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6. Main text (subtitles)
7. References (listed according to the rules of ICME)
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Comparison of obstetric outcomes of pregnant women with isolated proteinuria according to proteinuria severity

Mehmet Özgür Akkurt¹, Bora Coşkun², Tuğberk Güçlü¹, Kaan Pakay¹, Engin Korkmazer¹

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²Gynecology and Obstetrics Clinic, Gülhane Training and Research Hospital, Ankara, Turkey

Abstract

Objective: To compare the obstetric outcomes of women who were found to have isolated gestational proteinuria (IGP) according to the severity of 24-hour proteinuria.

Methods: The women who were found to have IGP between January 1, 2014 and June 1, 2018 at the Bursa Yüksek İhtisas Training and Research Hospital were included in our retrospective study. The study population was divided into 3 groups according to the proteinuria severity: Group 1: Proteinuria at physiological level (<300 mg/day, n=60); Group 2: Mild proteinuria (between 300 mg and 3000 mg/day, n=49); Group 3: Proteinuria at nephrotic level (≥3000 mg/day, n=28).

Results: There was no difference among 3 groups in terms of maternal age, gravidity and the number of living children. The mean proteinuria amount was the highest in the group with nephrotic level (216±73 mg/day in Group 1, 849±119 mg/day in Group 2, and 9055±1011 mg/day in Group 3, respectively; p<0.05). Preeclampsia (PE) incidence was higher in Group 3 (6.6% in Group 1, 47% in Group 2 and 64% in Group 3, respectively; p<0.05). The period elapsed between the diagnoses of IGP and PE was the shortest in Group 3 (21.2±4.9 days in Group 1, 16.4±4.7 days in Group 2, and 7.8±2.2 days in Group 3, respectively; p<0.05). There was no significant correlation between proteinuria severity and birth weight and the period elapsed between the diagnoses of IGP (r=0.68) and PE (r=0.79).

Conclusion: While IGP increases the incidence of poor perinatal outcomes such as intrauterine growth retardation, low birth weight and iatrogenic preterm birth, it was also found that PE incidence is higher, diagnosis week is earlier and the period between IGP and PE diagnoses are shorter in women with proteinuria at nephrotic level than those with less severe proteinuria.

Keywords: Low birth weight, interval, isolated gestational proteinuria, preeclampsia.
Introduction

During pregnancy, detecting proteinuria ≥300 mg/dl in 24-hour urine and/or finding proteinuria +1 and above in the urinalysis by dipstick method is considered abnormal and defined as isolated gestational proteinuria (IGP). Although clean and fresh urine sample can be collected by urinary dipstick method, it is affected by many clinical conditions such as protein content, infection and/or blood contamination in urine. Therefore, determining protein amount in 24-hour urine is the most appropriate method for preeclampsia.

It has not been clarified yet if proteinuria is an indicator of preeclampsia which will develop in the following steps of pregnancy or a physiological change in the kidneys associated with the pregnancy or not. Although proteinuria is accepted the late finding of preeclampsia today, Morikawa et al. suggest that isolated proteinuria is an early clinical finding of PE.

Until the preeclampsia report prepared by ACOG (American College of Obstetricians and Gynecologists) in 2013, proteinuria was among the diagnostic criteria of preeclampsia. After this report, proteinuria was removed from the absolute criteria of preeclampsia. In this report, it was highlighted that in 10% and 20% of pregnant women who were found to have preeclampsia or eclampsia, respectively, did not have proteinuria during the diagnosis.

Hypertensive diseases are still among the major reasons of maternal and perinatal deaths, and isolated proteinuria is one of the risk factors defined for PE. Therefore, following up such patients in terms of PE development is very important. Our aim in this study is to analyze the perinatal outcomes of pregnant women who were found to have preeclampsia or eclampsia, respectively, did not have proteinuria during the diagnosis.

Methods

Our study was conducted at Bursa Yüksek İhtisas Training and Research Hospital which is the biggest tertiary center in South Marmara. Pregnant women with isolated proteinuria during 54 months between January 1, 2014 and June 30, 2018 were included in the study. Proteinuria was measured in 24-hour urine of pregnant women who were found to have proteinuria +1 or above in the dipstick urinalysis according to the hospital protocol. The pregnant women with proteinuria level of 300 mg and above were included in the study. Since the study was based on the method of analyzing retrospective records, the approval of ethics committee was not obtained. The women with hypertension during the diagnosis, those with the history of renal and vascular diseases, the women diagnosed with diabetes before pregnancy, multiple pregnancies, the pregnant women with fetuses which had chromosomal or non-chromosomal genetic diseases and structural malformations, and the pregnant women who had risk factors for preeclampsia such as molar pregnancy were excluded from the study.

Without the history of a hypertensive disease, proteinuria and/or end organ damage accompanying to systolic blood pressure being 140 mmHg and above and/or diastolic blood pressure being 90 mmHg and above in the last 2 measurements with 4-hour intervals in the follow-ups after 20 weeks of gestation was defined as preeclampsia. The study group was separated into 3 groups according to the 24-hour proteinuria severity: Group 1: Physiological proteinuria (<300 mg/day); Group 2: Mild proteinuria (300–3000 mg/day); Group 3: Proteinuria at nephrotic level (3000 g and above). The maternal data (age, gravida, living child, 24-hour urine level, the week of proteinuria diagnosis, the week of preeclampsia diagnosis, the period elapsed between the diagnoses of proteinuria and preeclampsia) and perinatal data (the incidence of intrauterine growth retardation [IUGR], abdominal circumference [percentile], birth time, delivery type, birth weight, the rate of cesarean section due to fetal stress, newborn’s hospitalization duration at intense care unit, 1-minute and 5-minute APGAR scores and perinatal mortality rate) were obtained from the files of mothers and newborns and these data were compared among the groups.

The statistical analysis was performed by using SPSS 22.0 (IBM SPSS, version 22, IBM Corp. Armork, NY, USA). The descriptive data were expressed as mean and standard deviation. Kolmogorov-Smirnov test was used to determine the distribution of variables. For the analysis of quantitative and qualitative data, Mann-Whitney U and chi-square tests were used respectively. Fisher’s test was used when chi-square test could not meet the conditions. Spearman’s test was used for the correlation analysis and p<0.05 was considered significant.

Results

Isolated proteinuria was found in 77 pregnant women who admitted to our clinic during the study period. The
proteinuria was at nephrotic level in 28 of them (≥3000 mg/day) and at mild level in 49 of them. The patients with isolated proteinuria were separated into 3 groups according to their severity and when compared to the control group (n=60), no difference was found among 3 groups in terms of maternal age, gravida and the number of living child. Compared to the other groups, the mean proteinuria level was the highest in the group with nephrotic level (216±73 mg/day in Group 1, 849±119 mg/day in Group 2, and 9055±1011 mg/day in Group 3, respectively; p<0.05). In 4 pregnant women included in our study, proteinuria was found 10 g and above in 24-hour urine (range: 10.98 to 21.45 g/day). While all of these pregnant women also had hypertensive diseases, 2 of them had HELLP (hemolysis, elevated liver enzymes, thrombocytopenia).

In the group with proteinuria at nephrotic level, preeclampsia and growth retardation rates were also higher. Preeclampsia also developed at the earlier weeks of gestation in this group. The period elapsed between the diagnoses of proteinuria and preeclampsia was shorter in the group with proteinuria at nephrotic level compared to the other groups. In both groups with proteinuria, IUGR rate was higher and birth weight was lower than the control group. When perinatal outcomes were compared, the rate of cesarean section due to fetal stress and perinatal mortality rate was significantly higher in the group with proteinuria at nephrotic level (Table 1). When the correlation between 24-hour urine severity and birth weight, the week of preeclampsia diagnosis and the period elapsed between the diagnoses of proteinuria and preeclampsia was analyzed, a significant correlation was found between proteinuria severity and birth weight and diagnosis interval (Table 2).

### Table 1. The comparison of maternal and perinatal characteristics according to 24-hour proteinuria severity.

<table>
<thead>
<tr>
<th>Proteinuria level</th>
<th>Group 1 &lt;300 mg/day (n=60)</th>
<th>Group 2 300–3000 mg/day (n=49)</th>
<th>Group 3 ≥3000 mg/day (n=28)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td>27.6±4.1</td>
<td>28.9±4.7</td>
<td>26.4±3.2</td>
<td>0.12</td>
</tr>
<tr>
<td>Gravida</td>
<td>3.1±1.0</td>
<td>3.5±1.0</td>
<td>3.2±0.9</td>
<td>0.32</td>
</tr>
<tr>
<td>Number of living children</td>
<td>1.7±0.7</td>
<td>2.0±0.7</td>
<td>1.6±0.5</td>
<td>0.15</td>
</tr>
<tr>
<td>24-hour proteinuria amount (mg)</td>
<td>216±73</td>
<td>849±119</td>
<td>9055±1011</td>
<td>0.003</td>
</tr>
<tr>
<td>Week of proteinuria diagnosis</td>
<td>32.4±4.3</td>
<td>30.9±5.3</td>
<td>28.9±3.4</td>
<td>0.09</td>
</tr>
<tr>
<td>Preeclampsia incidence (n)</td>
<td>4 (%6.6)</td>
<td>23 (%47)</td>
<td>18 (%64)</td>
<td>0.004</td>
</tr>
<tr>
<td>Week of preeclampsia diagnosis</td>
<td>37.2±2.5</td>
<td>33.9±5.3</td>
<td>30.1±4.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Diagnosis interval of proteinuria-preeclampsia (day)</td>
<td>21.2±4.9</td>
<td>16.4±4.7</td>
<td>7.8±2.2</td>
<td>0.003</td>
</tr>
<tr>
<td>Incidence of growth retardation (n)</td>
<td>6 (%10)</td>
<td>9 (%18)</td>
<td>16 (%57)</td>
<td>0.001</td>
</tr>
<tr>
<td>Abdominal circumference (percentile)</td>
<td>35.4±5.9</td>
<td>24.8±4.6</td>
<td>10.5±3.1</td>
<td>0.03</td>
</tr>
<tr>
<td>Delivery time (week)</td>
<td>38.4±2.1</td>
<td>35.5±5.1</td>
<td>31.6±3.4</td>
<td>0.009</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3049±150</td>
<td>2570±371</td>
<td>1345±142</td>
<td>0.001</td>
</tr>
<tr>
<td>Vaginal delivery</td>
<td>36 (%60)</td>
<td>14 (%28.5)</td>
<td>4 (%14)</td>
<td>0.04</td>
</tr>
<tr>
<td>Cesarean section due to fetal stress</td>
<td>4 (%6.6)</td>
<td>7 (%14)</td>
<td>8 (%28)</td>
<td>0.03</td>
</tr>
<tr>
<td>1-minute APGAR</td>
<td>8.9±0.3</td>
<td>8.3±0.5</td>
<td>7.7±0.4</td>
<td>0.08</td>
</tr>
<tr>
<td>5-minute APGAR</td>
<td>9.5±0.2</td>
<td>9.2±0.4</td>
<td>8.6±0.3</td>
<td>0.16</td>
</tr>
<tr>
<td>Perinatal death (n)</td>
<td>0 (%0)</td>
<td>1 (%2)</td>
<td>2 (%7)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

### Table 2. The relationship between proteinuria severity and birth weight, week of preeclampsia diagnosis and development period.

<table>
<thead>
<tr>
<th>Proteinuria level</th>
<th>Birth weight</th>
<th>Week of preeclampsia diagnosis</th>
<th>Diagnosis interval of proteinuria-preeclampsia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteinuria &lt;300 mg/day (n=60)</td>
<td>r=0.25</td>
<td>r=0.38</td>
<td>r=0.16</td>
</tr>
<tr>
<td>Proteinuria ≥300 mg/day (n=77)</td>
<td>r=0.68*</td>
<td>r=0.22</td>
<td>r=0.79*</td>
</tr>
</tbody>
</table>

The relationship was calculated by Spearman’s correlation coefficient. Statistically significant values were expressed by the symbol *. While a moderate and significant correlation and significant correlation was found between proteinuria at nephrotic level and birth weight, there was a strong and significant correlation in the diagnosis interval between proteinuria and preeclampsia.
Discussion

Distinguishing isolated gestational proteinuria and preeclampsia is very important for the management of gestation. In a study performed, incidences for preterm labor, low birth weight, gestational diabetes and renal disease in women with IGP were found similar with the healthy women, and these women had term labor. On the other hand, preeclampsia is associated with increased maternal and perinatal morbidity. Our study is a retrospective case-controlled study performed in a tertiary center. According to our results, the risk of increased preeclampsia and intrauterine growth retardation increases in pregnant women who are found to have isolated proteinuria. Also, there is a significant correlation between proteinuria and birth weight and the period elapsed between the diagnoses of proteinuria and preeclampsia.

The most common method to determine the presence of proteinuria is the urinalysis by dipstick test. However, false positivity rate increases in some clinical conditions such as concentrated urine or concurrent infection. Although collecting urine in 24 hours and analyzing it as in our study is the golden standard for IGP, it usually cannot be tolerated by the patients since the procedure takes long. As found by Yamada et al., protein/creatinine rate above 0.27 in the spot urine is an easy and useful method for the diagnosis of IGP.

While the incidence of isolated proteinuria varied in the previous studies, it was seen in about 2% (range: 0.3 to 4%) of pregnancies and its importance could not be understood clearly. Proteinuria is not seen during the diagnosis in approximately 15–26% of pregnant women with new-onset hypertension, but it is found in the further phases of the pregnancies. As argued by Akaishi et al., preeclampsia develops in 2 different conditions: (1) when proteinuria is diagnosed much earlier than hypertension, or (2) proteinuria and hypertension are diagnosed at the same time. Increased body mass index, twin pregnancy, nulliparity, young maternal age which are among the well-known risk factors for PE are also the risk factors for GP, and supports this hypothesis.

The progression rate of PE in women with IGP varies among the studies. The reasons for this difference among the studies include the size of population and mean week of gestation, PE incidence and the risk factors of women in the study population. Morikawa et al. found PE in about 51% of the pregnant women diagnosed with isolated proteinuria in their retrospective review and this rate was 34% in the study of Ekiz et al. In the study of Yamada et al., the authors found that PE developed in 25% of the patients with IGP, and 20% of all PE patients developed PE after IGP was diagnosed. In our study, we diagnosed PE in later periods in 53% of the women with proteinuria level of 300 mg and above. In the sub-group analysis according to the proteinuria severity, we found that PE was concomitant in 64% of those with proteinuria at nephrotic level and in 47% of those with less severe proteinuria (between 300 and 3000 mg). In addition, the week of PE diagnosis was earlier and the period elapsed between the diagnoses of isolated proteinuria and preeclampsia was shorter in the group with proteinuria at nephrotic level. Many studies investigated the risk factors for this progression. Twin pregnancy, pregnancy after 40-year-old, preeclampsia history and nulliparous women are also in the risk group. In addition to these studies, we also found a significant correlation between proteinuria severity and the week of preeclampsia diagnosis and diagnosis interval.

The single-center study (n=37) of Morikawa et al. which included a limited number of pregnant women with IGP and the multi-centered large-scale study (n=130) of Yamada et al. similarly found PE about 2 weeks after diagnosing IGP. Unlike other studies, we found in our study that PE developed about 8 days later in the cases with proteinuria at nephrotic level and about 16.5 days later in the cases with less severe proteinuria. Our study contributes to the literature and shows that the period of PE development is also significantly correlated with the proteinuria severity.

Similar to the study of Ekiz et al. we showed that IGP is not only associated with the increased PE risk but also with the increased risk of growth retardation and low birth weight. This shows that further wide-scale studies investigating the relationship between IGP and increased poor obstetric outcomes are needed. The major limitation of study is its retrospective nature. Being single-centered and having limited number of patients are the factors affecting the incidence of preeclampsia. In addition, since it is retrospective, we could not obtain some information such as increased body-mass index, history of previous PE, weight gain during pregnancy, the history of aspirin use, increased resistance in uterine artery Doppler blood flow which may contribute to the development of preeclampsia. Also, we did not investigate maternal outcomes as we focused on perinatal outcomes. However, the studies in
the literature which estimate PE development according to the proteinuria severity are limited.

**Conclusion**

According to the findings of our study, women with IGP are in the risk group in terms of increased poor perinatal outcomes. In these women, the risk for preeclampsia, low birth weight and iatrogenic preterm labor is increased. PE incidence is higher, diagnosis week is earlier and the period elapsed between the diagnoses of IGP and PE is shorter in women with proteinuria at nephrotic level compared to the women with less severe proteinuria. Therefore, we recommend follow up the women with proteinuria at nephrotic level closely due to the increased risk of PE and growth retardation and expect the development of PE about 8 days after IGP diagnosis at nephrotic level.

**Conflicts of Interest:** No conflicts declared.

**References**


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Myomectomy during cesarean section: is it a safe procedure?

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Abstract

Objective: To evaluate the relationship between intraoperative and postoperative complications of the myomectomy procedure performed during cesarean section.

Methods: Our study included 280 patients who had undergone cesarean section at Obstetrics and Gynecology Clinic of Düzce University. The study group was comprised of 45 patients who had undergone myomectomy during cesarean section. The remaining 235 patients having had only cesarean section constituted the control group.

Results: When the groups were compared, the duration of the operation was longer in the group with both myomectomy and cesarean section (49.5 min vs. 44.3 min; p=0.002). No statistically significant difference was found between the groups in terms of postoperative hemoglobin levels, decrease in hemoglobin levels or intraoperative and postoperative complications.

Conclusion: Myomectomy during cesarean section was not associated with increased blood transfusion, postpartum hemorrhage or postoperative complications and only differed from the cesarean section group in the duration of the operation. Myomectomy during cesarean section performed by experienced surgeons can be a safe surgical procedure.

Keywords: Cesarean section, hemorrhage, myomectomy, leiomyoma.

Introduction

Leiomyomas are the most common uterine neoplasms and are detected using various imaging modalities in almost 40% of women during their reproductive period. Most of these women are asymptomatic, but 1 in 4 requires treatment. The incidence of uterine leiomyomas during pregnancy varies depending on the time of assessment. In various publications this rate ranges from 0.37% to 12%. Given that maternal age for pregnancy is increasing and that the incidence of myoma increases with age, obstetricians are more likely to encounter pregnant patients with myomas and be required to treat complications related to them.

Myomectomy during cesarean section (C/S) is still a controversial subject. The main concern here is the...
excessive bleeding and increased morbidity that may occur during the operation. Many sources still object to routinely performed myomectomy during C/S for these reasons. Recent literatures states that, however, studies and meta-analyses have been carried out suggesting that C/S myomectomy is a safe surgical procedure and that positive results may be obtained for subsequent pregnancy outcomes. For this reason, this combined surgical procedure has been introduced more frequently by many surgeons.

In this study, we aimed to examine C/S myomectomy cases performed at our center and evaluate the effects of this procedure on intraoperative and postoperative morbidity.

Methods
This study is a retrospective cohort study conducted at a single medical center. Cesarean section patients admitted to the Düzce University Medical Faculty Hospital between January 2015 and June 2018 were included in the study. Records of patients who were operated on within this period were obtained from patient files and the hospital’s automation system. This study was approved by the local ethics committee (IRB no. 2018/0069).

Study population was divided into 2 groups. Group 1 included those who had undergone myomectomy during C/S and Group 2 (control group) included those who had undergone C/S only. Patient data recorded included age, gravida, parity, gestational week of operation, duration of operation, length of hospital stay, indications for cesarean section and localization and number of myomas. Informed consent was obtained from patients diagnosed with myomas before the cesarean section.

Our primary goal in this study was to evaluate the effect of myomectomy performed during C/S on intraoperative and postoperative outcomes. For this purpose, we evaluated blood loss during the operation, uterine atony, major organ injuries and need for blood transfusion or relaparotomy.

Estimated blood loss was calculated according to the formula:

\[ \Delta \text{hemoglobin concentration} = \text{baseline hemoglobin concentration} - \text{postoperative 6th hour hemoglobin concentration} \]

The duration of surgery was calculated in minutes – from skin incision to skin closure. The decision for blood transfusion was made according to the patient’s symptoms, including tachycardia, hypotension or changes in postoperative hemoglobin level.

All C/S operations were performed using transverse lower uterine segment incisions, while myomectomy was carried out using the serosal incision technique. If the myoma was close to the C/S incision, it was excised from that incision, otherwise it was removed from a different incision.

Between the dates mentioned above, there were 4280 births in our hospital and 2300 of them were via C/S. Forty-five of these patients had undergone myomectomy during C/S and these were included in the study group. The control group was randomly selected and included 10% of the patients having had only C/S.

The operations were performed by surgeons experienced in the field of myomectomy operations and trained in the management of postpartum hemorrhage.

Statistical analysis
Descriptive statistics for continuous variables were expressed as mean ± standard deviation or median (minimum–maximum) and nominal variables were expressed as number and percentage (%). For each group, differences in mean values and differences in median values were evaluated using the Student’s t-test and Mann-Whitney U-test, respectively. The chi-square distribution test was used to compare categorical data, with p-values of ≤0.05 considered as statistically significant. Statistical analysis was performed using SPSS for Windows version 22 software (SPSS, Inc., Chicago, IL, USA).

Results
Between January 2015 and June 2018, a total of 4280 deliveries occurred in our hospital, of which 2300 were delivered via C/S. Myomectomy was performed during C/S in 1.95% (n=45) of the 2300 C/S cases. The characteristics of these patients are summarized in Table 1. There were no significant differences found between the two groups in terms of baseline characteristics.

When cesarean indications were considered, a previous cesarean was the first among all indications (37.8% vs. 48.1%), followed by non-cephalic presentation and cephalopelvic disproportion (Table 2). The groups were similar in terms of indications for C/S.
When the myomectomy during C/S group was compared with the C/S group, the duration of operation in the C/S myomectomy group was longer and this difference was statistically significant (49.5 min vs. 44.3 min; p=0.002). Preoperative, postoperative and Δ hemoglobin concentrations were similar, with no statistically significant difference found between the groups (p=0.056, p=0.548, p=0.177, respectively). Although the need for transfusion was greater in the C/S myomectomy group, this difference was not statistically significant (6.7% vs. 2.6%; p=0.152). There was no difference between groups in terms of hospitalization time. No relaparotomy, visceral organ injury or major vascular complications developed in either group (Table 3).

A hematoma developed in the suture line of the myomectomy site in two patients in the C/S myomectomy group. One of these patients had a myoma 6 cm in diameter on the anterior wall which was removed transendometrially. No additional surgical intervention was performed on these patients and with only expectant management, these hematomas were spontaneously resolved over time.

Discussion
The end result of our study was that the myomectomy performed during C/S was not associated with a decrease in hemoglobin level, an increase in the need for transfusion, increased uterine atony or postoperative morbidity, and only differed from the C/S group in the prolongation of the operation time.

Most myomas are asymptomatic during pregnancy. In symptomatic pregnancies, pain, a feeling of pelvic pressure, or vaginal bleeding may occur due to myoma size or degenerative changes associated with pregnancy. Obstetric complications such as abortion, preterm birth, placental abruption, dystocia and increased frequency of Cesarean deliveries may also be associated with the uterine leiomyomas seen in pregnancy. Akkurt et al. reported that C/S myomectomy may have positive effects on subsequent pregnancies, that myoma recurrence was not common after the operation and that there was no serious operation-related adhesion formation. In this respect, C/S myomectomy can have a number of advantages. The incision required for myomectomy during C/S will be smaller than the incision made for the non-pregnant uterus, and technically it may be easier to identify the cleavage plane to be used for myomectomy. Due to the increased elasticity of the pregnant uterus, the suturation process can be performed more easily without damaging the tissue, and at the same time postpartum uterine contractions and uterine involution contribute to reduction of hemorrhaging. In our study,

<table>
<thead>
<tr>
<th>Table 1. Baseline characteristics of patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myomectomy group (n=45)</td>
</tr>
<tr>
<td>Age (year)</td>
</tr>
<tr>
<td>Gravidity</td>
</tr>
<tr>
<td>Parity</td>
</tr>
<tr>
<td>Abortion</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
</tr>
<tr>
<td>Gestational age (week)</td>
</tr>
</tbody>
</table>

Values are stated as median (minimum–maximum).

<table>
<thead>
<tr>
<th>Table 2. Indications for C/S in both groups.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myomectomy group (n=45)</td>
</tr>
<tr>
<td>Previous C/S</td>
</tr>
<tr>
<td>Maternal request</td>
</tr>
<tr>
<td>Non-cephalic presentation</td>
</tr>
<tr>
<td>Cephalopelvic disproportion</td>
</tr>
<tr>
<td>Fetal distress</td>
</tr>
</tbody>
</table>

Values are stated as number (%). *<.05 indicates statistical significance.

<table>
<thead>
<tr>
<th>Table 3. Intraoperative and postoperative outcomes.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myomectomy group (n=45)</td>
</tr>
<tr>
<td>Operation time (min)</td>
</tr>
<tr>
<td>Preoperative Hb level (g/dl)</td>
</tr>
<tr>
<td>Postoperative Hb level (g/dl)</td>
</tr>
<tr>
<td>Δ Hemoglobin level (g/dl)</td>
</tr>
<tr>
<td>Uterine atony</td>
</tr>
<tr>
<td>Transfusion requirement</td>
</tr>
<tr>
<td>Relaparotomy</td>
</tr>
<tr>
<td>Visceral organ injury</td>
</tr>
<tr>
<td>Major vascular complications</td>
</tr>
<tr>
<td>Hospital stay (hours)</td>
</tr>
</tbody>
</table>

Values are stated as means±SD or as number (%). *<.05 indicates statistical significance. N.A: not available.
we did not find any difference in terms of postoperative hemoglobin levels or estimated blood loss between the C/S myomectomy patients and the C/S patients without myomas.

Another advantage of the myomectomy performed during C/S is that two separate operations are performed in one session. Moreover, the possible risks of re-operation are prevented, while at the same time the cost is also reduced.\textsuperscript{[20]} As a matter of fact, in their study, Liu et al. reported that 40% of the myoma cases where myomectomy was not performed during C/S, were re-operated on within 6 to 38 months postoperatively.\textsuperscript{[20]}

Some factors to consider for myomectomy during C/S include the number, size and localization of the myomas, the possible effects on uterine contractility, the experience of the surgeon and the facilities at the health institution where the operation is performed. For this reason, in order to safely perform C/S myomectomy, experience in appropriate surgical techniques should be attained and training in surgical methods to reduce bleeding should be obtained. If these considerations are taken into account, myomectomy can be performed safely during C/S. Senturk et al. in their evaluation of 212 C/S myomectomies reported that at first they applied this procedure to the smaller myomas, and after gradually gaining more experience, they excised the larger and more numerous myomas during the C/S. In that study, they also evaluated 66 C/S myomectomy patients having myomas of 5 cm or more in diameter along with 31 non-myomectomy patients and reported that no differences were found between the C/S myomectomy group and the non-myomectomy group in terms of lowered hemoglobin levels, necessary blood transfusions or operation-related complication rates.\textsuperscript{[31]} We achieved similar results in our study.

Intraoperative hemorrhage is the most common complication of C/S myomectomy.\textsuperscript{[11]} For this reason, some sources suggest applying vasopressin infusion, bilateral uterine artery ligation or uterine tourniquet to reduce blood loss.\textsuperscript{[22],[23]} We applied oxytocin infusion and methylergonovine injection, but did not use any of the above methods in our patients. Only 6.7% of the patients with C/S myomectomy required blood transfusions and there was no difference in the hemoglobin level drop between C/S myomectomy and the non-myomectomy operations; nevertheless, the small sample size used in this study could have led to insufficient statistical power to detect differences between groups, resulting in a type II error. Dedes et al. did not report significant differences in estimated blood loss, decline in hemoglobin, and need for additional uterotonics.\textsuperscript{[24]} Hence, it remains unclear whether the number, site, and size of leiomyomas should influence decision-making. Future studies with multivariable analyses of these characteristics should specifically investigate the effect of myomectomy during cesarean delivery on intraoperative and postoperative outcomes.

Hatrnaz et al. reported that the disadvantages of the C/S myomectomy include increased operative time, extensive myometrial damage and possible post-operative adhesion formation, which they stated are more often related to the serosal surface incision for myomectomy. Therefore, they described the endometrial surface myomectomy incision techniques they performed in order to reduce these complications and which shortened the operation time compared to the classic C/S myomectomy. They were also able to reduce blood loss and adhesion formation on the endometrial surface.\textsuperscript{[13]} Two of our patients had undergone endometrial myomectomy with anterior placement of intramural myomas, and one of them developed a hematoma in the myoma localization, but this hematoma was monitored under expectant management. The patient did not need a blood transfusion and the resulting hematoma was spontaneously resolved.

The study we conducted had some limitations. These mainly included the retrospective nature of the study, the relatively low number of patients involved. We performed a power analysis on the data relative to the transfusion requirement. This data indicate that a sample of 220 patients in each arm could detect an efficacy of myomectomy between the groups, with 80% power and an error of 5%. There were 235 patients in the non-myomectomy group but we had 45 patients in the myomectomy group. Therefore we planned to include all eligible patients in myomectomy group. Lack of information on long-term patient outcomes and subsequent pregnancies was among the limitations of the study. Another limitation was that patients who had myomas detected during C/S and did not undergo myomectomy were not included in the study. In our view, the strongest aspect of our study was that the operations were performed by surgeons trained in surgical treatment of obstetric hemorrhage and having a high volume of surgical experience.
Conclusion
Myomectomy C/S carried out by experienced surgeons may be a safe surgical procedure and can be applied without increasing intraoperative and postoperative complications. Moreover, in this instance, the patient does not need a second operation after C/S. Large-scale prospective randomized controlled studies are needed that include long-term outcomes and the method of delivery in subsequent pregnancies.

Conflicts of Interest: No conflicts declared.

References
Conventional Doppler myocardial performance index, tricuspid and mitral annular plane systolic excursions in the assessment of fetal heart functions

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Abstract

Objective: Tei index and TAPSE & MAPSE are very useful and reliable non-invasive methods to assess the global myocardial systolic and diastolic functions, and right and left ventricular longitudinal myocardial functions, respectively. In this study, we aimed to assess fetal right and left ventricle (RV and LV) functions by myocardial performance index (Tei index) and tricuspid and mitral annular plane systolic excursions (TAPSE and MAPSE).

Methods: The findings of fetal echocardiographies performed in our center for control purposes between December 2015 and April 2017 were assessed. By obtaining appropriate positions in 152 fetuses which are at eligible weeks of gestation, Tei index and TAPSE and MAPSE measurements were recorded. Repeating echocardiographies were excluded from the study.

Results: Of all fetuses included in the study, LV Tei index was 0.47±0.16, RV Tei index was 0.52±0.17, TAPSE was 0.47±0.1 cm, and MAPSE 0.36±0.07 cm. Seventy-two fetuses were at 20+3–26 weeks of gestation, and 80 fetuses were at 26+3–37+3 weeks of gestation. Both groups were measured separately and they were compared. While there was no significant increase in LV and RV Tei indices and mitral valve gradient during the advanced weeks of gestation, significant difference was observed in TAPSE and MAPSE values (p=0.001 for both).

Conclusion: Tei index, and TAPSE and MAPSE are reliable non-invasive methods for global heart functions and annular plane systolic longitudinal functions of right and left ventricles, respectively, which are easily used on fetuses as well as children who are healthy or with congenital heart disease; and these methods also can be used in the routine practice.

Keywords: Fetal heart functions, Tei index, TAPSE, MAPSE.

Özet: Fetal kalp fonksiyonlarının değerlendirilmesinde konvansiyonel Doppler miyokardiyal performans indeksi, triküspid ve mitral kapak anüler düzlem sistolik hareketleri

Amaç: Tei indeksi, global miyokardiyal sistolik ve diastolik fonksiyonları, TAPSE ve MAPSE, sağ ve sol ventriküler longitudinal miyokardiyal fonksiyonların değerlendirilmesinde oldukça yararlı, güvenilir, non-invaziv yöntemlerdir. Bu çalışmada fetal sağ ve sol ventrikül (RV ve LV) fonksiyonlarının miyokardiyal performans indeksi (Tei indeksi); triküspid ve mitral kapak anüler düzlem sistolik hareketleri (TAPSE ve MAPSE) ile değerlendirilmesi amaçlanmıştır.


Bulgular: Çalışmaya alınan tüm fetüslerin; LV Tei indeksi 0.47±0.16, RV Tei indeksi 0.52±0.17, TAPSE 0.47±0.1 cm, MAPSE 0.36±0.07 cm idi. Yetişimi iki fetüs 20+3–26. hafta, 80 fetüs 26+3–37+3 hafta arasında bulunuyordu. Ölçümler bu iki grup için ayrı ayrı gerçekleştirildi ve karşılaştırıldı. İlerleyen gestasyon haftasında LV ve RV Tei indeks ve mitral kapak gradyanında anlamlı artış bulunmamakta, TAPSE ve MAPSE değerlerinde anlamlı artış olduğu görüldü (her ikisi için p<0.001).

Sonuç: Tei indeksi, global kalp fonksiyonlarının, TAPSE ve MAPSE ise sağ ve sol ventriküllerin anüler düzlem sistolik longitudinal fonksiyonlarının non-inziv olarak değerlendirilmesinde, sağlıklı ve konjenital kalp hastalığı bulunan çocuklarda olduğu gibi, fetüslerde de kolay uygulanabilen, rutinde de kullanılabilir, güvenilir yöntemlerdir.

Anahtar sözcükler: Fetal kalp fonksiyonları, Tei indeksi, TAPSE, MAPSE.
Introduction

Myocardial performance index (Tei index), which was first defined in healthy individuals and adult patients with dilated cardiomyopathy and for which many studies have been performed so far on children who were normal, healthy and had congenital heart disease, is an echocardiographic assessment method which is obtained by Doppler echocardiographic measurements and has a significant role for the assessment of global myocardial systolic and diastolic functions.\(^\text{[1–5]}\)

For about two decades, echocardiography, radionuclide studies and various methods such as magnetic resonance imaging as well as right ventricular functions which were considered to be “neglected” in the past have been the subjects of many studies. Tricuspid annular plane systolic excursion (TAPSE) is an echocardiographic method which has been studied well in all age groups, a wide range of patient groups and healthy children, of which mean and z-score values have been determined for age groups, which is reliable and easy to perform, can be obtained by M-mode measurements, useful for the assessment of right ventricular longitudinal myocardial function and which is independent from heart rate, ventricle size and geometry.\(^\text{[6–8]}\)

Mitral annular plane systolic excursion (MAPSE) is a reliable and easy-to-perform non-invasive method to assess left ventricular longitudinal myocardial functions which is performed on adults and children who are healthy or have disease, obtained by M-mode measurements, of which mean and z-score values have been determined, and for which many studies have been performed so far.\(^\text{[9–11]}\)

There are a limited number of studies where annular plane systolic excursions of atrioventricular valves (TAPSE and MAPSE) and Tei index are assessed in healthy fetuses by M-mode echocardiography during fetal period.\(^\text{[12–15]}\)

In this study, we aimed to assess fetal right and left ventricle (RV and LV) functions by conventional Doppler myocardial performance index (Tei index) and tricuspid and mitral annular plane systolic excursions (TAPSE and MAPSE) in healthy fetuses by M-mode echocardiography during fetal period.

Methods

Patient group

The findings of fetal echocardiographies performed in our center for control purposes between December 2015 and April 2017 were assessed. The pregnant women who were 18–40 (mean: 27.7±5.17) years old, of which 72 (47.4%) were at 20+3 – 26 weeks of gestation and 80 (52.6%) at 26+3 – 37+3 weeks of gestation were assessed by fetal echocardiography. By obtaining appropriate positions in 152 fetuses which were at 20+3 – 37+3 weeks of gestation and did not have congenital heart disease, dysrhythmia, myocarditis, pericardial effusion and valve insufficiency, Tei index measurements, and pulse wave Doppler measurements of atrioventricular and semilunar valves were performed. The pregnant women were asked to be full before the fetal echocardiography.

Echocardiography

Echocardiography measurements of all fetuses were performed by the same investigator (Dr. ŞP) via Phase Array pediatric transducer S8-3 mHz of 2005 HD11-XE device (©Philips Medical System Nederland BV, Best, the Netherlands). The measurements were done separately for each valve. Sample volume was obtained by placing on the farthest ends of atrioventricular valve leaflets on apical 4 chamber position. The mean of three consecutive valve flow measurements was calculated. All valve flow rates were obtained while sweep rate was 50 mm/sec. E and A waves of mitral and tricuspid valves, E/A rates, aortic and pulmonary artery flows were obtained. Fetal heart rates were measured four times when calculating the flows of mitral valve, aortic valve, tricuspid valve and pulmonary valve. Ejection fraction (EF) and fractional shortening (FS) values, TAPSE and MAPSE measurements, and minimum and maximum heart rates were recorded.

Statistical analysis

All data were recorded to Excel (2010; Microsoft Office Corp., Redmond, WA, USA), and transferred to SPSS 15.0 SPSS for Windows v.15.0; IBM-SPSS Inc., Chicago, IL, USA) for statistical analysis. The difference between mean values among independent groups was analyzed by independent sample test. The values were given as standard +/- deviation (SD). Pearson correlation and linear regression analyses were used to find the relationship between the variables. As the correlation coefficient, r<0.25 was considered poor, 0.25–0.49 was considered average, 0.50–0.74 was considered strong and >0.75 was considered very strong.
Results

Mean parameter values of all fetuses included in the study were as following: LV Tei index: 0.47±0.16, RV Tei index: 0.52±0.17, EF: 75±4.7%, FS: 39.84±4.2%, TAPSE: 0.47±0.1 cm, MAPSE: 0.36±0.07 cm, mitral E/A: 0.624±0.09, tricuspid E/A: 0.656±0.08, aortic valve flow: 71.43±12.53 cm/sec, pulmonary valve flow: 66.16±8.61 cm/sec, minimum heart rate: 137.2±7.99/min, maximum heart rate: 148.73±7.05/min.

The fetal assessments were done during the first pregnancy in 21.7% of the patients, during the second pregnancy in 30.3% of them, during the third pregnancy in 14.5% of them, during the fourth pregnancy in 8.6% of them, during the fifth pregnancy in 0.7% of them, and during the sixth pregnancy in 1.3%. Pregnancy information could not be obtained in 23% of the patients.

The mean values in the second trimester group (Group 1) were as following: LV Tei index: 0.46±0.16, RV Tei index: 0.51±0.16, mitral E/A: 0.624±0.09, tricuspid E/A: 0.656±0.08, aortic valve flow: 68.05±12.5 cm/sec, pulmonary valve flow: 66.16±8.61 cm/sec, minimum heart rate: 139.23±7.24/min, maximum heart rate: 149.37±6.48/min.

The mean values in the third trimester group (Group 2) were as following: LV Tei index: 0.47±0.15, RV Tei index: 0.53±0.18, mitral E/A: 0.65±0.1, tricuspid E/A: 0.67±0.08, aortic valve flow: 74.38±11.86 cm/sec, pulmonary valve flow: 67.72±8.0 cm/sec, minimum heart rate: 135.62±8.27/min, maximum heart rate: 148.17±7.5/min.

When we investigated to find whether there is any statistically significant difference between two groups in terms of all parameters assessed during advanced weeks of gestation, we found that there was no significant difference among LV Tei index, RV Tei index, and mitral valve mean gradient values while there was a significant increase in TAPSE and MAPSE values (p=0.001 and p=0.001, respectively) (Figs. 1–4). Also, we found a significant increase in aortic and pulmonary valve flows and tricuspid valve mean gradient value (p=0.002, p=0.017).

### Table 1. General characteristics of all fetuses.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Second trimester (Group 1)</th>
<th>Third trimester (Group 2)</th>
<th>All fetuses (Group 1+2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean gestational age (week)</td>
<td>23.8±1.41</td>
<td>29.95±2.89</td>
<td>27.05±3.83</td>
</tr>
<tr>
<td>LV Tei index</td>
<td>0.46±0.16</td>
<td>0.47±0.15</td>
<td>0.47±0.16</td>
</tr>
<tr>
<td>RV Tei index</td>
<td>0.51±0.16</td>
<td>0.53±0.18</td>
<td>0.52±0.17</td>
</tr>
<tr>
<td>MV E/A</td>
<td>0.59±0.07</td>
<td>0.65±0.1</td>
<td>0.624±0.09</td>
</tr>
<tr>
<td>TV E/A</td>
<td>0.63±0.07</td>
<td>0.67±0.08</td>
<td>0.656±0.08</td>
</tr>
<tr>
<td>Minimum heart rate (min)</td>
<td>139.2±7.24</td>
<td>135.6±7.77</td>
<td>137.2±7.99</td>
</tr>
<tr>
<td>Maximum heart rate (min)</td>
<td>149.37±6.48</td>
<td>148.17±7.5</td>
<td>148.73±7.05</td>
</tr>
<tr>
<td>TAPSE (cm)</td>
<td>0.44±0.08</td>
<td>0.52±0.11</td>
<td>0.47±0.1</td>
</tr>
<tr>
<td>MAPSE (cm)</td>
<td>0.32±0.07</td>
<td>0.39±0.07</td>
<td>0.36±0.07</td>
</tr>
<tr>
<td>EF (%)</td>
<td>74.99±4.48</td>
<td>75.01±4.93</td>
<td>75±4.70</td>
</tr>
<tr>
<td>FK (%)</td>
<td>39.56±3.84</td>
<td>40.1±4.52</td>
<td>39.84±4.20</td>
</tr>
</tbody>
</table>

Fig. 1. Difference between the groups in terms of LV Tei index.
and $p=0.001$, respectively). In terms of heart rates, minimum heart rate was significantly different between two groups ($p=0.006$) while maximum heart rate was similar in both groups. The correlations between RV and LV Tei indexes and the week of gestation were $r=0.091$; $p=0.298$ and $r=0.137$; $p=0.097$, respectively. There was a strong and statistically significant correlation between TAPSE and the week of gestation ($r=0.537$; $p=0.001$). There was also a strong and statistically significant correlation between MAPSE and the week of gestation ($r=0.523$; $p=0.001$). There was an average and statistically significant correlation between TAPSE and RV Tei index ($r=0.322$; $p=0.001$). However, there was a negative, poor and statistically significant correlation between MAPSE and LV Tei index ($r=-0.157$; $p=0.208$).

Mean TAPSE and MAPSE values and LV and RV Tei index values ± SD of the fetuses between 22 and 32 weeks of gestation are shown in Table 2.

Table 2. The mean TAPSE, MAPSE, RV and LV Tei index values of the fetuses between 22 and 32 weeks of gestation.

<table>
<thead>
<tr>
<th>Week of gestation</th>
<th>TAPSE (cm)</th>
<th>MAPSE (cm)</th>
<th>LV Tei index</th>
<th>RV Tei index</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>0.39±0.07</td>
<td>0.39±0.12</td>
<td>0.49±0.14</td>
<td>0.53±0.17</td>
</tr>
<tr>
<td>23</td>
<td>0.43</td>
<td>0.25</td>
<td>0.56</td>
<td>0.53</td>
</tr>
<tr>
<td>24</td>
<td>0.44±0.06</td>
<td>0.32±0.05</td>
<td>0.42±0.19</td>
<td>0.48±0.20</td>
</tr>
<tr>
<td>25</td>
<td>0.42</td>
<td>0.25</td>
<td>0.48</td>
<td>0.61</td>
</tr>
<tr>
<td>26</td>
<td>0.47±0.07</td>
<td>0.37±0.08</td>
<td>0.55±0.10</td>
<td>0.61±0.14</td>
</tr>
<tr>
<td>27</td>
<td>0.45</td>
<td>0.37</td>
<td>0.50</td>
<td>0.58</td>
</tr>
<tr>
<td>28</td>
<td>0.55±0.05</td>
<td>0.33±0.00</td>
<td>0.45±0.15</td>
<td>0.57±0.24</td>
</tr>
<tr>
<td>29</td>
<td>0.51</td>
<td>0.39</td>
<td>0.42</td>
<td>0.53</td>
</tr>
<tr>
<td>30</td>
<td>0.47±0.12</td>
<td>0.35±0.04</td>
<td>0.52±0.17</td>
<td>0.49±0.11</td>
</tr>
<tr>
<td>31</td>
<td>0.56</td>
<td>0.28</td>
<td>0.46</td>
<td>0.65</td>
</tr>
<tr>
<td>32</td>
<td>0.57±0.07</td>
<td>0.37±0.01</td>
<td>0.52±0.17</td>
<td>0.46±0.15</td>
</tr>
</tbody>
</table>
Discussion

Assessing fetal myocardial functions properly is critically significant to identify high-risk fetuses. When assessing systolic and diastolic functions, Tei index which is independent from the size and shape of ventricle and heart rate is one of the important parameters determining the fetal heart health. Some studies have reported that it increases in advanced weeks of gestation while some other studies have argued that there is no such correlation and there is even a negative correlation. In our study, we did not observe a significant increase in advanced weeks of gestation. When calculating Tei index, some authors measured ventricle entrance (mitral and tricuspid valves) and exit (aortic and pulmonary) pulsed Doppler records separately while some authors only measured time intervals that they obtained from a single Doppler record placed on an appropriate position. In our study, we measured aortic and mitral, tricuspid and pulmonary valve flows consecutively and separately and we took the mean value of three different measurements. Friedman et al. studied Tei index on 74 healthy pregnant women whose mean gestational age was 24±3.4 (range: 18–31) weeks, and they found the mean LV Tei index 0.53±0.13, Tsutsumi and Eidem et al. reported LV Tei index 0.62±0.07 (range: 18–26) week and 0.35±0.03 in their studies, respectively. Mori et al. reported RV Tei index 0.35±0.07 and showed that it did not change during gestation. In our study, mean RV Tei index was 0.52±0.17 and LV Tei index was 0.47±0.08 in the entire group. In the following weeks, RV and LV Tei index did not exhibit any statistically significant increase.

It has been reported that Tei index values increased in fetal ventricular dysfunction cases (such as intrauterine growth retardation, twin-to-twin transfusion syndrome, maternal diabetes mellitus, preeclampsia, and congenital heart diseases). Diastolic dysfunction which provides information about compliance and relaxation capacity of myocytes can be assessed by the flow pattern of tricuspid and mitral valves. In our study, mean mitral and tricuspid E/A values for the entire group were 0.62±0.09 and 0.65±0.08, respectively. E/A rate is usually <1, and it exhibits a constant increase during gestation. E wave is early or passive filling wave and it is associated with the relaxation function of myocardium and the negative pressure applied by the ventricles. A wave is atrial, active or late wave, and it reflects the atrial contraction during ventricular filling. Chronic hypoxia and cardiac overload can be given as the examples changing this rate. While mitral E/A was 0.62±0.09 and tricuspid E/A was 0.65±0.08 in our study, Parasuraman et al. reported LV E/A and RV E/A values 0.68±0.07 and 0.716±0.109, respectively. In the intrauterine growth retardation, the rates are lower in the fetuses with same gestational ages compared to the normal ones. The values found were at 10–25 percentile values for mitral E/A and tricuspid E/A according to the reference values determined by Parasuraman et al. Also, the aortic valve flow was 71.43±12.53 cm/sec and pulmonary valve flow was 66.16±8.61 cm/sec in the entire group. These values were at 10–25 percentile values for aortic and pulmonary valve flows according to the reference values determined in a previous report. Messing et al. compared conventional fetal TAPSE and spatiotemporal image correlation (STIC)-TAPSE methods, and they reported high correlation for both methods (r=0.904). In their study, conventional fetal TAPSE value was 0.36±0.11 cm at 21 weeks of gestation while it was 0.86±0.15 cm at 39 weeks of gestation. The mean TAPSE and MAPSE values according to the gestational age reported by Koestenberger et al. in different studies and the mean TAPSE and MAPSE values we found in our study according to the week of gestation were consistent. It has been reported that TAPSE value was higher than MAPSE value at any week of gestation due to the fact that dominant ventricle is the right ventricle in fetus and due to the structural characteristics of myocardial fibril distribution. In our study, we found TAPSE value higher than MAPSE value, and TAPSE/MAPSE ratio was 1.37 at the second trimester while it was 1.33 at the third trimester. It is known that TAPSE value decreases in pathological conditions. It has been reported that MAPSE value decreases in adult patients, and cardiovascular disease and extracardiac pathological conditions.

Conclusion

Tei index, and TAPSE and MAPSE are reliable noninvasive methods for global heart functions and annular plane systolic longitudinal functions of right and left ventricles, respectively, which are easily used on fetuses as well as children who are healthy or with con-
genital heart disease; and these methods also can be used in the routine practice. Knowing normal values in healthy fetuses and children will help to understand cardiac and extracardiac pathological conditions better where these parameters increase and decrease. We believe that TAPSE, MAPSE, LV Tei and RV Tei values that we found according to the gestational age will provide an insight for the studies to be performed by advanced techniques.

Conflicts of Interest: No conflicts declared.

References


The distribution of primary cesarean section indication at a university hospital: ten-year experience and potential lessons to be taken to decrease cesarean section rates

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Abstract

Objective: Although cesarean section can be a life-saving practice for pregnant woman and fetus, great increase in the rates of cesarean section in the recent years has made its indications questionable. Primary cesarean section (PCS) is the main source of total cesarean section pool. In our study, we aimed to investigate the distributions of PCS indications and to determine the case characteristics of the groups.

Methods: A full cohort of delivery room records for PCS carried out between January 1, 2007 and January 1, 2017 at the Hospital of Dokuz Eylül University was analyzed. PCS cases were separated into two groups as singleton and multiple pregnancies first, and then singleton pregnancies were separated into term-preterm and primiparous-multiparous groups for advanced sub-group analyses.

Results: A total of 3284 PCS cases from a ten-year period were accessed. Of the cases, 263 (8.0%) were twin pregnancy, 11 (0.3%) were triplet pregnancy, and 3010 (92.7%) were singleton pregnancy. Of 494 (15.0%) preterm cases, 105 (21.3%) were in multiple pregnancy group and 389 (78.7%) were in the singleton pregnancy group. While dystocia (41.6%) was the most common indication among term cases, it was fetal distress (35.4%) among the preterm cases. When the cases were compared according to the parity, the rank and frequency of the indication were varying significantly. Dystocia (40.2%) was the most common indication among the multiparous cases while it was fetal distress (23.0%) among the multiparous cases.

Conclusion: Dystocia, which is the greatest indication among PCS categories, is the hardest indication to standardize due to the fact that its diagnosis criteria are controversial and determining these criteria is very subjective. A different path should be followed for the solution of fetal distress issue since it is the most common indication in preterm labor cases. Breech presentations and the suspected macrosomic infant seem to be the first goal of the measures to be taken to decrease the need of cesarean section.

Keywords: Primary cesarean section, dystocia, fetal distress, macrosomia.

ÖZET: Bir üniversite hastanesinin primer sezaryen endikasyon dağılımı: On yila ait tecrübe ve sezaryen doğum oranlarını azaltma yönelik çıkarılabilecek dersler

Amaç: Gebe ve fetus için hayat Kurtarıcı olabilmesine rağmen sezaryen yoğunluk oranında son yıllarda büyük artış, endikasyonlarının sorgulanmasını günde getirmiştir. Primer sezaryen (PS) doğum toplam sezaryen doğum havuzunun ana kaynağıdır. Araştırılmazda PS endikasyon dağılımlarının incelemesi ve gruplara ait olgu özelliklerinin belirlenmesi amaçlanmıştır.

Yöntem: Dokuz Eylül Üniversitesi Hastanesi'nin'de 1 Ocak 2007 ile 1 Ocak 2017 tarihleri arasında gerçekleştirdilmiş olan PS doğumlara ait doğumhane kayıtlarını tam bir kohortu incelendi. PS olguları daha sonra tekil gebelikler ve çoğul gebelikler, tekil gebelikler de term-preterm ve primipar-multipar olarak iküye ayrılarak ileri alt grup analizleri yapıldı.

Bulgular: On yıllık bir dönemde 3284 PS doğuma ait bilgilere ulaşıldı. Olguların 263’ü (%8.0) ikiz gebelik, 11’i (%0.3) üçüz gebelik olup 3010 (%92.7) ise tekil gebeliklere aitti. Preterm olguların sayısı 494 (%15.0) olup bu olguların 105’i (%21.3) çoğul gebelik, 389 olgu (%78.7) tekil gebelikler grubunda yer alıyordu. Term olgularında distosi (%41.6), preterm olgularında ise fetal distres (%35.4) en sık rastlanan endikasyonlar olarak saptandı. Pariteye göre karşılıklı oldukça endikasyon sralaması ve sıkılıkları önemli değişiklikler göstermektedi. Primipar olgularında distosi (%40.2%), çoğul olgularında ise fetal distres (%23.0) en büyük endikasyon grubunu oluşturuyor makuluzdur.

Sonuç: PS kategorilerinin en büyük olduğu distosi, tani kriterlerinin tartışmalı olması ve bu kriterlerin saptanmasındaki özellikle boyutu nedeniyle en zor standartize edilecek endikasyon olarak öne çıkmaktadır. Fetal distres preterm doğum olgularında en sık rastlanan endikasyon grubu olması nedeni ile çözümünde farklı bir yol izlemesi gereken bir başlıktr. Makat prezentasyonlar ve makrozmik bebek süphesi olguları sezaryen doğum ihbarını azaltmaya yönelik tedbirlerin ilk hedefi olarak görünektedir.

Anahtar sözcükler: Primer sezaryen, distosi, fetal distres, makrozomi.
Introduction

The rates of cesarean section have been increasing in Turkey as in the entire world and even much more rapidly.\[1,2\] According to OECD data, Turkey has become the number one country as of 2015 with the highest rate for cesarean section with its rate of 531 cesarean section out of 1000 live births.\[2\] Cesarean sections can be categorized in two groups which are primary and repeat.\[9\] Primary cesarean section is defined as the first occurrence of cesarean section, and it is called “repeat” when the patient has a history of cesarean section or “former” cesarean section as it is preferred in Turkey.

Therefore, primary cesarean sections (PCS) are the main source of total cesarean section pool.\[10\] Barber et al. reported that PCS cases are responsible for 50% of the increase in cesarean section rates.\[4\] PCS have widely-accepted indications;\[10,13\] however, the distribution of the indications may vary depending on the countries, centers and even the physicians.\[10\]

Cesarean section has higher morbidity and mortality rates than the vaginal labor.\[9\] Cesarean section increases the risks of uterine rupture, placenta previa, placenta accreta, hemorrhage, hysterectomy and maternal mortality in the further pregnancies.\[7\] Therefore, decreasing PCS rates in a safe way without risking maternal and fetal health is among the primary health targets in the world\[10\] and Turkey.\[5\]

PCS indications are considered in two main topics which are maternal and fetal indications.\[10,11\] The analysis of the distribution of these indications has a critical significance to determine effective strategies for decreasing PCS needs. Among these indications, the most common and subjective one is dystocia\[10,10\] and it is an indication also used as non-progressive labor or cephalopelvic disproportion in the clinical practice. Electronic fetal monitorization (EFM), which is routinely used for the evaluation and follow-up of the well-being of fetus during labor, is criticized for increasing PCS rates without providing any significant improvement in the newborn outcomes.\[12\] The changes and patterns seen in fetal heart rates during labor follow-up and interpreted as fetal distress are the second greatest category among PCS indications.\[10,10,11\] Multiple pregnancies increase as assisted reproductive technologies improve and become prevalent.\[11\] Multiple pregnancies and breech presentations constitute a significant part of PCS indications, and represent an aspect of obstetrics which diminishes slowly.

Delivering all twin pregnancies by cesarean section is an important question of debate whether it decreases perinatal mortality or not.\[14\] One of the focuses in the studies to decrease PCS rates safely is the safety of external cephalic version in breech presentations.\[4\] In breech presentations, trying vaginal labor in both nulliparous and multiparous pregnant women is an important question of debate.\[16,17\] Large infant (macrosomic fetus) is included in the top 5 PCS indication category in clinical practice.\[19\] Another aspect of macrosomic fetus category is that it may be included in a different scenario in PCS labors due to dystocia except PCS labors directly due to macrosomic fetus. While fetal weights which is 4500 g and above for diabetic pregnant women and 5000 g and above for non-diabetic pregnant women are required for the macrosomia definition in the standard treatment guidelines, an expected birth weight of 4000 g is chosen as a more common cautionary threshold in practice.\[18,19\]

The medicolegal concerns related with shoulder dystocia especially and brachial plexus paralysis and asphyxia which may develop afterwards compel many obstetricians to make the decision for cesarean section as from expected fetal weight of 400 g.\[18,19\] Evaluating PCS indication category due to macrosomic fetus and determining its relative weight will support the efficacy of labor induction efforts to decrease PCS rates safely in pregnancies with fetuses over the expected weights which are close to the term, and the determination of sub-groups where it can be successful.

Methods

This study analyzed the full cohort of delivery room records for PCS cases carried out between January 1, 2007 and January 1, 2017 at the Department of Obstetrics and Gynecology of Dokuz Eylül University. For that purpose, all PCS cases with indications which were seen clearly were included in the study. PCS cases were separated into two groups as singleton and multiple pregnancies, and then singleton pregnancies were separated into term-preterm and primiparous-multiparous groups for advanced sub-group analyses. Former cesarean section and postmortem cesarean section cases were excluded from the study. In order to comply with the terminology in the literature, exceptional cases below 500 g and 24 weeks of gestation were not included. The study was approved by Ethics Committee for Non-Invasive Researches of Dokuz Eylül University (4087-GOA-2018/16-06).
Statistical analyses

Statistical analyses were performed by using SPSS v.22 (SPSS Inc., Chicago, IL, USA). The compatibility of variables to normal distribution was analyzed by visual and analytical methods (Kolmogorov-Smirnov / Shapiro-Wilk tests). Descriptive statistics were presented by selecting mean and standard deviation values for the variables exhibiting normal distribution. The mean values of constant variables were compared by one-way ANOVA test among the groups more than two. The homogeneity of variances was analyzed by Levene’s test. When significant difference was found between the groups, post-hoc pairwise comparisons were done by Tukey and Games-Howell tests. When constant variables did not exhibit any normal distribution, they were compared by Kruskal-Wallis test. The presence of difference among the groups in frequency analyses were compared by using either chi-square or Fisher’s test. When p value was below 0.05, the results were considered statistically significant.

Results

A total of 3284 PCS labors were carried out between January 1, 2007 and January 1, 2017 in a period of ten years. Of these cases, 263 (8.0%) were twin pregnancy, 11 (0.3%) were triplet pregnancy, and 3010 (92.7%) were singleton pregnancy. The total number of preterm cases was 494 (15.0%), and 105 (21.3%) of them were in multiple pregnancy group while 389 (78.7%) of them were in the singleton pregnancy group. While 38.3% of the multiple pregnancies resulted in preterm labor, only 12.9% of the singleton pregnancies resulted in preterm labor. When all cases were considered, mean gestational age was 29.2±5.3 (range: 15.0 to 51.0), and mean birth weight of newborns was 3123±812 (range: 502 to 5580) g. Of the cases, 2106 (64.1%) were primigravida and 1178 (35.9%) were multigravida. Considering the cases in terms of previous history of live birth, 2604 (79.3%) cases were primiparous and 680 (20.7%) cases were multiparous. 16.7% of the pregnant women (548 cases) were 35 years old or above.

PCS indication categories are presented in Table 1. The number of obstetric indication categories with frequency of 1% and above was 9 (Table 1). The greatest category in this group and the greatest group among PCS’ was dystocia (36.0%). In our clinic, cephalopelvic disproportion and non-progressive labor were referred as two sub-definitions for dystocia indication. Due to maternal problems, PCS practices were categorized under 6 main topics (Table 1). The greatest indication category in this group was severe preeclampsia (78 cases, 2.4%). Indication types with lower than 1% frequency were categorized under 15 topics (Table 1). Placenta previa marginalis was the greatest group among these rare reasons. When they were all considered, 25 indication types were seen (Table 1).

In term cases, dystocia was found to be the most common indication category in all years (Table 2 and Fig. 1). The frequency of dystocia indication was the highest (48.4%) in 2011 while it was the lowest (19.5%) in 2016 (Table 2). The ranking of dystocia, fetal distress, breech presentation, twin pregnancy and macrosomic fetus changed after first 2 years and macrosomic fetus category reached to rank 4 in 2009, 2010 and 2011, and rank 2 in 2016 (Table 2 and Fig. 1). Twin pregnancies regressed to rank 5 as of 2009, and stayed at this rank except 2012 where it was not within top 5 (Table 2). Although the absolute number of twin pregnancies seemed to decrease beginning from 2010, the decrease was not statistically significant: Ninety-six cases between 2007 and 2010 vs. 69 cases between 2011 and 2016 (p=0.06).

In preterm cases, fetal distress was found to be the most common indication category except 2009 (Table 2 and Fig. 2). While fetal distress had a rate of 3.3% among all PCS’ in preterm cases in 2007, it increased to 8.0% in 2016. Dystocia, which was the greatest category of term cases, could only manage to be in top 5 groups of preterm cases between 2007 and 2012 (Table 2). Although the ranks changed in some years, fetal distress, breech presentation and twin pregnancies were top three categories in preterm cases (Table 2 and Fig. 2). Unlike term cases, placental attachment anomalies and detachment were always in top 5 categories in preterm pregnancies.

When primiparous and multiparous cases were compared, top 5 indication ranks and their frequencies were varying significantly. While the top five indications for primiparous cases were dystocia (40.2%), fetal distress (18.9%), breech presentation (11.2%), twin pregnancies (8.3%) and macrosomic fetus (5.6%), they were fetal distress (23.0%), dystocia (19.9%), breech presentation (14.5%), macrosomic fetus (13.6%) and twin pregnancies (6.6%) for multiparous cases. When the groups with maternal age above and below 35-year-old were com-
pared, top 3 categories were same (dystocia, fetal distress, breech presentation); however, 4th category was twin pregnancies in the group with maternal age of <35 while it was macrosomic fetus in the group with maternal age of ≥35. The rate of macrosomic fetus was 6.9% in cases with the maternal age of <35 and 8.9% in cases with the maternal age of ≥35. Dystocia was the greatest category in both groups (36.4% vs. 34.1%; p=0.422), and first 5 indication ranking did not change.

When maternal, fetal and obstetric characteristics of top 5 indication groups were compared among the groups, there was no significant difference among the groups in terms of mean maternal age (Table 3). Newborn weight was significantly higher in macrosomic fetus group than all other groups (p<0.0001), and it was significantly higher in dystocia group than fetal distress (p<0.0001) and breech presentation (p<0.0001) groups.

Primiparous case rate was higher in fetal distress, breech presentation and macrosomic fetus groups than dystocia and twin pregnancy groups (Table 4). Male fetus rate was higher in macrosomic fetus group than breech presentation group. Preterm case rate was higher in twin pregnancy and fetal distress groups than the other groups. Preterm case rate was also higher in twin pregnancy group than the fetal distress group (p=0.008) (Table 4). The rate of pregnancy obtained by assisted reproductive technologies was higher than all other groups; the rates of pregnancies obtained by spontaneous pregnancy and in vitro fertilization / intrauterine insemination were not different among other groups (Table 4).

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### Table 1. The distribution of indications of primary cesarean section cases in total cohort.

<table>
<thead>
<tr>
<th>Indication categories for primary cesarean section</th>
<th>Number of cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication categories for primary cesarean section</strong></td>
<td>Number of cases (%)</td>
</tr>
<tr>
<td><strong>Dystocia</strong></td>
<td>3284 (100)</td>
</tr>
<tr>
<td>Cephalopelvic disproportion</td>
<td>795 (24.2)</td>
</tr>
<tr>
<td>Non-progressive labor</td>
<td>387 (11.8)</td>
</tr>
<tr>
<td><strong>Fetal distress</strong></td>
<td>648 (19.7)</td>
</tr>
<tr>
<td><strong>Breech presentation</strong></td>
<td>390 (11.9)</td>
</tr>
<tr>
<td><strong>Twin pregnancies</strong></td>
<td>263 (8.0)</td>
</tr>
<tr>
<td>** Macrosomic fetus**</td>
<td>239 (7.3)</td>
</tr>
<tr>
<td><strong>Fetal anomaly</strong></td>
<td>109 (3.3)</td>
</tr>
<tr>
<td>Transverse fetal position</td>
<td>44 (1.3)</td>
</tr>
<tr>
<td>Placenta previa partialis and totalis</td>
<td>42 (1.3)</td>
</tr>
<tr>
<td>Ablatio placentae</td>
<td>35 (1.1)</td>
</tr>
<tr>
<td><strong>Maternal problems</strong></td>
<td>159 (4.8)</td>
</tr>
<tr>
<td>Severe preeclampsia</td>
<td>78</td>
</tr>
<tr>
<td>Cardiac diseases</td>
<td>36</td>
</tr>
<tr>
<td>Lumbar disc herniation</td>
<td>14</td>
</tr>
<tr>
<td>Neuromuscular diseases</td>
<td>11</td>
</tr>
<tr>
<td>Vaginismus</td>
<td>11</td>
</tr>
<tr>
<td>Other various diseases</td>
<td>9</td>
</tr>
<tr>
<td><strong>Rare indications (with &lt;1% rate)</strong></td>
<td></td>
</tr>
<tr>
<td>Placenta previa marginalis</td>
<td>27 (0.8)</td>
</tr>
<tr>
<td>Previous uterine surgery</td>
<td>21 (0.6)</td>
</tr>
<tr>
<td>Feet presentation</td>
<td>21 (0.6)</td>
</tr>
<tr>
<td>Genital wart</td>
<td>20 (0.6)</td>
</tr>
<tr>
<td>Oblique fetal position</td>
<td>18 (0.5)</td>
</tr>
<tr>
<td>Cord prolapse</td>
<td>12 (0.4)</td>
</tr>
<tr>
<td>Eclampsia</td>
<td>11 (0.3)</td>
</tr>
<tr>
<td>Triplet pregnancy</td>
<td>11 (0.3)</td>
</tr>
<tr>
<td>Face presentation</td>
<td>10 (0.3)</td>
</tr>
<tr>
<td>HELLP syndrome</td>
<td>9 (0.3)</td>
</tr>
<tr>
<td>Hand presentation</td>
<td>5 (0.2)</td>
</tr>
<tr>
<td>Arm prolapse</td>
<td>2 (&lt;0.1)</td>
</tr>
<tr>
<td>Forehead presentation</td>
<td>2 (&lt;0.1)</td>
</tr>
<tr>
<td>Genital herpes</td>
<td>2 (&lt;0.1)</td>
</tr>
<tr>
<td>Asynclitism</td>
<td>2 (&lt;0.1)</td>
</tr>
</tbody>
</table>
Table 2. Distribution of top 5 indication categories of primary cesarean section in term and preterm cases by years.

<table>
<thead>
<tr>
<th>Years / Number of primary cesarean section cases (% in cohort)</th>
<th>Top 5 indication groups in term cases Number of cases (%)</th>
<th>Top 5 indication groups in preterm cases Number of cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007 / 436 (13.2)</td>
<td>1. Dystocia 189 (43.3) 2. Fetal distress 62 (14.2) 3. Breech presentation 43 (9.9) 4. Twin pregnancy 26 (5.6) 5. Macrosomic fetus 19 (4.4)</td>
<td>1. Fetal distress 17 (3.9) 2. Twin pregnancy 14 (3.2) 3. Breech presentation 7 (1.6) 4. Dystocia 3 (0.7) 5. Placenta previa 2 (0.5)</td>
</tr>
<tr>
<td>2008 / 381 (11.6)</td>
<td>1. Dystocia 124 (32.5) 2. Fetal distress 74 (19.4) 3. Breech presentation 48 (12.6) 4. Twin pregnancy 26 (6.8) 5. Macrosomic fetus 10 (2.6)</td>
<td>1. Fetal distress 23 (6.0) 2. Twin pregnancy 15 (4.1) 3. Breech presentation 3 (0.8) 4. Transverse fetal position 2 (0.5) 5. Ablatio placenta 2 (0.5)</td>
</tr>
<tr>
<td>2009 / 329 (10.0)</td>
<td>1. Dystocia 90 (27.4) 2. Fetal distress 79 (24.0) 3. Breech presentation 32 (9.7) 4. Macrosomic fetus 24 (7.3) 5. Twin pregnancy 16 (4.9)</td>
<td>1. Twin pregnancy 19 (5.8) 2. Fetal distress 18 (5.5) 3. Breech presentation 9 (2.7) 4. Ablatio placenta 5 (0.9) 5. Fetal anomaly 4 (0.7)</td>
</tr>
<tr>
<td>2010 / 538 (16.4)</td>
<td>1. Dystocia 204 (37.9) 2. Fetal distress 84 (15.6) 3. Breech presentation 40 (7.4) 4. Breech presentation 32 (5.9) 5. Twin pregnancy 28 (5.2)</td>
<td>1. Fetal distress 24 (4.5) 2. Twin pregnancy 17 (3.2) 3. Breech presentation 9 (1.7) 4. Ablatio placenta 5 (0.9) 5. Fetal anomaly 4 (0.7)</td>
</tr>
<tr>
<td>2011 / 337 (10.3)</td>
<td>1. Dystocia 163 (48.4) 2. Fetal distress 33 (9.8) 3. Breech presentation 29 (8.6) 4. Macrosomic fetus 16 (4.8) 5. Twin pregnancy 10 (2.9)</td>
<td>1. Fetal distress 20 (5.9) 2. Breech presentation 6 (1.8) 3. Twin pregnancy 5 (1.5) 4. HELLP syndrome 2 (0.6) 5. Placenta previa 2 (0.6)</td>
</tr>
<tr>
<td>2012 / 183 (5.6)</td>
<td>1. Dystocia 70 (38.2) 2. Fetal distress 17 (9.3) 3. Breech presentation 15 (8.2) 4. Fetal anomaly 9 (4.9) 5. Macrosomic fetus 8 (4.4)</td>
<td>1. Fetal distress 12 (6.6) 2. Breech presentation 6 (3.3) 3. Twin pregnancy 4 (2.2) 4. Dystocia 3 (1.6) 5. Ablatio placenta 2 (1.1)</td>
</tr>
<tr>
<td>2013 / 217 (6.6)</td>
<td>1. Dystocia 81 (37.3) 2. Breech presentation 24 (11.1) 3. Fetal distress 18 (8.3) 4. Macrosomic fetus 17 (7.8) 5. Twin pregnancy 10 (4.6)</td>
<td>1. Fetal distress 9 (4.1) 2. Breech presentation 7 (3.2) 3. Twin pregnancy 5 (2.3) 4. Ablatio placenta 2 (0.9) 5. Placenta previa 2 (0.9)</td>
</tr>
<tr>
<td>2014 / 290 (8.8)</td>
<td>1. Dystocia 96 (33.1) 2. Macrosomic fetus 47 (16.2) 3. Fetal distress 35 (12.1) 4. Breech presentation 28 (9.7) 5. Twin pregnancy 12 (4.1)</td>
<td>1. Fetal distress 14 (4.8) 2. Breech presentation 8 (2.8) 3. Twin pregnancy 6 (2.1) 4. Fetal anomaly 4 (1.4) 5. HELLP syndrome 2 (0.7)</td>
</tr>
<tr>
<td>2015 / 286 (8.7)</td>
<td>1. Dystocia 87 (30.4) 2. Fetal distress 45 (15.7) 3. Breech presentation 30 (10.5) 4. Macrosomic fetus 19 (6.6) 5. Twin pregnancy 16 (5.6)</td>
<td>1. Fetal distress 15 (5.2) 2. Twin pregnancy 5 (1.7) 3. Breech presentation 4 (1.4) 4. Cord prolapse 2 (0.7) 5. Placenta previa 2 (0.7)</td>
</tr>
<tr>
<td>2016 / 287 (8.7)</td>
<td>1. Dystocia 56 (19.5) 2. Macrosomic fetus 47 (16.3) 3. Breech presentation 38 (13.2) 4. Fetal distress 26 (9.1) 5. Twin pregnancy 21 (7.3)</td>
<td>1. Fetal distress 23 (8.0) 2. Breech presentation 7 (2.4) 3. Twin pregnancy 4 (1.4) 4. Placenta previa 4 (1.4) 5. Ablatio placenta 4 (1.4)</td>
</tr>
</tbody>
</table>
The distribution of primary cesarean section indication at a university hospital

Fig. 1. Top 5 indication categories of primary cesarean section in term cases.

Fig. 2. Top 3 indication categories of primary cesarean section in preterm cases.
When the changes in categories of the top 5 indication group for PCS cases were analyzed by the years, it was seen that dystocia group started to decrease after 2011, and regressed to 19.5% from 48.4% (p<0.0001) (Table 1 and Fig. 1). Fetal distress category expanded between 2007 and 2009, narrowed between 2010 and 2013 (p<0.0001) and then remained same relatively among other groups (Table 1 and Fig. 1). There was no significant change in the rate of PCS due to breech presentation during the study period; it reached its lowest level (7.4%) in 2010 and its highest level (13.2%) in 2016; however, this change was not statistically signifi-

### Table 3. Comparison of maternal, fetal and obstetric characteristics in top 5 indication categories.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Dystocia (n=1182)</th>
<th>Fetal distress (n=648)</th>
<th>Breech presentation (n=390)</th>
<th>Twin pregnancy (n=263)</th>
<th>Macrosomic fetus (n=239)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (year)</td>
<td>29.2±4.9 (15–47)</td>
<td>28.8±5.2 (16–46)</td>
<td>29.1±5.4 (17–44)</td>
<td>29.6±5.7 (17–51)</td>
<td>29.3±5.4 (17–42)</td>
<td>0.793</td>
</tr>
<tr>
<td>Newborn weight (g)</td>
<td>3417±462 (1400–5160)</td>
<td>2640±893 (502–4750)</td>
<td>2945±760 (700–4900)</td>
<td>4138±316 (3590–5580)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Parity condition</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1047 (88.6)</td>
<td>492 (75.9)</td>
<td>292 (74.9)</td>
<td>218 (82.8)</td>
<td>147 (61.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>135 (11.4)</td>
<td>156 (24.1)</td>
<td>96 (25.1)</td>
<td>45 (17.2)</td>
<td>92 (38.5)</td>
<td></td>
</tr>
<tr>
<td>Fetal sex</td>
<td>Female</td>
<td>537 (45.4)</td>
<td>298 (46.0)</td>
<td>197 (50.5)</td>
<td>99 (41.4)</td>
<td>0.026</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>638 (54.6)</td>
<td>350 (54.0)</td>
<td>193 (49.5)</td>
<td>90 (58.6)</td>
<td></td>
</tr>
<tr>
<td>Week of gestation</td>
<td>Preterm</td>
<td>22 (1.9)</td>
<td>175 (27.0)</td>
<td>63 (16.2)</td>
<td>94 (35.7)</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>Term</td>
<td>1160 (98.1)</td>
<td>473 (73.0)</td>
<td>327 (83.8)</td>
<td>169 (64.3)</td>
<td>&lt;0.008</td>
</tr>
<tr>
<td>Conception type</td>
<td>Spontaneous</td>
<td>1142 (96.6)</td>
<td>628 (96.9)</td>
<td>379 (97.2)</td>
<td>163 (62.0)</td>
<td>235 (98.3)</td>
</tr>
<tr>
<td></td>
<td>Assisted</td>
<td>40 (3.4)</td>
<td>20 (3.1)</td>
<td>11 (2.8)</td>
<td>100 (38.0)</td>
<td>4 (1.7)</td>
</tr>
</tbody>
</table>

### Table 4. Procedures to be performed and actions to be taken to decrease the rates of primary cesarean section safely.

<table>
<thead>
<tr>
<th>Indication category of primary cesarean section and the rate in total number</th>
<th>Recommendation and procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dystocia</td>
<td>Improving diagnosis criteria and determining reliable threshold values for the definition of failure to progress</td>
</tr>
<tr>
<td></td>
<td>Accurate timing for hospitalization at delivery room</td>
</tr>
<tr>
<td></td>
<td>Active labor follow-up</td>
</tr>
<tr>
<td></td>
<td>Determining induction and augmentation criteria</td>
</tr>
<tr>
<td>Fetal distress</td>
<td>Determining induction and augmentation criteria</td>
</tr>
<tr>
<td></td>
<td>Standard guidelines and management algorithms for correct interpretation of fetal heart rate traces</td>
</tr>
<tr>
<td></td>
<td>Amnioinfusion applications for repetitive variable decelerations</td>
</tr>
<tr>
<td></td>
<td>Preventing preterm labor</td>
</tr>
<tr>
<td></td>
<td>Protecting placental function and preventing fetal growth retardation</td>
</tr>
<tr>
<td>Breech presentation</td>
<td>External cephalic version efforts</td>
</tr>
<tr>
<td>Twin pregnancies</td>
<td>Proper selection and correct implementation of fertility support treatments</td>
</tr>
<tr>
<td></td>
<td>Optimizing embryo transfer numbers</td>
</tr>
<tr>
<td></td>
<td>Maintaining vaginal labor option in vertex-vertex presentations</td>
</tr>
<tr>
<td>Macrosomic fetus</td>
<td>Proper nutrition during pregnancy</td>
</tr>
<tr>
<td></td>
<td>Training for movement and lifestyle during pregnancy</td>
</tr>
<tr>
<td></td>
<td>Glucose intolerance and diabetes screening</td>
</tr>
<tr>
<td></td>
<td>Strict glycosmic control in gestational diabetes cases</td>
</tr>
<tr>
<td></td>
<td>Screening and following up thyroid functions</td>
</tr>
<tr>
<td>Severe preeclampsia and eclampsia</td>
<td>Preeclampsia prediction and prophylaxis studies</td>
</tr>
<tr>
<td>Fetal anomalies</td>
<td>Randomized controlled studies for the safety of vaginal labor in fetal anomaly types</td>
</tr>
<tr>
<td></td>
<td>Establishing centers specialized on the delivery of fetuses with anomaly</td>
</tr>
</tbody>
</table>
The distribution of primary cesarean section indication at a university hospital

cant (p=0.109). Twin pregnancies remained stable between 2007 and 2010; it decreased as absolute number after 2010, but its rate within other groups did not change relatively (p=0.051). PCS labors performed due to the indication of macrosomic fetus increased greatly during 2013–2014, and reached its highest level (16.3%) in 2016 (p<0.0001) (Table 1 and Fig. 1).

Discussion

In order to understand to what extent the rates of cesarean section labors can be decreased, it is necessary to determine the reasons for primary cesarean section. In their major retrospective cohort analysis within the scope of Safe Labor Consortium in the USA, Boyle et al. assessed 34,484 indications of primary cesarean section.① As the most common PCS indications, they reported non-progressive labor (35.4%), non-reassuring fetal heart rate trace (27.3%) and fetal malpresentations (18.5%), and stated that the distributions varied according to the parity.①,② 45.6% of all PCS labors were carried out on cases which were primiparous term singleton pregnancies and had cephalic presentation. This rate represents PCS cases which can be prevented somehow.

In a study conducted on more than 200,000 cesarean section cases in 19 hospitals between 2002 and 2008 in the USA, dystocia (47.1%) was found as the most common indication of intrapartum cesarean section labors.③ Dystocia was followed by non-reassuring fetal heart rate traces (27.1%) and malpresentations (7.5%). In cesarean sections performed before labor started, previous history of cesarean section (45%) was followed by breech and other malpresentations (17.1%).④ Our study was consistent with the literature and top 3 categories of PCS indications were dystocia, fetal distress and breech presentation (Table 1 and Fig. 1).

Dystocia is consisted of the combination of two sub-indications, which are the opinion of cephalopelvic disproportion and failure to progress.⑤ Failure to progress also has two sub-phases which are the failure of progress during the active stage of labor and failure to descend at the second stage of labor.⑥ Failure to progress is partially subjective and controversial diagnosis. Instead of waiting for 2 hours, which was the criterion used traditionally before proceeding with cesarean section when there were sufficient uterine contractions, waiting for 4 hours has helped to decrease the number of failure to progress diagnosis without any worsening in maternal and perinatal outcomes.⑦ In a report presented by Safe Labor Consortium in the USA argued that the definitions of labor progression should be updated and they should be extended slightly.⑧ Unlike the information based on classical Friedman’s curves, it was observed that 0.5 cm/h dilatation rate is normal sub-limit for cervical dilatation during active phase in both nulliparous and multiparous cases, and it can be seen during safe labor.⑨ In another study investigating the first stage of labor, it was concluded that the definition of failure to progress under 5 cm should not be used.⑩ Safe Labor Consortium recommends 6 cm for this diagnosis.⑪ Similar studies were conducted for the definition of duration of the second stage of labor and it was reported that keeping the maternal pushing effort as long as fetal heart rates are reassuring decreases the rates of cesarean section labors due to dystocia without any worsening in maternal and fetal outcomes.⑫ When considered from this point of view, dystocia is one of the most subjective indications due to the reasons such as being controversial in terms of diagnosis criteria among PCS indications and being open for personal opinions for considering whether a case have these criteria or not.⑬ The lack of reliable and high quality evidences particularly for the definition of non-progressive labor makes this diagnosis subjective.⑭ In this regard, it would be widely accepted that dystocia is one of the most difficult topics for decreasing the number of PCS (Table 4).

The greatest 2nd category among PCS indications is the cesarean sections carried out due to fetal distress and non-reassuring fetal heart rate traces.⑮ Labor follow-up by EFM has been almost a routine practice in the world and Turkey and this increased PCS rates without any provable improvement in the neonatal outcomes.⑯ In our study, we analyzed and interpreted fetal distress cases according to triple category system of ACOG except for 2007. After its recommendation update, ACOG grouped fetal heart rate traces under 3 categories.⑰ Category 3 is an abnormal category which requires intervention, because fetal heart rate patterns in this category may be associated with the pH of abnormal neonatal umbilical cord, encephalopathy, and cerebral palsy.⑱ When corrective primary approaches (positioning pregnant woman on side-lying, investigating and eliminating hypotension and tachysystole, and ruling out acute reasons such as cord prolapse) do not improve fetal heart rates, rapid interventions including cesarean section are required.⑲ Fetal heart rate traces which are
recorded most frequently during labor are the patterns included in Category 2. These traces are usually temporary and require follow-up, but they frequently turn into Category 1 safe traces. Category 3 traces being rare is interpreted in a way that PCS labors due to fetal distress are carried out mostly by Category 2 indication. The decision of emergency cesarean section in the presence of Category 2 fetal heart rate traces is based on medicolegal concerns. Lack of valid scientific evidences on the capacity of these traces to predict newborn's condition and the absence of studies supporting the efficiency of corrective intrauterine approaches indicates that it is not easy to decrease the number of PCS practices under this matter in the near future. Doppler evaluation of prenatal arterial and venous areas and cerebroplacental rate evaluations in cases which require labor induction offers first promising evidences to decrease the number of PCS practices.

The fetus to be born being 4000 g and above seems to be among other indications and affect them. In the cases which underwent PCS due to macrosomia, 90 (6.1%) fetuses were ≥4000 g and 338 (28.6%) fetuses were ≥3700 g. Considering the entire cohort, 277 (8.5%) cases were born ≥4000 g, and 705 (21.4%) cases were born ≥3700 g. Fetuses having such weights may contribute to all diagnosis groups, and particularly non-progressive labor and cephalopelvic disproportion. The rates of preferring cesarean section deliveries in twin pregnancies have increased gradually, and this increase has reached to 70% even in cases where presenting fetus is on vertex position. As in head presentation of presenting fetus, it is known that cesarean section does not improve perinatal outcomes in twin pregnancies.

In twin pregnancies, particularly in cases where first fetus is on vertex position, vaginal delivery should be recommended to pregnant women. During obstetrics specialization and residency, sufficient training and upskilling on delivery of twin pregnancies should be provided, and continuing education programs should be established to preserve this experience (Table 4).
The rates of cesarean section labors are higher both in premature preterm cases (<34 weeks) and late preterm cases (34–36 weeks) than term cases. In the large-scale cohort of Boyle et al., 21.6% of the cesarean section cases were preterm cases (<37 weeks and 0/7 day(s)). In our study, 15.0% of the cases were preterm cases (Table 2).

The studies investigating the potential relationship between cesarean section rates and characteristics of pregnant women showed that there was no correlation between PCS rates and ages, weights and ethnic origins of pregnant women. We also did not find any significant difference in our study between the groups in terms of the mean age of pregnant women (Table 3).

In our study, we did not analyze the cases by the subcategories such as spontaneous labor and labor induction. Labor induction was considered as a risk factor for labor by cesarean section until recent prospective randomized controlled studies and their meta-analyses. However, when labor induction cases are compared to with the cases who are just followed up and are the actual equivalents instead of the spontaneous labor cases, it is seen that the rates of cesarean section did not increased but decreased on the contrary.

**Conclusion**

World Health Organization reported that ideal rate of cesarean section is about 15%, and recommended to keep PCS rates under control to reach this rate. Investigating PCS indication categories is the first step to take in order to reach this goal. The data to be obtained in this way may contribute to the development of strategies to decrease PCS rates.

**Conflicts of Interest:** No conflicts declared.

**References**

Retrospective analysis of the preeclampsia cases delivered in our clinic between 2013 and 2017

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Abstract

Objective: The aim of our study is to analyze and compare obstetric, maternal and fetal outcomes of the cases who delivered with the diagnoses of early-onset and late-onset preeclampsia.

Methods: The data of 149 patients with preeclampsia who delivered between January 2013 and August 2017 were collected and analyzed at Derince Training and Research Hospital. Of the cases, 65 were established with the diagnosis of early-onset preeclampsia and 84 were established with the diagnosis of late-onset preeclampsia. The demographic characteristics, biochemical changes, and perinatal, maternal and obstetric outcomes of both groups were compared.

Results: Between the patient groups with early-onset and late-onset preeclampsia, there was no statistically significant difference in terms of age, gravida, parity, systolic and diastolic blood pressures, laboratory values (liver function tests, hemogram, thrombocyte count), and delivery types (p>0.05). There was statistically significant difference between serum creatinine values (p=0.045). There was statistically significant difference between two groups against early-onset preeclampsia in terms of newborn weight, low birth weight infant, newborn’s need for intensive care, maternal complication and intrauterine death (p<0.001).

Conclusion: Our data show that the rates of perinatal and maternal complications are higher in the patients with early-onset preeclampsia. We believe that using new predictive biomarkers is necessary for early diagnosis and labor decision in women with preeclampsia diagnosis. Considering the genetic factors and racial and ethnic differences, multi-centered studies are needed to evaluate preeclampsia-related maternal and fetal complications.

Keywords: Preeclampsia, early-onset preeclampsia, late-onset preeclampsia, maternal outcomes, newborn outcomes.

 Özet: Çalışmamızın amacı, erken başlangıçlı ve geç başlangıçlı preeklampsi tanısı ile doğumu gerçeklesten olguların obstetrik, maternal ve fetal sonuçlarını değerlendirip ve karşılaştırmaktır.

Yöntem: Ocak 2013 – Ağustos 2017 arasında doğum yapan preeklampsi hastalarından toplandığı veriler, Derince Eğitim ve Araştırma Hastanesi’nde değerlendirildi. Her ikisi grup arasında, yenidoğan ağırlığı, düşük ağırlıkli bebek, yenidoğan, gelişir ve intrauterin ölüm açısından erken başlangıçlı preeklampsi aleyhitine istatistiksel olarak anlamlı fark saptandı (p<0.001).

Sonuç: Verilerimiz erken başlangıçlı preeklampsi hastalarında perinatal ve maternal komplikasyonların daha yüksek olduğunu göstermektedir. Preeklampsi tanısı konan kadınlarda erken tanı ve doğum kararları için yeni ön görgüci biyobelirtilerinin kullanılmasını gerektiği olduğunu düşünüyoruz. Genetik faktörler, ırk ve etnik farklılıklar göz önüne alındığında, preeklampsi ile ilişkili maternal ve fetal komplikasyonları değerlendirilirken için çok merkezli çalışmalarla ihtiyaç vardır.

Anahtar sözcükler: Preeklampsi, erken başlangıçlı preeklampsi, geç başlangıçlı preeklampsi, anneye ait sonuçlar, yenidoğana ait sonuçlar.
**Introduction**

Preeclampsia is a gestational disease affecting about 5–10% of pregnant women and increasing the rates of maternal and fetal mortality significantly. Hypertensive disorders are responsible for 14% of maternal mortality rates in the world. Due to the insufficient access to antenatal care services in the underdeveloped and developing countries, mortality rate related with preeclampsia and its complications increases much more.

Measuring blood pressure during prenatal period, the early gestational period or second trimester is quite important to establish the diagnosis of preeclampsia which may develop during pregnancy. High blood pressure and the presence of proteinuria which are found after 20 weeks of gestation in a pregnant woman used to be known normotensive is defined as preeclampsia. However, the presence of proteinuria is not always a must for preeclampsia diagnosis. In the lack of proteinuria, preeclampsia finding can also be established in cases where systemic findings (renal failure, liver dysfunction, pulmonary edema, cerebral and visual symptoms, hemolysis and the presence of thrombocytopenia) accompany hypertension.

The week of gestation when preeclampsia is identified is the most important clinical variable to predict both maternal and prenatal outcomes. When preeclampsia develops before 32 weeks of gestation, it causes 20 times higher maternal mortality than the term pregnancy. Increased maternal and fetal risks observed in the early-onset preeclampsia support the opinion that the pathophysiology of early-onset preeclampsia is different. It has been also reported that the risks of developing cardiovascular disease in the further lives of women who were diagnosed with early-onset preeclampsia are increased. Moreover, early-onset preeclampsia also affects fetal prognosis negatively. Placental dysfunction, intrauterine growth retardation, abnormal uterine and umbilical artery Doppler evaluation, low birth weight and multiple organ dysfunctions may be concurrent with fetal outcomes associated with prenatal death. Late-onset preeclampsia is considered mainly as a maternal disorder. It is frequently associated with a normal placenta, normal fetal development, normal uterine and umbilical artery Doppler evaluation, normal birth weight and more positive maternal and neonatal outcomes. Therefore, the opinion that early-onset preeclampsia mostly has more severe clinical course gains importance.

In pregnancies complicated with preeclampsia, many life-threatening maternal complications from ablation placenta, intracranial bleeding, liver failure, kidney failure, and disseminated intravascular coagulation to death can be seen. As it is a progressive disease, the only treatment option is to complete the pregnancy by delivery in order to prevent fetal and maternal complications. Delivery timing and delivery type should be determined according to the gestational age, preeclampsia severity, and maternal and fetal well-being.

The aim of this study is to compare patients who were diagnosed with early-onset and late-onset preeclampsia and delivered in our clinic according to their biochemical changes and prenatal and maternal outcomes.

**Methods**

The medical records of 223 patients who were diagnosed with preeclampsia and delivered in the Clinic of Gynecology and Obstetrics of Derince Training and Research Hospital, Health Sciences University between 2013 and 2018 were analyzed retrospectively. The medical records of 149 patients whose files were accessed from hospital database and patient files were analyzed and 13 of them were excluded from the study due to their concomitant diseases (diabetes, autoimmune disease, chronic hypertension).

The diagnosis of preeclampsia was established according to the criteria of ACOG (American College of Obstetricians and Gynecologist). According to these criteria, (1) the presence of 140–159 mmHg or higher persistent systolic blood pressure (BP) or 90–109 mmHg or higher diastolic BP which develops after 20 weeks of gestation in a woman who previously had normal blood pressure, (2) concomitant systemic findings (proteinuria >300 mg/24-hour, thrombocytes <100,000/ dL, at least 2 times increase of transaminase level, creatinine value >1.1 mg/dL, presence of pulmonary edema, presence of cerebral or visual symptoms) in addition to blood pressure of 160/100 mmHg or above with an interval of 15 minutes, and (3) measuring blood pressure ≥160/100 mmHg with 4-hour interval in addition to minimum one systemic finding were considered preeclampsia. When it was found that hemolysis, lactate dehydrogenase was >600 IU/L, total bilirubin was >1.2 mg/dL, aspartate aminotransferase (AST) was >70 IU/L, and thrombocytes were <100,000 cell/mm³ in a patient with preeclampsia, the diagnosis of HELLP syndrome was
established. The cases found to have new-onset grand mal seizures were considered eclampsia.

All blood pressure measurements were carried out by a sleeve sphygmomanometer at sitting position as the arm is on heart level.

Although the presence of proteinuria is not among the definitive diagnosis criteria of preeclampsia, we included proteinuria values of our patients in our study. The protein amount in 24-hour urine obtained from patients was measured with precipitation method by using trichloroacetic acid (TCA) (the collected urine amount was measured and 5 ml of it was put in graduated conic tube; by adding 2.5 ml TCA, it was centrifuged at 3500–4000 rpm; the precipitation level obtained was measured and its equivalent value in nomogram was recorded as g/l). Presence of protein more than 300 mg/L in 24-hour urine was considered proteinuria. The presence of proteinuria was evaluated by dipstick test in patients who admitted under emergency conditions and taken to delivery room for labor. In dipstick proteinuria test, the presence of protein $\geq 1+$ was considered proteinuria.

Week of gestation was determined according to crown-rump length (CRL) measurement performed between 8 and 16 weeks of gestation. The patients were categorized in 2 groups according to the week of gestation when preeclampsia developed. The preeclampsia developed before 34 weeks of gestation was defined early-onset, and it was defined late-onset when it developed after 34 weeks of gestation.

Of the pregnant women in both groups, the weeks of gestation when the patients were diagnosed with preeclampsia, their blood pressure measurements when they were diagnosed with preeclampsia, weeks of gestation at labor, delivery types, birth weights, fetal (low birth weight, newborn’s need for intensive care unit, intrauterine death) and maternal (eclampsia, detachment, HELLP syndrome) complications were recorded. The data of the patients on hemogram, routine biochemistry (liver function tests, kidney function tests, total), and the presence of proteinuria which were obtained by file screening were recorded.

All data obtained from the study were analyzed by using “Statistical Packages for the Social Science” (SPSS) 11.5 (SPSS Inc., Chicago, IL, USA) statistics software on Windows operating system. After definitive statistical analyses (frequency, percentage distribution, mean±standard deviation), the conformity of variables to normal distribution was evaluated by Shapiro-Wilks test. Pearson’s chi-squared test was used for the comparisons of categorical variables. $p<0.05$ was considered statistically significant.

**Results**

The demographic characteristics and laboratory findings of the patients in the early-onset preeclampsia and late-onset preeclampsia groups included in the study are shown in Table 1. Fifty-one (78.5%) patients diagnosed

<table>
<thead>
<tr>
<th></th>
<th>Early-onset PE</th>
<th>Late-onset PE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±SD</td>
<td>Min–max</td>
</tr>
<tr>
<td>Age (year)</td>
<td>30.1±6.7</td>
<td>-</td>
</tr>
<tr>
<td>Gravida</td>
<td>2.1±1.5</td>
<td>-</td>
</tr>
<tr>
<td>Parity</td>
<td>0.9±1.2</td>
<td>-</td>
</tr>
<tr>
<td>Week of gestation at diagnosis</td>
<td>31.3±2.6</td>
<td>23–34</td>
</tr>
<tr>
<td>SBP (mm/Hg)</td>
<td>161.5±17.7</td>
<td>130–220</td>
</tr>
<tr>
<td>DBP (mm/Hg)</td>
<td>100.9±10.9</td>
<td>80–130</td>
</tr>
<tr>
<td>SGOT (IU/L)</td>
<td>26.3±43.3</td>
<td>6–234</td>
</tr>
<tr>
<td>SGPT (IU/L)</td>
<td>29.4±34.5</td>
<td>10–198</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.6±0.1</td>
<td>0.3–1.4</td>
</tr>
<tr>
<td>LDH (IU/L)</td>
<td>289.8±122.7</td>
<td>148–762</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>11.8±1.4</td>
<td>8.3–14.3</td>
</tr>
<tr>
<td>Thrombocyte (cell/m$^3$)</td>
<td>204.5±73.8</td>
<td>32–448</td>
</tr>
</tbody>
</table>

DBP: diastolic blood pressure; LDH: lactate dehydrogenase; PE: preeclampsia; SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamic pyruvic transaminase; SBP: systolic blood pressure.
with early-onset preeclampsia and 84 (100%) patients diagnosed with late-onset preeclampsia had proteinuria (p<0.001). Compared to the infants of pregnant women diagnosed with late-onset preeclampsia, the infants of pregnant women diagnosed with early-onset preeclampsia had higher rates of newborn’s need for intensive care and intrauterine death, which was statistically significant. Similarly, maternal complication rate was higher in the group diagnosed with early-onset preeclampsia (Table 2).

Discussion

Preeclampsia is a progressive disease specific to the last half of pregnancy. Examining symptoms and findings specific to the disease during routine antenatal visits is important in terms of preventing maternal and fetal mortality and morbidity.[8]

In our study, we defined the preeclampsia developing before 34 weeks of gestation as “early-onset” while the preeclampsia developing after 34 weeks of gestation as “late-onset”. While some studies have used this classification,[10,11,15] some studies defined early-onset preeclampsia when it developed before 37 weeks of gestation.[16]

In our study, 43.6% (n=65) of preeclampsia patients were early-onset and 56.4% (n=85) of them were late-onset. The studies performed in the past years support the idea that early-onset preeclampsia and late-onset preeclampsia may be different diseases associated with different biochemical markers, risk factors, clinical characteristics and hemodynamic conditions.[17,18]

Although the etiology of preeclampsia has not been fully clarified yet, one of the most prominent hypotheses is placental angiogenesis and uteroplacental failure associated with the incomplete placental development.[19] In the early-onset preeclampsia, abnormal placentation and insufficient remodeling in spiral artery are seen specifically; however, these conditions are rarely seen in late-onset preeclampsia.[20]

The previous studies showed that early-onset preeclampsia is significantly associated with high rates of perinatal mortality and morbidity.[20] Quaker et al. found that stillbirth rate decreases as the week of gestation progresses. In their studies, the authors reported that the rate of stillbirth associated with preeclampsia is 0.52%, and that the risk of fetal death associated with preeclampsia starts when preeclampsia becomes clear clinically.[21] In the study of Kumru et al., the authors found the rate of intrauterine death 6.1% in severe preeclampsia cases.[22] Consistent with the literature, we observed intrauterine death in 4 (6.2%) of the cases with early-onset preeclampsia in our study while there was no stillbirth in late-onset preeclampsia group.

Table 2. Labor characteristics and maternal and fetal outcomes of two groups.

<table>
<thead>
<tr>
<th></th>
<th>Early-onset PE</th>
<th></th>
<th>Late-onset PE</th>
<th></th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=65</td>
<td>Mean±SD</td>
<td>Min–max</td>
<td>n=84</td>
<td>Mean±SD</td>
</tr>
<tr>
<td>Week of gestation during labor</td>
<td></td>
<td>33.3±2.8</td>
<td>26–39</td>
<td>38.1±1.3</td>
<td>35–42</td>
</tr>
<tr>
<td>Newborn’s birth weight (g)</td>
<td></td>
<td>1959.0±81.7</td>
<td>510–2880</td>
<td>3240±565.1</td>
<td>2015–5210</td>
</tr>
<tr>
<td>Delivery type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSD</td>
<td>4</td>
<td>6.2</td>
<td>10</td>
<td>11.9</td>
<td>0.270</td>
</tr>
<tr>
<td>CS</td>
<td>61</td>
<td>93.8</td>
<td>74</td>
<td>88.1</td>
<td>0.347</td>
</tr>
<tr>
<td>Primary CS</td>
<td>50</td>
<td>78.1</td>
<td>59</td>
<td>70.2</td>
<td></td>
</tr>
<tr>
<td>Fetal complication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low birth weight</td>
<td>17</td>
<td>26.2</td>
<td>10</td>
<td>12.0</td>
<td>0.270</td>
</tr>
<tr>
<td>Newborn’s need for ICU</td>
<td>25</td>
<td>38.5</td>
<td>4</td>
<td>4.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intrauterine death</td>
<td>4</td>
<td>6.2</td>
<td>0</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maternal complication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Eclampsia</td>
<td>3</td>
<td>4.6</td>
<td>1</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Abruptio</td>
<td>3</td>
<td>4.6</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>HELLP syndrome</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1.2</td>
<td></td>
</tr>
</tbody>
</table>

CS: cesarean section; ICU: intensive care unit; NSD: normal spontaneous delivery; PE: preeclampsia.
Some investigators argue that early-onset preeclampsia is a part of severe preeclampsia. In our study, we found significantly high rate of maternal complication in the early-onset preeclampsia group. We found ablato placentae and eclampsia in 3 (4.6%) of the patients in the early-onset preeclampsia group, but they were uncontrollable complications as these patients were not being followed up. While there was no difference between the incidences of early-onset and late-onset preeclampsia complicated with HELLP syndrome, we found HELLP syndrome only in 1 patient in the late-onset preeclampsia group in our study.

In 2014, Doddamani et al. reported in their study that perinatal mortality rate increase in direct proportion to the severity of preeclampsia and that the newborn's need for intensive care is 26.6%. In terms of the newborn's need for intensive care unit, we found this rate 38.5% in the cases with early-onset preeclampsia and 4.8% in the cases with late-onset preeclampsia. We believe that the high rate of newborn's need for intensive care in the early-onset preeclampsia group according to the literature is associated with the high rate of cesarean section.

A retrospective cohort study conducted in 2002 reported that birth weights of the newborns of mothers diagnosed with preeclampsia were lower compared to the weeks of gestation in a statistically significant level, but the birth weights of the newborns delivered by preeclamptic pregnant women at 37 weeks of gestation were within normal range. In our study, 17% of the pregnant women with early-onset preeclampsia and 10% of the pregnant women with late-onset preeclampsia delivered newborns with low birth weights. However, these results did not reach a statistically significant level (p<0.270). The literature does not support this result of our study. We think that this result depends on the impacts of ethnic, environmental and genetic factors on newborn birth weights and the low number of patients included in our study group.

It is known that the only treatment option of preeclampsia is to complete the pregnancy by delivery. However, if the labor is completed on time and delayed, maternal (cerebral hemorrhage, hepatic rupture, kidney failure, pulmonary edema, DIC, ablato placentae, etc.) and fetal complications (intrauterine growth retardation, intrauterine death, etc.) become inevitable. NICE clinical guidelines and ACOG recommend conservative treatment by close fetal and maternal monitorization if fetal and maternal conditions are stable during early weeks of gestation in order to avoid fetal sequels associated with premature labor. However, conservative treatment may also cause complications such as maternal mortality and intrauterine death since the preeclampsia is a progressive disease. In our study, we did not find maternal mortality in either group despite the increased newborn’s need for intensive care due to the increased rate of premature labor.

There is different information in the literature about delivery types of preeclampsia cases. Zhang et al. carried out labors by cesarean section in more than half of their patients with preeclampsia and eclampsia. Kumru et al. reported labor by cesarean section in 51.5% of the severe preeclamptic cases. In our study, cesarean section rate is quite higher than the rates reported in the literature. The primary cesarean section rate in study was 78.1% in the early-onset preeclampsia group and 70.2% in the late-onset preeclampsia group. We believe that the patients that we followed up due to preeclampsia should be reconsidered in terms of delivery type in the light of the literature.

It is known that preeclampsia is a multisystemic disease which can develop with liver and kidney dysfunctions. During gestation, blood urea nitrogen (BUN), creatinine and uric acid levels are reliable markers to evaluate the glomerular filtration rate. The studies performed in the past years showed that blood urea nitrogen, creatinine and uric acid are significantly higher in pregnant women who were diagnosed with early-onset and late-onset preeclampsia presenting with severe hypertension than the healthy pregnant women. However, there is no statistically significant difference in the renal functions between the early-onset and late-onset preeclampsia patients. In our study, we found creatinine levels statistically higher in the early-onset preeclampsia group (p=0.045). We think that this statistical difference in the creatinine levels is caused by higher maternal complication rates in the early-onset preeclampsia group. However, new biomarkers are needed to predict the early diagnosis of preeclampsia and to guide us for labor decision.

**Conclusion**

In our study, we showed that perinatal outcomes (intrauterine death, newborn’s need for intensive care) and maternal complications (ablato placentae, eclampsia)
are higher in the patients with early-onset preeclampsia. We believe that the patients should be followed up closely in primary and secondary hospitals in terms of early diagnosis in order to decrease the rates of maternal complications associated with preeclampsia much more. In order to decrease the newborn’s need for intensive care that we found higher rates in our study compared to the literature and to prevent associated fetal complications, hospitalizing patients and following up closely, determining time and type of delivery according to the progression will contribute to the decrease of maternal and fetal mortality rates.

Conflicts of Interest: No conflicts declared.

References

Evaluation of the use of iodized salt by pregnant women and their knowledge on the use of iodized salt

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2Department of Nursing, Faculty of Health Sciences, Tokat Gaziosmanpaşa University, Tokat, Turkey
3Department of Nursing, Faculty of Health Sciences, Erciyes University, Kayseri, Turkey

Abstract

Objective: The aim of our study is to evaluate the use of iodized salt by pregnant women and their knowledge on the use of iodized salt.

Methods: The study is of descriptive type. The sample of the study consisted of 347 pregnant women. The data of the study was collected by using a data form developed by researchers. The data obtained by the study was analyzed by means of SPSS package software.

Results: Of the pregnant women included in the study, the mean age was 27.38±6.44 years old, 41.8% were living in urban areas, 34.6% were graduated from secondary school, 50.4% had income equal to their expenses, and 43.8% had husbands who were workers. It was found that 74.1% of the pregnant women had no knowledge on iodine deficiency and associated diseases, 65.7% of them did not know the importance of protection against iodine deficiency, and 68.6% of the pregnant women did not receive information for the use of iodized salt during pregnancy.

Conclusion: In conclusion, we found that the use of iodized salt during pregnancy and knowledge on the use of iodized salt are insufficient. We can say that pregnant women need training on the use of iodized salt, the time for adding salt into meals and methods for preserving salt.

Keywords: Pregnancy, iodized salt, iodine insufficiency.

Introduction

Cardiovascular system (14.6%) and endocrine system diseases (14.5%) are the leading diseases threatening women’s health. Thyroid gland diseases are the most common disorders among endocrine system diseases with a rate of 5.6%.[1]

Physiological changes during pregnancy affect the activities of thyroid gland. The incidence of hypo-
hypothyroidism during pregnancy is reported 2–3%. [5] However, the incidence of undiagnosed hypothyroidism and hyperthyroidism is higher. The rate of hypothyroidism during pregnancy is consistent with the literature in two studies performed in Turkey; [14,15] however, Güzel et al. found it 15.8% in their studies. [5] Hypothyroidism during pregnancy affects maternal and fetal health negatively. The most common reason for hypothyroidism is iodine deficiency. The synthesis of thyroid hormones depends on the penetration of sufficient amount of iodine into thyroid, normal iodine metabolism in the thyroid and normal thyroglobulin synthesis. [6] Insufficient iodine intake may cause maternal hypothyroidism, insufficient fertilization, pre eclampsia, postpartum hemorrhage, anemia, miscarriage risk, low birth weight, stillbirth, congenital anomalies, fetal neurological development disorders, microcephaly, cretinism and similar outcomes. [16,17] It may also cause goiter and congenital hypothyroidism in the newborn. [18,19] It is reported that iodine deficiency is the most common reason for preventable mental retardation in the world. [20] It is also reported that there is an increase in the mortality risk of newborns associated with the iodine deficiency. [10,11,12] Congenital hypothyroidism is one of the most common endocrine diseases of newborns. [13] Chronic thyroid hormone deficiency is seen in one per 3500–4000 newborns in the world and per 2525 children in Turkey. [14,15]

Iodine need increases during pregnancy and therefore iodine intake should be increased to meet increasing need. [21] World Health Organization recommends 250 mcg of iodine intake daily for pregnant women. [14] Urinary iodine, which is the best indicator for iodine level, should be >100–200 mcg/L in pregnant women, and therefore it is recommended to take 250–300 mcg iodine daily by means of iodized salt, sea products and iodine-rich foods. [2] However, it is seen that mean daily iodine intake is 66.4 mcg for pregnant women and 65.7 mcg for breastfeeding women in Turkey. [17] It has been found in the studies performed in Turkey that pregnant women have iodine deficiency. [2,18–21]

In Turkey, iodine deficiency is an endemic problem in all regions and iodine deficiency is associated with the insufficient intake by diet. “The Program of Preventing Iodine Deficiency Diseases and Iodizing Salt” has been carried out since 1995 in Turkey to fight against iodine deficiency, and it has been made obligatory to iodize table salt by legal regulations as of 1998 in accordance with this program. Food industry salt is not iodized. It is highlighted that the iodine needs (200–250 mcg/day) of women planning pregnancy, pregnant women and breastfeeding women whose salt intake should be restricted due to various reasons should certainly be met. [17]

Although it has been 20 years for the obligatory iodization of salt, it is seen in various studies that iodine deficiency is still a risk for the health of mothers and children. This shows us that the process of iodizing salt is not sufficient alone to eliminate iodine deficiency, and that it is necessary to inform individuals / pregnant women about the use of iodized salt. It is considered that determining the use of iodized salt by pregnant women and their knowledge on the use of iodized salt in order to prevent thyroid dysfunctions associated with iodine insufficiency and to protect the health of mothers and newborns would guide the initiatives to be planned for identifying and resolving the problem.

Methods

The study is of descriptive type and it was conducted in the Maternity Clinic of Nevşehir State Hospital of Nevşehir Public Hospital Association. The sample of the study consisted of 3637 pregnant women who admitted to this hospital in a year. The sample size was calculated by using the method of sampling from known population. As the number of individuals in the population is known, sample size was calculated by the following formula:

\[ n = \frac{N \cdot t^2 \cdot pq}{d^2 \cdot (N-1) + t^2 \cdot pq} \]

\( n \) = sample size, \( N \) = number of individuals in the target population (3637), \( n \) = number of individuals to be sampled, \( p \) = prevalence of the case investigated (probability of occurrence) (0.50), \( q \) = non-prevalence of the case investigated (probability of non-occurrence) (0.50), \( t \) = theoretical value found from t table at a particular independent level and identified margin of error was considered 1.96 at 95% significance level, \( d \) = desired level according to the prevalence ± deviation, 0.05 margin of error (5% deviation)

Random sampling method was used to collect the data. The data of the research was collected by using a data collection form prepared by reviewing the literature by the researchers. Pregnant women who knew Turkish and had no problems with verbal communication were included in the study. The data was collected by face to
face interview in the maternity clinic by the researchers. The participation in the study was on voluntary basis, and the purpose of the study and participation on voluntary basis were explained to the pregnant women. Pregnant women who accepted to participate were applied data collection form. SPSS package software was used to analyze the study data. Descriptive statistics (number and percentage) were used to evaluate the data.

It was paid attention to comply with ethical principles in all stages of the study. Before starting the study, the ethics committee approval (no. 2014.12.05) was obtained from Ethics Committee of Nevşehir Hacı Bektaş Veli University and written approval was obtained from Nevşehir State Hospital of Nevşehir Public Hospital Association. Also, before filling data forms, the verbal consents of pregnant women were obtained after informing them about the purpose of the research.

Results
Of the pregnant women who participated in the study, 24.2% were between 21 and 25 years old, 41.8% were living in city center, 34.6% were graduated from secondary school, 80.7% were housewives, 50.4% had income equal to their expenses, and 43.8% had husbands who were workers. It was also found that it was first pregnancy in 27.7% of the pregnant women, 35.4% of them had 4 and more pregnancy, 11% of them had preterm labor, 27.7% of them had the history of miscarriage/curettage, and 3.5% of them had stillbirth.

It was found that 4.9% of the pregnant women had thyroid disorder, all pregnant women who had thyroid disorder had hypothyroidism (n=17), and 9.8% of them had a history of thyroid disorder in their families and the mothers of 76.5% of these pregnant women had a history of disease.

Of the pregnant women who participated in the study, 35.7% stated that they did not know the importance of protecting themselves against iodine deficiency and 65.7% stated that they did not know the necessity of using iodized salt during pregnancy. Of the pregnant women who knew the necessity of using iodized salt during pregnancy, 43.6% stated that it was necessary for the brain development of baby. Although 55.9% of the pregnant women reported that they were using iodized salt, 62% of them said that they did not pay attention if the salt they purchase is iodized or not. Also, 40.2% of the pregnant women using iodized salt said that they did not know why they need to use iodized salt (Table 1).

While 45.9% of the pregnant women using iodized salt kept it in glass jar with lid and 69.6% of them paid attention to keep iodized salt away from the sunlight, only 46.1% of them could properly explain why it should be kept away from sunlight (as vitamin/mineral would be lost, chemical structure of iodine would be damaged) (Table 2).

### Table 1. The distribution of pregnant women in terms of iodized salt use (n=347).

<table>
<thead>
<tr>
<th>Use of iodized salt</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>I use</td>
<td>194</td>
<td>55.9</td>
</tr>
<tr>
<td>I do not use</td>
<td>153</td>
<td>44.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Paying attention to purchase iodized salt</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>132</td>
<td>38.0</td>
</tr>
<tr>
<td>No</td>
<td>215</td>
<td>62.0</td>
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</table>

<table>
<thead>
<tr>
<th>Salt type used at home</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rock salt</td>
<td>144</td>
<td>41.5</td>
</tr>
<tr>
<td>Sea salt</td>
<td>7</td>
<td>2.0</td>
</tr>
<tr>
<td>Himalayan salt</td>
<td>2</td>
<td>0.6</td>
</tr>
<tr>
<td>Iodized salt</td>
<td>194</td>
<td>55.9</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>The reason for using iodized salt (n=194)</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>I do not know why I have to use it</td>
<td>78</td>
<td>40.2</td>
</tr>
<tr>
<td>I believe that it is healthier</td>
<td>67</td>
<td>34.5</td>
</tr>
<tr>
<td>Because it is beneficial</td>
<td>32</td>
<td>16.5</td>
</tr>
<tr>
<td>Because it is good for goiter</td>
<td>17</td>
<td>8.8</td>
</tr>
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<table>
<thead>
<tr>
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<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Always</td>
<td>142</td>
<td>73.2</td>
</tr>
<tr>
<td>From time to time</td>
<td>48</td>
<td>24.7</td>
</tr>
<tr>
<td>I started to use during pregnancy</td>
<td>4</td>
<td>2.1</td>
</tr>
</tbody>
</table>

### Table 2. The distribution of iodized salt according to proper using/keeping conditions among pregnant women using iodized salt.

<table>
<thead>
<tr>
<th>Location where iodized salt is kept (n=194)</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original packaging</td>
<td>6</td>
<td>3.1</td>
</tr>
<tr>
<td>Glass jar with lid</td>
<td>89</td>
<td>45.9</td>
</tr>
<tr>
<td>Light-proof jar with lid</td>
<td>85</td>
<td>43.8</td>
</tr>
<tr>
<td>Open salt shaker</td>
<td>14</td>
<td>7.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Paying attention to keep iodized salt away from sunlight (n=194)</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pays attention</td>
<td>135</td>
<td>69.6</td>
</tr>
<tr>
<td>Does not pay attention</td>
<td>59</td>
<td>30.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>The reason for keeping iodized salt away from sunlight (n=194)</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No reason</td>
<td>27</td>
<td>13.9</td>
</tr>
<tr>
<td>I do not know</td>
<td>37</td>
<td>19.1</td>
</tr>
<tr>
<td>To keep away from moisture</td>
<td>36</td>
<td>18.6</td>
</tr>
<tr>
<td>Because vitamin/mineral would be lost</td>
<td>18</td>
<td>9.3</td>
</tr>
<tr>
<td>Because chemical structure of iodine would be damaged</td>
<td>68</td>
<td>35.0</td>
</tr>
<tr>
<td>Its odor would change under sunlight</td>
<td>8</td>
<td>4.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time to add salt into meals (n=347)</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>After the meal is cooked</td>
<td>58</td>
<td>16.7</td>
</tr>
<tr>
<td>During the cooking</td>
<td>289</td>
<td>83.3</td>
</tr>
</tbody>
</table>
Of the pregnant women, 69.7% use tap water as drinking water, 92.5% use tap water in their meals while 72.1% do not know iodine-rich foods. Of those who know iodine-rich foods, 79.4% believe that sea products are iodine-rich, but 73.2% of the pregnant women do not pay attention to consume iodine-rich foods during pregnancy (Table 3).

On the other hand, it was found that the pregnant women rarely consume foods which are poor in iodine (kale, cabbage, turnip, white turnip), and only consume milk and dairy products more frequently as iodine-rich foods.

Of the pregnant women, 31.4% stated that they were informed about the use of iodized salt during pregnancy and 67.9% of these pregnant women were informed by healthcare professionals. Also, 58.7% of the pregnant women stated that they were informed about the benefits of iodine on health.

**Discussion**

Preventing iodine deficiency is important to protect the health of mother and baby. Using iodized salt has an important role on the prevention of iodine deficiency diseases. The Communique of Turkish Food Codex on Edible Salt was published in 1998. With this communique, it was obliged to enrich table salt by iodine in Turkey. In our study, 55.9% of the pregnant women stated that they use iodized salt. It is seen in the studies on the use of iodized salt during pregnancy that the rate of using iodized salt varies between 26.1% and 96% among the pregnant women.

In our study, we found that almost half of the pregnant women were not using iodized salt. This result of our study is important in terms of showing the fact that the knowledge on the use of iodized salt by pregnant women is insufficient or these pregnant women are not aware of its importance.

In our study, 51% of the pregnant women stated that they are using iodized salt as it is more beneficial and healthier. In the study of Şenbayram, 50% of pregnant women explained the reason for using iodized salt as it is beneficial and healthy. Seventy-seven percent of the pregnant women in the study of Kirkizoglu and Pekcan and 93.9% of the pregnant women in the study of Köksal and Pekcan stated that they did not know why they should use iodized salt. In our study, almost half of the pregnant women use iodized salt and half of those using iodized salt do not know why they use it. This result shows that pregnant women have insufficient knowledge about the use of iodized salt. Iodine deficiency is a significant condition for the health of mother, fetus and newborn. Iodine deficiency may cause insufficient fertilization, preeclampsia, postpartum hemorrhage, anemia, and miscarriage risk in women, and low birth weight, stillbirth, congenital anomalies, microcephaly, cretinism and similar outcomes in fetuses. It may also cause goiter and hypothyroidism in the newborn. In our study, 70.9% of the pregnant women stated that they did not know the importance of protection against iodine deficiency and they did not do anything for it. This rate was 12% in the study of Şenbayram. Compared to the study of Şenbayram, we believe that this difference in the rates might be because of the low education and employment levels of women in our study.

Iodized salt should be kept in a cool, dry environment without light and in dark colored glass containers in order to prevent iodine loss. In our study, 45.9% of the pregnant women expressed that they are keeping salt in glass jar with lid. While 71.6% of the pregnant

<table>
<thead>
<tr>
<th>Table 3. The distribution of pregnant women in terms of iodine intake and nourishment characteristics (n=347).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Using tap water (n=347)</strong></td>
</tr>
<tr>
<td>Bottle water</td>
</tr>
<tr>
<td>Tap water</td>
</tr>
<tr>
<td>Purified water</td>
</tr>
<tr>
<td><strong>Water added into meals (n=347)</strong></td>
</tr>
<tr>
<td>Bottle water</td>
</tr>
<tr>
<td>Tap water</td>
</tr>
<tr>
<td>Purified water</td>
</tr>
<tr>
<td><strong>The knowledge about iodine-rich foods (n=97)</strong></td>
</tr>
<tr>
<td>She knows</td>
</tr>
<tr>
<td>She does not know</td>
</tr>
<tr>
<td><strong>The foods known as iodine-rich (n=97)</strong></td>
</tr>
<tr>
<td>Dairy products</td>
</tr>
<tr>
<td>Sea products</td>
</tr>
<tr>
<td>Green vegetables</td>
</tr>
<tr>
<td>Legumes</td>
</tr>
<tr>
<td>Red meat and meat products</td>
</tr>
<tr>
<td><strong>Paying attention to consume iodine-rich foods during pregnancy (n=347)</strong></td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td><strong>Iodine-rich foods consumed by pregnant women (n=93)</strong></td>
</tr>
<tr>
<td>Dairy products</td>
</tr>
<tr>
<td>Sea products</td>
</tr>
<tr>
<td>Green vegetables</td>
</tr>
<tr>
<td>Legumes</td>
</tr>
<tr>
<td>Red meat and meat products</td>
</tr>
</tbody>
</table>
women in the study of Akın were keeping salt in glass jar,[25] 76% of the pregnant women in the study of Özkan were keeping salt in a cool, closed environment without any sunlight.[26] 19.1% of the pregnant women in the study of Şenbayram and 13.9% of the pregnant women in the study of Ulu stated that they were keeping salt in light-proof jars which are the ideal containers.[1,2,25] In our study and many other studies, we can see that most of the pregnant women do not keep salt under proper conditions. Iodine loss occurs in salts which are not kept under proper conditions, and it results in the problems associated with iodine deficiency even iodized salt is used.

Iodine is a substance which is affected by heat, moisture and other climatic conditions. Since iodized salt loses approximately 50% of its content when cooked, it is recommended to add iodized salt after the meal is prepared.[11] In our study, 83.3% of the pregnant women reported that they add salt into the meal during cooking. Of the pregnant women, 67.7% in the study of Ulu[25] and 91.5% in the study of Özkan[26] stated that they add salt into meal before starting to cook. In the study of Şenbayram, 16.3% of the pregnant women said that they add salt into the pot after the meal is cooked.[11] It is seen both in our study and other studies conducted on this topic that iodized salt is not added during the recommended times. The presence of iodine deficiency despite the high consumption of salt in Turkey shows that the salt used is not iodized and/or individuals have insufficient knowledge about the proper use of iodized salt.

Iodine is a trace element which penetrates into the structure of thyroid hormones and is essential for the normal activity of thyroid hormones that are necessary for the normal growth and neurological development of fetus during the pregnancy.[2] According to the report of WHO/ICCIDD in 2007, the best method for iodine replacement in pregnant women is to iodize salt.[14] Turkey is a region with moderate/severe level of iodine deficiency and endemic goiter.[15] Iodine need increases during pregnancy, and iodine deficiency during pregnancy may disrupt thyroid hormone production, affect physical and mental development of fetus negatively, and increase mortality risk of newborn.[11] In our study, 25.4% of the pregnant women expressed that the use of iodized salt during pregnancy is necessary and 8.8% of them associated this necessity with thyroid gland.

In our study, 4.9% of the pregnant women had hypothyroidism. Bostancı and Taşkesen reported in their study conducted on pregnant women that the rate of hypothyroidism was 2.8%.[14] This rate was 15.8% in the study of Güzel et al.,[16] 2.8% in the study of Şenbayram,[15] and 1.8% in the study of Fadayev et al.[11] According to 2017 report of Turkish Endocrinology and Metabolism Society, hypothyroidism prevalence during pregnancy was 0.3–0.5% for overt hypothyroidism and 2–3% for sub-clinical hypothyroidism.[2] Hypothyroidism rate of pregnant women in our study was higher than other studies. The iodine concentration of local drinking water is also another indicator of the iodine content of soil. While the iodine content in iodine-poor regions is usually below 2 μg/L, it is 9.0 μg/L and above in the regions which are not iodine-poor.[25] The Public Health Laboratory of the region where the study was conducted reports that the tap water of the city has insufficient iodine. In our study, 92.5% of the pregnant women stated that they use tap water. Of the pregnant women, 46.6% in the study of Akın, 50.5% in the study of Özkan and 37.8% in the study of Ulu were using tap water.[25,27,28] Absence of iodine in the tap water is important in terms of revealing iodine deficiency and iodine-related problems. This finding of the study highlights the importance of planning and providing training about the use of iodized salt to people who live in iodine-poor regions. The iodine need of fetus is met by maternal iodine transferred transplacentally.[14] Iodized salt, sea products and particularly fish, milk and dairy products are the most important iodine resources.[15] The rate of the cases consuming dairy products daily is 56.5% in our study. According to the results of 2016 Turkish Nourishment and Health Survey (TBSA), the rate of those drinking milk daily was 28.4%.[17] Yavuz and Akyut found in their study that 48.8% of the pregnant women were consuming appropriate amounts of milk and dairy products.[28] While 82.9% of the pregnant women in the study of Noğay were consuming milk,[17] this rate was 69.6% in the study of Akın.[25] The studies carried out have similar results compared to our study, and the rate of pregnant women consuming milk and dairy products is insufficient. Consuming insufficient amount of milk and dairy products is a significant indicator showing insufficient intake of iodine resources.

Antithyroid compounds in some foods may cause iodine deficiency by blocking iodine transfer in thyroid gland. The most important resources for antithyroid compounds are cauliflower, cabbage, Brussels sprout, turnip, white turnip and similar vegetables.[27] The pregnant women in our study rarely consume these vegeta-
bles. In the study of Akin, the authors reported that 45.1% of the pregnant women consume cabbage, 13.4% of them consume white turnip and 38.2% of them consume turnip. Excessive consumption of these vegetables cause insufficient intake or use of iodine by the body; however, the consumption of these vegetables is not considered as risky as causing iodine deficiency in terms of consumption frequency. Iodine mainly exists in the soil; most of the iodine in the world is taken from the surface by glaciers, snow and rains and carried into oceans by winds, rivers and floods. Therefore, seaweeds and sea products are rich in iodine. In our study, 14.1% of the pregnant women were consuming fish for a few days per week. According to 2010 data of Turkish Nourishment and Health Survey, 79% of the pregnant women consume sea products. In the study of Noğay, 87.1% of the pregnant women were consuming fish and only 52.9% of them were consuming fish for 1–2 times a week. In the previous studies and our study, it is seen that pregnant women do not consume iodine-rich sea products regularly and sufficiently. Of the pregnant women, only 31.4% stated that they were informed about the use of iodized salt during pregnancy and 67.9% of these informed pregnant women received this information from healthcare professionals. In our study, 14.1% of the pregnant women were consuming fish at least once during their pregnancy. Akin et al. reported in their study that 73.9% of the pregnant women consume sea products. In the study of Şenbayram, these rates were 73% and 37%, respectively. The fact that approximately one third of the pregnant women were informed about the use of iodized salt and two third of informed pregnant women received this information from healthcare professionals indicates that the information they receive may be insufficient and incorrect. The low level of iodized salt use and insufficient level of knowledge about the significance of iodized salt can be explained with the insufficient information received.

**Conclusion**

We found in our study that 74.1% of the pregnant women had no knowledge on iodine deficiency and associated diseases, 35.7% of them did not know the importance of protection against iodine deficiency, and 65.7% of them did not know the necessity of using iodized salt during pregnancy. Also, we found that 44.1% of the pregnant women included in the study did not use iodized salt, 56.2% of those using iodized salt did not keep it in a proper way, and 16.7% of them added iodized salt into their meal after prepared. We found that 68.6% of the pregnant women did not receive information for the use of iodized salt during pregnancy. In conclusion, we found that the use of iodized salt during pregnancy and knowledge on the use of iodized salt are insufficient.

Beginning from the pregestational period, pregnant women and their families should be informed about the use and importance of iodized salt during pregnancy, studies should be planned to determine the knowledge of healthcare professionals about the use of iodized salt, nurses should perform house visits to inform pregnant women and observe the use of iodized salt conditions on-site and repeat their trainings if necessary.

**Conflicts of Interest:** No conflicts declared.

**References**


The impact of using thromboprophylactic medication by pregnant women on the hemodynamics of fetus and uterus

Emre Zafer

Department of Gynecology and Obstetrics, Faculty of Medicine, Aydın Adnan Menderes University, Aydın, Turkey

Abstract

Objective: To define potential effects of anticoagulants at prophylactic doses due to various reasons during pregnancy on the blood flow of fetus and uterus.

Methods: In this prospective monocenter study, blood flow parameters of umbilical artery (UmA), middle cerebral artery (MCA) and uterine artery (UtA) of pregnant women, who were at second and third trimesters and were using anticoagulants (low-molecular-weight heparin-LMWH and/or acetylsalicylic acid-ASA), were evaluated by Doppler ultrasonography. The pregnant women who were at similar ages and weeks of gestation and not using anticoagulants were selected as the control group. Two groups were compared by “independent samples t-test” and “Mann–Whitney U test” in terms of clinical, demographic and Doppler findings. In the sub-group analysis, only the cases using LMWH and LMWH+ASA were compared to the control group.

Results: A total of 63 cases were included in the study. No statistically significant difference was found in the comparison of demographic and clinical data of 36 (57.1%) pregnant women using anticoagulant and 27 (42.9%) pregnant women not using any anticoagulant except the presence of poor obstetric history (p<0.001). There was no difference between two groups in terms of Doppler data on the arteries studied (p>0.005). However, when the groups were compared in terms of their trimester period, it was found that 3rd trimester MCA PSV values of anticoagulant group was significantly different than of the control group (p<0.005). It was found in the anticoagulant sub-group analysis that the concomitant use of LMWH and ASA caused a significant change in MCA PSV values (p=0.006).

Conclusion: We found that the use of LMWH or ASA during pregnancy did not cause any significant change which can be seen by Doppler in the hemodynamics of umbilical artery, fetal middle cerebral artery and uterine artery. However, we considered that the concomitant use of both anticoagulants has a more distinguishable effect on MCA value during 3rd trimester of pregnancy.

Keywords: Anticoagulant, pregnancy, Doppler, umbilical artery, uterine artery, middle cerebral artery.

Özet: Gebelikte tromboprofilaktik ilaç kullananının fetüs ve uterus kan akış dinamiklerine etkisi

Amaç: Gebelikleri süresince çeşitli nedenlerle profilaktik dozda antikoagülayışın başlanan olguların fetal ve uterus kan dolaşımındaki olası etkileri tanımlamak.

Yüntem: Prospektif yapılan bu tek merkezli çalışmada antikoagu-ylan (düşük molekül ağırlıklı heparin-DMAH ve/veya asetilsalisilik asit-ASA) kullanan, ikinci ve üçüncü trimesterdeki gebelere, umbilikal arter (UmA), orta serebral arter (MCA) ve uterus arteri (UtA) kan akış parametreleri Doppler ultrasonografi ile değerlendirildi. Antikoagülayan kullanılan ve benzer yaş ve gestasyonel hafifdaki gebeler ise kontrol grubu olarak seçildi. İki grup klinik, demografik ve Doppler bulguları açısından “bağımız grup t testi” ve “Mann–Whitney U testi” ile karşılaştırıldı. Alt grup analizinde, sadece DMAH ve DMAH ile beraber ASA kullananlar kontrol grubu ile karşılaştırıldılar.

Bulgular: Çalışmaya toplam 63 olgu dahil edildi. Antikoagülayan kullanılan 36 (%57.1) gebe ile herhangi bir antikoagülayan kullanılan 27 (%42.9) gebe 40'ıktaki obstrüktif özgeçmiş varlığındaki (p=0.001) demografik ve klinik verilerinin karşılaştırılmasında istatistiksel açıdan anlamlı bir fark bulunmadı. Çalışmanın damarlardaki Doppler verileri açısından da alt grup arasında farklı izlenmedi (p>0.005). Ancak trimester ayrimiy yapıldığında antikoagüyan grubunun 3. trimester MCA PSV değerlerinin kontrol grubundan an- lamlı derecede farklı olduğu izlandı (p=0.037). Antikoagüyan alt grup analizinde ise DMAH ve ASA’nın birlikte kullanmanın MCA PSV değerlerinde anlamlı değişimde neden olduğu bulundu (p=0.006).

Sonuç: Gebelikte DMAH veya ASA kullananın umbilikal, fetal orta serebral arter ve uterus arteri akış dinamiklerinde Doppler ile izlenemebilir anlamlı bir değişikliğe yol açtığı gözlemlendi. Ancak her iki antikoagülayanın birden kullanınının, gebeliğin 3. trimesterinde MCA üzerinde farklı edilebilir bir etki gösterebilceği düştü.

Anahtar sözcükler: Antikoagülayan, gebelik, Doppler, umbilikal arter, uterus arteri, orta serebral arter.
Introduction

Thromboprophylaxis during pregnancy usually aims one of two major goals: Maternal thromboembolism prophylaxis and preventing poor obstetric outcomes. The potential roles of coagulative changes in maternal-fetal combination and congenital thrombophilia on recurrent first trimester miscarriages, second-third trimester fetal deaths, ablatio placentae and even intrauterine growth retardation have been investigated frequently.\(^1\) By the recommendations published by different professional societies and organizations on this popular topic, it has been aimed to prevent anticoagulant use during pregnancy through incorrect and/or missing indications.\(^2,3\)

The usage areas of Doppler ultrasonography have been expanding day by day thanks to its superiority in analyzing hemodynamics. Changes in fetal-placental and uterine hemodynamics can be identified without requiring an invasive procedure on many positions of circulation system, particularly umbilical artery, fetal middle cerebral artery and uterine artery, for topics such as intrauterine growth retardation, fetal anemia follow-up and management, preeclampsia and even the prediction of poor obstetric outcomes.\(^4,5\)

Uterine artery provides blood flow to uterine and therefore to placenta during pregnancy. In recent years, uterine artery Doppler (UtAD) ultrasonography has been used particularly for the prediction of the development of severe preeclampsia.\(^6\) Significant parameters reflecting placental resistance in particular are obtained with the analysis of umbilical artery by Doppler ultrasonography (UmAD). Thanks to these parameters, fetal-neonatal mortality in the management of intrauterine growth retardation can be decreased significantly.\(^6\) Hemodynamics of fetal middle cerebral artery (MCA) are very important for the antenatal follow-up and management of clinical problems such as feto-maternal hemorrhages and Rh incompatibility in terms of the brain sparing effect defined as centralization and therefore the intrauterine follow-up of fetal anemia.\(^7\) It is also very important to predict the poor obstetric outcomes as a component of “cerebro-placental ratio” (CPR) which has been investigated frequently in the recent years.\(^8\)

Although the parameters measured by Doppler ultrasonography technique, which is commonly used in obstetrics and reassures clinical evaluation, vary according to the user due to technical reasons such as angle of insonation and broadness of samples, their standardization is quite simple. However, apart from the techniques of ultrasonography use, these parameters can be affected by the clinical characteristics of patients. Therefore, it is worth investigating how anticoagulants affect fetal and placental hemodynamics during the pregnancy. While there is particularly a considerable amount of pregnant women who use anticoagulant due to the subjective criterion of “poor obstetric history”\(^9\), potential effects of anticoagulants on Doppler parameters can be crucial.

Therefore, we aimed to compare uterine, umbilical and fetal middle cerebral artery Doppler parameters between the pregnant women who started to use anticoagulant due to the subjective criterion of poor obstetric history and the pregnant women who did not use anticoagulant and to investigate the effects of anticoagulant at prophylactic dose on the outcomes in this study.

Methods

Study population

The study group consisted of the cases who admitted to the maternity clinic of Application and Research Hospital, Medicine Faculty, Aydin Adnan Menderes University and for whom thromboprophylaxis was initiated by another center during the first trimester of their pregnancies. The inclusion criterion was “continuing to use low-molecular-weight heparin (LMWH) at prophylactic dose and/or low-dose acetylsalicylic acid (ASA) at second or third trimester since the first trimester”. The exclusion criteria were determined as pregnancies below 18-year-old, multiple pregnancies, known fetal genetic or other anomalies, using anticoagulant due to indications (i.e. deep vein thrombosis or prosthetic heart valve, anticardiolipin antibody positivity, presence of lupus anticoagulant) except poor obstetric history, using anticoagulant irregularly, and starting to use anticoagulant before pregnancy or after first trimester.

The approval of Ethics Committee of Non-Invasive Clinical Researches, Medicine Faculty, Aydin Adnan Menderes University (protocol no. 2015/38) was obtained before the study. During routine obstetric ultrasonography, umbilical, uterine and middle cerebral artery Doppler ultrasonography evaluations
were done in all patients and the values were recorded together with other demographic and clinical data. As clinical and demographic data, age, gravida, parity, week of gestation, smoking habit, blood pressure, anticoagulant use and type, medication use for chronic reasons other than anticoagulants, presence of poor obstetric history and obstetric and non-obstetric problems in the current pregnancy were investigated. Two or more first trimester pregnancy loss in previous pregnancies, second or third trimester fetal death, ablatio placentae, and hypertensive diseases during gestation were considered “poor obstetric history”. The conditions in pregnancy during study such as pregestational or gestational diabetes, hypertensive diseases of gestation, chronic hypertension, ablatio placentae, and epilepsy were classified as “presence of current clinical problems”. Presence of congenital thrombophilia (i.e. factor V Leiden mutation) was not taken into consideration.

Doppler ultrasonography

Doppler measurements were carried out by an ultrasonography device with 7 MHz convex probe (C3-7IM, Accuvix V20, Samsung- Medison, Gyeonggi, South Korea). For UtAD measurements, it was paid attention to keep insonation angle below 30 degrees at every measurement. Pulsatility index (PI), resistance index (RI), and systole/diastole ratio (S/D) were recorded bilaterally. The mean of right and left measurements was taken during the analysis. In UmAD samplings, the sampling was done on the area close to the placental end, and PI, RI and S/D values were recorded. Insonation angle was kept below 10 degrees in MCA measurements, and peak systolic velocity (MCA PSV) and PI values were recorded.

Statistics

When the statistical power analysis was performed for the study by taking the study of Bar et al. as reference, it was calculated that at least 20 cases should be studied in each group to conduct the research as effect size would be 0.3, alpha would be 0.05 and statistical power would be 80% for UmA PI variable. Kolmogorov-Smirnov test was used for the normal distribution analysis of numerical variables. The comparison between the groups for numerical variables exhibiting normal distribution was done by “independent samples t-test” and the data were presented as mean±standard deviation. Mann-Whitney U test was used to compare numerical variables without normal distribution, and descriptive statistical data were presented as median (25th–75th percentile). Chi-square test was used for the analysis of categorical data. The cases where “p-value” is below 0.05 were considered statistically significant.

Results

A total of 56 cases using anticoagulant and 27 cases not using anticoagulant were analyzed for the study. Of the cases using anticoagulant, 2 were excluded from the study due to DVT history, 5 due to multiple pregnancy, 4 due to anticoagulant use after first trimester and 9 due to irregular use of anticoagulant. The data of remaining 36 (57.1%) cases using anticoagulant were analyzed as study group. Similarly, the data of 27 (42.9%) pregnant women not using any type of anticoagulant were recorded as the control group. The study population consisted of a total of 63 pregnant women.

Except the parameter of “presence of poor obstetric history” (p<0.001), no statistically significant difference was found in the comparison of demographic and clinical data of the study group using anticoagulant and the control group not using any anticoagulant (p>0.05, Table 1). No significant difference was found when the groups were compared in terms of Doppler parameters analyzed (UmA PI, UmA SD, UtA PI, MCA PI and MCA PSV) (p>0.05, Table 2).

When the cases were compared only in terms of third trimester Doppler data, it was found that MCA PSV values of the study group were lower than the control group (p=0.037, Table 3).

When the cases were analyzed by grouping according to the anticoagulant type they used, LMWH, ASA and LMWH+ASA sub-groups were identified. However, the cases using only ASA were not included in the analysis as their number was low (n=4). It was observed that MCA PSV values of the cases using LMWH+ASA were lower than those of the control group (p=0.006). There was no significant difference in other sub-groups and other parameters (Table 4).

When sub-analysis was performed according to the anticoagulant type and trimester simultaneously, the only sub-group reaching sufficient number for statistical analysis was the sub-group consisting of cases at their third trimester and using only LMWH (n=15).
There was no significant difference between this subgroup and the control group in terms of Doppler data (p>0.05, no data was presented).

### Discussion

In this study, we aimed to analyze potential changes in Doppler dynamics of uterine, fetal middle cerebral and umbilical arteries in pregnant women who started to use anticoagulant due to the subjective criterion of “poor obstetric history”. We observed that the concomitant use of low-molecular-weight heparin (LMWH) and acetylsalicylic acid (ASA) may be associated with the low MCA PSV values.

Anticoagulants are commonly used in many poor obstetric problems such as intrauterine fetal death, ablation placentae, early-severe preeclampsia and intrauterine growth retardation but early pregnancy losses in particular. Moreover, it is also known that anticoagulant is prescribed in pregnancies achieved by assisted reproductive technologies. However, it has not been shown that such common use of anticoagulants improved the outcomes. In obstetrics practice, the area of use of Doppler ultrasonography has become quite popular and it has proved its positive contribution on perinatal outcomes in many clinical scenarios. Although different results

### Table 1. Comparison of the demographic and clinical data of the groups.

<table>
<thead>
<tr>
<th></th>
<th>Anticoagulant group (n=36)</th>
<th>Control group (n=27)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)*</td>
<td>31.05±6.06</td>
<td>30.14±5.97</td>
<td>0.556</td>
</tr>
<tr>
<td>Week of gestation†</td>
<td>30 (26–34)</td>
<td>32 (28–34)</td>
<td>0.611</td>
</tr>
<tr>
<td>Second trimester‡</td>
<td>12 (33.3)</td>
<td>6 (22.2)</td>
<td></td>
</tr>
<tr>
<td>Third trimester‡</td>
<td>24 (66.6)</td>
<td>21 (77.8)</td>
<td></td>
</tr>
<tr>
<td>Parity‡</td>
<td>1 (0–1)</td>
<td>1 (0–2)</td>
<td>0.953</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)†</td>
<td>110 (104.2–118.7)</td>
<td>110 (100–130)</td>
<td>0.713</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)†</td>
<td>70 (61.25–70.0)</td>
<td>70 (65–80)</td>
<td>0.360</td>
</tr>
<tr>
<td>Cases with poor obstetric history§</td>
<td>26 (72.2)</td>
<td>6 (22.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoker cases§</td>
<td>6 (14.8)</td>
<td>4 (16.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>Cases using non-anticoagulant medication due to chronic disease§</td>
<td>4 (11.1)</td>
<td>10 (37.0)</td>
<td>0.032</td>
</tr>
<tr>
<td>Anticoagulant type§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH only</td>
<td>20 (55.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH+ASA</td>
<td>11 (30.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA only</td>
<td>5 (14)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Mean±standard deviation; †median (25th–75th percentile); ‡n (%). ASA: acetylsalicylic acid; LMWH: Low-molecular-weight heparin.

### Table 2. Comparison of Doppler parameters between two groups.

<table>
<thead>
<tr>
<th></th>
<th>Anticoagulant group (n=36)</th>
<th>Control group (n=27)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCA PSV*</td>
<td>38.59±9.02</td>
<td>43.17±10.5</td>
<td>0.071</td>
</tr>
<tr>
<td>MCA PI†</td>
<td>1.85 (1.58–2.06)</td>
<td>2.11 (1.55–2.43)</td>
<td>0.209</td>
</tr>
<tr>
<td>UmA PI†</td>
<td>1.09 (0.96–1.47)</td>
<td>1.25 (1.00–1.36)</td>
<td>0.484</td>
</tr>
<tr>
<td>UmA SD†</td>
<td>3.06 (2.69–4.20)</td>
<td>3.38 (2.67–4.00)</td>
<td>0.526</td>
</tr>
<tr>
<td>UtA PI†</td>
<td>1.27±0.50</td>
<td>1.21±0.39</td>
<td>0.576</td>
</tr>
</tbody>
</table>

*Mean±standard deviation; †median (25th–75th percentile). MCA PSV: medium cerebral artery peak systolic velocity; PI: pulsatility index; SD: systole/diastole; ratio; UmA: umbilical artery Doppler; UtA: uterine artery Doppler.

### Table 3. Comparison of third trimester Doppler data between the anticoagulant group and the control group.

<table>
<thead>
<tr>
<th></th>
<th>Control group (n=20)</th>
<th>Anticoagulant group (n=24)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCA PSV*</td>
<td>47.37±7.49</td>
<td>42.3±6.61</td>
<td>p=0.037</td>
</tr>
<tr>
<td>MCA PI†</td>
<td>2.1 (1.5–2.46)</td>
<td>1.9 (1.65–2.3)</td>
<td>p=0.524</td>
</tr>
<tr>
<td>UmA PI†</td>
<td>1.2 (1.0–1.4)</td>
<td>1.0 (0.9–1.4)</td>
<td>p=0.364</td>
</tr>
<tr>
<td>UmA SD†</td>
<td>3.2 (2.4–3.9)</td>
<td>2.9 (2.5–3.3)</td>
<td>p=0.364</td>
</tr>
<tr>
<td>UtA PI†</td>
<td>1.2 (0.9–1.4)</td>
<td>1.3 (1.0–1.5)</td>
<td>p=0.448</td>
</tr>
</tbody>
</table>

One third trimester control case was not included due to missing data. *Mean standard deviation; †median (25th–75th percentile). MCA PSV: medium cerebral artery peak systolic velocity; PI: pulsatility index; SD: systole/diastole; ratio; UmA: umbilical artery Doppler; UtA: uterine artery Doppler.
can be obtained due to “user factor” as in all ultrasonographic evaluations, it is possible to standardize it by measurement criteria and user trainings. However, apart from the user factor, the impact of demographic and clinical variables on Doppler parameters is a topic which is investigated less. In a cross-sectional study published very recently, it has been shown that demographic and clinical characteristics may significantly affect Doppler parameters. Although there are some studies investigating the impacts of medications, which affect artery physiology or intravascular volume during pregnancy, on Doppler data, there are fewer studies on the potential relationship between anticoagulant use during pregnancy and Doppler parameters.

For example, a study conducted on 178 pregnancies of 51 cases with hereditary thrombophilia using LMWH reported that fewer abnormal Doppler results (UmA and MCA) were observed in the cases using anticoagulant compared to those not using anticoagulant. This study claimed that LMWH might have an impact on Doppler values in the group with hereditary thrombophilia. However, the population of this study also includes thromboembolism unlike our study.

Bar et al. compared the pregnant women who started to use LMWH due to poor obstetric history to the pregnant women who started to use LMWH+ASA due to hereditary thrombophilia concurrent with poor obstetric history. They reported a significant decrease in UtA PI values of the group using LMWH+ASA compared to the control group. Similarly, we did not observe any significant change in UtAD parameters of pregnant women by anticoagulant at prophylactic doses in our study. In a recent study conducted on 139 pregnant women with hereditary thrombophilia, the authors reported that there was no difference between the cases using LMWH and the cases using LMWH+ASA in terms of uterine and umbilical artery Doppler parameters. Therefore, it can be considered that uterine and umbilical artery Doppler values are not different among the pregnant women using LMWH and/or the pregnant women using LMWH+ASA. We also found in our study that the anticoagulant use due to subjective criteria did not cause a significant change in UtAD and UmAD values.

The number of studies concluding that ASA use during pregnancy has no significant impact on Doppler parameters is high. For example, a prospective research reported that there was no significant difference between placebo and ASA in terms of UmAD values. Similarly, it was reported that UmAD and UtAD values of pregnant women who had anticardiolipin antibody positivity and used ASA were not different than normal pregnant women.

MCA Doppler ultrasonography, which has important areas of use in pregnancy, is important for the management of fetal and fetoplacental problems which are especially defined as brain sparing effect and concomitantly developed with the transformation of cerebral high resistant flow into low resistant. In their randomized study, Grab et al. concluded that the use of ASA did not cause a significant difference in MCA and other (UmA, UtA) Doppler values. In their study, the authors selected pregnant women with the history of intrauterine growth retardation or chronic hypertension.

Table 4. Distribution of Doppler data according to anticoagulant type.

<table>
<thead>
<tr>
<th></th>
<th>Control group (n=36)</th>
<th>LMWH only (n=27)</th>
<th>LMWH+ASA (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCA PSV*</td>
<td>43.1±10.5</td>
<td>42.3±8.1 (p=0.751)</td>
<td>32.7±8.5 (p=0.006)</td>
</tr>
<tr>
<td>MCA PI†</td>
<td>2.1 (1.5–2.4)</td>
<td>1.9 (1.6–2.3) (p=0.748)</td>
<td>1.8 (1.6–1.9) (p=0.219)</td>
</tr>
<tr>
<td>UmA PI†</td>
<td>1.2 (1.0–1.4)</td>
<td>1.0 (0.9–1.5) (p=0.535)</td>
<td>1.1 (1.0–1.5) (p=0.973)</td>
</tr>
<tr>
<td>UmA SD†</td>
<td>3.9 (2.7–4.0)</td>
<td>2.9 (2.6–4.0) (p=0.394)</td>
<td>3.1 (2.9–4.7) (p=0.666)</td>
</tr>
<tr>
<td>UtA PI†</td>
<td>1.2 (1.0–1.4)</td>
<td>1.0 (0.9–1.4) (p=0.235)</td>
<td>1.4 (1.1–1.6) (p=0.149)</td>
</tr>
</tbody>
</table>

*Mean±standard deviation; †median (25th–75th percentile). ASA: Low-dose acetylsalicylic acid; LMWH: Low-molecular-weight heparin; MCA PSV: medium cerebral artery peak systolic velocity; PI: pulsatility index; SD: systole/diastole ratio; UmA: umbilical artery Doppler; UtA: uterine artery Doppler.
as the study group. In our study, the number of pregnant women using ASA only was very low so it was not possible to derive a statistically significant result; however, we observed a significant decrease in MCA PSV median values of the cases using LMWH+ASA than those not using medication. On the other hand, Younis et al. reported in their study that MCA Doppler values were normal in the pregnant women who had thrombophilia and used LMWH+ASA.[22] However, their results should be interpreted carefully as they did not have a control group.

When the studies published in English in PubMed database are reviewed, it can be seen that a couple of studies published in this database on this topic were conducted usually on pregnant women with the history of thrombophilia and thromboembolism or with the problems such as intrauterine growth retardation during study period. We could not find any study investigating the potential impact of off-label anticoagulant use on the Doppler parameters during pregnancy. Therefore, the heterogeneity of pregnant women population among other studies and our study makes it difficult for making a clear deduction. One of the limitations of our study is the sampling size. Even though we reached sufficient number of cases by performing statistical power analysis before the study, this number may not be enough to provide a reliable result when a secondary analysis is performed by grouping according to anticoagulant sub-types. Thus, this factor should be taken into consideration when interpreting our results.

Conclusion
Apart from the current indications, we did not find a significant difference in umbilical artery, uterine artery and fetal cerebral artery Doppler parameters of pregnant women using LMWH due to the subjective criterion of “poor obstetric outcome” compared to the control group. However, the concomitant use of LMWH and ASA may cause changes measurable by Doppler ultrasonography in the hemodynamics of fetal middle cerebral artery.

Conflicts of Interest: No conflicts declared.

References


Cesarean scar pregnancies and their management: case series

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Introduction

Cesarean scar ectopic pregnancy (CSP) is one of the rare types of ectopic pregnancies. CSP incidence has been reported as 1/1800–1/2200 pregnancies. But, it is increasing progressively due to the increased cesarean section rates and assisted reproductive techniques. Early diagnosis is crucial to avoid severe complications such as uterine rupture and severe hemorrhage. Maternal morbidity such as uterine rupture, hemorrhage and hysterectomy is possible in case of undiagnosed cases. The diagnosis is usually made by ultrasound, showing the following with these criteria such as an empty uterine cavity and cervical canal, a gestational sac located anteriorly at the isthmus, and evidence of a functional trophoblastic/placental circulation on color Doppler at the late pregnancy weeks. Invasion of the bladder is possi-
ble complication. Morbidly adherent placenta is another end of abnormal placentation spectrum. Also, there is a focal thinning in myometrium at cesarean area. Pregnancy may protrude through the scar and if pregnancy is viable it can implant on abdominal organs. Magnetic resonance imaging can used to assess depth of placental invasion.\[4\]

There is only one patient which was reported who reached 35 weeks of gestation. She was complicated with massive hemorrhage and disseminated intravascular coagulopathy at cesarean operation and she underwent hysterectomy for life saving purposes.\[5\]

There are no guidelines for the optimal treatment of CSP in patients who are hemodynamically stable. There are many conservative treatment modalities described in the literature including systematic methotrexate, local methotrexate, combined intra cardiac potassium chloride injection and systemic methotrexate, bilateral uterine artery embolization (UAE), and combined UAE and local methotrexate. Uterine artery embolization could be indicated for the intractable bleeding.\[6–9\] Potassium chloride injections by vaginal route can be performed by ultrasound-guided needle, if fetal cardiac activity is positive.\[10–13\] We reported five cases of cesarean scar pregnancies which treated by various local therapies.

**Case Report**

Clinical features, treatments and outcomes of cases summarized in Table 1.

### Case 1

Thirty-three-year-old woman who had gravida 4 para 2 admitted to our outpatient clinic with symptoms of amenorrhea. She has a history of two deliveries by cesarean section 8 and 6 years ago and the history of cesarean scar pregnancy 2 years ago. She presented at 5 weeks pregnancy at her first visit. Beta HCG levels are raised as 417, 2357, 3512 mIU/ml. In the first visit, ultrasound revealed gestational sac with yolk sac (Fig. 1a) which located between the isthmus cervix borders (Fig. 1b) in the previous cesarean section scar. Longest diameter of gestational sac was 6 mm with yolk sac. Endometrium was 5.6 mm. Systemic methotrexate was performed intramuscularly (50 mg/m\(^2\)). HCG level was 7267 mIU/ml at methotrexate administration day. Dislocated gestational sac was detected by ultrasound at the control exam. Ultrasound-guided evacuation of gestational sac was performed. HCG levels dropped down sharply following evacuation.

### Case 2

Thirty-two-year-old gravida 3 para 1 woman admitted to emergency service with bleeding and amenorrhea. She has a history of delivery by cesarean section at 35 weeks of gestation. Also, she reported pressure in the midline just over bladder. HCG level was 22,976 mIU/ml. Ultrasound revealed both embryo and yolk sac which located in the lower uterine segment and gestational sac has been extended to the former cesarean section scar (Fig. 2a). Crown-rump length (CRL) was 4.76

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**Table 1.** Clinical features of cesarean scar pregnancy cases.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Number of previous C-section</th>
<th>HCG at diagnosis</th>
<th>Sac diameter</th>
<th>Treatment</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33</td>
<td>2</td>
<td>3512</td>
<td>6 mm with yolk sac</td>
<td>Systemic Mtx+ US guided evacuation</td>
<td>Successful term delivery in the next pregnancy</td>
</tr>
<tr>
<td>2</td>
<td>32</td>
<td>1</td>
<td>22,976</td>
<td>CRL: 4.76 mm, cardiac activity (+)</td>
<td>Systemic and local Mtx by OPU needle</td>
<td>Successful term delivery in the next pregnancy</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>1</td>
<td>9000</td>
<td>8 mm</td>
<td>Local Mtx by OPU needle + US guided evacuation</td>
<td>Successful, no further therapy</td>
</tr>
<tr>
<td>4</td>
<td>48</td>
<td>1</td>
<td>33,734</td>
<td>40 mm</td>
<td>US guided evacuation and haemostatic balloon</td>
<td>Successful, no further therapy</td>
</tr>
<tr>
<td>5</td>
<td>24</td>
<td>2</td>
<td>62,316</td>
<td>CRL: 8 mm, cardiac activity (+)</td>
<td>Systemic Mtx+ US Guided Intracardiac KCl</td>
<td>Successful, no further therapy</td>
</tr>
</tbody>
</table>

mm and cardiac activity was seen (Fig. 2b). In the power Doppler, low resistance-high velocity peripheral blood flow was seen around gestational sac in the previous cesarean section incision site (Fig. 2b). Gestational sac even bulged to the bladder not invaded (Fig. 3) CRL increased to 8 mm progressively one week later. Sequential systemic methotrexate (1 mg/kg) performed four times intramuscularly with folinic acid rescue. Intracavitary methotrexate (1 mg/kg) was performed by transvaginal oocyte pick-up (OPU) needle. One week later fetal cardiac activity was negative and bleeding was started. Evacuation of cavity was not performed. HCG level decreased progressively. One month later after intracavitary methotrexate administration, disrupted gestational sac was seen as $27 \times 24$ mm (Fig. 4a) diameter. However, obvious peripheral blood flow was seen (Fig. 4b). Two months later following methotrexate, HCG level was 13 mIU/ml. Gestational sac disappeared

Fig. 1. The gestational sac with yolk sac (a) located between the isthmus cervix borders (b) in the previous cesarean section scar.

Fig. 2. Both embryo and yolk sac located in the lower uterine segment and gestational sac extended to the former cesarean section scar (a) and cardiac activity (b). In the power Doppler, low resistance-high velocity peripheral blood flow was seen around gestational sac in the previous cesarean section incision site (b-bottom).
and replaced with hematoma. Its diameter was 3×4 cm (Fig. 4c). 4 months later following local treatment, uterus was normal and hematoma resolved (Fig. 4d). One year later, patient became pregnant again spontaneously. Gestational sac located at fundus.

**Case 3**

Forty-year-old gravida 2 para 1 woman admitted with secondary amenorrhea. We performed transvaginal ultrasound to reveal 8 mm gestational sac, which possibly placed within the former cesarean section scar and protrude to the bladder. Her abdomen was soft and not distended. There was no vaginal bleeding and the cervix was closed on speculum examination. Intracavitary methotrexate (1 mg/kg) was introduced by OPU needle (16 Gauge) by transvaginal ultrasound guide. Then it was aspirated by same needle. After methotrexate, gestational sac dislocated through to cervical canal and vaginal bleeding begun. In the follow-up, ultrasound-guided aspiration of gestational sac was performed by Pipelle cannula because of gestational sac did not abort.

**Case 4**

Thirty-eight-year-old gravida 2 para 1 women admitted with bleeding and pain. She has a history of one lower segment cesarean section delivery. Bright blood from external cervical os was seen during speculum exam. Cervix was tender by digital exam. Serum HCG titer was 33,734 mIU/ml. Ultrasound revealed gestational sac just located over former cesarean section site and extend to the isthmic region of uterus. It has 4 cm largest diameter. Hemoglobin level was 12.8 g/dl at the
first admittance. After the 6 hours follow-up it was drop down to the 11.4 g/dl. Suction curettage was performed by number 4 Karman cannula with negative pressure under ultrasound guidance. Transcervical 16 F Foley catheter was inserted and balloon was inflated 30 cc sterile saline and traction was performed to achieve haemostasis. It was remained 12 hours and deflated carefully and removed. Patient was discharged 24 hours following the suction curettage. Serum HCG titer was 2460 mIU/ml postoperative 7th day and 161 mIU/ml postoperative 17th day.

Case 5
Twenty-four-year-old gravida 3 para 2 woman referred by possible diagnosis of cervical pregnancy. She has two previous cesarean section operation, last one 10 months before. Basal serum HCG level was 62,316 mIU/ml. Transvaginal ultrasound revealed a bulging cystic mass located in the isthmic region. It was 42×33 mm and consisted of cardiac activity visible embryo (CRL: 8 mm). Both cervical canal and uterine cavity were empty. Continuity of anterior uterine wall was disappeared and myometrium was thin and irregular in the gestational sac region. By the diagnosis of cesarean section pregnancy, as a first step intracardiac 2 ml 10% potassium chloride applied by 20 G spinal needle under the real-time ultrasound guidance transabdominally. In the second step, systemic methotrexate was performed intramuscularly (1 mg/kg) in Day 1-3-5-7 with folinic acid rescue (0.1 mg/kg). HCG level was 70,074 mIU/ml in the day 3. Scar pregnancy started to shrinkage and disappeared 3–4 weeks later following the last dose of methotrexate.

Fig. 4. Disrupted gestational sac was seen as 27×24 mm (a). The obvious peripheral blood flow was seen (b). Two months later following methotrexate, gestational sac disappeared and replaced with hematoma (c). 4 months later following local treatment, uterus was normal and hematoma resolved (d).
Discussion

We reported clinical outcomes of five cases of cesarean scar pregnancy following local treatment by methotrexate. Cesarean scar pregnancy is a rare type of ectopic pregnancy. In recent years, ectopic scar pregnancies have progressively increased due to the assisted reproductive techniques and previous abdominal delivery. Furthermore, loss of fertility, life threatening bleeding, morbidly adherent placenta and maternal death are among the maternal morbidities related with cesarean scar pregnancy.

Delayed diagnosis and treatment may increase uterine rupture risk and causes severe hemorrhage. To diagnose the ectopic pregnancy, physical examination is the first step and transvaginal ultrasound is easy and cheap route to determine the location of gestational sac. Magnetic resonance imaging for differential diagnosis is rarely indicated.

Generally single agent pharmacologic therapy is the first choice, rarely surgery indicated. Treatment by methotrexate is the best for early-diagnosed cases. If the fetal cardiac activity present, we need intra-cardiac potassium chloride to sustain treatment success. Sometimes medical treatment may be failed because of very high HCG levels and in the presence of cardiac activity. Dilatation and suction curettage or laparoscopic resection in first trimester may be treatment choices if the initial treatment fails. If gestational sac bigger than 2.5 cm and HCG level is bigger than 10,000 IU/ml furthermore there is fetal cardiac activity positive at ectopic focus we absolutely need KCl injection.

Uterine closure at cesarean section may be a factor for uterine rupture and future cesarean scar pregnancy. Uterine double-layer closure may be safe for avoiding from complications like scar pregnancies. Multiple pregnancies, absence of the first stage of labor, and cephalopelvic disproportion might be the risk factors for the occurrence of CSP. In some cases, surgical resection for removing ectopic pregnancy and repair former cesarean section defect are logical options. Although we did not need hysterectomy in our patients, hysterectomy is a treatment choice for the severe hemorrhage following initial treatment. Also, patients must be counseled about abnormal placentation for next pregnancies.

In our small case series, we achieved elimination of cesarean scar pregnancy by local treatment with methotrexate due to early diagnosis. Local treatment is better than systemic treatment because of fewer side effects. Totally in twenty days HCG levels decreased progressively, but we needed systemic methotrexate and folic acid in two cases (Cases 1 and 5). Ultrasound-guided evacuation performed 3 cases (Cases 1, 3 and 4). Ultrasound-guided or blind curettage or evacuation is not successful alone. Following the local methotrexate administration, greater than 35% reduction in HCG after uterine artery embolization and local methotrexate injection can be used as an indicator to perform dilation and curettage as complementary treatment.

There was no severe hemorrhage in our patients in this respect, for this reason blood transfusion was not required. In the Case 4 from our small series, we performed balloon compression by Foley catheter and it was removed 12 hours later to achieve hemostasis.

Every woman who had a cesarean section history must be checked carefully due to cesarean section pregnancy following delayed menstruation and positive pregnancy test. Various cesarean section pregnancy treatment modalities have been reported, however the best approach for this is still under debate. Management and follow-up should be individualized for each patient.

Conclusion

In conclusion, local treatment of cesarean scar pregnancy could be achieved by combination of local techniques in carefully selected cases.

Conflicts of Interest: No conflicts declared.

References


Gestational management of the patient with osteogenesis imperfecta: a case report

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Introduction

Osteogenesis imperfecta (OI), which is also known as glass bone disease, is a genetic disorder with different dominantly or autosomal recessively inherited subtypes. In Types I, II, III and IV patients, the synthesis of type I collagen, which is an important structural protein for bones, tendons, ligaments and many connective tissues, is defective due to the mutations in COL1A1 and COL1A2 genes, and therefore fragility in bones, decreased bone density and skeletal anom-
Gestational management of the patient with osteogenesis imperfecta

Alies are seen in affected individuals. In addition, short height, scoliosis and spinal deformities, joint laxity, tendency to muscle and connective tissue injury, blue sclera, odontologic deformities, conductive hearing loss, hyperthermia, hyperhydrosis, platelet dysfunction, congenital cardiomyopathy, and fragility in other tissues such as joint, vessel and skin can be seen.

Today, it has been shown that about 20 different genes except COL1A1 and COL1A2 genes, which have a major role in the pathology, may cause OI. Although OI has 4 sub-groups classically, up to 15 different types have been reported according to clinical and radiological findings and underlying genetic reasons. Type I is the common one which has a better prognosis. Type II is the most slow-progressing form. Its usual prevalence is up to 6–7 in 100,000 and most of them are new mutations.

In our case report, we aimed to present the gestational follow-up and management of a patient with type I OI and to discuss potential complications.

**Case Report**

Thirty-six-year-old patient diagnosed with Type I OI admitted to our infertility center for preconceptional genetic diagnosis. The patient whose height was 148 cm and weight was 48 kg had the history of cholecystectomy and many surgeries for bone fracture; she had no known disease other than OI and migraine. In her family, only her brother had OI. It was planned to transfer healthy embryo by performing intracytoplasmic sperm injection and preimplantation genetic diagnosis (PGD) in order to eliminate the possibility of OI in her baby to be born. When planning the treatment process, the patient got pregnant spontaneously and the gestational follow-up was initiated for her. New generation full gene sequencing analysis was performed for the molecular genetic diagnosis; a mutation was identified in COL1A1 gene located on 17q21.33 chromosome region [p.R697 (c.2089C>T) (heterozygous)], but her COL1A2 gene located on 7q21.3 region was normal. Chorionic villus sampling was performed when she was at 12 weeks and 3 days of gestation according to her last menstrual period. Normal karyotype was seen in the karyotyping examination and sequencing analysis, and also it was found that COL1A1 gene was normal. No anomaly was observed in the detailed ultrasonographic examinations of the patient at 11–14 and 18–22 weeks of gestation. Oral glucose tolerance test was within normal range. The results of blood count, thyroid, liver and kidney function tests were normal. The patient was followed up for calcium, vitamin D, phosphor, and ferritin. The patient was followed up under the control of physiotherapy and rehabilitation department and nutritionist, and her daily oral vitamin D intake was arranged as 2000 IU and diet calcium as 1000 mg. Her weight was kept under control; the patient who was 48 kg before pregnancy was 54 kg during the delivery. Her blood pressure measurements were within normal ranges during all follow-ups. However, she had severe nausea and vomiting since the beginning of the pregnancy and she also had frequently repeating headache. As the week of gestation progressed, she frequently suffered stomachache and shortness of breath occasionally. Her complaint of being unable to eat due to gastric irritation, nausea and vomiting continued during the entire pregnancy period. The symptoms of the case were followed up until they regressed by routine follow-ups and sometimes several hospitalization after admitting to emergency service and also by intravenous hydration only under observation occasionally. By considering the possibility of preterm labor as the patient did not have any pain and had contractions in the tocography when she was at 27 weeks and 4 days of gestation, she was administered 2 doses of 12 mg Betamethasone (Celestone Chronodose, 1 ml, Schering Plough Turkey, Istanbul) with 24-hour interval. The case did not have any cervical dilatation during the follow-up, her contractions regressed and the patient was discharged from the hospital and her gestational follow-up was continued. As her complaints increased as the week of gestation progressed, the patient underwent amniocentesis after 34 weeks of gestation was completed and her lecithin/sphingomyelin ratio was evaluated. This ratio was found 8 and her labor was planned considering that fetal lung maturation was completed. When she was at 35 weeks and days of gestation according to the last menstrual period, her labor was carried out by cesarean section under general anesthesia considering that the patient, whose contractions increased and had cervical effacement and 2 cm dilatation, would be less traumatized physically and psychologically compared to normal delivery. A singleton living female baby with a weight of 2330 g and height of 46 cm was born with 1-minute and 5-minute Apgar...
scores of 9 and 10, respectively. It was seen during the cesarean section that her skin, subcutaneous tissues, uterus muscle tissues and other connective tissues were very soft and fragile, so suturation was done carefully and gently. As the newborn was premature and had minimal respiratory distress, it was monitored in the intense care unit for 24 hours for observation purposes and then delivered to the mother. The patient had no hemorrhage during postoperative period, her hemoglobin values were stable, and she was administered Enoxaparin (Clexane 4000 anti-Xa IU, Sanofi Turkey, Istanbul) on the postoperative 1st day to prevent thromboembolism risk. When the patient had subfebrile fever (37.8°C) on the postoperative second day, her CRP value was checked and found high, and therefore broad-spectrum intravenous antibiotic treatment was initiated; her urine and blood culture tests were normal, and no infection focus was found. The patient whose CRP value regressed by the treatment was discharged from the hospital on the postoperative 4th day as her general condition was good and her vital signs were stable.

**Discussion**

The pregnancy of a patient with the diagnosis of osteogenesis imperfecta is a difficult process physically and psychologically. The concern of transferring defective genetic structure to the next generation, difficulty of carrying pregnancy due to anatomic deformity, frequent gestational complications such as antepartum bleeding, ablatio placenta, preterm labor and intrauterine growth retardation, frequent labor complications such as bleeding, uterine atony and stress fractures, thromboembolism and anesthesia risks are the problems that can be seen during the pregnancy of an OI patient. When offering genetic consultancy to such patients, the healthcare professionals should know the family history well, identify gene mutation and find out by appropriate methods if they are transferred to fetus or not. A healthy embryo can be transferred by PGD to a patient seen before the conception. However, more common method referred is to investigate current genetic mutation in mother’s cells obtained by chorionic villus sampling or amniocentesis. Mutation is found in 70% of COL1A1 gene and in 30% of COL1A2 gene in OI cases associated with COL1A1-COL1A2. If no mutation is identified in COL1A1 and COL1A2 genes, autosomal recessively inherited and OI-associated genes (CRTAP and LEPRE1) which are responsible for some of the cases are studied by also considering the family history.

OI diagnosis can also be established by USG examinations carried out during antenatal period. NT increase in early pregnancy, echogenicity decrease in long bones, bending and shortening of heights should bring OI to mind. The diagnosis of OI type I can be established by USG at the 17 weeks of gestation at the earliest; OI type II can be diagnosed at 13 weeks of gestation. In types III and IV, there may be bending without any shortening in the bone length or decrease in its mineralization, and this may delay the diagnosis as it will be clear in the further weeks of gestation. When type III or IV OI is suspected, the results of repeating USG examinations should be compared. In order to confirm the diagnosis, fetal magnetic resonance imaging may also help in necessary cases.

Due to the increase of body weight and change of the center of gravity during pregnancy, musculoskeletal system problems such as back pain, spinal deformities, scoliosis, and disk hernia increase. Bisphosphonates used routinely by this patient group is contraindicated for the pregnancy as they may cause fetal skeletal anomalies or congenital malformations, and many studies recommend discontinuing them after conception. However, these problems may be mitigated by calcium and vitamin D support and keeping weight gain under control. It has been shown that checking the values of calcium, phosphate, vitamin D, parathyroid hormone, LDH, CK, CRP, and kidney and liver function tests by a 3-month laboratory analysis would help the management of treatment.

The rates of gestational complications such as antepartum bleeding, ablatio placenta, preterm labor and intrauterine growth retardation are also higher in OI patients. It was shown in the previous years that the individuals with OI are more prone to bleeding and this may be associated with the platelet disorder.

Ruiter-Ligeti et al. reported that antepartum bleeding or ablacio placenta risk may be associated with collagen defect or coagulation defect, but they did not find any increase in the risk of postpartum bleeding. In the same study, the authors found the risk of venous thromboembolism higher in women with OI and they associated it with the high rates of cesarean section and
prolonged immobilization related with postnatal skeletal problems.\[1\]

Also, the studies showing that calcium metabolism has a role in the pathogenesis of preeclampsia indicate that the risks for preeclampsia and intrauterine growth retardation are increased in these patients.\[2\]

The increase in preterm labor risk may be associated with antenatal bleeding, ablatio placentae, premature rupture of membrane or intrauterine growth retardation as well as maternal complications.\[1,6\] In our case, tightness and abdominal pain felt by the mother as the uterine got bigger, back and lumbar pain, shortness of breath and gastric irritation findings such as severe nausea and reflux made maintaining the pregnancy difficult; therefore, after we confirmed the fetal pulmonary maturation, we informed the family that newborn might need intense care support as it was a premature baby, and we planned the labor by obtaining the approval of the family.

Although there is no certain suggestion for the delivery type for patients with OI, cesarean section is usually preferred for the delivery as an effort to decrease labor trauma. Maternal fracture incidence does not increase during pregnancy; however, small traumas due to obstetric manipulations may increase the fracture risk. Stress fractures related with bone demineralization can be seen both in vaginal labors and cesarean section labors. It has been reported that such fractures can be minimized by careful positioning during delivery or surgery and performing preconceptional bisphosphonate treatment.\[1,3,6,7\] In addition, spontaneous uterine rupture was also reported during labor.\[8\] Labor induction is not recommended since it is not possible to predict how uterine contractions will develop in the presence of defective collagen.\[9\] Feng et al. reported that a patient with OI who prefers vaginal labor should be managed as if she is a patient with a scarred uterus, and they highlighted that postpartum bleeding risk is high depending on the uterine atony, laceration or thrombocyte disorder.\[10\] Presentation anomalies and cephalopelvic disproportion associated with maternal skeletal anomaly can be cesarean section indications. Labor by cesarean section can also be considered for a fetus established with OI diagnosis in order to minimize the labor trauma. However, the studies show that cesarean section do not decrease the rates of newborn fractures during labor.\[1,3,9\]

In addition, labor by cesarean section should not be considered as free of risk, and it should be remembered that it may increase the risks such as thrombosis, uterine atony, and postpartum bleeding.\[2\] We decided that labor by cesarean section would be more appropriate for our case considering pelvic or vertebral fracture or uterine rupture risks.

For anesthesia, all general, epidural and spinal anesthesia methods can be used; however, both general and regional methods may have risks. Cardiopulmonary condition of the patient should be evaluated well. In the general anesthesia, difficult intubation due to skeletal deformities, mandibular or dental fractures may occur; malign hyperthermia risk should also be considered. In regional anesthesia, the procedure related with spinal deformities is technically difficult, and it may also get hard to adjust block level.\[2,3\]

Breastfeeding of the patients with OI may also be considered contraindication relatively. Although there is no full consensus, it is recommended to avoid long-term breastfeeding periods particularly in patients who have vertebral fracture in order to shorten this process which may cause a certain decrease in the bone density.\[10\]

Conclusion

Osteogenesis imperfecta is a condition with high maternal morbidity risk during pregnancy. Preconceptional consultancy and medical and genetic evaluation should be offered to all women with OI.

The type and severity of the disease and general clinical condition of patient should be considered in order to minimize the complications, and these patients should be followed up at fully equipped tertiary hospitals through a multidisciplinary approach.

Conflicts of Interest: No conflicts declared.

References


Dear Editor,

Preterm labor is the most significant reason of perinatal mortality in the world. Although the major reason for morbidity and mortality in preterm fetuses is respiratory distress of the newborn, short-term outcomes such as necrotising enterocolitis, intraventricular hemorrhage, newborn retinopathy and patent ductus arteriosus and long-term outcomes such as cerebral palsy, bronchopulmonary dysplasia and short bowel syndrome also should be considered. While prevention of preterm labor is the major action to prevent these problems, different pharmacological treatments should also be taken into account in cases where preterm labor cannot be prevented. In the last four decades, corticosteroids provided a significant decrease in the neonatal mortality and morbidity rates. In 1994, NICHD (National Institute of Child Health and Development) recommended using them to prevent prematurity-related respiratory distress in preterm labors.\(^1\) It has been reported that antenatal steroids also decrease the rates of newborn mortality, intraventricular hemorrhage and necrotising enterocolitis. In this regard, the use of antenatal steroid between 24 and 34 weeks of gestation in pregnant women with high risk of preterm labor has been recommended, and this recommendation has also been supported by ACOG. Current antenatal steroid administration is conducted by two different protocols, and dexamethasone and betamethasone are used for this purpose.\(^2\) The effects of two different molecules on lung maturation and intraventricular hemorrhage rate are similar. While dexamethasone is a molecule which is cheap and easy to obtain, the binding rate of betamethasone to albumin is lower and this increases the transplacental transition rate.

Optimal efficacy of antenatal steroids starts 24 hours after the last administration and continues for 7 days, and it starts to wear off afterwards. Therefore, in cases where preterm labor does not occur, a repeat or rescue dose should be administered when same problem is faced again in the future. Steroid administrations in repeat doses suppress maternal hypothalamic-hypophyseal axis, disrupt glycemic control in diabetic pregnant women by leading hyperglycemia, and may cause lung edema by its concomitant use with beta-mimetics in particular. In terms of newborn, hypoglycemia and hyperbilirubinemia are the major problems. As long-term and repeat doses of antenatal steroids may cause cerebral atrophy, microcephaly and low birth weight in fetus, administrating repeat doses is not recommended.\(^3\)

It was shown in a meta-analysis\(^4\) evaluated 30 studies and published in Cochrane database that steroids decreased the rates of perinatal mortality (RR: 0.72), neonatal death (RR: 0.69), respiratory distress syndrome (RR: 0.66), intraventricular hemorrhage (RR: 0.66), and necrotising enterocolitis.

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0.55), necrotising enterocolitis (RR: 0.5), and the need for ventilator support (RR: 0.6).

Although the use of antenatal corticosteroids before 24 weeks of gestation is controversial, the lower limit can be 22–23 weeks of gestation since the outcomes of newborn intense care get better in the extreme preterm group with very low birth weight. While this group decreases the mortality rates in newborns, it does not affect morbidity rates.

Chorioamnionitis and multiple pregnancies are not contraindicated for the use of antenatal steroid, and its administration scheme is similar to singleton pregnancies. While the administration threshold for antenatal steroids was 34 weeks of gestation until two years ago, it was shown in a randomized controlled study which was supported NIH that extending administration time up to 37 weeks of gestation led to a decrease in newborn respiratory distress. Therefore, ACOG updated its guidelines in August 2017 and extended the upper limit for administration up to 37 weeks of gestation. In the same guidelines, rescue treatment is recommended for pregnant women below 34 weeks of gestation who were previously administered corticosteroid in cases where the time elapsed since the last dose is longer than 14 days and where preterm labor condition arises and becomes inevitable in the next 7 days.

In conclusion, antenatal steroids should be administered in order to decrease neonatal morbidity and mortality in singleton and multiple pregnancies where preterm labor is inevitable between 24 and 34 weeks of gestation. The lower limit can be as low as 22 weeks of gestation depending on the newborn intense care capabilities, and the upper limit can be extended up to 37 weeks of gestation according to the recent literature data. The mode of administration is the same in singleton and multiple pregnancies. It should be remembered that its effects start within 24 hours after the last dose and continue for 7 days, and routine repeat doses should be avoided (Table 1). Since almost 2/3 of the preterm labor cases still do not result with preterm labor 1 week later, repeat doses should be referred only in cases where preterm labor is inevitable considering the fetal-neonatal and maternal adverse effects.

Conflicts of Interest: No conflicts declared.

### Table 1. Administration scheme of antenatal steroid.

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Administration week</th>
<th>Protocol</th>
<th>34–37. weeks of gestation</th>
<th>22 weeks – 23 weeks and 6 days of gestation</th>
<th>Repeat dose administration</th>
<th>Premature rupture of membrane</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACOG (2017)</td>
<td>24–34 weeks of gestation</td>
<td>Dexamethasone 6 mg - a total of 4 administrations every 12 hours or betamethasone 12 mg - 2 administrations every 24 hours</td>
<td>It can be administered</td>
<td>It can be administered after 23 weeks of gestation</td>
<td>If the time elapsed after the last dose is 14 days and more</td>
<td>Indicated</td>
</tr>
<tr>
<td>SOGC (2018)</td>
<td>24 weeks – 34 weeks and 6 days of gestation</td>
<td>Dexamethasone 6 mg - a total of 4 administrations every 12 hours or betamethasone 12 mg - 2 administrations every 24 hours</td>
<td>Controversial</td>
<td>Controversial</td>
<td>If the time elapsed after the last dose is 14 days and more</td>
<td>Indicated</td>
</tr>
<tr>
<td>NICE (2015)</td>
<td>26 weeks – 33 weeks and 6 days of gestation</td>
<td>Dexamethasone 6 mg - a total of 4 administrations every 12 hours or betamethasone 12 mg - 2 administrations every 24 hours</td>
<td>It can be administered between 34 weeks and 35 weeks and 6 days of gestation</td>
<td>Discuss with the family between 22 weeks and 23 weeks and 6 days of gestation; consider between 24 weeks 25 weeks and 6 days of gestation</td>
<td>-</td>
<td>Indicated</td>
</tr>
<tr>
<td>Turkish Ministry of Health (2014)</td>
<td>24–34 weeks of gestation</td>
<td>Dexamethasone 6 mg - a total of 4 administrations every 12 hours or betamethasone 12 mg - 2 administrations every 24 hours</td>
<td>By the decision of obstetrician</td>
<td>By the decision of obstetrician</td>
<td>By the decision of obstetrician</td>
<td>Single dose before 32 weeks of gestation, by doctor decision between 32 and 34 weeks of gestation</td>
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