies have investigated the effects of SCH on pregnancy outcomes. Ball et al. (18) evaluated 238 patients with ultrasonographically detected SCH in a retrospective casecontrol study and reported a significant association between SCH and miscarriage and preterm delivery rates. They also reported increasing pregnancy loss rates with increasing SCH size. Similarly Nagy et al. (19) compared 187 patients who had SCH with 6488 controls, and they found increased miscarriage, intrauterine growth restriction, and preterm delivery rates in the presence of SCH. However, they failed to show an association between the size and location of the SCH and ongoing pregnancy outcome measures. In a retrospective cohort study, Norman et al. (20) evaluated 63,966 patients who had an ultrasonographic evaluation before 22 weeks of gestation and reported that the incidence of SCH was 1.7%. They found that the detection of an SCH during routine second-trimester ultrasonography was associated with more than a 2-fold increased risk of placental abruption, regardless of whether the woman reported bleeding in the early half of pregnancy. They also identified that women with SCH were at increased risk of preterm delivery. However, in the aforementioned studies, SCHs were defined during the routine first- or second-trimester ultrasonography, and not all patients with an SCH had threatened abortion. Vaginal bleeding occurs in 25% of pregnancies in the first 20 weeks, and half of these result in miscarriage (16). Hence, it is important to identify the risk factors of threatened abortion and the factors that can affect the outcome. In a retrospective cohort trial, Ben-Haroush et al. (21) assessed 2556 pregnant patients who were admitted with vaginal bleeding during the first 20 gestational weeks. The incidence of SCH was 9%. They reported that gestational age at diagnosis, size of SCH, and duration of bleeding did not affect the pregnancy outcome. They also reported significantly decreased miscarriage rates with bed rest. However, Bennett et al. (17) reported that increasing SCH size increases the risk of miscarriage. In a prospective cohort study, Pedersen and Mantoni followed up 342 pregnancies with vaginal bleeding between 9 to 20 gestational weeks, in which 18% had SCH (12). They found no association between the presence of SCH and miscarriage or preterm delivery risks. In another retrospective case-control study, Johns et al. (22) reported that first-trimester vaginal bleedings were associated with adverse pregnancy outcomes, but the presence of SCH had no effect on the prognosis. According to the results of a recent meta-analysis evaluating 1735 patients with SCH from 7 studies, the presence of SCH increases the risks of early and late pregnancy loss, miscarriage, and preterm premature rupture of membranes (15).

In a prospective study from Turkey, the size of the SCH was suggested to be the primary risk factor for miscarriage in patients with first-trimester vaginal bleeding (23). Uluğ et al. (24) reported that first-trimester bleedings were associated with preterm delivery and low birth weight. However, they found no relationship between the prognosis and presence or size of the SCH. In another Turkish case-control study, Özkaya et al. (25) reported the outcomes of 43 patients with SCH, and they found that the presence of SCH increases the risks of miscarriage and intrauterine growth restriction but not preterm delivery. The results of our study were partially concordant with the literature, as we could only show that the presence of SCH increased the risk of miscarriage. However, we failed to show any significant relationship between the presence of SCH and ongoing pregnancy outcome measures.

The underlying mechanism of how SCH causes adverse pregnancy outcomes is still controversial. One of the possible mechanisms is the premature perfusion of the intervillous space, as occurs with subchorionic hemorrhage, before the development of placental adaptations to cope with oxidative stress (26). Another possible mechanism might be the underlying cause of the subchorionic bleeding and secondary mechanical effects of the hematoma. Shallow trophoblast invasion and impaired angiogenesis with resultant friable blood vessels may predispose one to subchorionic hemorrhage, as well as adverse outcomes (15). The presence of a hematoma, especially in a retroplacental location, may create an area of weakness, where further separation of the placenta from the uterine wall may occur, resulting in placental abruption (15). Our results support the estimated mechanical effect of SCH that can cause miscarriage. The presence of an SCH and detachment of the gestational sac from the endometrium may result in miscarriage. However, if the gestational sac survives, reattachment to the endometrial wall might be enough for further progression of the pregnancy without any other adverse effects.

In conclusion, SCH in patients with threatened abortion during the first half of the pregnancy increases the risk of miscarriage. However, it is not absolute if the presence of an SCH increases the adverse pregnancy outcome risk in ongoing pregnancies or not, because almost all of the previously reported studies were retrospective. Large prospective randomized studies are required to determine the true role of SCH in the prognosis of ongoing pregnancies.

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# Left lateral position and common gynecologic examining position in anal manometry measurements for evaluation of urogynecologic patients

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## Abstract

**Objective:** The aim of this study is to compare the anometrical parameters obtained in the left lateral position, which is the conventional position of anal manometry, with the same measurements taken in the common gynecologic examining position (45° sitting position in a birthing chair with maximum hip flexion).

**Material and Methods:** Twenty-one patients with lower urinary tract symptoms (LUTS) were enrolled into this prospective cohort study. Basal mean resting pressure (BMRP), maximum squeeze pressure (MSP), rectal sensation, rectal compliance, and recto-anal inhibitory reflex (RAIR) were compared between the gynecologic examining position and left lateral position.

**Results:** There was no statistically difference between the anal manometric measurements of the left lateral and gynecologic examining positions (paired t-test, p>.05).

**Conclusion:** It can be concluded that it seems to be unnecessary to change the examination chair and/or patient position in urogynecological patients who need an anorectal assessment. (J Turk Ger Gynecol Assoc 2014; 15: 243-4)

**Key words:** Anal manometry, lower urinary tract symptoms, gynecologic examining position

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## Introduction

The reported prevalence of anal incontinence in women with urogynecologic problems ranges from 20% to 54%; therefore, the significance of anorectal function assessment has become more important in the evaluation of patients suffering from urogynecologic problems (1, 2). Among the various tests that are available, anorectal manometry is an essential clinical tool. Anorectal manometry has almost always been performed with the patient in the left lateral position (3, 4). However, the left lateral position does not permit one to examine the pelvic organs properly and is not suitable for a urogynecologic evaluation. Ideally, assessing the condition of a patient with urogynecological complaints should be in a one-step fashion, with minimal discomfort and without unnecessary time and costs. Changing the patient's position and the examination chair while performing a urogynecological examination causes discomfort, time loss, and additional costs.

The aim of this study is to compare the anometrical parameters obtained in the left lateral position, which is the conventional position of anal manometry, with the same measurements taken in the common gynecologic examining position (45° sitting position in a birthing chair with maximum hip flexion), which is the standard of a urogynecological investigation.

## Material and Methods

This prospective cohort study included 21 patients with lower urinary tract symptoms (LUTS). The study was approved by the hospital's ethics committee. Informed consent forms were obtained from all patients. All patients underwent anorectal manometry (Rectoscan, Aymed, İstanbul, Turkey). Each patient was investigated first in the left lateral and then in the gynecologic examining position. Anorectal manometry measurements included basal mean resting pressure (BMRP), maximum squeeze pressure (MSP), rectal sensation, rectal compliance, and recto-anal inhibitory reflex (RAIR). The manometric catheter used was a water-perfused, 4-mm, four-channeled, polyvinyl chloride catheter (Aymed, İstanbul, Turkey). The catheter was connected to a pneumohydraulic capillary infusion system. Each capillary tube was connected

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**Table 1. The anal manometric measurements of left lateral and gynecologic examining position**

| | Left lateral position | Gynecologic examining position | p |
|---|---|---|---|
| Basal mean resting pressure (mmHg) | 54.4±12.9 | 53.9±17.2 | .860 |
| Maximum squeeze pressure (mmHg) | 85.2±31.3 | 91.6±30.6 | .152 |
| Rectal compliance (cc/mmHg) | 13.1±2.4 | 12.3±1.9 | .542 |
| First sensation volume (cc) | 40.6±11.2 | 41.3±12.7 | .684 |
| First urge volume (cc) | 69.1±14.6 | 78.1±20.5 | .053 |
| Modest sensation volume (cc) | 102±18.2 | 109.7±24.9 | .125 |
| Maximum tolerated volume (cc) | 180±19.3 | 180.6±18.7 | .847 |
| The Paired t-test was used. P<0.05 was statistically significant. | | | |

to a computer via a Digitrap. A continuous pull-through technique was used to perform the manometry. BMRP, MSP, rectal sensation, rectal compliance, and the presence of RAIR and vector volume were measured in all patients in both positions. The statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) v. 11.5 for Windows (SPSS, Inc., Chicago, IL, USA). Paired t-test was used to assess the difference between paired datasets. P<.05 was considered to be statistically significant.

## Results

The mean age of the patients was 50.2±3.4 years. There were no statistical differences between BMRP, MSP, the presence of RAIR, rectal compliance, and rectal sensations obtained in the left lateral position and in the common gynecologic examining position (Table 1). The additional time required to change the examination chair and patient position was 3.6±.92 minutes.

## Discussion

In the present study, there were no significant changes in manometric variables, including BMRP, MSP, RAIR, rectal compliance, and rectal sensation between the left lateral and common gynecologic examining positions.

The effect of body position on anal manometric parameters has been widely investigated in the medical literature. Comparative studies of the conventional anometric left lateral position with the erect and/or sitting positions have been reported with various results (4, 5). To our knowledge, the present study is the first to compare the left lateral position with the standard gynecologic position in women with LUTS. The results of this study show that the gynecological examining position is as reliably effective as the left lateral position in assessing anorectal functions in women with LUTS. Not altering the patient's examination chair and position resulted in less time spent and less discomfort, also allowing the examination of the patient in one-step fashion. Furthermore, women with LUTS are commonly elder people, usually with some physical restrictions, causing difficulties while changing their positions. Often, a health professional is needed to help the patient overcome these physical problems in these women. The rectoanal assessment is becoming more and more a part of the examination in women with LUTS. This study shows that performing an anorectal examination in the gynecologic examining position in women with LUTS is practical and has many benefits. This approach will allow one to evaluate a patient by means of the POP-Q system and urodynamics and anorectal manometry without interfering with the patient's comfort in less time. It can be concluded that it seems to be unnecessary to change the examination chair and/or patient position in urogynecological patients who need an anorectal assessment.

***Ethics Committee Approval:*** *Ethics committee approval was received for this study.*

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

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# Maternal and obstetrical factors associated with a successful trial of vaginal birth after cesarean section

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## Abstract

**Objective:** To detect the maternal and obstetrical factors associated with successful trial of vaginal birth among women with a previous cesarean delivery.

**Material and Methods:** A total of 122 women who were eligible for a trial of labor after cesarean section (TOLAC) according to departmental protocol were included in this comparative prospective study. After informed consent, the women included in this study were subjected to a thorough history to detect maternal and obstetric characteristics and a standard examination to estimate fetal weight, engagement of the fetal head, intra-partum features of fetal membranes, and cervical dilatation. After delivery, data on duration of labor, labor augmentation, mode of delivery, birth outcome, and neonatal intensive care (NICU) admission were recorded and analyzed.

**Results:** Trial of labor after cesarean section was successful in 72.13% and was unsuccessful in 27.87%. Body mass index (BMI) was significantly lower in the successful TOLAC group compared to the unsuccessful group (23.8±0.03 versus 26.2±0.02 kg/m$^2$), and the number of women with BMI >25 kg/m$^2$ was significantly high in the unsuccessful group; also, mean gestational age was significantly lower in the successful TOLAC group compared to the unsuccessful group (37.5±0.04 versus 38.5±0.03 weeks), and the number of women admitted in labor with gestation ≥40 weeks was significantly high in the unsuccessful group. The number of women admitted with >2/5 of fetal head palpable abdominally and fetal head station ≥-2 was significantly high in the unsuccessful TOLAC group.

**Conclusion:** In carefully selected cases, TOLAC is safe and often successful. Presence of BMI >25 kg/m$^2$, gestation ≥40 weeks, and vertex station ≥-2 were risk factors for unsuccessful TOLAC. (J Turk Ger Gynecol Assoc 2014; 15: 245-9)

**Key words:** Factors, successful trial, vaginal birth, cesarean section

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## Introduction

Repeat cesarean deliveries are associated with pelvic adhesions, morbidly adherent placenta, bladder injury, and increased cumulative hysterectomy rates (1, 2). A World Health Organization (WHO) survey in Latin America identified that women with singleton cephalic pregnancy with prior cesarean section, despite their smaller pool, were the greatest contributors to the overall cesarean section rate (3). Successful trial of labor and vaginal birth after cesarean section (VBAC) results in decreased maternal morbidity in terms of blood transfusion, hysterectomy, and febrile morbidity as compared to repeat cesarean sections (3, 4).

Vaginal delivery after the first cesarean confirms pelvic adequacy for vaginal birth and improves the chances of subsequent vaginal deliveries, resulting in a reduction of repeat cesarean and consequent morbidities. Previous studies concluded that the success rates of vaginal birth after cesarean section were 74% (ranging from 68%-77%) (4-6). There have been many studies conducted following a first cesarean section to examine trial of labor after cesarean section (TOLAC), irrespective order of birth (7-11). TOLAC for a second delivery is a much-needed option in developing countries to reduce the cost and morbidities of repeat cesarean deliveries. This study was designed to detect maternal and obstetrical factors associated with a successful trial of vaginal birth among women with a previous cesarean delivery.

## Material and Methods

This comparative prospective study was conducted in Ahmadi Hospital, Kuwait Oil Company (KOC), after approval of the study protocol by the institutional ethical committee. TOLAC is routinely offered at our hospital to women meeting the standard criteria for a TOLAC, according to departmental protocol. According to departmental protocol, the eligibility for TOLAC

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includes women with one previous lower segment cesarean section for nonrecurrent cause (fetal distress, placenta previa, post-term pregnancy, failed induction, malpresentation, malposition), those without severe medical disorders (severe hypertension, uncontrolled diabetes, or acute liver disorder), singleton pregnancy with cephalic presentation, clinically estimated fetal weight ≤3.5 kg, adequate pelvis on clinical assessment and in spontaneous labor in the absence of maternal or fetal compromise (ante-partum hemorrhage, fetal distress), and those willing to undergo a trial of scar. According to departmental protocol, the decision for augmentation of labor was taken by a consulting obstetrician (Ibrahim A. Abdelazim). One hundred twenty-two women with singleton pregnancy and cephalic presentation at $37\text{-}41^{+6/7}$ weeks of gestation, with spontaneous onset of labor were eligible for TOLAC according to departmental protocol and were included in this study after informed consent. Women with previous upper segment cesarean, previous myomectomy, placenta previa, severe medical disorders, intrauterine growth restriction, estimated fetal weight >3.5 kg, and post-term pregnancy (≥42 weeks) were excluded from this study.

Trial of labor after cesarean section is defined as an attempt at vaginal delivery in women with a previous cesarean section. A successful TOLAC is defined as spontaneous or instrumental (assisted by vacuum or low forceps) delivery to a woman undergoing TOLAC. An unsuccessful TOLAC is defined as failure to achieve a vaginal birth after cesarean section in women undergoing a TOLAC and the delivery ending by emergency cesarean section.

Augmentation of labor is defined as the use of oxytocin infusion to achieve four to five uterine contractions, each lasting for 45-60 seconds, in 10 minutes.

After informed consent, the women included in this study were subjected to a thorough history to detect maternal and obstetric characteristics (age, height, weight, body mass index (BMI), gestational age, date, and indication of previous cesarean) and a standard examination to estimate fetal weight, engagement of fetal head, intra-partum features of the fetal membranes, and cervical dilatation. After the delivery, data on the duration of labor (from 4 cm dilatation until delivery), labor augmentation, mode of delivery, birth outcome, neonatal intensive care unit (NICU) admission, and APGAR score at 1 and 5 minutes of birth were recorded and statistically analyzed. For women admitted at cervical dilatation >4 cm, total duration of labor was estimated after recognizing the onset of the active phase, from the history of regular painful and increasingly intense contractions.

**Sample size justification**

The required sample size was calculated using G* Power software, version 3.17 for sample size calculation (*Heinrich Heine Universität; Düsseldorf; Germany), setting the α-error probability at 0.05, power (1-β error probability) at 0.95%, and effective sample size (w) at 0.3. The effective size (w) was calculated as follows $w=\sqrt{X^2/N}$, where $X^2$ is the chi-square test and N is the total sample size. The number of participants needed to produce a statistically acceptable figure was 111 patients, and assuming a 10% dropout rate (11 cases), 122 women were included in this prospective comparative study.

**Statistical analysis**

After delivery, the collected data on admission were statistically analyzed using Statistical Package for Social Sciences (SPSS; Chicago, IL, USA), version 16. Numerical variables were presented as mean and standard deviation (±SD), while categorical variables were presented as number and percentage. Chi-square (X2) test was used for the comparison between groups with regard to qualitative variables, while using unpaired student t)-test was used for the comparison between groups as regards quantitative variables. Also, logistic regression analysis was done to detect maternal and obstetrical factors associated with a successful trial of vaginal birth after cesarean section. A difference with a p value <0.05 was considered statistically significant; otherwise, it was insignificant.

## Results

One hundred twenty-two (122) women were eligible for TOLAC according to departmental protocol and were included in this study after informed consent. TOLAC was successful in 88 (72.13%) women (8 (9%) of them were instrumental) and was unsuccessful in 34 women (27.87%). The mean age of women included in this study was 26.7±4.09 years, the mean gestational age was 38.2±1.22 weeks, mean age of the last born was 2.2±0.88 years, mean cervical dilatation was 4.5±2.1 cm (70 (57.4%) women presented with cervical dilatation of ≥4 cm and 52 (42.6%) presented with cervical dilatation <4 cm), and mean duration of active labor was 6.1±2.11 hours. Mean BMI was significantly lower in the successful TOLAC group compared to the unsuccessful group (23.8±0.03 versus 26.2±0.02 $Kg/m^2$), mean gestational age was significantly lower in the successful TOLAC group compared to the unsuccessful group (37.5±0.04 versus 38.5±0.03 weeks), and duration of active labor was significantly lower in the successful TOLAC group compared to the unsuccessful group (6.4±0.33 versus 8.4±0.22 hours); cervical dilatation on admission was significantly higher in the successful TOLAC group compared to the unsuccessful group (5.1±0.9 versus 4.0±0.7 cm) (Table 1).

The number of women with BMI >25 Kg/m2 was significantly higher in the unsuccessful TOLAC group compared to the successful group (20 (58.8%) versus 18 (20.5%)), and the number of women admitted in labor with gestation ≥40 weeks was significantly higher in the unsuccessful TOLAC group compared to the successful group (12 (35.3%) versus 8 (9.1%)); also, the number of women with inter-delivery interval <2 years was significantly higher in the unsuccessful TOLAC group compared to the successful group (24 (70.6%) versus 20 (22.7%)) (Table 2).

The number of women admitted with >2/5 of fetal head palpable abdominally and with fetal head station ≥-2 was significantly higher in the unsuccessful TOLAC group compared to the successful group (26 (76.5%) versus 20 (22.7%)), and the number of women admitted with cervical dilatation <4 cm was significantly higher in the unsuccessful TOLAC group compared to the successful group (24 (70.6%) versus 17 (19.3%)); also, the number of women with duration of labor ≥7 hours was significantly higher in the unsuccessful TOLAC group compared to the successful group (19 (55.9%) versus 15 (17.0%)) (Table 2).

**Table 1. Maternal characteristics, cervical dilatation, duration of active labor, and birth outcome**

| Variable | Successful TOLAC (number=88) Mean±SD | Unsuccessful TOLAC (number=34) Mean±SD | p value (95% confidence interval of difference) |
|---|---|---|---|
| Age (years) | 26.8±4.28 | 26.3±3.56 | 0.12** (-0.99, 1.99) |
| Body mass index (BMI) (kg/m$^2$) | 23.8±0.03 | 26.2±0.02 | 0.005* (-2.41, -2.39) |
| Height (cm) | 156.8±3.7 | 157.4±5.6 | 0.99** (-2.63, 1.43) |
| Weight (kg) | 58.8±7.8 | 64.6±10.6 | 0.98** (-9.71, 1.89) |
| Gestational age (weeks) | 37.5±0.04 | 38.5±0.03 | 0.03* (-1.01, -0.99) |
| Delivery interval (hours) | 2.32±0.9 | 2.02±0.8 | 0.58** (-0.05, 0.65) |
| Cervical dilatation on admission (cm) | 5.1±0.9 | 4.0±0.7 | 0.05* (0.7988, 1.4012) |
| Duration of active labor (hours) | 6.4±0.33 | 8.4±0.22 | 0.005* (-2.0511, -1.8489) |
| Birth weight (kg) | 2.9±0.3 | 3.0±0.4 | 0.99** (-0.28, 0.028) |
| APGAR score 1 minute | 7.2±0.8 | 6.9±0.9 | 0.86** (-0.05, 0.65) |
| APGAR score 5 minutes | 8.6±0.8 | 7.5±0.8 | 0.32** (0.79, 1.41) |

*significant
**non-significant
TOLAC: trial of labor after cesarean section

**Table 2. Comparison between maternal and obstetrical factors in the two studied groups**

| Variable | Unsuccessful TOLAC Number=34 Number (%) | Successful TOLAC Number=88 Number (%) | p value Test used ($X^2$=Chi-square test) |
|---|---|---|---|
| **Maternal Factors** | | | |
| Body mass index (BMI >25 kg/m$^2$) | 20 (58.8%) | 18 (20.5%) | 0.004* (<0.05) |
| Height <155 cm | 7 (20.6%) | 12 (13.6%) | 0.42** (>0.05) |
| Gestational age on admission ≥40 weeks | 12 (35.3%) | 8 (9.1%) | 0.03* (<0.05) |
| Inter-delivery interval < 2 years | 24 (70.6%) | 20 (22.7%) | 0.001* (<0.05) |
| **Obstetrical Factors** | | | |
| Estimated fetal weight (EFW >3 -3.5 kg) | 7 (20.6%) | 14 (15.9%) | 0.61** (>0.05) |
| Fetal head >2/5 palpable abdominally | 26 (76.5%) | 20 (22.7%) | 0.001 * (<0.05) |
| Cervical dilatation <4 cm | 24 (70.6%) | 17 (19.3%) | 0.0004* (<0.05) |
| Fetal head station ≥-2 | 26 (76.5%) | 20 (22.7%) | 0.01 * (<0.05) |
| Premature ruptured membranes | 7 (20.6%) | 18 (20.5%) | 0.81** (>0.05) |
| Duration of labor ≥7 hours | 19 (55.9%) | 15 (17.0%) | 0.002* (<0.05) |
| Augmentation of labor | 10 (29.4%) | 15 (17.0%) | 0.17** (>0.05) |

*significant
**non-significant
TOLAC: trial of labor after cesarean section

Logistic regression analysis was done to detect the maternal and obstetrical factors associated with a successful trial of vaginal birth after cesarean section in this study and showed that estimated fetal weight ≤3.5 kg was associated with a successful TOLAC (adjusted odds ratio (AOR) 3.89 (confidence interval (CI); 0.28, 3.50), p<0.05), while presence of BMI >25 kg/m$^2$ (AOR 5.008 (CI; 1.96,12.74), p<0.05), gestation ≥40 weeks (AOR 5.45 (CI; 1.66,17.88), p<0.05), vertex station ≥-2 (AOR 3.83 (CI; 1.26,11.62), p<0.05), and cervical dilatation <4 cm (AOR 5.90 (CI; 2.17, 15.98), p<0.05) were risk factors for an unsuccessful TOLAC.

## Discussion

One hundred twenty-two women eligible for a TOLAC according to departmental protocol were included in this study after informed consent. TOLAC was successful in 88 ((72.13%) women (8 (9%) of them were instrumental) and was unsuccessful in 34 women (27.87%) in this study.

Also, an 83.47% (96 women) successful vaginal birth rate after cesarean and 16.5% (19 women) failure rate were recorded in Balachandran et al. (12), while a 50% (95/190) successful vaginal birth rate after cesarean section and 50% (95/190) failure rate were recorded in Ugwu et al. (13); a 66% (344/522) successful vaginal birth rate after cesarean section was recorded by Dunwald et al. (14).

One hundred women were included in Raja and colleagues' study, and they were scored according to six variables (maternal age, gestation, indications of previous cesarean, history of vaginal birth, Bishop score, and BMI). Raja and colleagues found that the rates of successful vaginal birth after cesarean increased from 38% in women having a score of 0-3 to 58% in patients scoring 4-6. Among those having a score of 7-9 and 10-12, the success rates were 71% and 86%, respectively. Raja and colleagues concluded that increasing scores correlated with the increasing probability of vaginal birth after cesarean, and they also concluded that the admission VBAC scoring system is useful in counseling women with a previous cesarean for the option of induction of labor or repeat cesarean delivery (15).

In this study, there was no significant relation between maternal height (<155 cm) and success of TOLAC, although Sylvia Kirchengas et al. (16) reported that short stature was significantly associated with a higher incidence of operative deliveries and cesarean sections.

In this study, BMI was significantly lower in the successful TOLAC group compared to the unsuccessful group, and the number of women with BMI >25 kg/m$^2$ was significantly higher in the unsuccessful group; also, mean gestational age was significantly lower in the successful TOLAC group compared to the unsuccessful group, and the number of women admitted in labor with gestation ≥40 weeks was significantly higher in the unsuccessful group. Landon et al. (17) reported a significantly lower success rate of vaginal birth after cesarean section (68.4%) in obese (BMI ≥30) than non-obese women (76.9%), and Juhasz et al. (18) reported decreasing chances of a successful TOLAC with increasing BMI; also, Tessmer et al. (19) concluded that VBAC success was independently associated with age <30 years, body mass index <30, prior vaginal delivery, and prior VBAC.

Smith et al. (20) concluded that a TOLAC was likely to be unsuccessful at 41 weeks or 42 weeks gestation compared to a TOLAC at 40 weeks, and Coassolo et al. (21) reported a 31.3% TOLAC failure rate at 40 weeks or beyond, against 22% in <40 weeks; also, Tita et al. (22) concluded that the risks of maternal morbidities and cesarean delivery, but not neonatal morbidity, increased significantly among laboring nulliparous women beyond 39 weeks.

Cervical dilatation in the studied cases on admission was significantly higher in the successful TOLAC group compared to the unsuccessful TOLAC group, and the number of women admitted with cervical dilatation <4 cm was significantly higher in the unsuccessful TOLAC group; also, the duration of active labor was significantly lower in the successful TOLAC group. This was similar to findings reported in the literature; also, Durnwald et al. (14) reported increased chances of a successful vaginal birth after cesarean section in women admitted with cervical dilatation of more than 1 cm.

The number of studied women with an inter-delivery interval <2 years was significantly higher in the unsuccessful TOLAC group compared to the successful group, and the number of women admitted with >2/5 of the fetal head palpable abdominally and the number of women admitted with fetal head station ≥-2 were significantly higher in the unsuccessful TOLAC group.

Logistic regression analysis was done to detect the maternal and obstetrical factors associated with a successful trial of vaginal birth after cesarean section in this study and showed that estimated fetal weight ≤3.5 kg was associated with a successful TOLAC, while the presence of BMI >25 kg/m$^2$, gestation ≥40, vertex station ≥-2, and cervical dilatation <4 cm were risk factors for an unsuccessful TOLAC.

One hundred (100) women were included in Raja and colleagues' study, and they were scored according to six variables (maternal age, gestation, indications of previous cesarean, history of vaginal birth, Bishop score, and BMI). Raja and colleagues concluded that increasing scores correlated with an increasing probability of vaginal birth after cesarean (15).

In this study, neonatal intensive care admission was significantly higher in the unsuccessful TOLAC group (2 due to birth asphyxia and 2 due to meconium aspiration and sepsis) compared to the successful group (1 case due to birth asphyxia). Ball et al. and Tan et al. reported increases in risks of neonatal morbidities and hypoxic ischemic encephalopathy (HIE) after an unsuccessful TOLAC (6, 23).

Scar dehiscence was found in 1 (0.9%) case of unsuccessful TOLAC, impending rupture was found in another case (0.9%) of unsuccessful TOLAC, and the presence of premature rupture fetal membranes and/or use of oxytocin for augmentation does not affect the success of TOLAC in this study. Also, 0.2%-0.7% risk of scar dehiscence in women undergoing TOLAC was reported in the literature and by Cahill and colleagues (4, 7). Careful decision on the use of augmentation during a TOLAC is needed, and spontaneous onset of labor in women with a previous cesarean section increases the chance of a successful TOLAC.

Smith et al. (20) concluded that women with a failed vaginal birth after a trial of scar and who delivered by emergency cesarean section are subjected to increased risk of uterine rupture and catastrophic rupture, leading to perinatal death. Hochler and colleagues reported a 0.3% risk of uterine rupture; 2 cases ended in a hysterectomy during their retrospective study to evaluate the safety of trial of labor after cesarean delivery in grand multiparous women. They concluded that neither induction nor augmentation of labor increased the risk for uterine rupture, and they also concluded that trial of labor after cesarean delivery in the first labor after a prior cesarean delivery conferred a higher risk for hysterectomy (24).

In carefully selected cases, TOLAC is safe and often successful. Estimated fetal weight ≤3.5 kg was associated with a successful TOLAC, while the presence of BMI >25 kg/m$^2$, gestation ≥40 weeks, vertex station ≥-2, and cervical dilatation <4 cm were risk factors for an unsuccessful TOLAC. A careful decision in the augmentation of labor during a TOLAC is needed, and spontaneous onset of labor in women with a previous cesarean section increases the chance of a successful TOLAC.

***Ethics Committee Approval:*** *Ethics committee approval was received for this study from Ahmadi Hospital.*

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

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

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

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# A new biological marker candidate in female reproductive system diseases: Matrix metalloproteinase with thrombospondin motifs (ADAMTS)

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## Abstract

Playing a key role in the pathophysiology of many diseases, A Disintegrin-like and Metalloproteinase with Thrombospondin type-1 motif (ADAMTS) proteinases have been attracted more attention in obstetrics and gynecology. First discovered in 1997, this zinc-dependent proteinase family has 19 members today. These enzymes, which are located in the extracellular matrix (ECM), have a lot of very important functions, like matrix formation and resorption, angiogenesis, ovulation, and coagulation. In addition, in the pathogenesis of cancer, inflammation, arthritis, and connective tissue diseases, ADAMTS proteinases have crucial roles. The purpose of this review is to collect previous studies about obstetrics and gynecology that are related to ADAMTS enzymes and discuss the subject in many aspects to give an idea to the investigators who are interested in the subject. (J Turk Ger Gynecol Assoc 2014; 15: 250-5)

**Key words:** ADAMTS, reproductive diseases, biological marker

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## Introduction

A Disintegrin-like and Metalloproteinase with Thrombospondin type-1 motif (ADAMTS) proteinases, which are released outside the cell (soluble), have very critical roles in damage and repair of extracellular matrix (ECM) processes (remodeling) (1). The ADAMTS family, which degrades ECM structural substrates, such as collagen, aggrecan and versican, has 19 family members (2). These enzymes, which are associated with a great deal of vital physiological processes in the ECM, are inhibited by tissue inhibitors of metalloproteinases (TIMPs) (3, 4). Family members of this group are divided into various subgroups according to their tasks in the ECM (Figure 1).

ADAMTS1 (METH-1), which was identified for the first time in colon adenocarcinoma, is associated with inflammation (5) and shows anti-angiogenic properties with ADAMTS8 (METH-2) (6, 7). Especially in the physiology of ovulation, there is interest in these proteases. ADAMTS1 also takes important roles in the process of normal growth, fertility, and organogenesis (8). ADAMTS 2, 3, and 14, also known pro-collagen N-proteinases, have important roles in collagen synthesis in the ECM. Various connective tissue diseases are seen in ADAMTS2 deficiency in this group (9). ADAMTS1, -4, -5, -8, -9, -15, -16, and -18 degrade aggrecan, which is the one of the main components of the ECM; so, they are called as aggrecanases (1). ADAMTS1, -4, and -5 degrade brevican and versican, other structural ECM components (10). Versican helps hyaluronan, which is the basic element of the ECM, to stabilize the matrix (11). ADAMTS5 and -6, expressed specifically in the placenta, are thought to be responsible for implantation (12). ADAMTS7 and -12 degrade Cartilage oligomeric matrix protein (COMP), which is an essential glycoprotein in cartilage matrix (13). ADAMTS10 has important roles in the development of tissues of skin and lens. In ADAMTS10 mutations, autosomal recessive Weill-Marchesani syndrome is seen (14).

Known as von Willebrand cleaving protease, ADAMTS13 has effects on coagulation and homeostasis. This protease degrades ultralarge VWF multimers that are localized in endothelial surfaces; so, it prevents thrombus formation (9). Thrombotic thrombocytopenic purpura (TTP), a serious problem during pregnancy, occurs in ADAMTS13 deficiency (15). Increased by follicle-stimulating hormone (FSH) and luteinizing hormone (LH), ADAMTS16 degrades α-2 macroglobulin in the ECM (16). ADAMTS17 is involved in estrogen-induced apoptosis in cancer cells (16). ADAMTS9 and -20 are known

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as Gon-ADAMTS (17). ADAMTS10 and ADAMTS19, whose roles are unknown today, are called orphan ADAMTS proteases (1).

## ADAMTS in the Physiology of Obstetrics and Gynecology

### Ovarian physiology and ADAMTS

For successful ovulation, cumulus oocyte complex (COC) formation and rupture of ovarian surface epithelium must occur properly (18). While COC formation occurs, the synthesis of basic ECM components, like versican and hyaluronic acid (HA), is increased (18).

The synthesis of proteoglycans, such as aggrecan, versican and brevican, which bind to HA, increases in the ovaries after an LH surge (10, 19). These proteoglycans are basic components of the ECM, together with HA. Versican, a substrate of ADAMTS1, -4, and -5, has roles in ECM remodeling, movement of cumulus cells, and maintaining the structural and functional integrity of the matrix (10, 18). In the peri-ovulatory period, ADAMTS1, -4, and -5 degrade versican, resulting in the expansion of the COC (18, 19). For successful ovulation, this destruction must occur (10, 16, 17).

Progesterone (PG) and its receptor (PR) are two genes that are activated by LH in ovaries. PG binds to receptors (PGR) on the granulosa cell resulting in increased ADAMTS1 (8, 9, 20, 21) (Figure 2). In disorders of PR, which controls expression of ADAMTS1, ovulation and fertility problems are observed. Ovulation does not occur successfully and fertility rates are reduced (7, 22). ADAMTS1 has critical roles in the degradation of versican, expansion of COC formation, ovulation and angiogenesis. In ADAMTS1-null mice, oocyte and ovarian vascular degeneration and reduction in ovarian network organization were determined (6, 9). Human chorionic gonadotropin (hCG), another hormone in ovulation, also stimulates secretion of ADAMTS1 in ovaries (23).

Tissue inhibitor of metalloproteinases (TIMPs), which specifically inhibit ADAMTS1, are also involved in ovulation. The balance between ADAMTS1 and TIMP3 is important for the development and regression of the corpus luteum (24).

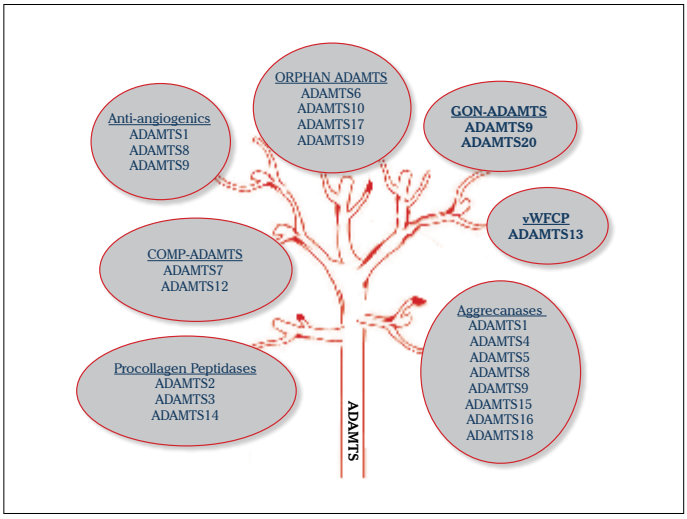


**Figure 1. ADAMTS tree: Classification of ADAMTS proteinase according to their functions**

Although other ADAMTS proteinases, like ADAMTS 4, -5, -9, -16, and -17 were identified in ovaries, only ADAMTS1 has been examined in detail so far (9). For these reasons, other ADAMTS proteinases are thought to have important tasks in ovulation (2, 10).

In a study about mice that had defective leptin hormone, the levels of gonadotropin-releasing hormone were reduced, and consequently, hypogonadism and anovulation were shown. Leptin increases ADAMTS1; so, ovulation occurs (25).

The expression of PACAP (pituitary adenylate cyclase-activating polypeptide), which is an endogenous peptide found in the placenta and uterus, is increased after stimulation of LH/gonadotropins in ovaries. This hormone is critical for steroidogenesis, oocyte maturation and survival of granulosa cells in ovaries (26, 27).

As a result of this information, ADAMTS1 is a new candidate marker that indicates the competence of oocytes and the capacity of fertilization (23).

### Menstrual cycle and ADAMTS

Various structural changes in the endometrial ECM are seen in the menstrual cycle. These changes are quite important for successful implantation and placental development (28). ADAMTS1, one of the considerable structures that are responsible for these changes, is effective in all uterine tissues throughout the menstrual cycle (12). ADAMTS1 has a role in matrix remodeling. The expression of ADAMTS1, which is responsible for the degradation of proteoglycans, like syndecan and perlecan, in the ECM, is increased by gonadal steroids, such as PG, estrogen, and androgens (28, 29). ADAMTS1, responsible for ECM remodeling, also has critical roles in the initiation and successful maintenance of decidualization (29). In ADAMTS1 knockout mice, the uterus develops, but successful implantation does not occur (12, 28).

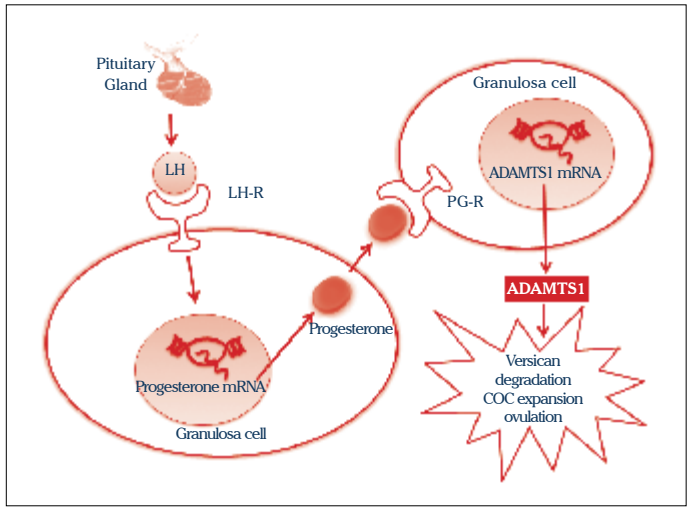


**Figure 2. Luteinizing hormone (LH) secreted from the pituitary gland, increases secretion and expression of progesterone and progesterone receptor (PG-R) in granulosa cells. Progesterone leads to increased expression of ADAMTS1 by binding to its receptors (PG-R) on the granulosa cells. ADAMTS1 degrade versican. This degradation causes to expand COC formation and ovulation (8, 9, 20, 21)**

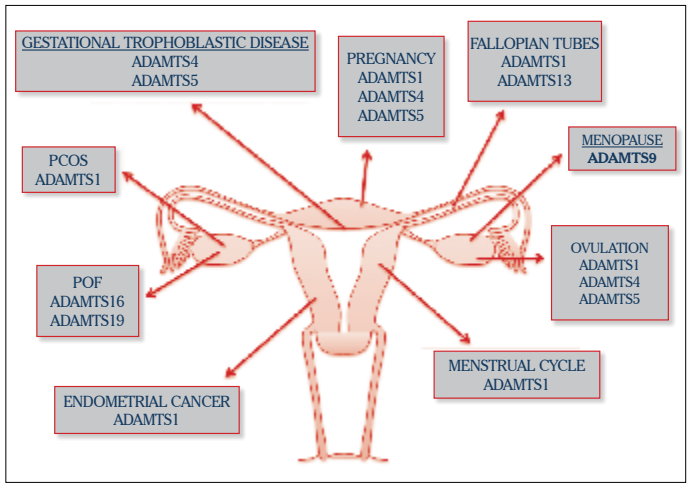


**Figure 3. The role of the ADAMTS: A new biological marker candidates in physiological and pathological processes in female reproductive system**

Although the expression of ADAMTS1 and -13 is increased in the fallopian tube during the menstrual cycle, there is no functional work reported in the literature (30).

**Pregnancy and ADAMTS**

Placenta formation for the occurrence of pregnancy is the most fundamental step. For successful placentation, the transformation cytotrophoblasts into intermediate trophoblast and the invasion of these cells into maternal tissues are needed (31). During placenta formation, extravillous trophoblasts lose their cell-cell interactions and secrete various proteases, including ADAMTS1. The functions of these cells, which invade surrounding tissues and the endometrium, are controlled very tightly. ADAMTS1 is responsible for the degradation of the ECM and the invasion of the myometrium and endometrium (32, 33). Interleukin 1 beta (IL-1β) and transforming growth factor beta (TGF-β) are two cytokines that affect the expression and activity of ADAMTS1 (33). ADAMTS1 is also responsible for the formation of new blood vessels that supply the nutrients needed for the placenta and endometrium (34). In ADAMTS1 knockout mice, it was observed that the pregnancy rate declined (33). ADAMTS4 and -5 are expressed at very high levels, especially in the first-trimester placenta and are responsible for maternal tissue invasion (31).

ADAMTS5 presence in first-trimester decidual endometrial tissue was determined. IL-1β and TGF-β1 are two key cytokines that affect the expression of ADAMTS5. While IL-1β increases the expression levels of ADAMTS5, TGF-β1 decreases them (35). Expression of ADAMTS5 is associated with decidualization. ADAMTS5 is also thought to be responsible for the cytokine-mediated proteolytic degradation of decidual ECM (35). Gonadal steroids, like PG and dihydrotestosterone, regulate the expression of ADAMTS5, -8, and -9 in endometrium cell culture. These enzymes, which have critical roles in endometrial physiology, lead to decidualization in the endometrium. Defects in the synthesis of these proteases result in infertility (36).

In the symphysis pubis during pregnancy, several changes are seen. The expansion of the symphysis pubis is seen for the fetus to pass through the birth canal in a comfortable way. For this expansion, the synthesis of versican and HA is increased, and proteinases, like ADAMTS1, are decreased in the ECM (37). Cells obtained from amniotic fluid from pregnant women with fetuses who have neural tube defects do not make the storage of collagen. The expression of ADAMTS2 and -14 in these cells is lower (38).

In placental tissue samples taken from pregnant women in the first trimester, it was shown that ADAMTS12, independent of other metalloproteinases, was responsible for the invasion of trophoblastic cells. The expression of this protease is regulated by IL-1β and TGF-β1, like ADAMTS1 and -5. ADAMTS12 also regulates cell-ECM adhesion and invasion (39).

**Menopause and ADAMTS**

Menopause is an important physiological event closely related to women's health. Genetic studies have showed that various genes are associated with menopause. ADAMTS9 is one of these genes. The relationship between the ADAMTS9 and SMAD3 genes is associated with natural menopause age (40). Bone mineral densitometry (BMD), an examination method to determine osteoporosis, is influenced by several genetic and environmental factors. Although the peak level of BMD is influenced by diet and physical activity, genetic factors are also important. Studies about this issue showed that ADAMTS18 has been associated with femoral neck bone mineral density (41).

**ADAMTS in the Pathogenesis of Obstetrics and Gynecology Diseases**

**Thrombotic thrombocytopenic purpura/other diseases that are predisposed to thrombosis and ADAMTS**

Thrombotic thrombocytopenic purpura is a rare disease associated with thrombocyte aggregation secondary to thrombocytopenia, hemolytic anemia, and ischemic conditions. In TTP, which is an acute onset and quite fatal disease, there are hyaline thromboses in a great deal of tissue and organs (42). Although it is a rare disease, its incidence increases during pregnancy (43, 44). In the pathogenesis of the disease, ultralarge von Willebrand factor multimers, which must be degraded by ADAMTS13 (vWFCP) in circulation, have an essential role (42). This disease is more frequently seen in pregnancy. Pregnancy-related hypercoagulability and decline of ADAMTS13 levels are the reasons (45). Especially in severe ADAMTS13 deficiency, TTP develops during pregnancy (46). The risk of recurrence after pregnancy is high. For this reason, early diagnosis and treatment of TTP are needed (43).

In ADAMTS13 deficiency, the incidence of HELLP, preeclampsia, and hemolytic uremic syndrome (HUS) also increases (43). In HELLP syndrome (hemolysis, elevated liver enzymes and low platelet count), active plasma vWF levels and the propeptide/mature vWF ratio have been found to be higher than in normal pregnancy and preeclampsia. ADAMTS13 levels have been also found to be low (47). In the pathogenesis of HELLP syndrome (hemolysis, elevated liver enzymes and low platelet count), there is thought to be acute endothelial activity, like TTP (47).

Early diagnosis and treatment of TTP in pregnancy are crucial. Measurement of ADAMTS13 levels is helpful in the diagnosis. An ADAMTS13 level of no less than 5%, the absence of ADAMTS inhibitors, and expression of ADAMTS gene mutations will help confirm the diagnosis (48).

**Polycystic ovary syndrome (PCOS) and ADAMTS**

Polycystic ovary syndrome is a common disease that affects mostly women of reproductive age. In this disease, common cysts in the ovaries, oligo-anovulation, hyperandrogenism, hyperinsulinism and insulin resistance are seen. Abnormal steroidogenesis/folliculogenesis and developmental disorders in the dominant follicle result in impairment of ovarian function. The expression of ADAMTS1 is reduced in PCOS. This is thought to be associated with the failure of ovulation, impairment of oocyte quality, and declined fertilization rate (49).

**Premature ovarian failure (POF) and ADAMTS**

Premature ovarian failure, one of the most important diseases that cause female infertility, is a disease characterized by amenorrhea occurring before the age of 40 and hypergonadotropic hypogonadism. In the development of POF, the dysfunction and destruction of follicles are important physiological events. In genomic studies, ADAMTS19 has a role in ovarian development. It is thought ADAMTS19 may be important in the pathogenesis of POF (50, 51). Insulin-like growth factor (IGF-2) increases the number of FSH receptors in granulosa cells. IGF-2 and FSH induce steroidogenesis in these cells. IGF-2 is a useful marker to identify high-risk POF patients. In the pathogenesis of POF, there is a relationship between ADAMTS19 and IGF-2 receptors (50).

Activin A is an effective hormone that provides germ cell proliferation and survival in ovaries. In the pathogenesis of POF, there is a relationship between ADAMTS19 and activin type II receptors (ACVR2) (52).

Thyroid-stimulating hormone (TSH) induces steroidogenesis induced by gonadotropin. In thyroid dysfunctions, estrogen metabolism disorders, menstrual disorders and infertility are seen. In previous studies, there was a relationship between ADAMTS16 and the TSHβ gene. This relationship is associated with POF pathogenesis (53).

**Gynecologic cancers and ADAMTS**

Endometrial adenocarcinoma composes 80% of endometrial cancers, which are the most frequently seen gynecologic cancers in women. In these tumors, while angiogenesis increases, invasiveness also increases. ADAMTS1 plays an important role in invasiveness associated with tumor cell migration and metastasis. Increased in endometrial adenocarcinomas, ADAMTS1 is related to epithelial cell invasion and endothelial cell function (54).

ADAMTS4 and -5 are highly expressed in gestational trophoblastic diseases. These proteinases are closely related to the biological behavior of gestational trophoblastic disease. It is suggested that the staining pattern of these proteinases may help make the distinction between normal gestation, early complete mole, invasive mole, and choriocarcinoma (31).

Epithelial ovarian cancer composes 90% of ovarian cancers, which are the most disastrous gynecologic cancers in women. Several epigenetic changes were detected in these tumors. Methylation of DNA is one of these epigenetic mechanisms. The activity of hypermethylated genes reduces. Although HOXA9, HOXB5, CRABP1, and SCGB3A1 have been shown to be hypermethylated in ovarian carcinomas, the ADAMTS1 gene is not methylated (55).

## Conclusion

We tried to point out the importance of ADAMTS proteinases, which have been hugely popular in recent years, in obstetrics and gynecology. These enzymes have very critical roles in the physiology of the female reproductive system, including ovulation and the pathogenesis of obstetric and gynecology diseases (56) (Figure 3). There are not enough studies about this subject in obstetrics and gynecology. A great deal of studies are required to analyze the ADAMTS gene promoter, discover signaling pathways and point out single-nucleotide polymorphisms (1). In these studies, the functions of this family, in the ECM context will be studied in the female reproductive system, like other tissues and organs.

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

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# Complete hydatidiform mole presenting as placenta previa in a twin pregnancy with a coexisting normal foetus: Case report

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## Abstract

We present a case of a patient with a complete hydatidiform mole co-existing with a normal foetus (CMCF) who had a caesarean section in week 32 of gestation, resulting in a live female infant weighing 1590 grams. The mother, with a normal bleeding pattern, did not require any surgical intervention. She was discharged from hospital on the third post-operative day. Premature termination is recommended in this type of pregnancy because of the risks associated with molar pregnancies. However, with the close follow-up of these pregnancies, good maternal and perinatal results may be obtained. (J Turk Ger Gynecol Assoc 2014; 15: 256-8)

**Key words:** Twin pregnancy, complete hydatidiform, placenta previa

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## Introduction

A complete hydatidiform co-existing with a live foetus (CMCF) is extremely rare. It is difficult to estimate the incidence of such pregnancies because the diagnosis can only be made by histological examination (1). Pre-eclampsia, hyperemesis gravidarum, vaginal haemorrhage, intrauterine foetal demise and increased risk of persistent trophoblastic disease are the most common complications (1-4). Careful clinical assessment, detailed ultrasound examination and chromosome analysis are essential for prenatal diagnosis. Patients with CMCF may have an increased risk of persistent trophoblastic disease. These pregnancies may have an aggressive biological course even after they have been terminated. The rate of trophoblastic tumours after such pregnancies has been reported to be 50 to 60% (1). However, there is no consensus on the diagnosis and management of such pregnancies. We present here a case of a CMCF who was delivered at 32 weeks of gestation.

## Case Presentation

A 21-year-old nulliparous woman suffering from vaginal haemorrhage in the early second trimester of her pregnancy was referred to the Obstetrics and Gynecology Department of Ege University Hospital. Gestational age was 17 weeks and 4 days according to her last menstruation date at the time of admission. A live foetus and a placenta with multi-cystic heterogeneous appearance and increased anteroposterior diameter were observed on ultrasound examination (Voluson e8 Ultrasound Device, Buckinghamshire, United Kingdom) (Figure 1). Serum levels of β-hCG and haemoglobin were 77.509 mIU/mL and 11 g/dL, respectively. The thyroid function tests, amniotic fluid volume, umbilical artery Doppler flow velocimetry, foetal growth and the maternal blood pressure were all within normal limits. A normal karyotype (46, XX) was found based on the results of amniocentesis. The pregnant woman and her family were informed about molar pregnancy and written informed consent was obtained from the patient for this study. The termination of the pregnancy was recommended as an option because of the probable risks of molar pregnancy; however, the family refused this intervention. The mother was discharged after being advised to have bed-rest with subsiding symptoms, and was scheduled to have follow-up visits.

No apparent foetal abnormality was detected in the twenty first week of gestation during the second trimester obstetric ultrasound examination. The β-hCG level was 67.265 mIU/mL at the twenty first week of gestation. Magnetic resonance imaging (MRI) examination was performed because of the presence of low-lying placenta during her next follow-up visit. Many cystic structures with diameters of up to 2 cm were observed on the placenta. Both placenta previa totalis and placenta acreata were detected on MRI examination (Figure 2).

In the follow-up period, the patient was admitted to our hospital with the complaint of vaginal haemorrhage in week 32

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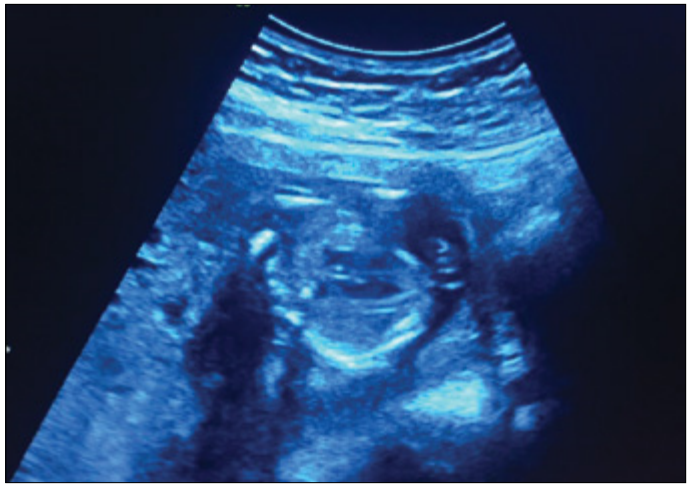

**Figure 1. The ultrasound appearance of the foetus and the placenta**

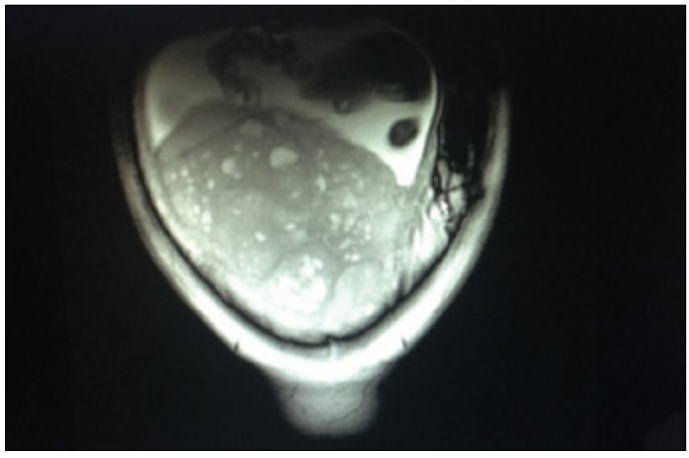

**Figure 2. Magnetic resonance imaging of the foetus and the placenta**

of gestation. The patient was hospitalised with the diagnosis of placenta previa totalis and preterm labour. Antenatal betamethasone for foetal lung maturation and intravenous $MgSO_4$ as a tocolytic agent were administered to the patient. The patient was taken urgently to the operation room for labour due to excessive vaginal haemorrhage at the gestational age of 32 weeks on the fourth day of hospitalisation. A female infant weighing 1590 g was successfully delivered by caesarean section. APGAR scores at the 1st and 5th minutes were 7 and 9, respectively. The surgery took place smoothly and none of the expected complications, such as significant uterine bleeding, were encountered during the operation. The serum β-hCG and haemoglobin levels were 30.134 mIU/mL and 9.7 g/dL, respectively, on post-operative day 1. Placentomegaly, hydropic degeneration and many vacuoles were observed to be compatible with complete hydatidiform mole in the placenta (Figure 3). The pathological examination confirmed the initial diagnosis of CMCF. The infant was admitted to the newborn intensive care unit because of prematurity. The mother was discharged on the third post-operative day. Serum β-hCG levels were both zero on the sixth post-operative week and on the monthly follow-up, until six months after delivery.

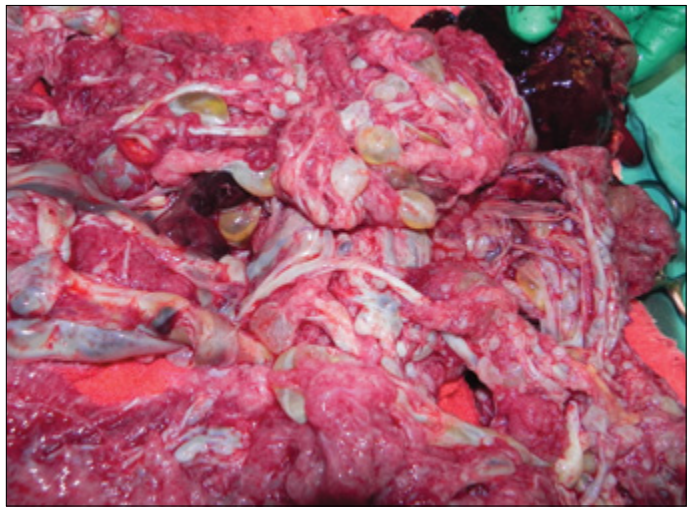

**Figure 3. The morphological appearance of the placenta**

## Discussion

In several studies, the incidence of CMCF has been reported to be between 1/10000 and 1/100000 (1-4). Diagnosis is usually made by first-trimester ultrasound examination (2). In those cases, vaginal haemorrhage was found to be most common complaint at admission to the hospital (1-4). Serum levels of β-hCG are usually high at the time of admission, but it should be kept in mind that β-hCG levels may be high in multiple gestations (2). A high level of β-hCG at the time of admission may be an indication of poor prognosis of the disease (1).

Partial and complete molar pregnancies have obvious foetal and maternal risks (2). Thus, such pregnant women should be followed more carefully in specialised centres. It is usually recommended to terminate a partial or complete hydatidiform mole if it is detected early in the course of pregnancy (1, 2). Written informed consent should be taken from the family because of probable risks of these pregnancies if they choice to maintain the pregnancy (2).

Ongura et al. (5) presented a case who had a complete mole coexistent with a twin foetus. Her pregnancy was terminated by hysterectomy due to massive haemorrhage. The second patient published by Suri et al. (6) presented to hospital in the 28th week of gestation with signs of intrauterine infection. Her pregnancy was terminated in week 28 of gestation by hysterectomy following the development of systemic inflammatory response and a live male infant was born. Pathological examination supported molar pregnancy and bacterial abscess. Klatt et al. (7) reported a case in the third gestational week with vaginal haemorrhage. Her pregnancy was terminated on the 31st gestational week by hysterectomy upon increasing vaginal haemorrhage and foetal distress; an intrauterine balloon was inserted prophylactically for postpartum haemorrhage.

It is appropriate to evaluate the placenta by Doppler ultrasound examination in early gestational weeks to exclude placenta accreta; occasionally, MRI may be needed for the posterior side placenta and it may be necessary for the assessment of the depth of myometrial and parametrial involvement (8).

The optimal management of CHCF is controversial, especially when the pregnancy is desired. The management may be altered due to coexisting complications, such as hypertension, pre-eclampsia, thyrotoxicosis and vaginal haemorrhage. The aim of the management should be to avoid complications and to plan delivery at the most appropriate time for both maternal and foetal well-being. Performing the surgical intervention by an experienced surgical team would be more appropriate for avoiding complications that could occur during operation. One should be alert for severe and serious postpartum haemorrhage that may be caused by placenta previa as well as molar pregnancy and the necessary surgical instruments and materials should be prepared prior to operation.

In conclusion, we can say that it should be advised to terminate such pregnancies in order to prevent maternal and foetal risks. However, one should keep in mind that such pregnancies may result in live births with careful follow-up. Also, one should be alert for the possibility of gestational trophoblastic neoplasia following termination of the pregnancy.

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

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# Bicuspid aortic valve and severe aortic stenosis in a newborn exposed to carbamazapine during pregnancy

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## Abstract

The use of antiepileptic drugs increases the risk of major congenital malformations during pregnancy. Here, we report an infant who had a history of in-utero carbamazepine exposure and who was born with a cardiac malformation. The infant was born at 39 weeks of gestation vaginally to an epileptic mother who had been treated with carbamazepine throughout her pregnancy. He was referred due to cardiac murmur in the second week of his life. The mother had not received folic acid supplementation. Transthoracic echocardiography revealed bicuspid aortic valve, mild aortic stenosis, patent ductus arteriosus, patent foramen ovale and the renal ultrasound revealed mild left hydronephrosis. Follow-up echocardiography performed 14 weeks later showed increased severity of aortic stenosis and percutaneous balloon aortic valvuloplasty was performed. To our knowledge, there is only one case report in the literature mentioning the association of a bicuspid aortic valve and aortic stenosis with oxcarbazepine exposure, which is a structural derivative of carbamazepine. However, there are no reports for association with carbamazepine itself. Bicuspid aorta and aortic stenosis may be among the cardiac malformations that result from the teratogenic effect of carbamazepine. (J Turk Ger Gynecol Assoc 2014; 15: 259-61)

**Key words:** Aortic stenosis, bicuspid aortic valve, carbamazepine, pregnancy

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## Introduction

Antiepileptic drugs (AEDs) received during pregnancy have potential adverse effects on foetal development. In the United States alone, over 25,000 children have a history of in-utero AED exposure each year (1), which increases the risk of major congenital malformations in the foetus from 3.3% to 7.7% (2, 3). Cardiovascular malformations, neural tube defects, cleft palate and urogenital abnormalities are among the congenital abnormalities that can develop secondary to in-utero AED exposure. Multicystic dysplastic kidney, hydronephrosis, ureteropelvic junction stenosis and hypospadias are the abnormalities of the urinary system that are reported to be associated with maternal AED use during pregnancy (2, 3). Cardiac malformations associated with antenatal exposure to an AED have been reported to have a prevalence of 7.8% in infants of mothers with epilepsy (4) and include ventricular septal defect, atrial septal defect, tetralogy of Fallot, patent ductus arteriosus, pulmonary stenosis, tricuspid regurgitation and transposition of great arteries (2-4).

Carbamazepine (CBZ) is among the most commonly used AEDs during pregnancy. Major congenital malformations reported to be associated with CBZ use in the cohort studies are several cardiovascular malformations, spina bifida, cleft lip with or without cleft palate, hypospadias, inguinal hernia, diaphragmatic hernia, hypertrophic pyloric stenosis, ectopic and hypoplastic thyroid (2-4).

This report describes the presence of bicuspid aortic valve, aortic stenosis and unilateral mild hydronephrosis in a newborn exposed to CBZ during pregnancy. To the best of our knowledge, this is the first case describing the possible association of bicuspid aortic valve and aortic stenosis with in-utero CBZ exposure.

## Case Presentation

A 14 day-old male infant born from a mother using AED during pregnancy was referred to the paediatric cardiology department due to cardiac murmur. He was born in the 39th gestational week to a 29 year-old healthy mother (G5P2) and a 31 year-old healthy father. Both parents were of Turkish descent and were not related. The mother had been receiving antiepileptic therapy for seven years with CBZ (Tegretol CR, Novartis, İstanbul, Turkey), at a dose of 1000 mg/day (600 mg in the morning, 400 mg in the evening). The medical history was negative for using folic acid, drug abuse, alcohol consumption or smoking. There was no parental history of congenital anomalies. The pregnancy had a normal course and the

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mother had no epileptic seizures throughout the pregnancy. At 39 weeks of gestation, she delivered a male infant with spontaneous vaginal delivery with a 1st and 5th minute Apgar score of 8 and 10, respectively. The infant's birth weight was 3050 grams, head circumference was 34.5 cm, and height was 50 cm, all of which were appropriate for the gestational age at delivery. Physical examination revealed systolic ejection murmur (grade III/VI) at the upper right sternal border and laryngomalacia. There were no additional abnormalities. The phenotype of the infant was not suggestive of known genetic syndromes. Transthoracic echocardiography showed a bicuspid aortic valve (BAV) (functionally bicuspid), mild aortic stenosis, patent foramen ovale, and patent ductus arteriosus. There were no other cardiac lesions. Renal ultrasound revealed mild left hydronephrosis without evidence of posterior urethral valve. Blood count, electrolytes, renal function tests, liver enzymes, thyroid hormones and cranial ultrasound were normal.

Repeat echocardiography performed in the 14th week of life showed an increased severity of aortic stenosis. Doppler ultrasound revealed severe aortic stenosis with a mean gradient of 70 mmHg (Figure 1). Aortography showed aortic stenosis with BAV (Figure 2). Upon these findings, percutaneous balloon aortic valvuloplasty was performed with a 9 mm BAV catheter. Peak systolic gradient of aortic valve decreased from 86 mmHg before the procedure to 33 mmHg after the procedure. Echocardiographic follow-up at 6 months showed spontaneous closure of the patent foramen ovale, a small patent ductus arteriosus, BAV, mild aortic stenosis (peak gradient 36 mmHg) and mild aortic regurgitation (Figure 3). Paediatric assessment revealed normal growth and development. Written informed consent was obtained from the parents for this study.

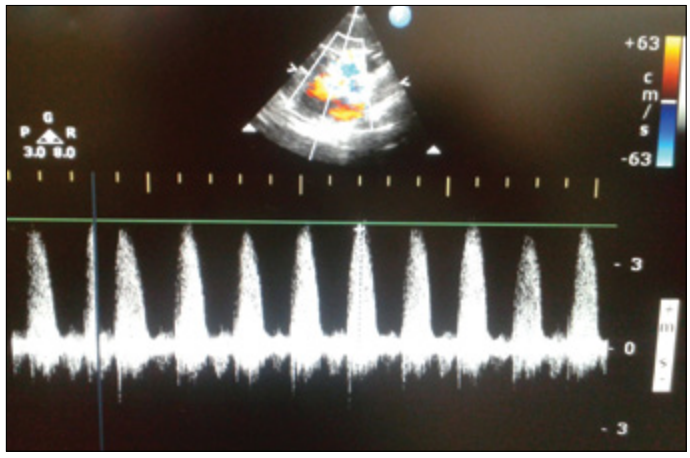


**Figure 1. Echocardiographic image of the gradient across the aortic valve before the balloon valvuloplasty procedure**

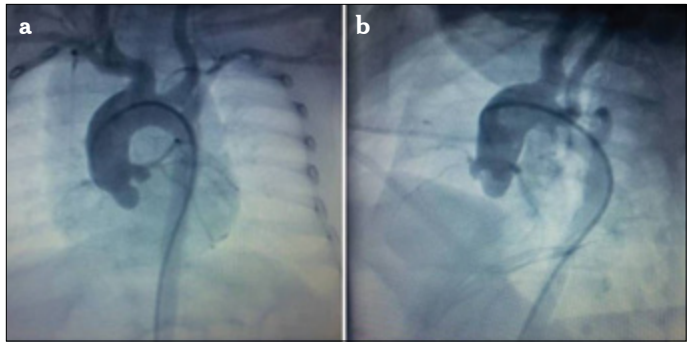


**Figure 2. a, b. Appearance of bicuspid aortic valve in the aortography**

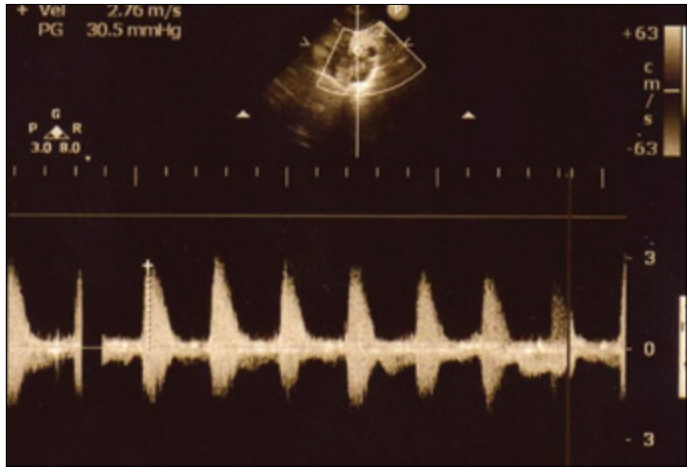


**Figure 3. Echocardiographic image of the gradient across the aortic valve after the balloon valvuloplasty procedure**

## Discussion

Some studies have proposed that the mother's epilepsy plays an important role in development of foetal malformations (4). However, recent studies have suggested that AED therapy is the main cause of neural tube and cardiac defects. Their association with other birth defects is not clear. Moreover, the congenital malformation rate increases during the first trimester of pregnancy (2, 4, 5). Folic acid supplementation in the periconceptional period is shown to be associated with a reduced risk of congenital malformations, especially of neural tube defects, heart defects, cleft palate and limb defects (2, 5, 6). On the other hand, there is no evidence to suggest that additional folic acid supplementation decreases the risk of congenital malformations associated with in-utero AED exposure (4, 7).

During pregnancy, AEDs should be used at the lowest possible dose that is compatible with the maternal disease. The dose of the AEDs should be reduced beginning from the periconceptional period to the first 8 weeks of gestation to avoid any unwanted effect on organogenesis (2, 8). CBZ at doses greater than 400 mg per day increase the risk of congenital anomalies (8). Besides the dose of the AEDs, the risk of major congenital malformations is also affected by other variables such as parental history of congenital anomalies. Moreover, cardiovascular malformations were significantly more frequent in premature infants of mothers with epilepsy (4). The mother in the present case had not only used a high dose of CBZ, but had also not used folic acid supplementation, which might be one of the possible causes of the congenital malformation seen in this infant. However, BAV seen in our case could also be an isolated finding which was not associated with drug exposure since BAV is the most common cardiac lesion seen in the newborn population.

Carbamazepine shows its antiepileptic effect by blocking voltage-gated sodium channels and stabilizing neuroexcitatory tissues. It has been suggested that CBZ is relatively safer than other AEDs during pregnancy (3). Cohort studies evaluating the teratogenic effects of CBZ have shown a significantly increased risk only for spina bifida (2, 3). Cardiovascular malformations associated with in-utero CBZ exposure include ventricular septal defect, hypoplastic left ventricle, transposition of the great arteries and anomalous pulmonary venous return (2-4, 9). Akar et al. (10) have reported a case of foetal CBZ syndrome presenting with facial dysmorphism, skeletal abnormalities, congenital heart defect, renal agenesis, anal atresia, ambiguous genitalia, and right hemihypoplasia of the entire body. Rolnitsky et al. (11) reported an infant with congenital abnormalities (BAV, mild aortic stenosis, patent ductus arteriosus, patent foramen ovale, and severe unilateral hydronephrosis due to ureteropelvic junction stenosis), hyponatraemia, and a withdrawal syndrome following in-utero oxcarbazepine exposure. There is another case report which mentions an association of aortic stenosis with antenatal use of oxcarbazepine (2). The infant also developed hyponatremia and a withdrawal syndrome, which has not been reported in infants exposed to CBZ during pregnancy.

To the best of our knowledge, BAV that may be associated with exposure to CBZ during pregnancy has not been previously described. BAV includes a spectrum ranging from critical aortic stenosis to an asymptomatic finding which is not associated with aortic stenosis or regurgitation. In the present case, severe aortic stenosis developed during follow-up, and valvuloplasty was performed. There was no hyponatraemia or neonatal withdrawal syndrome. With the present clinical findings, known genetic syndromes associated with abnormalities of the vascular system such as Marfan disease, Turner, Loeys-Dietz, Williams and other syndromes were excluded.

We presented a case of BAV and severe aortic stenosis in an infant who had a history of in-utero CBZ exposure. Although it could be just a coincidence of an isolated BAV with an in-utero drug exposure, this possible association should be kept in mind by obstetricians and paediatricians during follow-up of infants exposed to AEDs during pregnancy. In appropriate cases, the AEDs should be reduced to the lowest possible dose beginning from the preconception period and supplementation of folic acid should be considered.

***Ethics Committee Approval:*** *N/A.*

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

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

***Author contributions:*** *All authors contributed equally during the preparation of this manuscript.*

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

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# What is your diagnosis?

A 68-year-old woman, affected by a vulvar tumor that was accompanied by burns, was referred to our department. The vulvo-vaginal examination revealed a voluminous blackish clitoral lesion, measuring around 30 mm, and pigmented areas on the labia majora and minora, also affecting the clitoral prepuce and the vulvar vestibule (Figures 1, 2). The patient underwent a total body exam, which did not reveal any other localization.

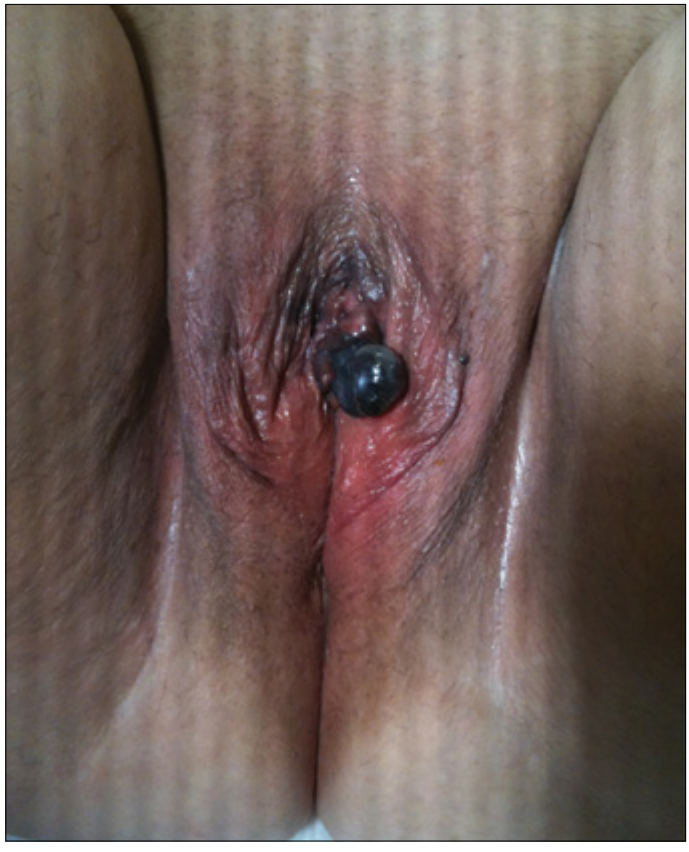

**Figure 1. Macroscopic aspect of the vulvar tumor**

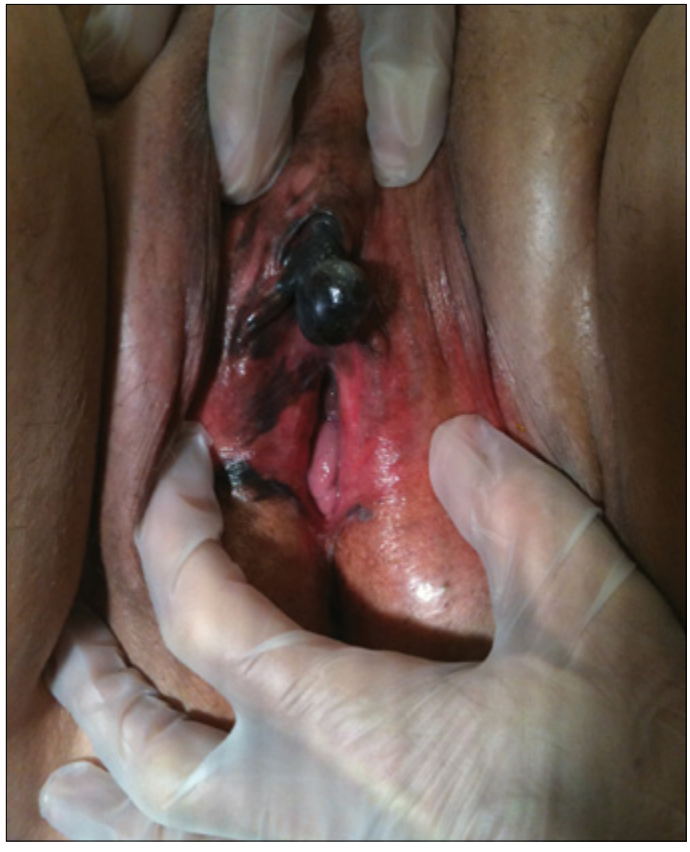

**Figure 2. Genital examination findings - pigmented lesions**

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## Answer

An excisional biopsy on the clitoral lesion and multiple biopsies on the pigmented area were performed. The pathologic report of the tumor of the clitoris revealed melanoma with a desmoplastic component (Breslow tumor thickness of 25 mm and Clark level of invasion of 5) (Figure 3). The microscopic resection was incomplete. The other biopsies revealed an aspect of atypical lentigo. The full-body computed tomography and positron emission tomography were normal. After a multidisciplinary consultation, adjuvant radiotherapy was performed in light of the many studies that have revealed that radical surgery does not improve the survival rate with advanced tumors and can be associated with physical disabilities (1). In this case, complete surgical management would require an anterior pelvectomy, which was not justified insofar as the local extension of disease was important. Because the tumor thickness and its level of invasion were elevated, the risk of local and/or metastatic recurrence was high. Radiotherapy appeared as an alternative management. All of this information was given to the patient and her family. After 36 months, no local and metastatic clinical and radiological evolution occurred.

The density of melanocytes appears greater in the head, face, and neck but also in the genital areas (2). Malignant melanoma represents less than 5% of all skin cancers deriving from melanocytes but is nevertheless responsible for 75% of skin cancer-related mortality (3). Vulvar melanoma is a rare variant with a poor prognosis. It should be staged surgically using the American Joint Committee on Cancer (AJCC) staging system, which incorporates the Clark and Breslow scores (4). Desmoplastic melanoma is a rare entity that is more difficult to recognize insofar as the cytomorphology and the immunohistochemical features are non-specific. It is usually composed of non-pigmented fusiform melanocytes with unusual phenotypic profiles resembling fibroblasts. Its early detection and en bloc large surgical excision with safety margins and regional lymphadenectomy were considered, until recently, the standard therapeutic modality (1). Malignant melanoma appears historically to be radiation-resistant. However, adjuvant radiation therapy can be used in situations of increased risk for locoregional recurrence, like thickness, ulceration, desmoplastic or neurotropic features, and certain anatomic locations (5).

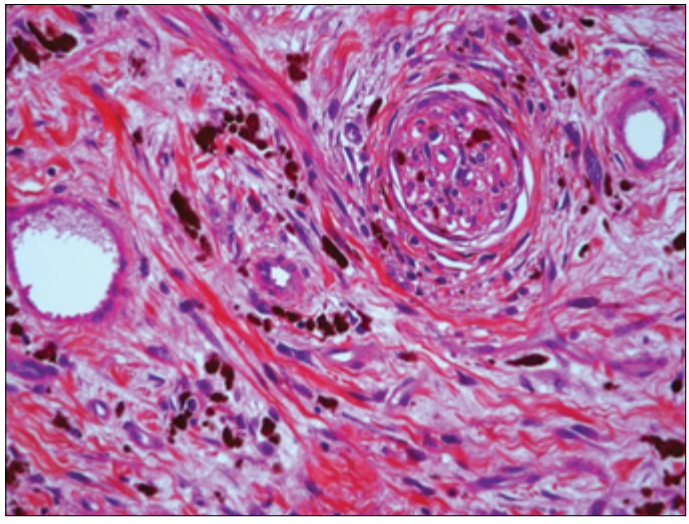

**Figure 3. Microscopic view (x200) of the desmoplastic component with important fibrosis**

**Erdogan Nohuz[1,2], Maël Albaut[1], Sharif Kullab[3], Mayssam Fattouh[1], Stefano Tamburro[4], Marie-Melanie Dauplat[5], Céline Benoît[6], Xavier Durando[3]**

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# Maternal vitamin D supplementation and its impact on allergy

To the Editor,

With great interest, we read the recent article by Gur et al. (1), "The effect of place of residence and lifestyle on vitamin D deficiency in pregnancy: Comparison of eastern and western parts of Turkey". The authors discussed the prevalence and the predictive factors of vitamin D deficiency in pregnancy and the compliance with "The National Vitamin D Support Program" in Turkey's easternmost and westernmost provinces. They found that clothing style, seaside holiday duration, consuming fish, living in high-altitude cold regions, and 1200 IU/day vitamin D supplementation affected vitamin D levels. They also showed that vitamin D deficiency in pregnancy is high in Turkey. They recommended increasing compliance with "The National Vitamin D Support Program" at the follow-up of all pregnant women.

Vitamin D supplementation in early life is recommended to prevent vitamin D deficiency in many countries, raising important questions about the safety and benefit for immune development and the implications for allergic risk. The impact of vitamin D deficiency on the risk of developing an allergy and a child's immune status in childhood has been controversial and lacking. We want to mention that vitamin D supplementation during pregnancy may promote the evolution of allergic diseases in offspring during childhood.

In recent studies, vitamin D was found to be positively associated with the risk for the development of allergic diseases in children during their first 2 years of life. Weisse et al. demonstrated that in pregnancy and at birth, higher levels of vitamin D may contribute to a higher risk for allergic outcomes. A questionnaire was answered by parents during pregnancy and yearly thereafter about children's atopic findings in the first 2 years of life. They also found a positive association between maternal and cord blood vitamin D concentrations with children's risk for food allergy within the first years of life (2).

In a prospective study, 596 pregnant women's vitamin D concentrations were evaluated in pregnancy, and their children were followed about allergic diseases and growth parameters. An association was not found between maternal vitamin D level and the child's anthropometric data or intelligence. Children whose mothers had a higher concentration of vitamin D had an increased risk of atopic dermatitis and asthma compared to children whose mothers had a lower concentration of vitamin D (3).

Rothers et al. (4) found that those with cord blood vitamin D ≥100 nmol/L, when compared to children with cord vitamin D 50-74.9 nmol/L, had a greater risk of a positive response to a skin prick test. They also reported a non-linear relationship between cord vitamin D and IgE (allergen-specific and total). The highest levels of IgE were identified in children with a cord vitamin D concentration <50 nmol/L and ≥100 nmol/L. Increased risk of aeroallergen sensitization and elevated total IgE levels are associated with both low and high levels of vitamin D in cord blood.

Nielsen et al. (5) reported that postpartum depression is associated with high levels of 25(OH)D3. They speculated that 24-hydroxylase is the main determinant of this situation. High levels of 25(OH)D3 stimulate the 24-hydroxylase enzyme, which degrades the active form of vitamin D, 1,25(OH)2D3, to the inactive 1,24,25-trihydroxyvitamin D3 metabolite. This results in low concentrations of intracellular 1,25(OH)2D3. So, they propose that either a low level of 25(OH)D3 or high level of 25(OH)D3 cause a low level of 1.25(OH)2D and subsequent insufficient stimulation of vitamin D receptors.

Although the data to support this are still limited and heterogeneous, according to data, especially large doses of vitamin D supplementation during pregnancy should be used carefully.

We hope that the items mentioned above will add to the value of the well-written article of Gur et al. (1) regarding vitamin D deficiency in pregnancy.

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## Author's Response

We appreciate and thank the authors, because they made an interpretation about the study we performed. There are studies indicating that high serum levels of vitamin D can lead to negative health outcomes, like low levels, as the writers state in this letter. However, there is very little information regarding the subject that a high maternal serum vitamin D level in pregnancy can have fetal or maternal side effects. In the study of Rother et al. that the writers give reference to, the relationship between high umbilical cord vitamin D level (≥100 nmol/L =40 ng/mL) seen in 24 of 214 pregnant women and vitamin D replacement was not mentioned. Furthermore, cord blood vitamin D levels presented in this study are surprisingly high according to our national data. In the study performed by Halıcıoglu et al., it was found that the mean cord blood vitamin D level was 11.5±6.8 ng/mL, whereas they encountered normal (≥30 ng/mL) levels of vitamin D in only 2.3% of fetuses (1).

There are no clear data in pregnancy about the vitamin D replacement dose that will ensure normal maternal serum vitamin D levels. However, it was put forth that 400 IU/day of vitamin D replacement that the health authorities proposed is far from meeting the increasing need in pregnancy. The subject that the safe upper limit for pregnant women is 4000 IU/day has been reported by The National Health Institution. Wagner et al. showed that the mean umbilical cord blood vitamin D level was 27.0±13.3 ng/mL in pregnant women to whom they gave 4000 IU/day of vitamin D replacement in their prospective study (2). In addition, it was stated that there were no findings of toxicity in these pregnant subjects. The subject that vitamin D addition of 1000 IU/day during the last trimester of pregnancy resulted in only an augmentation of 5 to 6 ng/mL in moving around of vitamin D levels in maternal and cord serum was reported by Mallet et al. (3). It has been seen in pregnant and lactating women that it is necessary to take doses exceeding 1000 IU/day of vitamin D (2000-10,000 IU/d) for the purpose of obtaining robust nutritional vitamin D status (2).

As a result, new data are needed to find the ideal replacement dose of vitamin D during pregnancy. However, it is being seen that the dose replacement of 1200 IU/day proposed in the National Health Program in our country in the current conditions is an appropriate and logical approach.

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# Acknowledgements for the Year 2014

(Reviewers contributed at the review process in 2014)

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

**Prominent Reviewers in 2014**

We would like to acknowledge, with special thanks and appreciation, the following reviewers for their remarkable contributions to peer review process of the *Journal of The Turkish German Gynecological Association* in 2014. We extend our sincere gratitude for their timely, scholarly and critically evaluations.

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We are also grateful for the help of the reviewers who devoted time and effort to the *Journal of The Turkish German Gynecological Association* in 2014.

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Özlem Moraloğlu, Turkey
Özlem Pata, Turkey
Özlem Seçilmiş Kerimoğlu, Turkey
Polat Dursun, Turkey
Pushan Kundu, India
Ramazan Dansuk, Turkey
Recep Has, Turkey
Roel De Heus, Netherlands
Ruşen Aytaç, Turkey
Rüya Deveer, Turkey
Sabri Cavkaytar, Turkey
Şafak Olgan, Turkey
Şahin Zeteroğlu , Turkey
Salih Taşkın, Turkey
Saritha Shamsunder, India
Sean Kehoe, United Kingdom
Şebnem Özyer, Turkey
Seetha Ramamurthy Pal, India
Selçuk Özden, Turkey
Selim Büyükkurt, Turkey
Sema Yıldız, Turkey

# JTGGA CME/CPD CREDITING

## Questions on the article titled *"A new biological marker candidate in female reproductive system diseases: Matrix metalloproteinase with thrombospondin motifs (ADAMTS)"* within the scope of CME/CPD

1. Which of the following ADAMTS is different from the others according to classification of ADAMTS?
   a) ADAMTS1
   b) ADAMTS2
   c) ADAMTS4
   d) ADAMTS5
   e) ADAMTS18

2. Which ADAMTS proteinases are included in the pathogenesis of premature ovarian failure (POF)?
   a) ADAMTS1-ADAMTS5
   b) ADAMTS4-ADAMTS5
   c) ADAMTS16-ADAMTS4
   d) ADAMTS16-ADAMTS19
   e) ADAMTS19-ADAMTS20

3. Which events related to ovulation pathogenesis that are described below are not associated with ADAMTS1?
   a) Release of LH from the pituitary gland
   b) Progesterone release from granulosa cells
   c) The degradation of versican
   d) Expansion of the cumulus oocyte complex (COC)
   e) The reduction of expression ADAMTS1

4. In the pathogenesis of thrombotic thrombocytopenic purpura (TTP), preeclampsia, and the HELLP syndrome (hemolysis elevated liver enzymes and low platelets), which ADAMTS enzyme is important?
   a) ADAMTS1
   b) ADAMTS13
   c) ADAMTS16
   d) ADAMTS19
   e) ADAMTS5

5. Which of the following enzymes are associated with the destruction of COMP, an important structure located in the cartilage extracellular matrix?
   a) ADAMTS4 and -5
   b) ADAMTS2 and -3
   c) ADAMTS7 and -12
   d) ADAMTS1 and -4
   e) ADAMTS2 and -14

6. Which of the following two are involved in regression of the corpus luteum?
   a) ADAMTS1 and TIMP3 (tissue inhibitor of metalloproteinase-3)
   b) IL-1-beta and TGF-beta
   c) ADAMTS2 and TGF-beta
   d) ADAMTS2 and ADAMTS13
   e) ADAMTS2 and TIMP3

# JTGGA CME/CPD CREDITING

## Answer form for the article titled *"A new biological marker candidate in female reproductive system diseases: Matrix metalloproteinase with thrombospondin motifs (ADAMTS)"* within the scope of CME/CPD

| 1st Question | | | | |
|---|---|---|---|---|
| A | B | C | D | E |

| 2nd Question | | | | |
|---|---|---|---|---|
| A | B | C | D | E |

| 3rd Question | | | | |
|---|---|---|---|---|
| A | B | C | D | E |

| 4th Question | | | | |
|---|---|---|---|---|
| A | B | C | D | E |

| 5th Question | | | | |
|---|---|---|---|---|
| A | B | C | D | E |

| 6th Question | | | | |
|---|---|---|---|---|
| A | B | C | D | E |

*People who answer these questions will receive "2 TMA-CME/CPD credits"*

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**Name** ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

**Surname** ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

**Signature** ..... **The City You Work In** .....

**Your Institution** .....

**IMPORTANT NOTE:** You may apply for Turkish Medical Association CME/CPD credits by answering the questions in the front page, filling in your personal information and sending this form to "Abdi İpekçi Cad. No: 2/7 34367 Nişantaşı, İstanbul" by post. This form should arrive to the above-mentioned address latest by February 28, 2014.

# CONGRESS CALENDAR

## INTERNATIONAL MEETINGS

| | |
|---|---|
| 4-7 December, 2014 | **20th World Congress on Controversies in Obstetrics, Gynecology & Infertility (COGI)**<br>Paris, France<br>www.cogi.org |
| 11-12 December, 2014 | **6th Annual Seminar on Minimally Invasive & Robotic Gynecologic Surgery**<br>New York, USA<br>www.sgo.org/education/sgo-meetings |
| 19-21 February, 2015 | **1st Meeting of the Fertility Control Club (FCC)-** ***Hormonal contraception methods: From basic research to clinical practice***<br>Barcelona, Spain<br>http://www.comtecmed.com/FCC/2015 |
| 5-7 March, 2015 | **Best of ESHRE & ASRM - A joint meeting of the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine**<br>New York, USA<br>http://www.asrm.org |
| 18-20 March, 2015 | **16th World Congress on Human Reproduction**<br>Berlin, Germany<br>http://www.humanrep2015.com/congress |
| 8-12 April, 2015 | **3rd Annual Middle East Society for Gynecologic Endoscopy (MESGE) Congress & 6th Annual Congress of Turkish Society of Gynecological Endoscopy (TSGE) Conjoint Meeting**<br>Antalya, Turkey<br>www.mesge2015.org |
| 15-18 April, 2015 | **8th International DIP Symposium on Diabetes, Hypertension, Metabolic Syndrome & Pregnancy**<br>Berlin, Germany<br>http://www.comtecmed.com/dip/2015 |
| 11-13 June, 2015 | **7th Annual SERG Meeting on Robotic Gynaecological Surgery**<br>İstanbul, Turkey<br>www.sergs2015.org |
| 14-17 June, 2015 | **31st Annual Meeting of ESHRE**<br>Lisbon, Portogual<br>http://www.eshre.eu |
| 16-19 June, 2015 | **11th AAGL International Congress on Minimally Invasive Gynecology & 15th Annual Meeting of the Israeli Society of Gynecologic Endoscopy - ISGE IL Conjoint Meeting**<br>Jerusalem, Israel<br>www.aagljerusalem2015.com |

## NATIONAL MEETINGS

| | |
|---|---|
| 5-8 March, 2015 | **12th Uludağ Obstetrics and Gynecology Winter Congress**<br>Bursa, Turkey<br>www.uludagkadindogum.org/ |
| 23-25 April, 2015 | **Perinatal Medicine 2015 (TMFTP and SEESPM)**<br>İstanbul, Turkey<br>www.perinatalmedicine2015.org |
| 11-15 May, 2015 | **13th TJOD National Obstetrics and Gynecology Congress**<br>Antalya, Turkey<br>http://www.tjodkongre2015.org/ |
| 15-18 October, 2015 | **15th National Congress of Perinatal Medicine**<br>Muğla, Turkey<br>www.perinatoloji2015.org |

# Türkçe Özler – Aralık 2014

Özgün Araştırma

*J Turk Ger Gynecol Assoc 2014; 15: 208-211 • DOI: 10.5152/jtgga.2014.14092*

# Preterm ve term doğum arasında serum granülosit koloni uyarıcı faktör düzeylerinin karşılaştırılması

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*Zekai Tahir Burak Kadın Sağlığı Eğitim ve Araştırma Hastanesi, Kadın Hastalıkları ve Doğum Anabilim Dalı, Ankara, Türkiye*

## ÖZ

**Amaç:** Erken doğum gelişmiş ülkelerdeki en önemli obstetrik sorundur, yenidoğan mortalite ve morbiditesinin çoğunluğundan sorumludur. Hematopoietik sitokin olan Granülosit koloni uyarıcı faktör (G-CSF), gebelikteki lökosit artışına sebep olur ve plasentasyonda rol oynayabilir. Takip eden spontan erken doğumlarla term doğum yapan sağlıklı gebe kadınlar arasındaki G-CSF seviyelerinin farklılıklarını araştırmayı amaçladık.

**Gereç ve Yöntemler:** Rutin 24-28. haftalar arası antenatal takip sırasında, tekil gebeliği olan toplam sağlıklı 600 gebeden G-CSF seviyelerini değerlendirilmek üzere kan örneği alındı. Spontan olarak 37. gebelik haftasından önce doğum yapan 40 gebe çalışma grubu olarak belirlendi. Kontrol grubu olarak 1/3 oranı gereği 120 gebe belirlendi. Student t testi, Ki-kare testi, Mann-Whitney U testleri ve preterm doğumu öngörmede Roc eğrisi grupların karşılaştırılması için kullanıldı. $P<0.05$ istatistiksel olarak anlamlı kabul edildi.

**Bulgular:** Çalışma ve kontrol grubu arasında maternal serum G-CSF düzeyinde ($p=0.28$) belirgin farlılık yoktu ancak anne Beyaz Kan Hücresi (WBC) açısından gruplar arasında anlamlı bir fark ($p=0.00$) vardı. Buna ek olarak, G-CSF erken doğumu öngörmede (AUC=0.419) yetersiz bulundu. Preterm ve term grubunda, WBC ve G-CSF arasında korelasyon bulunmadı ($p=0.165$ vs $p=0.703$).

**Sonuç:** Term ve preterm doğum yapan gebeler arasında serum G-CSF seviyelerinde farklılık yoktu. Serum G-CSF nin erken doğumu ön görmede rol yoktu.

**Anahtar kelimeler:** Erken doğum, Granülosit koloni uyarıcı faktör, Yenidoğan bebekler

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Özgün Araştırma

*J Turk Ger Gynecol Assoc 2014; 15: 212-216 • DOI: 10.5152/jtgga.2014.14045*

# Plasenta previa ile komplike olmuş gebeliklerde birinci trimester tarama testi parametrelerindeki değişiklikler ve hiperemezis gravidarum ile ilişkisi

*Fırat Tülek[1], Alper Kahraman[1], Salih Taşkın[1], Esra Özkavukçu[2], Feride Söylemez[1]*
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## *ÖZ*

**Amaç:** Plasenta previa ile komplike olan gebeliklerde bu bozukluğun erken dönemlerindeki değişimlere dair fikir verebileceğinden, ilk trimester tarama test parametrelerindeki değişimlerin incelenmesi ve hiperemezis gravidarum ile arasında bir ilişki olup olmadığının saptanması

**Gereç ve Yöntemler:** Mayıs 2006-Mayıs 2013 arasında plasenta previa ile komplike olmuş spontan konsepsiyon ile gerçekleşen 131 tekil gebelik doğum kayıtlarından değerlendirilmiştir. Aynı dönemde doğum yapan plasenta previa olmayan 90 kadın kontrol grubu olarak belirlenmiştir. Çalışma grubunda aşağı yerleşimli plasentası (n=52) olan vakalar ayrı bir grup olarak ele alınmıştır. Geri kalan vakalar tek bir grupta toplanmıştır.

**Bulgular:** Bhcg ve NT MoM değerleri plasenta previa grubunda aşağı yerleşimli plasenta ve kontrol gruplarına göre anlamlı ölçüde yüksek saptanmıştır. Hem 1. hem de 5. dakikalardaki apgar skorları plasenta previa grubunda anlamlı şekilde düşük saptanmıştır. Plasenta previa grubunda hiperemezis gravidarum sıklığı anlamlı oranda yüksek saptanmıştır.

**Sonuç:** Hiperemezis gravidarum aynı gebelikte plasenta previa gelişimi için bir risk faktörü olabilir. Hiperemezisli hastalarda aynı gebelikte plasenta previa gelişebileceği rutin gebelik takiplerinde akılda tutulmalıdır.

**Anahtar kelimeler:** Plasenta previa, hiperemezis gravidarum, birinci trimester tarama testi, Bhcg, PAPP-A

Özgün Araştırma

*J Turk Ger Gynecol Assoc 2014; 15: 217-221 • DOI: 10.5152/jtgga.2014.14072*

# Posterior reversibl ensefalopati sendromuna (PRES) yoğun bakım yaklaşımı: 7 olgunun analizi

İsmail Demirel[1], Burçin Salih Kavak[2], Ayşe B. Özer[1], Mustafa K. Bayar[1], Ömer L. Erhan[1]
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*[2]Fırat Üniversitesi Tıp Fakültesi, Kadın Hastalıkları ve Doğum Anabilim Dalı, Elazığ, Turkey*

## *ÖZ*

**Amaç:** Posterior reversible encephalopathy syndrome (PRES)'li obstetrik hastalara yoğun bakım ünitesinde uygulanan tedavilerin retrospektif olarak değerlendirilmesi amaçlandı.

**Gereç ve Yöntemler:** Temmuz 2011 ile Temmuz 2013 tarihleri arasında, PRES sendromu tanısı konan 7 gebe olgunun kayıtları retrospektif olarak incelendi. Hastaların klinik verileri, tedavi öncesi ve sonrası beyin manyetik rezonans (MR) görüntülemeleri ve nörofizyolojik testleri değerlendirildi.

**Bulgular:** Toplam 7 hastanın, 5' inde eklampsi, 1'inde ağır preeklampsi, 1'inde HELLP sendromuna sekonder PRES gelismisti. Kalsiyum kanal blokerleri ve β- blokerler antihipertansif olarak kullanıldı. Bütün hastalar parenteral magnesium sülfat tedavisi aldı. Yoğun bakım ünitesinde takip edilen tüm olguların nörolojik ve radyolojik bulgularının düzeldiği gözlendi.

**Sonuç:** PRES etyolojisi multifaktöriyeldir ve farklı klinik bulgulara sebep olabilen klinik bir durumdur. Radyolojik görüntüleme teknikleri PRES' in teshisi için kullanılabilir. Gebelik ve postpartum dönem sıklıkla bu sendroma yol açar. Bazı vakalarda, PRES irreversible nörolojik bozukluk yada ölüme sebep olabilir. Siddetli radyolojik bulguları olan hastalar için, antihipertansif ve magnesium sülfat tedavisine ek olarak thiopental'in erken dönemde infüzyon seklinde tedaviye eklenmesinin klinik sonuçları daha hızlı ve etkin bir sekilde düzeltebileceğini düsünmekteyiz.

**Anahtar kelimeler:** PRES, yoğun bakım, obstetrik hasta

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Özgün Araştırma

*J Turk Ger Gynecol Assoc 2014; 15: 222-227 • DOI: 10.5152/jtgga.2014.14076*

# Maternal mortalite ve DSÖ ramak-kala aracından (near-miss tool) çıkarımlar: Güney Hindistan'da on yıllık kurumsal deneyim

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## *ÖZ*

**Amaç:** Enstitümüzde Ciddi Maternal Akıbet (CMA) sürveyansı için Dünya Sağlık Örgütü (DSÖ)'nün ramak-kala yaklaşımının kullanılması öncesi, kurumsal düzeyde fizibilite ve kullanışlılığını saptamak amacıyla son 10 yılda gerçekleşen maternal ölüm vakalarında aracın pilot testini yaptık.

**Materyal ve Metot:** Bu, on yıl içinde Hindistan'da Hıristiyan Tıp Fakültesi Vellore'de maternal ölümlerin retrospektif bir gözden geçirilmesidir. Olgular kaydedildi ve DSÖ ramak-kala aracı kullanılarak analiz edildi. Maternal mortalite tanımı ve sınıflandırılması için Uluslararası Hastalık Sınıflandırması, 10. Revizyon kullanıldı.

**Bulgular:** Toplam 98139 doğum ve 212 kayıtlı maternal ölüm vardı. Toplam maternal ölümlerin%46.96'sını doğrudan nedenler, %51.40'ını dolaylı nedenler oluştururken %1.9'unu bilinmeyen olgular oluşturdu. Obstetrik dışı nedenler (%48.11) tek büyük gruptur. Puerperal sepsis dışındaki enfeksiyonlar (%19.8) önemli bir grup olarak kalmaktadır, akciğer tüberkülozu, çalılık tifüsü ve sıtma da başta gelenlerdendir. DSÖ ramak-kala kriterlerine göre, kardiyovasküler ve respiratuar disfonksiyonlar en sık organ disfonksiyonlarıdır. Koagülasyon disfonksiyon insidansı en yüksek obstetrik kanamalarda (%64) görülmektedir. Ölen tüm kadınlarda en az bir organ yetmezliği vardı; annelerin %90.54'ünde iki ve %38.52'sinde dört veya daha fazla organ tutulumu vardı.

**Sonuç:** DSÖ ramak-kala aracının tarama soruları Uluslararası Hastalık Sınıflandırması -Maternal Mortalite ötesinde sorununun kapsamlı bir değerlendirmesini elde etmede özellikle yararlıdır ve organ disfonksiyonunun laboratuvar tabanlı tanımlanması için gerekenleri ve kritik bakım tesislerinin acil ulaşılabilirliği ihtiyacını saptar. Süreç göstergeleri, diğer taraftan, daha fazla veya daha az yaygın olarak uygulanan ve bu nedenle kurumsal düzeyde hiçbir ilave bilgi vermeyen temel müdahaleleri sorgular.

**Anahtar kelimeler:** Maternal mortalite, DSÖ ramak-kala aracı, organ disfonksiyonu

Özgün Araştırma

*J Turk Ger Gynecol Assoc 2014; 15: 228-232 • DOI: 10.5152/jtgga.2014.14166*

# Over rezervine tamoksifenin etkisi: Bir fare modelinde randomize kontrollü değerlendirici-kör çalışma

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## *ÖZ*

**Amaç:** Tamoksifen (TMX) maruziyetinin over rezervinde kalıcı azalmaya neden olup olmadığını belirlemek.

**Materyal ve Metot:** Randomize kontrollü değerlendirici-kör çalışmaya 30 yetişkin dişi doğal BALB/C fare dahil edildi. TMX grubunda 15 fareye periton içi TMX 0.1 mg tek dozda verildi. Kontrol grubundaki 15 fareye periton içi, aynı hacimde tek bir doz vehikül verildi. İki döngü sonrası, anti-Müllerian hormon (AMH) seviyelerinin belirlenmesi için kan örnekleri toplandı ve fareler sakrifiye edildi. Gonadektomi sonrası, over boyutları ölçüldü ve ışık mikroskobu altında foliküller sayıldı.

**Bulgular:** Medyan serum AMH düzeyleri, kontrol ve TMX gruplarında sırasıyla 6.53 ve 6.14 ng/mL idi (p=0.03).Over boyutu TMX grubunda anlamlı olarak azaldı. Primordial (8'e karşılık 9), primer (3'e karşılık 6) ve sekonder (5'e karşılık 4.5) folikül sayıları benzer iken kontrol grubuna kıyasla TMX grubunda anlamlı olarak daha az preantral (11.5'a karşılık 6, p<0.01) ve antral (2'ye karşılık 1, p=0.03) folikül ve ayrıca korpus luteum (6'ya karşılık 3, p=0.04) vardı. Atretik folikül sayısı (2.5'e karşılık 5, p=0.048) TMX grubunda artmıştı.

**Sonuç:** Tamoksifen uygulaması gonadotropin duyarlı foliküllerin büyümesinin durmasına yol açar oysa duyarsız foliküller etkilenmeden kalır. TMX sadece bir endokrin engelleyicidir ve primordial folikül havuzunda bir azalmaya neden olmaz.

**Anahtar kelimeler:** Tamoksifen, anti-Müllerian hormon, over rezervi, folikülogenez, antral folikül sayısı

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Özgün Araştırma

*J Turk Ger Gynecol Assoc 2014; 15: 233-238 • DOI: 10.5152/jtgga.2014.14111*

# Farklı anestezi protokollerinin postpartum periyodda laktasyon üzerine etkileri

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## *ÖZ*

**Amaç:** Birçok faktör anne sütü salgılanmasınaı etkileyebilir.Sezeryan operasyonu emzirmenin başlangıcının geç ikmesi için bir risk faktörüdür.

**Gereç ve Yöntemler:** Çalışmamızda genel anestesi, spinal anestesi, epidural anestesi altında elektif sezeryan operasyonu ve normal vajinal doğum yaşları 18-40 ve ASA I-II olan toplam 84 olgu incelendi. Çalışma kapsamına alınan olgular rastgele 4 eşit guruba ayrıldı. (Grup G: genel anestezi, Grup S:spinal anestezi, Grup E: epidural anestezi ve Grup V: Spontan vajinal doğum yapan) .Bütün gruplardaki olguların, doğum öncesi ve sonrası oksitosin ile prolaktin, değerlerine bakıldı. Tüm olguların laktasyonlarının, doğumdan sonra kaçıncı saatte başladığı kaydedildi.

**Bulgular:** Tüm gruplarda prepartum periyodda hormone seviyelerinde belirgin bir farklılık gözlenmemiştir (p=0.350). Grup G'deki prolactin seviyeleri (p=0.011) ve Grup V'deki oksitosin seviyeleri (p=0.012) postpartum dönemde diğer gruplara göre belirgin yüksek bulunmuştur Grup G'de laktasyon başlangıcı belirgin olarak uzadığı gözlendi (p=0.003).

**Sonuç:** Elektif sezaryan olgularındaspinal, epidural anestezi uygulanan ve normal vajinal doğum yapan annelerin laktasyon başlama zamanları karşılaştırıldığında; genel anestezi uygulanan grupta diğer gruplara göre geciktiği izlenmiştir.Genel anestezi sonrasındaki derlenme ve kognitif fonksiyonlardaki geri dönüşün gecikmesi nedeniyle anne ve yenidoğan arasındaki iletişimi geciktirmekte ve buda laktasyonde gecikmeye neden olmaktadır.

**Anahtar kelimeler:** Anestezi tekniği, laktasyon, sezaryen, normal doğum

Özgün Araştırma

*J Turk Ger Gynecol Assoc 2014; 15: 239-242 • DOI: 10.5152/jtgga.2014.14170*

# Düşük tehdidi olan hastalarda gebelik akıbeti üzerine subkoryonik hematomun etkileri

*Yavuz Emre Şükür[1], Göksu Göç[1], Osman Köse[2], Gökhan Açmaz[3], Batuhan Özmen[1], Cem Somer Atabekoğlu[1], Acar Koç[1], Feride Söylemez[1]*
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*[3]Kayseri Eğitim ve Araştırma Hastanesi, Kadın Hastalıkları ve Doğum Anabilim Dalı, Kayseri, Türkiye*

## *ÖZ*

**Amaç:** Gebeliğin ilk yarısında vajinal kanaması olan hastalarda gebelik akıbeti üzerine ultrasonografik olarak tespit edilen subkoryonik hematomun etkilerini değerlendirmek.

**Materyal ve Metot:** Ocak 2009 ile Aralık 2010 tarihleri arasında ağrısız vajinal kanama nedeniyle düşük tehdidi tanısı alan ve ilk vajinal kanama sırasında yatan hasta servisinde takip edilen hastalar bu retrospektif kohort çalışmasına dahil edildi Hastalar subkoryonik hematom varlığına göre iki gruba ayrıldı. Düşük oranları ve devam eden gebeliklerde gebelik akıbeti gruplar arasında karşılaştırıldı.

**Bulgular:** Yaş, parite, önceki düşük öyküsü ve ilk vajinal kanama sırasındaki gebelik yaşı dahil olmak üzere demografik parametreler açısından gruplar arasında istatistiksel olarak anlamlı fark yoktu. Subkoryonik hematomu olan 44 gebelikten 13'ü (%29.5) düşükle sonuçlanırken, subkoryonik hematomu olmayan 198 gebeliğin 25'i (%12.6) düşükle sonuçlandı (p=0.010). Düşük sırasında gestasyonel yaş ve ilk vajinal kanama ile düşük arasındaki süre gruplar arasında benzerdi. Devam eden gebeliklerde doğum sırasında gebelik yaşı, doğum ağırlığı ve doğum yolu gibi akıbet ölçümleri de gruplar arasında benzerdi.

**Sonuç:** Ultrasonografik olarak saptanan subkoryonik hematom gebeliğin ilk 20 haftasında vajinal kanaması ve düşük tehdidi olan hastalarda düşük riskini artırır. Bununla birlikte, devam eden gebeliklerde gebelik akıbeti ölçümlerini etkilemez.

**Anahtar kelimeler:** Abortus, tehdit, düşük, spontan, gebelik akıbeti

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Özgün Araştırma

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# Ürojinekolojik hastaların değerlendirilmesinde anal manometri ölçümlerinde sol lateral pozisyon ve basit jinekolojik muayene pozisyonu

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## ÖZ

**Amaç:** Bu çalışmanın amacı, anal manometri için geleneksel pozisyon olan sol lateral pozisyonda elde edilen manometrik parametreleri, basit jinekolojik muayene pozisyonunda (maksimum kalça fleksiyonu ile doğum masasında 45° oturur pozisyonda) alınan aynı ölçümler ile karşılaştırmaktır

**Materyal ve Metot:** Alt üriner sistem semptomları (AÜSS) olan 21 hasta bu prospektif kohort çalışmasına alındı. Bazal ortalama istirahat basıncı (BOİB), maksimum sıkma basıncı (MSB), rektal his, rektal uyum ve rekto-anal inhibitör refleks (RAIR) jinekolojik muayene pozisyonu ve sol lateral pozisyon arasında karşılaştırıldı.

**Bulgular:** Sol lateral ve jinekolojik muayene pozisyonlarında anal manometrik ölçümler arasında istatistiksel bir fark yoktu (eşleştirilmiş t-testi, p>0.05).

**Sonuç:** Anorektal değerlendirme ihtiyacı duyulan ürojinekolojik hastalarda muayene masasını ve/veya hastanın pozisyonunu değiştirmek gereksiz gibi görünmektedir kanısına varılabilir.

**Anahtar kelimeler:** Anal manometri, alt üriner sistem semptomları, jinekolojik muayene pozisyonu

Özgün Araştırma

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# Sezaryen sonrası başarılı vajinal doğum denemesi ile ilişkili maternal ve obstetrik faktörler

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## *ÖZ*

**Amaç:** Önceden sezaryen ile doğum yapmış kadınlar arasında başarılı vajinal doğum denemesi ile ilişkili maternal ve obstetrik faktörleri tespit etmek.

**Materyal ve Metot:** Departman protokolüne göre Sezaryen sonrası doğum denemesi (SSDD) için uygun olan toplam 122 kadın bu karşılaştırmalı prospektif çalışmaya dahil edildi. Bilgilendirilmiş olur sonrası, çalışmaya dahil edilen kadınlar maternal ve obstetrik özellikleri tespit etmek için kapsamlı bir öykü almaya ve fetal ağırlık, fetal başın angajmanı, fetal membranların intra-partum özellikleri ve servikal dilatasyonu belirlemek için standart muayeneye tabi tutuldular. Doğumdan sonra, doğum sancı süresi, eyleme yardım, doğum şekli, doğum sonucu ve yenidoğan yoğun bakıma (YYBÜ) kabul hakkındaki veriler kaydedildi ve analiz edildi.

**Bulgular:** Sezaryen sonrası doğum denemesi %72.13'ünde başarılı ve %27.87'sinde başarısız oldu. Vücut kitle indeksi (VKİ) başarısız gruba kıyasla başarılı SSDD grubunda anlamlı olarak daha düşüktü (26.2±0.02'ye karşılık 23.8±0.03 kg/m2), ve VKİ> 25 kg/m2 olan kadınların sayısı başarısız grupta anlamlı derecede yüksekti; ayrıca, ortalama gebelik yaşı başarısız gruba kıyasla başarılı SSDD grubunda anlamlı olarak daha düşüktü (38.5±0.03'e karşılık 37.5±0.04 hafta), ve ≥40 haftalık gebelik ile doğuma başvuran kadınların sayısı başarısız grupta anlamlı derecede yüksekti. Fetal başın >2/5'i abdominal olarak palpe edilebilen durumda ve fetal baş duruşu ≥-2 olarak başvuran kadınların sayısı başarısız SSDD grubunda anlamlı derecede yüksekti.

**Sonuç:** Dikkatli seçilmiş olgularda, SSDD güvenli ve çoğu zaman başarılıdır. VKİ >25 kg/m2, gebelik ≥40 hafta, ve verteks duruş ≥-2 varlığı başarısız SSDD için risk faktörleridir. Al manometri, alt üriner sistem semptomları, jinekolojik muayene pozisyonu

**Anahtar kelimeler:** Faktörler, başarılı deneme, vajinal doğum, sezaryen

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Derleme

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# Kadın üreme sistemi hastalıklarında yeni biyolojik markır adayı: ADAMTS matriks proteinazlar

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## *ÖZ*

Birçok hastalığın patofizyolojisinde önemli rol oynayan A Disintegrin-like and Metalloproteinase with Thrombospondin type-1 motif (ADAMTS) proteinazlarının kadın doğum hastalıklarındaki önemi son yıllarda giderek artmaktadır. İlk olarak 1997 yılında keşfedilen bu çinko bağımlı enzimlerin günümüzde 19 üyesi mevcuttur. Ekstraselüler matrikste (ECM) yer alan bu enzimler, matriks yapım ve yıkımı, anjiyogenezis, ovulasyon ve pıhtılaşma gibi birçok önemli fizyolojik olayda görev alırlar. Buna ek olarak kanser, inflamasyon, artrit ve bağ dokusu hastalıkları gibi birçok hastalığın patogenezinde de hayati görevleri vardır. Bu derlemenin amacı, obstetrik ve jinekoloji sahasında daha önce yapılmış ADAMTS enzim çalışmalarını bir araya toplamak ve bu alanda ilgili araştırmacılara yeni fikirler sunmaktır.

**Anahtar kelimeler:** ADAMTS, üreme sistemi hastalıkları, biyolojik marker

Olgu Sunumu

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# Normal fetusun, komplet hidatiform molün ve plasenta previanın eşlik ettiği ikiz gebelik vakası: Olgu sunumu

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## *ÖZ*

Normal fetusa, komplet hidatiform molün ve plasenta previanın eşlik ettiği nadir görülen ikiz gebeliği olan vakamız, 32. gebelik haftasında sezeryan operasyonu ile 1590 gr ağırlığında, canli kız bebek doğurdu. Anne postoperatif 3. günde herhangi bir ek cerrahi işleme ihtiyaç duyulmaksızın taburcu edildi. Molar gebeliğin risklerinden dolayı genellikle erken terminasyon önerilen normal fetusun ve komplet hidatiform mole vakasının eşlik ettiği ikiz gebeliklerin yakın takibi ile maternal ve perinatal iyi sonuçlar alınabileceği olgu sunumuzda gösterilmiştir.

**Anahtar kelimeler:** İkiz gebelik, komplet hidatiform, plasenta previa

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Olgu Sunumu

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# Gebelik esnasında karbamazepine maruz kalan bir yenidoğanda biküspit aort kapağı ve ciddi aort darlığı

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## *ÖZ*

Gebelik esnasında antiepileptik ilaçların kullanımı major konjenital malformasyonların riskini artırmaktadır. Burada, intra-uterin karbamazepine maruz kalma öyküsü olan ve kardiyak malformasyon ile doğan bir bebeği sunduk. Bebek, 39. gebelik haftasında gebeliği boyunca karbamazepin ile tedavi edilen epileptik bir anneden vajinal olarak doğmuştu. Doğumunun ikinci haftasında kardiyak üfürüm nedeniyle refere edildi. Anne folik asit desteği almamıştı. Transtorasik ekokardiyografide biküspit aort kapağı, hafif aort darlığı, patent duktus arteriosus, patent foramen ovale ve renal ultrasonografide hafif sol hidronefroz saptandı. Takipte 14 hafta sonra yapılan ekokardiyografide aort darlığının şiddetinin arttığı görüldü ve perkütan balon aortik valvüloplasti uygulandı. Bildiğimiz kadarıyla, literatürde karbamazepinin yapısal bir türevi olan okskarbazepine maruz kalma ile biküspit aort kapağı ve aort darlığı ilişkisinden bahseden sadece bir olgu sunumu vardır. Fakat karbamazepinin kendisi ile bu anomalilerin ilişkisinden bahseden bir yayın yoktur. Biküspit aort kapağı ve aort darlığı karbamazepinin teratojenik etkisinden kaynaklanan kalp anomalileri arasında olabilir.

**Anahtar kelimeler:** Aort darlığı, biküspit aort kapağı, karbamazepin, gebelik