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The Results section should provide the main findings of the study. Data should be concisely presented, preferably in tables or graphs.

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Journal titles should be abbreviated according to the Index Medicus. All authors if six or fewer should be listed; otherwise, the first six and “et al.” should be written.

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3. Title (no unusual abbreviations)
4. Abstracts (max. 250 words for original research articles)
5. Key words (max. 5 keys for original research articles)
6. Main text (subtitles)
7. References (listed according to the rules of ICMJE)
8. Appendices such as tables, figures, drawings, pictures, videos, patient forms, surveys etc. (numbering, legends and headings; copyright info/permission)
9. Acknowledgement of Authorship and Transfer of Copyright Agreement
10. Conflicts of Interest Disclosure Statement (if necessary)
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Neurodevelopmental problems of late preterm fetuses and the factors affecting neurological morbidity

Adil Barut1, Ismail Burak Gültekin1, Elif Akkaş Yılmaz2, Murat Sabancı3, Faith Karšlı1, Osman Fadil Kara1, Ömer Kandemir1, Tuncay Küçüközkan1

Objective: We aimed to investigate neurodevelopmental prognosis of late preterm neonates (between 32 and 37 weeks) and to determine antenatal, natal and postnatal risk factors affecting pregnancy.

Methods: The study was carried out on a total of 200 children (100 premature and 100 mature born) with no known chronic disease from 6-month-old up to 6-year-old born between January 2008 and January 2013 in the obstetrics clinic of Health Ministry Dr. Sami Ulus Training and Research Hospital and being followed up routinely in the Pediatric Psychiatry Clinic. The information of the children was obtained by a questionnaire form completed by their first degree relatives. Antenatal and natal risk factors were listed by analyzing the files. Psychosocial and motor developments of the children were assessed with Ankara Development Screening Inventory (AGTE), and premature and mature babies were compared in terms of neurological development.

Results: While there was no statistically significant difference between the groups in our study in terms of chronological age and 1-minute and 5-minute Apgar scores (p>0.05), the difference between delivery week and birth weight was statistically significant (p<0.05). It was found that late premature babies had significantly high level of RDS, hyperthermia, hypoglycemia, jaundice, apnea and hospitalization period compared to mature babies (p<0.05). There was no significant correlation between AGTE and the week of gestation, birth weight, antenatal steroid prophylaxis, 1-minute and 5-minute Apgar score, maternal educational level, and socio-economic level (p>0.05). Among the groups, there was statistically no significant difference in terms of general development, language development, fine and gross motor development and personal-social development (p>0.05).

Conclusion: Although there was no significant difference between late premature and mature groups in terms of neurological development, late premature babies are under risk in terms of neonatal morbidity and mortality, and they encounter many problems. Therefore, delivery schedule should be planned carefully by considering prematurity risks against the maternal and fetal complication risks if it is decided to maintain pregnancy. In addition, the periods of follow-up besides mothers for late premature babies should be extended or these babies should be followed-up more closely in the first days after discharge.

Keywords: AGTE, late preterm, neurological development.
Introduction

Preterm labor is one of the leading reasons of neonatal mortality and morbidity in the world including developed countries. Thanks to the recent scientific and technological developments on neonatology and the increase in the quality of newborn intensive care units, the survival rates of premature babies have increased. However, despite all the improvements in neonatal and perinatal care, premature birth has still been a significant problem not prevented so far. Premature babies are the largest group under risk among newborns due to various reasons such as their different biological structures, various problems belonging to early neonatal period, their need for longer hospitalization and their tendencies to infections. Due to many risk factors associated, preterm labor increases both morbidity rates during natal and postnatal periods and neuro-developmental problems in the long-term. In premature babies, germinal matrix-intraventricular hemorrhage (GM-IVH) is the most significant factor which has a direct association with neurological development. GM-IVH has an impact on neonatal mortality, morbidity and long-term neuro-developmental problems.\(^{[1]}\) In the studies carried out, cerebral palsy, mental retardation, convulsion, blindness, hydrocephalus and deafness are considered as the major neurological sequelas. Except such neuromotor dysfunctions, some minor neurological problems such as speech delay, visual or verbal perception problems, learning disability, school and behavioral problems, hyperactivity and lack of attention may also be observed in some preterm cases.\(^{[2,3]}\)

Since permanent sequelas which develop depending on the complications cause serious social and economical problems for patients and their families, it is important to diagnosis the baby under risk as early as possible, to follow up regularly and to lead to the rehabilitation programs.\(^{[4]}\) By early diagnosis and support, the child can become more independent in the daily life and has the ability to deal with problems in school and game life, and many secondary social and emotional problems can be prevented or fixed.\(^{[5]}\)

This study was planned to investigate the neuro-developmental prognosis of premature babies (between 32 and 37 weeks) born in the obstetric clinic and followed up in the pediatric psychiatry clinic of Health Ministry Dr. Sami Ulus Obstetrics, Gynecology and Pediatrics Training and Research Hospital, and to determine antenatal, natal and postnatal risk factors affecting prognosis.

Methods

Çalışma, Sağlık Bakanlığı Dr. Sami Ulus Eğitim ve Araştırma Hastanesi, Sağlık Bakanlığı Dr. Sami Ulus Eğitim ve Araştırma Hastanesi, and the Pediatric Psychiatry Clinic of the same hospital. Risk factors during prenatal, natal and postnatal periods of the babies in study and control groups were obtained from the computer database and their medical files, and recorded to the forms. Babies with syndromes, congenital hydrocephaly, asphyxia and metabolic disease were excluded from the study. The approval of the ethics committee was obtained before the study. The families of premature babies included in the study were asked to visit the hospital. The families were informed about the research and the tests, and their written informed consents were received.

Information about the child was obtained preferably from the mother and/or father, otherwise from the first degree relatives who have the possibility to follow-up the child closely; and the information about child was obtained through a questionnaire form including questions such as child’s age, gender, birth weight, antenatal tests, birth information, previous diseases if any, the degree of person providing information (mother, father, grandmother etc.), their educational levels, educational level of mother, her profession and her current professional status. Antenatal and natal risk factors were listed by analyzing their files.

Psychosocial and motor developments of children included in the study were evaluated by Ankara Development Screening Inventory (AGTE) which is an assessment tool providing systematic and detailed information on the development of babies and children and applied to patients by physicians trained on this tool. This inventory, which is unique to our culture, can be applied to many participants in a short time and organized as reflecting the development of child in health screenings, consists of 154 items which are arranged according to various age groups and responded with “Yes / No / I don’t know” replies. The questions were arranged as representing different but associated parts of the development (a general assessment of abilities such as Language-Cognitive [LC]: language expressions, understanding the language and clearly expressing it; Fine Motor [FM]: visu-
al-motor skills; Gross Motor [GM]: movement and movement-related strength, balance and coordination; Social Skill - Self-Care [SS-SC]: Self-care habits [eating, drinking, toilet use and wearing] and independency, social interaction and initiative). The results reflect the current development of 0–6 y/o babies and children as 4 sub-tests stated above and total development scores. When applying AGTE in our study, only the questions relevant to the ages of children were asked and most appropriate responses were aimed by using an understandable language as much as possible and providing examples when necessary. Ages of children were calculated through months. In this calculation, AGTE recommendation was taken into consideration. If child have passed 15 days or more from one-month as of the date of questionnaire assessment, the age of that child was obtained by adding one to that month (the age of a child who was 20-month and 18-day-old was considered as 21-month-old, and age of a baby who was 8-month and 14-day-old was considered as 8-month-old). After questionnaire was completed, sub-test scores for Language-Cognitive [LC], Fine Motor [FM], Gross Motor [GM] and Social Skill - Self-Care [SS-SC] were calculated first, and General Development (GD) raw score was obtained by summing up these four scores. Raw score profile was used to interpret the raw scores of LC, FM, GM, SS-SC and GD. AGTE was preferred since it was a tool with completed validity studies, compared with the results of validity studies by other clinicians which was easy to apply and easy to assess.6

Data entries and analyses were done by SPSS software, version 15 (SPSS, Inc., Chicago, IL, USA). When analyzing the study data in terms of quantitative data comparison, one-way ANOVA test was used for intergroup comparisons and Student-t test for two-group comparison of the parameters not displaying normal distribution. Spearman correlation analysis was used for the comparison of the correlation among the parameters. For the qualitative data comparison, Chi-square test was used. The results were evaluated within 95% confidence interval and according to p<0.05 significance level.

### Results

Information about genders and birth types of children in the study group and educational and professional status of their mothers and smoking habit during pregnancy is shown in the Table 1. Comparison of the groups in terms of delivery data and maternal age are shown in the Table 2, and statistically no significant

<table>
<thead>
<tr>
<th>Table 1. Demographic information.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Delivery type</td>
</tr>
<tr>
<td>Vaginal</td>
</tr>
<tr>
<td>C/S</td>
</tr>
<tr>
<td>Educational level of mother</td>
</tr>
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</tr>
<tr>
<td>Secondary education</td>
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<tr>
<td>Higher education</td>
</tr>
<tr>
<td>Professional status of mother</td>
</tr>
<tr>
<td>Not working</td>
</tr>
<tr>
<td>Working</td>
</tr>
<tr>
<td>Smoking during pregnancy</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2. Distribution of fetal findings.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Delivery week (week)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
</tr>
<tr>
<td>Maternal age</td>
</tr>
<tr>
<td>Apgar score (1-minute)</td>
</tr>
<tr>
<td>Apgar score (5-minute)</td>
</tr>
</tbody>
</table>

*χ²: chi-square test; SD: standard deviation
difference was found between the groups in terms of chronological age and 1-minute and 5-minute Apgar scores (p>0.05). It was found that the difference between the delivery weeks and birth weights of the groups was statistically significant (p<0.05). The comparison of the groups in terms of fetal results and maternal findings is shown in the Table 3. The comparison of the groups according to the AGTE development test was shown in the Table 4 and statistically no significant difference was found among the groups in terms of general development, language development, fine and gross motor development and personal-social development (p>0.05).

**Discussion**

Unlike mature babies, premature babies are the largest group under risk among newborns due to various reasons such as their different biological structures, various problems belonging to early neonatal period, their

**Table 3.** The comparison of the groups in terms of fetal results and maternal findings.

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (≥37 weeks)</th>
<th>Group 2 (&lt;37 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Resuscitation</td>
<td>6 6</td>
<td>94 94</td>
</tr>
<tr>
<td>RDS</td>
<td>0 0</td>
<td>100 100</td>
</tr>
<tr>
<td>Apnea</td>
<td>20 20</td>
<td>80 80</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>8 8</td>
<td>92 92</td>
</tr>
<tr>
<td>Phototherapy</td>
<td>10 10</td>
<td>90 90</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>0 0</td>
<td>100 100</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>6 6</td>
<td>94 94</td>
</tr>
<tr>
<td>Anemia</td>
<td>2 2</td>
<td>98 98</td>
</tr>
<tr>
<td>Rh incompatibility</td>
<td>18 18</td>
<td>82 82</td>
</tr>
<tr>
<td>Mechanic ventilation</td>
<td>0 0</td>
<td>100 100</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>0 0</td>
<td>100 100</td>
</tr>
<tr>
<td>PROM</td>
<td>0 0</td>
<td>100 100</td>
</tr>
<tr>
<td>Celeston application</td>
<td>12 12</td>
<td>88 88</td>
</tr>
<tr>
<td>Gestational HT</td>
<td>8 8</td>
<td>92 92</td>
</tr>
</tbody>
</table>

**Table 4.** The distribution of AGTE test results.*

<table>
<thead>
<tr>
<th>AGTE parameters</th>
<th>Group 1</th>
<th>Group 2</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Abnormal</td>
<td>Normal</td>
</tr>
<tr>
<td>General development</td>
<td>n</td>
<td>92 8</td>
<td>84 16</td>
</tr>
<tr>
<td>%</td>
<td>%</td>
<td>92 8</td>
<td>84 16</td>
</tr>
<tr>
<td>Language development</td>
<td>n</td>
<td>92 8</td>
<td>84 16</td>
</tr>
<tr>
<td>%</td>
<td>%</td>
<td>92 8</td>
<td>84 16</td>
</tr>
<tr>
<td>Thin motor development</td>
<td>n</td>
<td>96 4</td>
<td>92 8</td>
</tr>
<tr>
<td>%</td>
<td>%</td>
<td>96 4</td>
<td>92 8</td>
</tr>
<tr>
<td>Gross motor development</td>
<td>n</td>
<td>96 4</td>
<td>92 8</td>
</tr>
<tr>
<td>%</td>
<td>%</td>
<td>96 4</td>
<td>92 8</td>
</tr>
<tr>
<td>Personal social development</td>
<td>n</td>
<td>96 4</td>
<td>92 8</td>
</tr>
<tr>
<td>%</td>
<td>%</td>
<td>96 4</td>
<td>92 8</td>
</tr>
</tbody>
</table>

*χ²: chi-square test
need for longer hospitalization and their tendencies to infections. In the international literature, there are many studies on long-term follow up of the premature babies. Due to the decreasing mortality rates of premature babies with very low birth weight, neurodevelopment retardation cases are seen frequently in the developed countries. On the other hand, morbidity rates and treatments of premature babies become more important increasingly as the number of neonatology units grows and mortality rates reach to the western levels in Turkey. It is crucial to reduce morbidity rate in terms of diagnosing the baby under risk as early as possible and the disabilities that would occur later. In the last two decades, premature birth rates increased significantly. Late premature births are the major reason for this increase. In 2003, 71% of all premature births in the USA were late premature cases. This study was planned to identify the developmental problems of late premature babies born in our hospital and followed up in the pediatric psychiatry clinic, and to reveal the correlation between these problems and risk factors during antenatal, natal and postnatal periods.

In our study group, RDS incidence in 32–36 week babies in our study group was consistent with the literature. While RDS incidence decreased significantly after 34 weeks of gestation, the risk continued in 35- and 36-week babies.[7] Escobar et al. reported that male gender, cesarean delivery, antenatal problem, being SGA and low week of gestation were among the risk factors which have a role in the development of respiratory distress syndrome.[8] In our study, the risk factors in terms of respiratory distress were similarly found as male gender, cesarean delivery, antenatal problem and being late premature. Before 37 weeks of gestation, the risk of respiratory distress occurrence increases together with each weekly decreases in the week of gestation, and this risk continues even gender, being SGA or LGA, race, antenatal problem, multiple pregnancy and birth weight are controlled.[9] Although respiratory distress is frequent in late premature cases, the reason is unclear. Insufficiency in fetal alveolar fluid resorption or having underdeveloped lungs may be the reason. Late premature babies are born when their lung developments are in saccular-alveolar period. In physiological development, the number of alveoli significantly increases after 32 weeks. These physiological insufficiencies in the lungs may also have a role in the respiratory distress of these babies.[9] Since respiratory distress (RDS in particular) is a significant morbidity reason in late premature babies, timing of the births of late premature babies becomes even more important. There is no sufficient study on the applicability and effectiveness of antenatal corticosteroid treatment after 34 weeks of gestation. Lewis et al. suggest to evaluate fetal lung maturity in the presence of PROM or early labor at 34 weeks of gestation and to delay delivery (conservative approach); however, state that such a practice is not necessary since RDS incidence is very low (0.6%) as of 35 weeks of gestation.[7] In our study, it is seen that antenatal corticosteroid application does not decrease respiratory distress problem. However, since the late premature rate applied antenatal corticosteroid is only about %10, the current data is insufficient to explain the relationship between antenatal corticosteroid application and respiratory distress. Our study and further studies including many late premature babies may clarify whether late premature babies will be candidates for antenatal corticosteroid applications.

In our studies, the jaundice rate was two times higher in late premature cases than mature cases. While phototherapy was applied to all patients with jaundice, none of them required blood transfusion. Jaundice was the second frequent reason for re-admitting to the hospital. Although there are few studies on this matter in the literature, current studies show that late premature babies compared to mature ones re-admitted to the hospitals and hospitalized more frequently due to jaundice.[8,10,11] Similarly, Wang et al. found in their study that late premature cases had jaundice 1.95 times more than mature cases.[12]

While 6% of late premature cases had hypothermia in our study, no hypothermia was observed in mature babies. Wang et al. reported hypothermia incidence as 10% in late premature cases and 0 in mature cases.[12] While it is possible that hypothermia may be the first finding of neonatal sepsis as well as it may develop depending on just prematurity, it should be cautious in terms of unnecessary sepsis evaluations and antibiotic treatment.

In accordance with the literature, hypoglycemia was 6 times higher in late premature cases than mature cases.[12] Carbohydrate metabolism is unclear in late premature cases and it is considered that glucose regulation has not grown to sufficient maturity in these babies since hypoglycemia is more frequent in them compared to mature cases.
The studies in the literature show that apnea incidence varies between 4 and 12% in late premature cases but it is below 1% in mature cases. In the study of Wang et al., there was statistically no significant difference, and apnea incidence was found higher in late premature cases (4.4%) than mature cases (0%). Although there was statistically no significant difference between the groups, the apnea incidence was found to be more frequent in late premature cases than mature cases but the apnea incidence we found in late premature cases was lower than those reported in the literature.

In the literature, major neuromotor sequela rate in the premature cases is higher in the group with low birth weight and varies between 7 and 30%. Cerebral palsy is indicated among the most common major neurological disorders. In 1997, McCormick reported cerebral palsy rate as 7.7% in babies with low birth weights. There is no clear consensus in the literature on the correlation between birth weight, week of gestation and development sequela. In the study of Thompson et al., no difference was found between birth weights below 1000 g and those above 1000 g in terms of neurodevelopmental problem. Özbek et al. stated in their study that mental scale was not affected in cases with low birth weight (LBW); however, motor function was affected by DDA negatively. In the same study, no difference was observed between 38–32 weeks and 32–36 weeks in terms of the impact of week of gestation. Lya den Ouden et al. carried out a study on 555 premature babies born below 32 weeks of gestation, and found neuromotor retardation in 60% of those born at 24–25 weeks of gestation, in 16% of those born at 26–27 weeks of gestation, in 22% of those born at 28–29 weeks of gestation, and in 15.5% of those born at 30–31 weeks of gestation. In the study of Chaudhari et al., neurodevelopmental status of 172 premature babies and 36 mature babies were compared at 18–24 weeks of gestation by Bayley Scales of Infant Development-II, and a positive correlation was found between birth weight and motor development. Similarly, in the study of Talge et al. carried out in the USA in 2012 on 6-year-old children of which 473 were born with low birth weight and 350 were born with normal birth weight, preterm labor is statistically and significantly associated with growth retardation and focusing problem. Unlike these studies, we found that the week of gestation of late preterm cases was not significant in terms of neuro-developmental growth.

We found in our study that week of gestation and birth weight did not make any difference in terms of general development, gross motor development, social development, mental scale and language development. Similar to our study, Vries et al. grouped preterm cases as those below 32 weeks and those above 32 weeks, and reported CP rate of those below 32 weeks as 5% and of those at 32–35 weeks as 6%, and therefore showed that week of gestation was insignificant in terms of neurodevelopmental prognosis. Similarly, in the study of Nepomnyaschy et al. carried on 315 cases between 1–5 y/o and born through late preterm labor and published in 2012, differences similar to our results were found which are not significant statistically.

Conclusion
The results of our study show that many problems are still unsolved for late premature babies in Turkey despite all progress in neonatal care. Prematurity is one of the most significant reasons of perinatal and neonatal morbidity and mortality. Delivery time should be determined by obstetricians and newborn experts jointly by considering the health of mother and baby, and in case that pregnancy is maintained despite the risks of prematurity, a profit-loss assessment should be done by considering the risk of complications that may occur in mother and fetus. In addition, either the periods of follow-up besides mothers for late premature babies should be extended or they should be followed-up more closely in the first days after discharge.

Conflicts of Interest: No conflicts declared.

References


Neurodevelopmental problems of late preterm fetuses and the factors affecting neurological morbidity

Evaluation of conservative and radical surgical outcomes in placenta previa and accreta cases

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Department of Obstetrics and Gynecology, Faculty of Medicine, Mustafa Kemal University, Hatay, Turkey

Abstract

Objective: To evaluate our 5-year clinical experience in the management of cases with placenta previa together with placental attachment anomalies and the activity of the hypogastric artery ligation (HAL) for the protection of uterus.

Methods: The cases who had cesarean section and were established the diagnosis of placenta previa and accreta between 2009 and 2014 in the Department of Obstetrics and Gynecology, Faculty of Medicine, Mustafa Kemal University were evaluated retrospectively. The medical files of the patients were analyzed and their demographic characteristics, and surgical and conservative approaches were evaluated. Hysterectomy rates after cesarean section of the patients who did and did not undergo hypogastric artery ligation were compared.

Results: In the evaluation of 67 placenta previa cases included in the study, 32 patients were applied post-cesarean hysterectomy, 40 patients were applied HAL, 12 patients were applied uterine sutures and 3 patients were applied Foley catheter. All of the patients who were applied uterine suture and Foley catheter were in the non-hysterectomy group. It was found that 27 (67.5%) of 40 patients who had HAL were applied post-cesarean hysterectomy and 5 of 27 patients who did not have HAL were applied post-cesarean hysterectomy, and there was statistically a significant difference between groups (p=0.001). In the pathology results of the patients who had hysterectomy, it was reported that 8 (25%) patients did not have accreta, 11 (34.4%) patients did not have increta, 10 (31.3%) patients did not have percreta and 3 (9.4%) patients did not have placental invasion. In terms of complications, it was found that 9 cases had bladder injury, one case had vaginal cuff hematoma and one case had disseminated intravascular coagulation. In neonatal outcomes, median delivery weight was 2674 g, 1-minute and 5-minute Apgar scores were 6.7 and 7.8, respectively. Fetal anomalies were observed in two newborns.

Conclusion: In cases with placenta previa in company with placental attachment anomaly, conservative surgical approach can be an alternative method. However, organ protection activity of HAL in such cases is considered to be suspicious.

Keywords: Placenta previa, hypogastric artery ligation, placental attachment anomaly.
Evaluation of conservative and radical surgical outcomes in placenta previa and accreta cases

Introduction

Placenta previa (PP) is defined as placental tissues being near or over internal cervical os. This condition with severe hemorrhage and early delivery potential has an incidence rate of 3.5–4.6 per 1000 deliveries. While its prevalence is reported more frequently in the early weeks of gestation, most of the cases recover spontaneously in the advanced weeks.[1] However, a dramatic increase has been observed recently in the incidence of placenta previa together with increased cesarean rates.[2] Although antenatal diagnoses have been improved by ultrasonography and magnetic resonance imaging (MRI), placenta previa and especially concomitant placental attachment anomalies may cause postpartum massive hemorrhage.[3,4] In patients with placenta accreta, an increase also in fetal mortality, disseminated intravascular coagulopathy (DIC) and infection can be observed. Standard approach in such patients is to carry out hysterectomy.[5] However, the information is limited for the most appropriate management in patients who especially request fertility. Uterine compression sutures and hypogastric artery ligation (HAL) or embolization appear as organ protection approaches in such patients.[6,7]

In this study, we aimed to evaluate the conservative and radical surgical approaches applied in our clinic, their outcomes and HAL’s activity in protecting uterus for patients who have placenta previa together with placental attachment anomaly.

Methods

The medical files of the cases who had cesarean section and were established the diagnosis of placenta previa and accreta in the Faculty of Medicine of Mustafa Kemal University between January 2009 and December 2014 were evaluated retrospectively. Cases with marginal and low-lying placenta previa were excluded from the study. Ages, gravida, parity, week of gestation, number of cesarean undergone, newborn weight, 1-minute and 5-minute Apgar scores and fetal anomalies (if any) of the patients were recorded. In addition, operation duration, transfusion need, hospitalization period, intense care need, operative complications, preoperative and postoperative hemogram and hematocrit values were also recorded. From the surgery notes of the patients, the incision type, whether they had HAL or not, uterine saturation, placing intraoperative Foley catheter to uterine lower segment and cervix, and post-cesarean hysterectomy condition were noted. The pathology reports of the patients who had post-cesarean hysterectomy were also reviewed.

Statistics

All statistical analyses of the data were done by using SPSS software, version 22.0 (SPSS, Inc., Chicago, IL, USA). In the evaluation of the data, mean±standard deviation was used. Availability of normal distribution in continuous variables was evaluated by Kolmogorov-Smirnov test. Descriptive statistics were analyzed via demographic characteristics. Paired samples t-test was used for the comparison of hemogram values while chi square test was used for the comparison of percentage values. p value below 0.05 was considered as statistically significant.

Results

Among 2276 pregnant women who delivered in the last 5 years, 8 of 81 patients with placenta previa were excluded from the study since they had marginal or low lying placenta previa. Six patients were also excluded from the study due to the missing information in their medical files. As a result, 67 (29/1000) cases were included in the study. The demographic characteristics of the patients are shown in the Table 1. Except four

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean*</th>
<th>Min.</th>
<th>Max.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>31.27±5.73</td>
<td>17</td>
<td>44</td>
</tr>
<tr>
<td>Gravida</td>
<td>3.78±1.42</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Parity</td>
<td>2.1±0.09</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Week of gestation</td>
<td>35.2±3.63</td>
<td>22</td>
<td>39</td>
</tr>
<tr>
<td>Number of cesarean section</td>
<td>1.9±0.97</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>2674±807</td>
<td>580</td>
<td>4580</td>
</tr>
<tr>
<td>1-minute Apgar score</td>
<td>6.7±2.4</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>5-minute Apgar score</td>
<td>7.8±2.5</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Erythrocyte (unit)</td>
<td>2.63±3.98</td>
<td>0</td>
<td>28</td>
</tr>
<tr>
<td>Operation duration (minute)</td>
<td>95±48</td>
<td>45</td>
<td>300</td>
</tr>
<tr>
<td>Hospitalization period (day)</td>
<td>4.9±4.3</td>
<td>1</td>
<td>30</td>
</tr>
<tr>
<td>Preoperative Hb (g/dl)</td>
<td>10.6±1.7</td>
<td>6.9</td>
<td>14.7</td>
</tr>
<tr>
<td>Preoperative Htc (%)</td>
<td>31.87±4.8</td>
<td>22.3</td>
<td>43.8</td>
</tr>
<tr>
<td>Postoperative Hb (g/dl)*</td>
<td>9.8±1.4</td>
<td>6.9</td>
<td>13.8</td>
</tr>
<tr>
<td>Postoperative Htc (%)*</td>
<td>29.44±4.5</td>
<td>21.8</td>
<td>43.8</td>
</tr>
</tbody>
</table>

* Mean variables and their standard deviations were provided.

†Postoperative hemoglobin value was found to be statistically and significantly lower than the preoperative value (p=0.001).

‡Postoperative hematocrit value was found to be statistically and significantly lower than the preoperative value (p=0.001).
patients, it was reported that all patients had cesarean history. A significant decrease was observed in the hemogram and hematocrit values of patients (p=0.001 and p=0.001, respectively). Pfannenstiel incision was applied in 53 (79%) patients while median hypogastric incision was applied in 14 (21%) patients. Twenty-two patients were applied post-cesarean hysterectomy, 40 patients were applied HAL, 12 patients were applied uterine sutures on placental implantation region and 3 patients were applied Foley catheter (Table 2). All of the patients who were applied uterine suture and Foley catheter were in the non-hysterectomy group. It was found that 27 (67.5%) of 40 patients who had HAL were applied post-cesarean hysterectomy and 5 of 27 patients who did not have HAL were applied post-cesarean hysterectomy, and there was statistically a significant difference between groups (p=0.001) (Fig. 1). It was found by the pathology results of the patients who had hysterectomy that 8 (25%) patients did not have accreta, 11 (34.4%) patients did not have increta, 10 (31.3%) patients did not have percreta and 3 (9.4%) patients did not have placental invasion. Fifty-one (76.1%) patients needed blood transfusion. Averagely, 2.63 units of erythrocyte suspension were administered. Also, 39 (58.2%) patients needed intense care. In terms of complications, 9 patients had bladder injury, 1 patient had vaginal cuff hematoma and 1 patient developed DIC. In the follow-up period of the patient who had DIC, the patient developed multi-organ failure and died on postpartum 30th day. In neonatal results, major anomaly was found in two newborns, one being multiple anomaly and other being hydrocephaly.

### Discussion

Together with the increase of previous cesarean rates recently, placenta previa cases have been observed more frequently. Indeed, we found placenta previa in 29 of 1000 deliveries in our study. It is seen that our rate is 7–8 times higher than the values 3.5–4.6 per 1000 deliveries reported in the literature. In terms of the demographic characteristics, our cases were in their 30s, their mean parity was two and almost all had previous cesarean history. Previous cesarean history and multiparity are also major risk factors for placenta previa in our study. It is also observed that Pfannenstiel incision is preferred more, operation durations reach 1.5 hour, patients are hospitalized about 5 days and more than half of them require intense care. It is seen that hemogram values decreased significantly after surgery and the patients were administered approximately 2.6 units of erythrocyte suspension.

Together with placenta previa, various rates of placental attachment anomalies were reported. Placental attachment anomaly was reported as 11–25% when there was single cesarean section history together with placental previa, 35–47% when there were two previous cesarean sections and about 40% when there were above three previous cesarean sections. In our study, we found attachment anomaly confirmed by histologically in about 43% among all the patients with placenta previa. It was seen that our patients had averagely 2–3 previous cesarean sections. Accreta was reported in 8 patients, increta in 11 patients and percreta in 10 patients. In the study of Sumigama et al., there were 18 placenta increta and 5 placenta percreta.

### Table 2. Conservative and radical surgical methods applied together with cesarean section.

<table>
<thead>
<tr>
<th>Method</th>
<th>Done (%)</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypogastric artery ligation</td>
<td>40 (59.7)</td>
<td>27 (40.3)</td>
</tr>
<tr>
<td>Postpartum hysterectomy</td>
<td>32 (47.8)</td>
<td>35 (52.2)</td>
</tr>
<tr>
<td>Uterine suture</td>
<td>12 (17.9)</td>
<td>55 (82.1)</td>
</tr>
<tr>
<td>Foley catheter</td>
<td>3 (4.4)</td>
<td>64 (96)</td>
</tr>
</tbody>
</table>

Fig. 1. Postpartum hysterectomy distribution in patients who did and did not undergo hypogastric artery ligation (HAL).
Evaluation of conservative and radical surgical outcomes in placenta previa and accreta cases

cases in 408 patients with previa. In the study of Grace Tan et al.,[15] 12 of 27 patients were reported to have placenta accreta, one to have placenta increta and 14 to have placenta percreta. It can be considered from the lower rate of placenta accreta in pathological reports that uterus could be protected much in these patients.

Placenta previa increases the risks for antepartum (RR=9.8), intrapartum (RR=2.5) and postpartum hemorrhage (RR=1.9).[16] Therefore, the need for blood transfusion in pregnant women with PP increased compared to those without PP (12% vs. 0.8%).[17] In our study, the need for blood transfusion was 76%. In order to control the hemorrhage, HAL was used the most among surgical procedures; however, post-cesarean hysterectomy was applied at a significant rate in these cases (Fig. 1). This has made us to consider that the intractable hemorrhage seen in PP and/or placental attachment anomalies were not got under control sufficiently by HAL, and therefore hysterectomy would be required in these patients. HAL was first applied to stop refractory hemorrhage seen in cervix cancer.[18] Although rational pelvic blood flow in HAL was decreased about 50% and arterial pressure was dropped in gynecologic and obstetric hemorrhages, blood flow rate decreases since venous pressure is kept stable.[19] The branches from external iliac artery to paravesical and vaginal areas after HAL can explain the failure of HAL in placental attachment anomalies. In some cases, massive blood flow was observed from external iliac artery to anastomosis lines, and even anastomoses with inferior epigastric and inferior mesenteric arteries contributed blood build up of uterus again through uterine artery.[20] It was also shown that the artery was recanalized after HAL, and blood flow in uterine, arcuate and ovarian arteries was sustained.[21] In the study of Iwata et al.,[19] the groups which did and did not have HAL were compared in the patients who had cesarean hysterectomy due to placenta accreta, and no difference was found between the groups in terms of hemostasis. It was emphasized in another study that HAL did not decrease morbidity in placenta accreta, expected blood loss or blood transfusion need, and that HAL was not required in the prophylactic routine practice in placenta accreta.[22] There are some studies with small populations suggesting prophylactic hypogastric artery embolization in patients suspected for placenta accreta.[23,24] In this study, HAL was applied before hysterectomy in all patients who had both HAL and hysterectomy.

In our study, among other surgical methods, square-shaped sutures were applied to uterus in 12 patients and Foley catheter was applied in 3 patients. Cho et al.[25] reported that applying square and circular sutures over uterus serosa on placental implantation localization contributed to hemorrhage control. In this study, all of the patients, who had saturation and applied Foley catheter even in a low rate, being in the non-hysterectomy group may be considered that these methods could be preferred first for hemorrhage on implantation region.

Mortality rates up to 7% were reported depending on the complications observed together with placenta previa such as ureter damage, infection and fistula formation in addition to intraoperative and postoperative massive blood loss and transfusion in placenta accreta.[26] In this study, a patient who developed DIC and sepsis after massive hemorrhage and transfusion died on postoperative 30th day. Sumigama et al.[14] reported in their study that one patient with placenta previa died due to massive hemorrhage. In our study, the most severe complication was bladder injury and found in 9 patients. Bladder injury in placenta previa was reported as 1/10,000 in the literature and it was stated that multidisciplinary approach might be required in such patients.[27]

Our neonatal results show mean week as 35, weight as 2600 g and almost normal Apgar scores. Similarly, O’Brien et al.[24] indicated in their study that the patients suspected for placenta accreta had post-hemorrhage delivery need after 35th week at a rate of 93% and 4 out of 8 maternal death were in labors delayed after 36th week. American College of Obstetricians and Gynecologists (ACOG) recommends planning preterm cesarean hysterectomy after 34 weeks of gestation in cases suspected for placenta accreta. Although we observed major anomaly in two fetuses in our study, it was also reported in the literature that placenta previa decreases Apgar score but it is not associated with congenital anomaly and fetal death.[28]

**Conclusion**

In cases with placenta previa in company with placental attachment anomaly, conservative surgical approach can be an alternative method. However, organ protection activity of HAL in such cases is considered to be suspicious.

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


The impact of amnioinfusion on fetal survival in second trimester oligohydramnios cases with intact membrane

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Abstract

Objective: Insufficient amount of amniotic fluid may cause various complications from intrauterine asphyxia to fetal death associated with fetal movement, fetal growth, lung development and cord compression. There are some studies showing that amniotic fluid restoration by amnioinfusion is helpful for the extension of gestation and survival in such patients. In this study, we aimed to present amnioinfusion results in second trimester oligohydramnios cases.

Methods: In this retrospective study, the medical records of the patients who had amnioinfusion in the Perinatology Department of Mustafa Kemal University between January 2013 and March 2015 were analyzed. All patients had detailed sonographic analysis results before and after the procedures. Ages, gravida values, parities, and weeks of gestation during amnioinfusion and after delivery of the patients were recorded. The patients were called by phone and information was obtained about the perinatal survival of the babies.

Results: Twenty-six of 34 patients who had amnioinfusion were included in the study. In these patients, the mean age was 29.2, gravida was 2.9, parity was 1.1 and the number of abortion was 0.7. It was found that the mean week of gestation for the procedure was 21.5 (range: 15.3 to 27.2) weeks, amniotic fluid index was 2.1 (range: 0.5 to 4) cm, the number of procedure was 1.6 (range: 1 to 5) and mean week of delivery was 26.4 (range: 18 to 35.4) weeks. Ten (45%) fetuses were born alive. It was reported that 6 of them died during perinatal period. Only 4 (18%) babies were alive. The mean period between the procedure and the delivery was 5.1 (range: 0 to16.7) weeks.

Conclusion: In cases without ruptures of membrane at second trimester, it seems that amnioinfusion is associated with perinatal survival at a rate of 18%. It is seen in these patients that amnioinfusion did not provide a certain improvement in poor prognosis.

Keywords: Amnioinfusion, oligohydramnios, second trimester.

Özet: Amniyoinfüzyonun membran intakt ikinci trimester olgularında fetal yaşam etkisi


Bulgular: Amniyoinfüzyon yapılan 34 hastadan 26’sı çalışmaya dahil edildi. Ortalama yaş 29.2, gravida 2.9, parite 1.1 ve abortus sayısı 0.7 olarak bulundu. İşlem yapılan ortalamada gebelik haftası 21.5 (ara: 15.3-27.2) hafta, amniyos svi indeksi 2.1 (ara: 0.5-4) cm, işlem sayısi 1.6 (ara: 1-5) ve ortalama ifllem haftaları 26.4 (ara: 18-35.4) hafta olarak bulundu. 10 (%45) fetüs canlandı. Bu bebeklerin %6'sının perinatal dönemde kaybedildiği rapor edildi. Toplam %4 (18) beşinin canli olduğu görüldü. Ortalama işlem ve doğum aralığı 5.1 (ara: 0-16.7) hafta olarak bulundu.

Sonuç: İkinci trimesterde membran rüptürü olmayan olgularda amniyoinfüzyon %18 oranında perinatal sağkalım sağlandı ile ilişkili görülmüştür. Bu hastalarda amniyoinfüzyonun kötü prognoza belirgin bir iyileşme sağlandığını görülmüştür.

Anahtar sözcükler: Amniyoinfüzyon, oligohydramnios, ikinci trimester.
Introduction

Oligohydramnios is the condition where amniotic fluid volume is less compared to the week of gestation. Second trimester oligohydramnios may be caused by fetal renal anomaly or obstructive uropathy, preterm premature rupture of membrane (PPRM), fetal growth retardation, placental insufficiency or unknown factors. Insufficient amount of amniotic fluid may cause various complications from intrauterine asphyxia to fetal death associated with fetal movement, fetal growth, lung development and cord compression. Second trimester oligohydramnios is seen in about 1% of all pregnancies. Mortality rate was reported as approximately 80–90% together with the lethal pulmonary hypoplasia. Therefore, early-onset oligohydramnios was mostly considered as a reason for termination in the past. In line with this information, it was determined to prevent potential risks of oligohydramnios and to increase perinatal survival by increasing the volume of amniotic fluid through antepartum transabdominal infusion. Despite the lack of randomized controlled studies, there are studies suggesting that amniotic fluid restoration by amnioinfusion helps the extension of gestation at least until pulmonary maturity is reached. In this study, we aimed to present our amnioinfusion results in second trimester oligohydramnios cases.

Methods

In this retrospective study, the cases that were at their 14–28 weeks of gestation and had amnioinfusion in the Perinatology Department of Mustafa Kemal University between January 2013 and March 2015 were evaluated. All patients had ultrasonographic anatomic analyses before and after amnioinfusion procedure. Ages, gravida values, parities, and weeks of gestation during amnioinfusion and after delivery of the patients and the complications developed after the procedure were recorded. The patients were called by phone and information was obtained about the perinatal survival of the babies. Amnioinfusion procedure was carried out in the direct guidance of ultrasonography after receiving consent forms signed by the patients. Amniotic cavity was reached by 15 mm 20–22 Gauge needle through the localization observed to have the highest volume of amniotic fluid. After it was confirmed that the needle was inside the cavity by about 1 ml fluid aspiration, Ringer’s lactate solution warmed at approximate body temperature was administered at 25–50 ml/min, as 10 ml per each week of gestation. After the procedure, patients had anatomic screening by ultrasonography. All patients had prophylactic antibiotic treatment. Also, the patients with negative Rh factor were applied anti-D prophylaxis.

Results

Six of 34 patients who had amnioinfusion were excluded from the study since their follow-up information could not be accessed, one patient was excluded due to the termination of gestation as fetal anomaly and trisomy 18 in karyotyping were found after the procedure and one patient was excluded since she had amnioinfusion at 31 weeks of gestation, and remaining 26 patients were included in the study. The demographic and clinical characteristics of the patients are shown in the Table 1.

It was found that the mean week of gestation for the procedure was 21.5 (range: 15.3 to 27.2) weeks, amniotic fluid index was 2.1 (range: 0.5 to 4) cm, the number of procedure was 1.6 (range: 1 to 5) and mean week of delivery was 26.4 (range: 18 to 35.4) weeks. Amnioinfusion was applied once in 18 patients, twice in 4 patients, three times in 2 patients, four times in one patient and five times in one patient. During the follow-up of the patients, termination was carried out in 4 patients by receiving the consent of the patient and her relatives due to the active amniotic fluid discharge during and immediately after the procedure. Nine (41%) fetuses died immediately after the birth, 10 (45%) fetuses were born alive and 2 (9%) of them were found to be intrauterine ex fetus after the post-procedure examination. One (5%) pregnancy resulted in abortion. It was reported that 6 of the live births died during perinatal period. Only 4 (18%) perinatal deaths were attributed to the procedure and complications developed after the procedure.
babies were alive. Demographic characteristics and perinatal survival rates of live births are shown in the Table 2. The mean period between the procedure and the delivery was 5.1 (range: 0 to 17) weeks.

Discussion

It is known that fetal urine contaminates amniotic sac in the beginning of the second trimester and fetus starts to swallow amniotic fluid. Therefore, disorders related with fetal urinary/renal system have a significant role in the etiology of oligohydramnios. Maternal and placental factors, rupture of placental membranes in particular, may cause oligohydramnios during second trimester. In our study, there was no case with fetal renal anomaly, and termination was carried out in 4 patients upon their requests due to active amniotic fluid discharge after amnioinfusion. Therefore, we found in our series including idiopathic oligohydramnios related with the reasons except EMR and renal anomaly that perinatal survival rate was 18% and mean week of gestation extended 5.1 weeks.

The survival rate of the fetuses with second trimester oligohydramnios was reported less than the rates of the cases found at third trimester (10.2%–14.4% vs. 57.7%–85.3%). Hadi et al. reported perinatal mortality rate as 90.1% in patients who admitted with PPRM at weeks 20–25 of gestation and had amniotic fluid below 2 cm during admission. It was reported in a review that only 8 (14%) of 57 babies had neonatal survival in second trimester oligohydramnios. However, an increase in the survival rates of fetuses after amnioinfusion was reported in the studies. Fisk et al. reported survival in 3 of 8 patients who were below 22 weeks of gestation and had weekly transabdominal amnioinfusion. In their study, Ogunyemi et al. done a series of amnioinfusion to a group consisting of patients with second trimester PPRM and did no treatment on the other group, and showed that the perinatal mortality rate decreased in the treatment group (83% vs. 33%). In another study performed on idiopathic oligohydramnios cases, it was seen that 8 of 12 cases died after the procedure.

Extending gestational age by amnioinfusion and improving gestational outcomes as a result were reported in various studies and their results are similar to our study. Ogunyemi et al. found that the period from antepartum amnioinfusion to delivery was approximately 33 days. Garzetti et al. found the latent period as 3 weeks in patients who had prophylactic amnioinfusion for PPRM below 25 weeks of gestation. In another study carried out on persistent oligohydramnios cases, it was found that the period up to delivery in cases which did not have amnioinfusion were significantly less. Turhan and Atacan showed that amnioinfusion extended the latent period but did not change perinatal outcomes. In their studies, they applied amnioinfusion to 15 of 29 women with oligohydramnios and followed up 14 of them spontaneously without any treatment and found that the latent period was extended 15 days in the amnioinfusion group while the extension was only 8 days in the other group.

### Table 2. Demographic characteristics and perinatal survival conditions of live birth cases after amnioinfusion.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Gravida</th>
<th>Parity</th>
<th>Amnioinfusion week</th>
<th>AFI (cm)</th>
<th>Birth week</th>
<th>Peripartum survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22</td>
<td>1</td>
<td>0</td>
<td>19.3</td>
<td>1.5</td>
<td>34</td>
<td>Live</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>2</td>
<td>0</td>
<td>23.3</td>
<td>4.0</td>
<td>35.4</td>
<td>Live</td>
</tr>
<tr>
<td>3</td>
<td>23</td>
<td>3</td>
<td>2</td>
<td>16.3</td>
<td>1.6</td>
<td>33</td>
<td>Live</td>
</tr>
<tr>
<td>4</td>
<td>34</td>
<td>4</td>
<td>2</td>
<td>19</td>
<td>1.8</td>
<td>27</td>
<td>Ex</td>
</tr>
<tr>
<td>5</td>
<td>23</td>
<td>1</td>
<td>0</td>
<td>26.3</td>
<td>1.9</td>
<td>26.6</td>
<td>Ex</td>
</tr>
<tr>
<td>6</td>
<td>39</td>
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<td>2</td>
<td>24</td>
<td>1.4</td>
<td>25</td>
<td>Ex</td>
</tr>
<tr>
<td>7</td>
<td>29</td>
<td>1</td>
<td>0</td>
<td>26</td>
<td>0.5</td>
<td>32</td>
<td>Live</td>
</tr>
<tr>
<td>8</td>
<td>27</td>
<td>5</td>
<td>3</td>
<td>23</td>
<td>1.2</td>
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<td>Ex</td>
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<tr>
<td>9</td>
<td>36</td>
<td>4</td>
<td>2</td>
<td>23</td>
<td>1.5</td>
<td>23</td>
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<td>28</td>
<td>2</td>
<td>1</td>
<td>27</td>
<td>1.1</td>
<td>29</td>
<td>Ex</td>
</tr>
</tbody>
</table>

AFI: amniotic fluid index
The first condition stating that amniofusion is beneficial in second trimester oligohydramnios is that fetal anomalies can be detected better. As oligohydramnios may spoil ultrasonographic examination under optimal conditions, it was reported that such cases could be screened better with approximately 200 ml amnioinfusion. In a review including unexplained second trimester oligohydramnios cases, it was reported that imaging fetal structures with amnioinfusion increased from 51% to 77%. Also, detection of obstructive uropathies with amnioinfusion increased from 12% to 31%. In our study, we found trisomy 18 findings in a patient and carried out termination procedure. Hsu et al. found fetal anomaly in 5 cases after amnioinfusion in their study. The second condition stating that amnioinfusion is beneficial is the facilitation of external cephalic version. However, there is no sufficient relevant data in the literature. Despite the insufficient data in the literature, it can be considered that the advantage provided by the amnioinfusion can be compensated with the high-resolution ultrasonography devices without any amnioinfusion thanks to the software such as 3D-HD live.

The third condition recommending amnioinfusion is the prevention of sequelae caused by oligohydramnios. It was shown in the sheep models developing full obstructive uropathy that pulmonary hypoplasia is prevented by intraamniotic port in those which had serial amnioinfusion compared to non-amnioinfusion group, and that their lung volumes were comparable compared to the sham group. Also, there are studies showing that meconium aspiration syndrome can be decreased by amnioinfusion lowering tracheal meconium volume in fetuses with meconium.

Complications such as chorioamnionitis, endometritis, ablatio placentae, preterm labor, fetal loss and fetal trauma due to the procedure were all reported in the literature. Hsu et al. reported intrauterine fetal loss in 4 of 17 patients within 2 weeks following amnioinfusion. In our study, we lost two fetuses and had an abortion in one patient after the procedure. However, no major maternal complication developed.

Lack of control group and not knowing long-term follow-up outcomes of the patients are the limitations of our study.

Conclusion

In conclusion, we found that antepartum amnioinfusion in early-onset oligohydramnios cases has a minimal risk for the mother except PPRM and renal anomaly; however, the prognosis was poor although a slight increase was observed in the fetal survival rates after the procedure.

Conflicts of Interest: No conflicts declared.

References


Inhibitory effects of isradipine on uterine contractions in pregnant rats

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Abstract

Objective: To investigate the effects of isradipine, which is a calcium channel blocker, on late pregnant rats' myometrium under in vitro conditions.

Methods: Stripes were obtained from the myometriums of pregnant rats which were decapitated on the 18 days of gestation. The effects of isradipine on myometrium were investigated in four groups and four cumulative doses: 1 ng/ml, 10 ng/ml, 0.1 µg/ml, 1 µg/ml. Group I: spontaneous myometrial contractions, Group II: myometrial contractions induced by oxytocin, Group III: myometrial contractions induced by prostaglandin, Group IV: myometrial contractions induced by oxytocin in calcium-free medium. Wilcoxon signed ranks test was used for the statistical analysis and p<0.05 was considered statistically significant.

Results: Group I: compared to the control group, 10 ng/mL and 0.1 µg/mL isradipine decreased the amplitude of uterine contractions. Group II: 0.1 µg/mL isradipine decreased the frequency of contractions (p=0.02). Isradipine decreased the amplitudes in the doses of 10 ng/mL and 0.1 µg/mL (p=0.02 for each dose). Group III: 0.1 µg/mL isradipine decreased the frequency of contractions (p=0.02). Isradipine decreased the amplitudes in the doses of 10 ng/mL and 0.1 µg/mL (p=0.02 for each dose). One µg/mL isradipine completely removed all spontaneous and induced contractions. Group IV: when compared to mediums with calcium, both amplitudes and frequencies of the contractions were found lower in this group (p<0.001). Isradipine was only used in the dose of 1 µg/ml and it completely removed all contractions.

Conclusion: Isradipine inhibits in vitro myometrial contractions in late pregnant rats and it may be effective in preventing early labor.

Keywords: Early labor, tocolytic, calcium channel blocker, isradipine, prostaglandin, rat.

ÖZET: Gebe ratlarda isradipinin uterus kontraksiyonları üzerine inhibitory etkileri

Amaç: Kalsiyum kanal blokörü olan isradipinin geç gebe rat miyometriumu üzerindeki etkilerini in vitro koşullarda araştırmaktır.

Yöntem: Gebelik 18. gününde dekapit edilen gebe ratların miyometriumlarından şeritler elde edildi. Isradipinin miyometrium üzerindeki etkileri dört grupta ve dört kümülatif dozda araştırıldı; 1 ng/ml, 10 ng/ml, 0.1 µg /ml, 1 µg /ml. Grup I: Spontan, Grup II: Oksitosinle induklenmiş, Grup III: Prostaglandinin ile induklenmiş, Grup IV: Kalsiyumuz ortamda oksitosinle induklenmiş miyometrial kontraksiyonlar. İstatistiksel analiz için Wilcoxon signed ranks testi kullanıldı ve p<0.05 istatistiksel olarak anlamlı kabul edildi.

Bulgular: Grup I: Kontrol grubu ile karşılaştırıldığında 10 ng/ml ve 0.1 µg/ml isradipin, uterus kontraksiyonlarının amplitüdünü azalttı. Grup II: 0.1 µg/mL isradipin, kontraksiyonların frekansını azalttı (p=0.02). Isradipin 10 ng/ml ve 0.1 µg/mL doz'da kontraksiyonların amplitüdlerini azalttı (her iki doz için p=0.02). Grup III: 0.1 µg/mL isradipin, kontraksiyonların frekansını azalttı (p=0.02). Isradipin 10 ng/ml ve 0.1 µg/mL doz'da kontraksiyonların amplitüdlerini azalttı (her iki doz için p=0.02). Isradipin 1 µg/mL tüm spontan ve induklenmiş kontraksiyonları tamamen ortadan kaldırdı. Grup IV: Kalsiyum bulunan ortamlarla karşılaştırıldığında bu grupta kontraksiyonların hem amplitüdleri hem de frekansları daha düşük bulundu (p<0.001). Isradipin sadece 1 µg/ml dozunda kullanıldı ve kontraksiyonları tamamen ortadan kaldırdı.

Sonuç: Isradipin, geç gebe ratlarda miyometrial kontraksiyonları in vitro inhibe etmektedir ve erken doğumun önlenmesinde etkili olabilir.

Anahtar sözcükler: Erken doğum, tokolitik, kalsiyum kanal blokörü, isradipin, prostaglandin, rat.
Introduction

Early labor is the most significant reason of neonatal mortality and morbidity in the world. Although significant improvements have been made in understanding the uterine physiology and developing new agents to prevent early labor, the incidence of early labor has been at the same level.\cite{1,2} More than half of the early labors occur either due to spontaneous contractions or early rupture of membrane. It is reported that about 75% of neonatal deaths and 50% of childhood neurological problems are associated with early labor.\cite{3}

Today, there are various agents used as tocolytic. Magnesium sulphate, prostaglandin synthesis inhibitors (i.e. indomethacin), nitric oxide or donors (i.e. nitroglycerine), atosiban as the oxytocin antagonist and calcium channel blockers (i.e. nifedipine, nicardipine) are used as tocolytic.\cite{4–8}

Calcium channel blockers are used quite commonly as tocolytic. In cases under early labor risk which use calcium channel blocker as tocolytic, it has been reported that less cases delivered within 7 days and under 34 weeks, the requirement to discontinue medication was less frequent, and less respiratory distress syndrome, necrotizing enterocolitis, intraventricular bleeding and jaundice were observed.\cite{9} Despite the activities of calcium channel blockers stated above, most effective and safest doses of these medications have not been found yet. As an addition, it was reported that nifedipine and nicardipine have serious adverse effects such as pulmonary edema.\cite{10,11} Under these conditions, new studies have been carried out to understand the most effective and safest doses of these medications and to investigate possible effects of new calcium channel blockers on the contractions of uterine myometrium.\cite{12,13,14,15}

Isradipine is one of the calcium channel blockers. There are some studies on the effects of this medication on myometrium.\cite{14,15} However, current methods are not strong enough to draw a conclusion about the effects of isradipine on myometrium and the suitability of using as a tocolytic. Under current information, this study was planned to investigate the effects of isradipine on the myometrium contractions in pregnant rats.

Methods

Experimental Animals, Tissue Preparation and Experiment Models

Approval from Local Ethics Committee of Firat University was obtained. For the experiments, female Wistar rats (220–240 g) supplied by Biomedical Researches Unit of Firat University were used. All of the experiments were carried out in the Physiology Laboratory of Faculty of Medicine, Firat University. The animals were kept under controlled temperature (22±1 °C) and light (lightning between 07:00 and 19:00) conditions. Food and water were provided as ad libitum. Daily vaginal smear test was carried out on animals and rats at pro-oestrus period were kept with sexually active and experienced male rats in the nights of such days. Vaginal smear test was carried out in the next day again and the day found sperm in the smear was considered as the day zero (the inception). All rats were decapitated on the 18 days of gestation. Four myometrial strips (1 mm in thickness, 2 mm in width and 12 mm in length each) were taken from each animal.

Four groups were established to test the effect of increasing doses of isradipine. Obtained muscle strips were put in organ bath filled with Krebs solution. Organ bath was aired regularly with 95% O2 – 5% CO2 mixture at 37 °C. The strips were attached to a fixed metal hook on the bottom and to an symmetric force displacement transducer (MAY; Commat Ltd., Ankara, Turkey) on the top. The signals coming from the transducer were amplified by an interface (MAY; Commat Ltd., Ankara, Turkey) and the data obtained were uploaded to a computer. For recording isometric tension, the strips were kept in balance for 30 minutes in 1 g resting tension. After spontaneous contractions occurred, myometrial contractions were induced either by oxytocin (10 mU/ml bath solution) or prostaglandin PGF2α, or they were just recorded as spontaneous contractions.

The effects of isradipine in increasing concentrations on myometrial contractions were investigated. Ten minutes before medication (predrug: spontaneous, pre-induction by oxytocin and PGF2α) were recorded as control for each strip. Amplitudes and frequencies of contractions (number of contractions observed within 10 minutes) were recorded both before applying isradipine and in increasing doses (1 ng/mL, 10 ng/mL, 0.1 µg/mL and 1 µg/mL) every 10 minutes for each dose. Further experiments were carried out to investigate the effects of isradipine on contractions induced by oxytocin in calcium-free mediums. For that purpose, single dose (1 µg/ml) isradipine was tested on contractions induced by oxytocin in calcium-free Krebs solution. Data were recorded and analyzed by computer software (Biopac System Inc, Goleta, CA, USA).
Experiments
The experiments were planned and carried out as 4 groups. Four different strips taken from a rat were used as 4 different groups.

**Group I:** The contraction period for the first 10 minutes was recorded as the control of each strip. Immediately after this control period, isradipine (Dynacirc SRO; Novartis, Istanbul, Turkey) was added cumulatively in 1 ng/mL, 10 ng/mL, 0.1 µg/mL and 1 µg/mL concentrations, respectively, as with 10-minute durations for each dose. Amplitudes and frequencies of contractions and the area under the curve were recorded both before the application of isradipine at different doses between 1 ng/ml and 1 µg/ml and every 10 minutes for each dose. The records were stopped 10 minutes after the application of the last dose.

**Group II:** In this group, it was waited until all spontaneous contractions stopped in myometrial strips. After spontaneous contractions stopped, the contractions were induced by adding approximately 0.0004 IU/mL oxytocin (Synpitan Forte; Deva Holding A.Ş., Istanbul, Turkey). Contractions induced by oxytocin were recorded as control. Immediately after this 10-minute control period, isradipine was added to the medium as indicated in the Group I above.

**Group III:** Just after spontaneous contractions disappeared, 1 µM d-cloprostenol (Dalmazin; Vetaş, Istanbul, Turkey) which is a synthetic PGF2α was added to the medium. The contraction induced by PGF2α was recorded as control for 10 minutes. After this control record, isradipine was added to the medium as indicated in the Group I above, and contractions were recorded.

**Group IV:** This group was created to find the amplitudes and frequencies of myometrial contractions in calcium-free medium and to test the effects of oxytocin and oxytocin+isradipine combination on these strips. In this group, the effects of isradipine on contractions induced by oxytocin in calcium-free medium were investigated. Before myometrial strips were placed, calcium-free Krebs solution was added to the medium and a calcium-free medium was obtained. In calcium-free medium, a single dose (1 µg/ml) of isradipine was added on contractions induced by oxytocin. Since spontaneous contractions disappeared after a few contractions, oxytocin (0.0004 IU/mL) was added to the medium as soon as contractions disappeared. Isradipine was added once in the dose of 1 µg/mL after contractions induced by oxytocin were recorded for 5 minutes. The record was ended at 15th minute of applying isradipine.

Statistical Analysis
All the data was presented as mean±standard error (M±SE). Non-parametric Wilcoxon signed ranks test was used for the analysis of the data. All statistical analyses of the data were done by using SPSS software, version 13.0 (SPSS, Inc., Chicago, IL, USA). A p-value <0.05 was considered as significant.

Results
**Group I:** The frequency of spontaneous contractions was calculated as 11.2±0.6/10 minutes. This value was measured as 11.0±0.6/10 minutes after 1 ng/mL isradipine was added and when contraction frequency was compared to the control group, the difference was not significant (p=0.317). After 10 ng/mL and 0.1 µg isradipine was added, the contraction frequency was measured as 10.7±0.5/10 and 6.3±2.0/10 minutes, respectively; these values was also not different than the control group (p=0.180 and p=0.68, respectively). By adding 1 µg isradipine, the spontaneous contractions disappeared completely (Figs. 1a and b).

**Group II:** After oxytocin application, the frequency of contractions was measured as 11.0±0.6/10 minutes after 1 ng/mL isradipine was added and when contraction frequency was compared to the control group, the difference was not significant (p=0.317). After 10 ng/mL and 0.1 µg isradipine was added, the contraction frequency was measured as 10.7±0.5/10 and 6.3±2.0/10 minutes, respectively; these values was also not different than the control group (p=0.180 and p=0.68, respectively). By adding 1 µg isradipine, the spontaneous contractions disappeared completely (Figs. 1a and b).

In this group, mean amplitude of control contractions was measured as 3416.3±560.3 mg. When isradipine was added in the dose of 1 ng/mL, this value was measured as 3281.5±494.3 mg and statistically no significant difference was found between these values (p=0.08). Adding 10 ng/mL and 0.1 µg isradipine caused a statistical significant decrease in the contraction frequencies (2834.8±324.2 mg and 1188.8±271.7 mg, respectively) (p=0.02 for both). Adding isradipine in the dose of 1 µg/mL caused spontaneous contractions disappear completely (Figs. 1a and c).

**Group II:** After oxytocin application, the frequency of contractions was measured as 14.3±0.3/10 minutes. Adding isradipine in the doses of 1 ng/mL and 10 ng/mL did not cause any significant change in contraction frequencies (14.3±0.3/10 and 13.3±1/10 minutes, respectively; p=1 and p=0.1). While isradipine in the dose of 0.1 µg/mL caused statistically a significant decrease to 1.50±1.50/10 minutes in the contraction frequency (p=0.02), isradipine in the dose of 1 µg/mL caused oxytocin-induced contractions to disappear completely (Figs. 2a and b).
Mean contraction amplitude in the control group was calculated as 2892.3±165.7 mg. By adding 1 ng/mL isradipine, this value reached 2894.7±176.0 mg and the difference was statistically not significant (p<0.05). By adding 10 ng/mL and 0.1 µg/mL isradipine, amplitude decreased to 2168.5±100.0 mg and 100.3±100.3 mg, respectively, and when these values were compared to the control group, the difference was statistically significant (p=0.02 for both). One µg/mL isradipine caused spontaneous contractions to disappear completely (Figs. 2a and c).

**Fig. 1.** The effects of isradipine (IS) with increasing concentrations on spontaneous myometrial contractions in late pregnant rats. Isradipine’s (a) peak frequency (number of contractions observed within 10 minutes), (b) peak amplitude level, (c) effects on spontaneous contractions. *p<0.05 when compared to the control group, Wilcoxon signed ranks test.

**Fig. 2.** The effects of isradipine (IS) with increasing concentrations on myometrial contractions induced by oxytocin in late pregnant rats. Isradipine’s (a) peak frequency (number of contractions observed within 10 minutes), (b) peak amplitude level, (c) effects on oxytocin-induced contractions. *p<0.05 when compared to the control group, Wilcoxon signed ranks test. OT: oxytocin.
**Group III:** In the control group induced by PGF2α, mean contraction frequency was calculated as $12.7 \pm 0.3/10$ minutes. Adding isradipine in the doses of 1 ng/mL and 10 ng/mL did not cause any significant decrease in contraction frequencies ($12.7 \pm 0.3/10$ and $11.7 \pm 0.8/10$ minutes, respectively; $p=1$ and $p=0.1$). Isradipine in the dose of 0.1 µg/mL caused a significant decrease in the frequency of contractions ($5.2 \pm 1.7/10$ minutes, $p=0.02$). The contractions induced by PGF2α disappeared completely by adding 1 µg/mL isradipine (Figs. 3a and b).

In the control group induced by PGF2α, mean amplitude of the contractions was calculated as $2787.2 \pm 471.9$ mg. Adding 1 ng/mL isradipine did not cause a significant decrease in the amplitude of contractions ($2756.2 \pm 469.3$ mg, $p=0.08$). Isradipine in the doses of 10 ng/mL and 0.1 µg/mL decreased the amplitudes of the contractions to $2474.8 \pm 535.7$ and $695.7 \pm 306.1$ mg, and the decrease was considered statistically significant compared to the control group ($p=0.02$ for both). The contractions induced by PGF2α disappeared completely by adding 1 µg/mL isradipine (Figs. 3a and c).

**Group IV:** In this group, contraction experiments carried out in calcium-free Krebs solution. It was observed that the contractions induced by oxytocin in the calcium-free medium continued at least for 30 minutes (records were not presented). After the contractions were induced by oxytocin, 1 µg/mL isradipine was added to the medium (at the 7th minute of oxytocin addition). By adding isradipine, all contractions disappeared (Fig. 4). Since the contractions did not continue as in the mediums including calcium, cumulative doses of isradipine were not applied in this group.

**Discussion**

Spontaneous preterm contractions are observed more frequently in multiple pregnancies and polyhydramnios cases. It is considered that extreme stress of uterine triggers the myometrial contractions. In vitro studi-
ies show that the stress of myometrial strips may also induce contractions similar to the extreme stress of uterine. It was reported that myometrial stress increased activator proteins (AP-1), connexin-26 and connexin-43 expressions, and decreased membrane potential.[14,17] The distinct result of this stress is the increase in intracellular calcium ion concentration and in the stimulability of myometrium.

In the current study, it was observed that isradipine inhibited the spontaneous myometrial contractions in myometrium of late pregnant rats depending on the dose. This observation seems consistent with the recommendations of Kantas et al.[18] It is considered that isradipine inhibits myometrium contractions by inhibiting L-type calcium channels, decreasing calcium release from intracellular repositories and facilitating intracellular calcium to move into extracellular area.[19,20]

Although it has been shown that isradipine inhibited myometrial contractions effectively in vitro, there is no study carried on pregnant women except the study presented by Wide-Swensson et al.[21] In this study, isradipine was used during the active phase of delivery and no inhibitory activity on uterine contractions was reported. We think that the active phase of delivery is resistant relatively to tocolytic agents and isradipine requires further studies to investigate its potential tocolytic effect.

It was observed in Group II of the study that isradipine inhibited oxytocin-induced myometrial contractions dose-dependently and removed completely in the highest dose. Çetin et al. reported that isradipine inhibited myometrial contractions in rat myometrium in vitro.[22] While it was observed in our study that isradipine removed contractions completely, this effect was not seen in the study of Çetin et al. It was thought that the highest dose used in this study was not strong enough to remove the contractions completely. The highest dose used in this study was $10^{-4}$ mol/L, and it was lower than the dose we used in our study.

It is known that oxytocin activates inositol triphosphate pathway by connecting to its own receptor to release calcium from intracellular repositories and hydrolyzes membrane phospholipids. Calcium release from intracellular repositories causes an increase in the calcium flow towards cytosol.[23] It is also known that oxytocin causes the depolarization of membranes by opening activated cation channels.[24] In this way, the use of isradipine inhibits calcium entrance into intracellular distance and calcium release from intracellular repository as in L-type calcium channel blockers[19,20] and therefore inhibits myometrium contractions induced by oxytocin.

In this study, it was shown for the first time that isradipine inhibits PGF2α-induced myometrial contractions in vitro. This is the first study investigating the effects of isradipine on PGF2α-induced myometrial contractions. Also, inhibitory effect of isradipine is dose-dependent and the highest dose caused PGF2α-induced myometrial contractions to disappear completely. Prostaglandins have a critical role in the inflammatory process of labor. Their effects were shown not only on myometrium but also on cervix and fetal membranes. They display their effects by increasing the number of gap-junctions between myocytes, the number of oxytocin receptors and by connecting to their own receptors.[25] Infections being the reason of 30–40% of early labors[26] and showing the distinct role of infections in early labor and suppression of PGF2α-induced myometrial contractions by isradipine make us think that isradipine may have an effect on the treatment of early labor.

Myometrial contractions in calcium-free medium had lower amplitude and frequency rates than those in the mediums with calcium. Isradipine in the dose of 1 µg/mL removed all myometrial contractions in calcium-free medium. This finding may indicate that our results are consistent with the study of Kaya et al.[27] and that isradipine in calcium-free medium displays activity by inhibiting calcium release from intracellular repositories.

**Conclusion**

In conclusion, the findings of this study show that in vitro isradipine inhibits dose-dependently the myometrial contractions occurring spontaneously, induced by oxytocin and induced by PGF2α. The results indicate that isradipine may have a tocolytic effect in spontaneous and infection-associated early labor cases. Further studies are required to establish the activity and safety of the medication.

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


Analysis of perinatal outcomes of the pregnant women applied magnesium sulfate due to severe preeclampsia and eclampsia

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Abstract

Objective: In this study, we aimed to analyze the perinatal outcomes of the pregnant women who were applied magnesium sulfate due to the diagnosis of severe preeclampsia and eclampsia in our clinic.

Methods: The patients hospitalized in our clinic and administered with magnesium sulfate due to diagnosis of severe preeclampsia and eclampsia between January 2011 and January 2015 were included in this retrospective study. The data of perinatal outcomes of the patients were reviewed retrospectively through hospital’s medical records. Ablation placenta, oligohydramnios, maternal acute renal failure, maternal neurological deficits, intracranial hemorrhage, which are the maternal complications of preeclampsia and eclampsia, and fetal intracranial hemorrhage, fetal growth retardation, newborn’s intense care need and neonatal necrotizing enterocolitis development, which are the potential fetal complications of preeclampsia and eclampsia, were considered as poor perinatal outcomes.

Results: A total of 207 patients were included in the study. When hospital records were reviewed, it was seen that 17 cases admitted to the hospital after eclamptic seizure, and 54 cases had eclamptic seizure when undergoing magnesium sulfate treatment due to the diagnosis of severe preeclampsia. Mean week of gestation was 32±2.4, and 30±1.5 in the eclampsia group. Mean hospitalization period of the patients with severe preeclampsia was 4±1.7 days while it was 6±2.2 days in patients with eclampsia.

Conclusion: The presence of severe preeclampsia and eclampsia is associated with poor maternal and fetal perinatal outcomes despite the appropriate treatment and close follow-up.

Keywords: Eclampsia, HELLP syndrome, magnesium, preeclampsia.

Özet: Ağır preeklampsi ve eklampsi nedeni ile magnezyum sülfat infüzyonu uygulanan gebelerin perinatal sonuçlarının incelenmesi

Amaç: Bu çalışmada kliniğimizde ağır preeklampsi ve eklampsi tanı ile magnezyum sülfat infüzyonu uygulanan hastaların perinatal sonuçlarını incelenmesi amaçlanmıştır.


Sonuç: Ağır preeklampsi ve eklampsi varlığı, uygun tedavi ve yakını takibe rağmen kötü maternal ve fetal perinatal sonuçlara iliskilidir.

Anahtar sözcükler: Eklampsi, HELLP sendromu, magnezyum, preeklampsi.
Introduction

Preeclampsia is the most common condition complicating pregnancy and it may occur at any period from the second half of pregnancy up to first two weeks after delivery.\(^1\) It is known that preeclampsia is caused by generalized vasospasm as a result of vascular endothelium injury and disorder of endothelium nitric oxide release due to the insufficiency of syncytiotrophoblasts in the invasion of spiral arterioles within myometrium during early weeks of gestation.\(^2\)

Depending on its severity, preeclampsia may cause many life-threatening organ and system damages such as renal failure, cerebral hemorrhage-edema, thrombocytopenia and liver function disorder in mother.\(^3\) Also, preeclampsia may cause baby to develop growth retardation, oligohydramnios, prematurity, increase in newborn intense care need, necrotizing enterocolitis and intracranial hemorrhage.\(^3\)

Addition of eclamptic seizure to severe preeclampsia may cause the increase in maternal mortality and morbidity.\(^5\) The treatment widely used to protect against eclampsia or to prevent its reoccurrence is magnesium sulfate infusion. Magnesium sulfate infusion complying with the protocol is a treatment accepted for its activity in the prophylaxis of eclampsia seizure.\(^4\)

Based on the association of preeclampsia and eclampsia with poor perinatal outcomes, we aimed in this study to review and analysis the perinatal outcomes of pregnant women undergoing magnesium sulfate treatment in our clinic with the diagnosis of severe preeclampsia and eclampsia between January 2011 and January 2015.

Methods

A total of 207 patients hospitalized in Ümraniye Training and Research Hospital and administered with magnesium sulfate between January 2011 and January 2015 due to diagnosis of severe preeclampsia and eclampsia were included in this study.

For the severe preeclampsia diagnosis, 2014 criteria of American College of Obstetricians and Gynecologists, which were the presence of arterial blood pressure over 140/90 mmHg after 20 weeks of gestation and/or proteinuria or target organ failure, were taken into consideration.\(^11\) Occurrence of tonic-clonic seizure in the presence of hypertension was considered as eclampsia. Conditions causing tonic-clonic seizure except the eclampsia were excluded from the study.

Before the magnesium sulfate treatment, blood hemoglobin levels, hematocrit count, platelet count, and serum liver enzyme levels of the patients are checked as a routine practice in our clinic. During the treatment, fetal well-being is checked every 4 hours by non-stress test (NST), daily biophysical profile and fetal umbilical Doppler (if necessary) examinations.

It was seen in the medical files of the patients included in the study that alpha-methyldopa and nifedipine were used as antihypertensive medication for patients appropriate for oral intake, and that magnesium sulfate infusion was performed to all patients in accordance with the protocol. The infusion was carried out as 2 g per hour after 4.5 g loading within 100 cc isotonic fluid in 20 minutes.

While the maternal reasons of labor indications were blood pressure being >160/110 mmHg despite the antihypertensive treatment, persistence and exacerbation of the symptoms, presence of severe acid, ablatio placenta, oliguria, pulmonary edema, premature rupture of membrane, HELLP syndrome and eclampsia, the fetal reasons were the variability loss in NST, presence of recurrent late decelerations, growth retardation, oligohydramnios, diastolic flow lost or presence of reverse flow in the umbilical Doppler screening.

Maternal age, gravida, parity, week of gestation and gestational outcomes were recorded. While ablatio placentae, oligohydramnios, maternal acute renal failure, maternal neurological deficits and maternal death were considered as poor maternal outcomes, fetal intracranial hemorrhage, growth restriction, newborn intense care need and neonatal necrotizing enterocolitis were considered as poor fetal outcomes.

The analysis of the data was done by SPSS 15.0 (SPSS Inc., Chicago, IL, USA). The data obtained were presented as percentage, mean and standard deviation.

Results

It was found that 71 of 207 patients included in the study had eclampsia seizure, and while 17 of these 71 patients admitted to hospital for eclampsia, other 54 patients had eclampsia seizure during magnesium sul-
fate treatment due to severe preeclampsia. Mean age of the patients diagnosed to have severe preeclampsia was 28±2.6, mean gravida was 2±1.1, and mean parity was 1±0.4. In the eclampsia group, mean age was 30±1.2, mean gravida was 2±0.8, and mean parity was 1±0.2 (Table 1). While 62 (29.9%) patients were primigravida, 21 patients had pregestational hypertension. One hundred and thirty-four patients were undergoing antihypertensive treatment due to the diagnosis of pregnancy-induced hypertension. Mean week of gestation was 32±2.4 in severe preeclampsia group and 30±1.5 in the eclampsia group, and two doses of betamethazone were administered with 24-hour interval to patients in accordance with the protocol whose pregnancy was less than 34 weeks of gestation.

Maternal death occurred due to disseminated intravascular coagulopathy (DIC) in one of the patients admitted after eclampsia seizure, and a mass was identified in the frontal lobe in another patient. In 8 (3.8%) patients, various levels of HELLP syndrome developed, and blood and blood product transfusion was carried out. Mean hospitalization period of the patients with severe preeclampsia was 4±1.7 days while it was 6±2.2 days in patients with eclampsia. A total of 95 (45.9%) patients who were decided to deliver due to severe preeclampsia diagnoses had a normal delivery while 46 (22.2%) patients due to previous cesarean section history and 68 (32.8%) patients due to ablatio placentae (n=13), fetal distress, eclampsia and maternal general condition disorder had cesarean section. All patients who had eclampsia underwent cesarean section.

Mean magnesium sulfate intake periods of the patients before delivery was calculated as 8±4.2 hours. During magnesium sulfate treatment, some patients complained about increased heat and decrease in baby movements. In order to monitor the toxic effect of the drug, hourly blood pressure, respiratory rate, urine volume, deep tendon reflexes (patella) of the patients were checked. Fetal well-being was checked every 4 hours by NST, and daily biophysical profile examination. Growth retardation was identified in 28 (13.5%) patients and oligohydramnios was identified in 38 (18.3%) patients. After the delivery, 94 (45.4%) babies needed follow-up in newborn intensive care unit.

Magnesium sulfate infusion continued for 24 hours after delivery for all patients. While all patients who underwent eclampsia were followed up in the intensive care unit after delivery, 15 (7.2%) patients diagnosed to have severe preeclampsia were hospitalized in the adult intensive care service for close monitoring purpose. While none of the patients who underwent severe preeclampsia had eclampsia seizure after the delivery, one case had eclampsia seizure in the intensive care unit and her magnesium sulfate treatment following the last eclampsia seizure was ended after 48 hours by consultant neurologist and diazepam treatment was initiated. Mean hospitalization period of the patients with severe preeclampsia was 4±1.7 days while it was 6±2.2 days in patients with eclampsia. Except the maternal death case, all cases were discharged with well-being after informing them about eclampsia risk and blood pressure follow-up information. Poor perinatal outcomes are summarized in the Table 2.

### Discussion

Severe preeclampsia and eclampsia are the most critical clinical conditions observed during pregnancy, and there are many studies in the literature about screening and preventing these conditions. Initiating acetylsalicylic acid by identifying Doppler abnormality during early weeks of gestation, reasonable use of antihypertensives, informing patients about symptoms before eclampsia are the methods for early diagnosis, treatment and prevention of these conditions. Despite all,

### Table 1. Comparison of the patients diagnosed with severe preeclampsia and eclampsia.

<table>
<thead>
<tr>
<th></th>
<th>Severe preeclampsia</th>
<th>Eclampsia</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>136</td>
<td>71</td>
</tr>
<tr>
<td>Mean age</td>
<td>28±2.6</td>
<td>30±1.2</td>
</tr>
<tr>
<td>Mean gravida</td>
<td>2±1.1</td>
<td>2±0.8</td>
</tr>
<tr>
<td>Mean parity</td>
<td>1±0.4</td>
<td>1±0.2</td>
</tr>
<tr>
<td>Mean week of gestation</td>
<td>32±2.4</td>
<td>30±1.5</td>
</tr>
<tr>
<td>Mean hospitalization period (day)</td>
<td>4±1.2</td>
<td>6±2.2</td>
</tr>
</tbody>
</table>

*Mean variables and their standard deviations were provided.

### Table 2. Comparison of the poor perinatal outcomes in patients diagnosed with severe preeclampsia and eclampsia.

<table>
<thead>
<tr>
<th>Poor perinatal outcomes</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ablatio placentae</td>
<td>13</td>
<td>6.2</td>
</tr>
<tr>
<td>Oligohydramnios</td>
<td>38</td>
<td>18.3</td>
</tr>
<tr>
<td>Newborn intensive care</td>
<td>94</td>
<td>45.4</td>
</tr>
<tr>
<td>HELLP</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>Growth retardation</td>
<td>28</td>
<td>13.5</td>
</tr>
</tbody>
</table>
the incidence rates of severe preeclampsia and eclampsia are among the leading reasons for maternal deaths worldwide while the rates are not clearly defined in Turkey.\(^8\)

Primiparity, young age and low socioeconomical status are the known risk factors for preeclampsia.\(^9\) In our study group, 62 of the cases were primigravida and the mean age of the patients was 28±2.6. Socioeconomical profiles of our patients were consistent with the literature, and it was found that 38 patients did not come to their antenatal follow-up visits during their pregnancies.

Maternal mortality and morbidity risk increases in pregnancies complicated with severe preeclampsia and eclampsia.\(10\) The most significant reasons for the increase of maternal morbidity are severe hemorrhage due to detachment, pulmonary edema development, acute kidney failure, cerebrovascular hemorrhage and liver rupture.\(10\) In 13 of the pregnant women that we monitor, emergency cesarean section was performed due to ablatio placentae, and it was found that one patient had cerebrovascular hemorrhage.

The addition of HELLP syndrome to the severe preeclampsia and eclampsia conditions increases the mortality risk. There are many studies in the literature supporting the maternal mortality increase where HELLP syndrome is added to the severe preeclampsia and eclampsia conditions.\(10\)

Severe preeclampsia may cause placental blood flow to decrease due to the insufficiency of trophoblastic invasion, and it results in fetal growth restriction and oligohydramnios.\(12\) Decreasing placental flow may appear as the loss of umbilical end diastolic flow and reverse flow in fetal Doppler screening.\(13\) We found that 28 of our patients included in the study had growth restriction and 38 of them were diagnosed with oligohydramnios by ultrasound measurements.

Although magnesium sulfate infusion is used successfully today for protecting against eclampsia, its adverse effects should be taken into consideration.\(14\) It is known that the medication, of which therapeutic serum level is with 4–6 mg/dL, causes renal function disorder and even respiratory distress. During the treatment, urination, deep tendon reflexes and respiratory rate should be followed up at serum level.\(14\) In our clinic, we carry out close follow-up for the patients undergoing magnesium sulfate treatment in terms of toxicity. Toxicity due to magnesium sulfate was not detected in any of the patients included in the study.

According to the previous studies, prematurity is among the poor fetal outcomes for severe preeclampsia and eclampsia.\(15\) Since the definite treatment of these conditions is delivery, premature labor rate increases. Mean delivery week of the patients, who underwent magnesium treatment due to severe preeclampsia and eclampsia in our clinic, was 32±2.4 and it was seen that 94 (45.4%) babies needed newborn intense care unit. Although it has been reported in the literature that the babies of women who underwent magnesium sulfate treatment had better neurological outcomes compared to the babies whose mothers did not undergo the magnesium treatment, all mortality and morbidity risk to be caused by prematurity will continue.\(16\)

**Conclusion**

In conclusion, the patients who underwent magnesium sulfate treatment in our clinic due to severe preeclampsia and eclampsia treatment were analyzed and poor perinatal outcomes were summarized. Based on our findings, it is required to highlight that these clinical conditions can be associated with poor maternal and fetal perinatal outcomes despite the appropriate treatment and close follow-up.

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

**References**

Assessment of the cases undergone peripartum hysterectomy in Kahramanmaraş city center in the last two years

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Abstract

Objective: The aim of this target is to determine the incidence, indications and risk factors of peripartum hysterectomy (PH) cases.

Methods: Twenty-five PH cases carried out between June 2013 and June 2015 in the Faculty Hospital of Medicine of Kahramanmaraş Sütçü İmam University and State Hospital were evaluated retrospectively.

Results: Peripartum hysterectomy incidence was found as 1.1 per 1000 deliveries. Total hysterectomy was performed in 22 of the cases due to placenta accreta and subtotal hysterectomy was performed in 3 cases due to atony. All of the placenta accreta cases had at least one previous cesarean section as well as placenta previa. Maternal mortality was identified in 2 (8%) cases and urinary tract injury was identified in 6 (24%) cases. It was found that blood transfusion was required in all cases.

Conclusion: Obstetric hemorrhages are life-threatening clinical conditions. PH is applied as a life-saving procedure. Placental invasion anomaly should be kept in mind if there is previous cesarean section history especially in placenta previa cases, and the operation should be carried out by preparing sufficient blood and blood products in a tertiary center capable of performing PH.

Keywords: Peripartum hysterectomy, cesarean section, placenta accreta.

Introduction

Obstetric hemorrhages are among the most significant reasons of maternal mortality worldwide. Despite the improvements in conservative medical and surgical treatment options, peripartum hysterectomy (PH) is applied as a life-saving surgical procedure.[1] Peripartum hysterectomy was first recommended in the end of 19th century to prevent maternal mortality, and first successful operation was performed in 1876.[2] Emergency peripartum hysterectomy (EPH) is defined as the hysterec-
Assessment of the cases undergone peripartum hysterectomy in Kahramanmaraş city center in the last two years

Tomies performed due to the hemorrhage which could not be brought under control by medical precautions within first 24 hours following the delivery. While PH incidence is 0.4 per 1000 deliveries in developed countries such as UK, it is about 5 per 1000 deliveries in underdeveloped countries and regions such as Nigeria and North Africa.\(^{[4–6]}\)

Peripartum hysterectomy is performed in persistent obstetric hemorrhages occurring due to lacerations during cesarean section and uterine atony, uterine rupture, placental pathologies and infections.

In the past, the most common reasons for PH were uterine atony and rupture. However, placenta accreta cases increased during last two decades have become the most common reason for PH.\(^{[7–9]}\)

In this study, we aimed to determine the incidence, indications, risk factors and complications of PH cases.

### Methods

In this study, 25 PH cases which were performed in the Kahramanmaraş Maternity Hospital and Gynecology & Obstetrics Clinic of Faculty of Medicine at Kahramanmaraş Sütçü İmam University between June 2013 and June 2015 were analyzed retrospectively.

Maternal age, gravida, parity, previous cesarean section history and week of gestation were recorded as the demographic data. Delivery type, type and indications of hysterectomy, complications, postoperative maternal outcomes and blood transfusion need were determined as clinical data.

### Results

Mean patient age was 33.72±4.53, gravida was 4.71±1.32, parity was 3.44±1.16 and week of gestation was 37.18±2.73, and all patients who underwent hysterectomy were multipara (Table 1). For the 2 years as the duration of the study, a total of 25 PH cases were identified among 21,214 deliveries carried out in 2 hospitals within Kahramanmaraş city center. While 2880 of these deliveries were carried out in the University Hospital, 18,334 of them were carried out in Maternity and Pediatric Hospital. Twenty-one of peripartum hysterectomy cases were carried out in the university hospital and the indication of all these cases was placenta accreta. While EPH was performed in 5 (24%) of these cases due to heavy antepartum hemorrhage, hysterectomy was performed in 16 (76%) of them following the planned cesarean section. In 3 out of 4 other hysterectomy cases had atony indication and the remaining one had placental accreta, therefore they underwent EPH in the State Hospital. Peripartum hysterectomy incidence was found as 1.1 per 1000 deliveries in our study.

All patients, who underwent PH due to placenta accreta, had previous cesarean section (PCS) history. Three of these cases had PCS history once, and remaining 19 patients had PCS history for two or more times. While two out of three patients, who underwent hysterectomy due to uterine atony indication, had hysterectomy after cesarean section, one patient had hysterectomy following the vaginal delivery. Hysterectomy type was determined as total in all cases with placenta accreta indication and as subtotal in cases with uterine atony indication (Table 2). Preoperative and postoperative hemoglobin values of the patients who undergone PH, hospitalization periods and blood and blood product amounts which were used in the transfusion were shown in the Table 2. The complications of PH cases are shown in the Table 3.

### Discussion

Peripartum hysterectomy is the last life-saving step in obstetric hemorrhages which cannot be brought under control by conservative medical and surgical methods. It has two types which are hysterectomy after cesarean (cesarean hysterectomy) and hysterectomy after vaginal delivery (postpartum hysterectomy). In our study, cesarean hysterectomy was carried out in 24 (96%) patients and postpartum hysterectomy was carried out in 1 (4%) patient. The indication in all cases who underwent cesarean hysterectomy was placenta accreta. It was found out that the rate of cesarean hysterectomy was higher than the results of other publications regarding to EPH in Turkey.\(^{[10,11]}\) This high rate can be associated with the rapid increase in placenta accreta cases in recent years.

Emergency hysterectomy rates vary between 0.2 and 2.7 per 1000 deliveries in different countries.\(^{[12,13]}\) In our study, we found EPH rate at university hospital as 7.2 per 1000 deliveries (21/2880), which was high. However, this high rate can be associated with the fact that the university hospital is a tertiary referral hospital and cases with high mortality and morbidity rates such
As in the world, cesarean section is the most common surgical procedure preferred by obstetricians also in Turkey. In our study, 22 (88%) of the cases had at least one PCS history. In a study performed, it was reported that at least one PCS history increased EPH risk 11 times.[3] It was also reported in various studies that placental invasion anomalies such as placenta accreta increase from 18 up to 110 times as the number of PCS increases.[14,15] Therefore, the incidence rate of placental invasion anomalies varies between 45 and 73%, and the incidence rate of atony varies between 20 and 43% in EPH cases.[13] It was also reported that hysterectomy risk was 16% in placenta previa if previous uterine surgery history is present but the risk decreases 3% if previous uterine surgery history is not present.[8]

In our study, the most common indication in 25 PH cases was placenta accreta (88%), which was consistent with the literature, followed by uterine atony (12%). All of the placenta accreta cases had at least one previous cesarean section before placenta previa. In this study, the reason for the lower rate of EPH cases associated with atony compared to the literature and even the non-presence of atony-associated EPH case in the university hospital may be our liberal use of balloon systems providing uterine tamponade as well as conservative medical and surgical treatments. ACOG recommends medical treatment by uterotonics first for atony-associated postpartum hemorrhages. In case of the failure of medical treatment, they recommend to tie up bilateral uterine artery and uteroovarian arteries and to use compression sutures. It is however reported that, in the presence of placental invasion anomaly such as placenta accreta, hysterectomy which is a life-saving procedure should be performed in no time.[16]

In our study, total hysterectomy was performed in 88% of the cases, and subtotal hysterectomy was performed in 12% of the cases. All of the patients who underwent total hysterectomy had placenta previa and placenta accreta. We looked for markers showing placental invasion anomaly in these cases such as vascularization increase in serosa after the clamping of umbilical cord. When we identified any marker, we closed uterine incision and initiated hysterectomy. Also when no marker was identified and placental separation could not be made, hysterectomy was initiated. In cases who underwent EPH due to atony, subtotal hysterectomy was performed since conservative medical and surgical procedures failed. Although it is controversial

### Table 1. Demographic data of the patients.

<table>
<thead>
<tr>
<th></th>
<th>Means±SD</th>
<th>Min.–Max.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>33.72±4.53</td>
<td>24–39</td>
</tr>
<tr>
<td>Gravida</td>
<td>4.71±1.32</td>
<td>2–9</td>
</tr>
<tr>
<td>Parity</td>
<td>3.44±1.16</td>
<td>2–7</td>
</tr>
<tr>
<td>Week of gestation</td>
<td>37.18±2.73</td>
<td>28.4–40.5</td>
</tr>
</tbody>
</table>

SD: standard deviation

### Table 2. Clinical data of the patients.

<table>
<thead>
<tr>
<th></th>
<th>Number of delivery</th>
<th>21214</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of emergency peripartum hysterectomy</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Placenta accreta</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Uterine atony</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Previous cesarean section history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placenta accreta</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>One cesarean section history</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>&gt;2 cesarean section history</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Uterine atony</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Delivery by cesarean</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Vaginal delivery</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hysterectomy type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

| Hemoglobin (g/dL)*                   |                    |       |
| Preoperative                         | 8.6±2.0            |       |
| Postoperative                        | 6.7±1.3            |       |

| Blood transfusion (unit)*            | 5.0±2.8            |       |

| Hospitalization period (day)†        | 5.8 (4–10)         |       |

*Mean±standard deviation
†Mean (Min.–Max.)

### Table 3. Complications.

<table>
<thead>
<tr>
<th>Patient number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>3</td>
</tr>
<tr>
<td>Bladder injury</td>
<td>6</td>
</tr>
<tr>
<td>Maternal mortality</td>
<td>2</td>
</tr>
<tr>
<td>Neonatal mortality</td>
<td>3</td>
</tr>
<tr>
<td>Transfer to intensive care unit</td>
<td>17</td>
</tr>
<tr>
<td>Wound site infection</td>
<td>4</td>
</tr>
<tr>
<td>Blood and blood product transfusion</td>
<td>25</td>
</tr>
</tbody>
</table>
in the literature about which type of hysterectomy should be performed in peripartum hysterectomies, there are publications recommending total hysterectomy to avoid hemorrhage which may occur through the cervical branch of uterine artery in obstetric hemor-

Lau et al.[19] reported the rate of urinary tract injuries as 25% in patients who underwent total hysterectomy due to obstetric hemorrhage, but as 12.5% in the patients who underwent subtotal hysterectomy. In our study, the rate of urinary tract injury was 24%, and all of them were in the total hysterectomy group.

Maternal mortality rates are high in obstetric hem-

The significant limitations of this study are the retro-

in the literature about which type of hysterectomy should be performed in peripartum hysterectomies, there are publications recommending total hysterectomy to avoid hemorrhage which may occur through the cervical branch of uterine artery in obstetric hemor-

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Maternal mortality rates are high in obstetric hem-

The significant limitations of this study are the retrospec-
tive design and low number of cases. Further studies are needed on this subject which have wider series of cases and designed prospectively.

Conclusion
Peripartum hysterectomy is performed as a life-saving procedure in heavy obstetric hemorrhages which are life-threatening conditions for maternal life. The patients with previous cesarean section history together with placenta previa are the most risky patient group for PH. Therefore, the deliveries of such patients should be carried out in tertiary centers which have sufficient amount of blood and blood centers and experienced surgeons.

Conflicts of Interest: No conflicts declared.

References


Anencephaly and coexisting malformations: analysis of 35 cases

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Department of Gynecology and Obstetrics, Faculty of Medicine, Dicle University, Diyarbakır, Turkey

Abstract

Objective: We aimed to analyze clinical and demographic characteristics of 35 cases hospitalized in our clinic with the diagnosis of fetal anencephaly and the correlation with other anomalies.

Methods: The patients hospitalized in the Gynecology and Obstetrics Clinic of the Faculty of Medicine at Dicle University for the termination of pregnancy due to the diagnosis of fetal anencephaly between June 2013 and May 2015 were included in this retrospective study. The information of patients such as age, gravida, parity, week of gestation, ultrasonographic findings and coexisting anomalies were accessed through their medical files.

Results: A total of 35 cases were included in the study. Mean age of the patients was 27.7±7.4. Their mean week of gestation during diagnosis was 17±4.6 weeks. In our study, we found the anomaly incidence associated with anencephaly as 65.7%. Polyhydramnios was found in 14.3% (n=5) of the cases; while 22 fetuses were female, 13 fetuses were male. The most common anomalies coexisting with anencephaly were spina bifida (n=12), pes equinovarus (n=4), iniencephaly (n=2), omphalocele (n=2), gastrochisis (n=1), and cleft palate/lip (n=2), respectively.

Conclusion: Anencephaly is the most common type of neural tube defects and there is additional anomaly in most of the cases. In our study, the anomalies coexisting with anencephaly are spina bifida, pes equinovarus, iniencephaly, omphalocele, gastrochisis, and cleft palate/lip.

Keywords: Anencephaly, iniencephaly, omphalocele, spina bifida.

Introduction

On the 4th week of embryonic development, dorsal neural tube being unable to get closed causes abnormal vascularization of embryonic exencephalic brain. [1] Nerve tissue than degenerates and the brain becomes a spongiiform vascular mass. [2] Rostral neural tube closes on 25th day after conception, and caudal neural tube closes 2 days later. [3] While anencephaly is the result of the incomplete closing of rostral neural tube on approximately postovulatory 25th day, spina bifida is the result of the incom-
plete closing of caudal neural tube on approximately postovulatory 27th day. Anencephaly is the heavy defect of cerebrospinal development. This malformation usually coexists with craniorachischisis (fissure in vertebral colon). Also, cleft palate/lip, and omphalocele may coexist. In this study, we analyzed the clinical and demographic characteristics and coexisting anomalies of 35 anencephaly cases hospitalizd in our clinic.

Methods
Approval for this retrospective study was obtained from the Ethics Committee for Non-Invasive Clinical Researches of Faculty of Medicine, Dicle University (12/06/2015; No. 269). Thirty-seven patients hospitalized in the Gynecology and Obstetrics Clinic of the Faculty of Medicine at Dicle University for the termination of pregnancy due to the diagnosis of fetal anencephaly between June 2013 and May 2015 were included in this study. The information of patients such as age, gravida, parity, week of gestation, ultrasonographic findings and coexisting anomalies were accessed through their medical files. The information such as maternal diseases, smoking habit, teratogenuos exposure, folic acid use, kin marriage, history of baby with neural tube defect were obtained from patients by phone. Two patients who could not be reached were excluded from the study. A total of 35 patients were included in the study. The analysis of the data was done by SPSS 18.0 (SPSS Inc., Chicago, IL, USA). The data was analyzed by definitive statistics. Continuous variables were given as mean±standard deviation.

Results
A total of 3621 live deliveries were carried out between June 2013 and May 2015 in the Gynecology and Obstetrics Department of the Faculty of Medicine, Dicle University, and 63 of them had neural tube defect (NTD). We found NTD incidence as 17.4 per 1000 live births in our study. Thirty-seven of 63 cases with NTD were diagnosed as anencephaly. We found anencephaly incidence as 10.2 per 1000 live births in our study. Mean age of the patients included in the study was 27.7±7.4. Mean week of gestation of the patients during hospitalization was 17±4.6 weeks. NTD history in previous pregnancies was found in 14.3% (n=5) of the patients. While no polyhydramnios was found in 85.7% (n=30) of the patients, 14.3% (n=5) of them had polyhydramnios. Fifteen (42.9%) patients were living in the city center while 20 patients (51.4%) were living in the district. Among the patients, 74.3% (n=26) of them were non-smokers and 25.7% (n=9) of them were smokers. Twenty-two fetuses were female and 13 fetuses were male (Table 1). The most common coexisting anomalies were spina bifida (n=12), pes equinovarus (n=4), iniencephaly (n=2), omphalocele (n=2), gastroschisis (n=1), and cleft palate/lip (n=2), respectively (Table 2).

Table 1. Demographic and clinical characteristics of the cases.

<table>
<thead>
<tr>
<th>Özellikler</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total case number</td>
<td>35</td>
</tr>
<tr>
<td>Maternal age</td>
<td></td>
</tr>
<tr>
<td>≤20-year-old (%)</td>
<td>20</td>
</tr>
<tr>
<td>≥35-year-old (%)</td>
<td>22.8</td>
</tr>
<tr>
<td>Gravida</td>
<td>1–8</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>3.5±2.4</td>
</tr>
<tr>
<td>Parity</td>
<td>0–6</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>2±1.9</td>
</tr>
<tr>
<td>Week of gestation during diagnosis (%)</td>
<td></td>
</tr>
<tr>
<td>1st trimester</td>
<td>22.9</td>
</tr>
<tr>
<td>2nd trimester</td>
<td>68.6</td>
</tr>
<tr>
<td>3rd trimester</td>
<td>8.6</td>
</tr>
<tr>
<td>Preconceptional folic acid use (%)</td>
<td></td>
</tr>
<tr>
<td>Yes (%)</td>
<td>22.9</td>
</tr>
<tr>
<td>No (%)</td>
<td>77.1</td>
</tr>
<tr>
<td>NTD history in previous pregnancy (%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>85.7</td>
</tr>
<tr>
<td>No</td>
<td>14.3</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>25.7</td>
</tr>
<tr>
<td>No</td>
<td>74.3</td>
</tr>
<tr>
<td>Kin marriage (%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>22.9</td>
</tr>
<tr>
<td>No</td>
<td>77.1</td>
</tr>
<tr>
<td>Residential area (%)</td>
<td></td>
</tr>
<tr>
<td>City center</td>
<td>42.9</td>
</tr>
<tr>
<td>District</td>
<td>51.4</td>
</tr>
<tr>
<td>Village</td>
<td>5.7</td>
</tr>
<tr>
<td>Polyhydramnios (%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>14.3</td>
</tr>
<tr>
<td>No</td>
<td>85.7</td>
</tr>
<tr>
<td>Fetal sex (%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>62.9</td>
</tr>
<tr>
<td>Male</td>
<td>37.1</td>
</tr>
</tbody>
</table>

NTD: neural tube defect; SD: standard deviation

Table 2. Coexisting anomalies of cases with anencephaly.

<table>
<thead>
<tr>
<th>Anomaly</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spina bifida</td>
<td>12</td>
</tr>
<tr>
<td>Pes equinovarus</td>
<td>4</td>
</tr>
<tr>
<td>Iniencephaly</td>
<td>2</td>
</tr>
<tr>
<td>Omphalocele</td>
<td>2</td>
</tr>
<tr>
<td>Gastroschisis</td>
<td>1</td>
</tr>
<tr>
<td>Cleft palate/lip</td>
<td>2</td>
</tr>
</tbody>
</table>

Yaman Tunç S et al.
Anencephaly and coexisting malformations

Discussion

Neural tube defects are among the most severe congenital anomalies in Turkey and epidemiological findings show that the prevalence varies according to regional and demographical characteristics. According to the studies conducted in various cities of Turkey, NTD incidence varies between 3 and 5.8 per thousand. In our study, we found NTD incidence about 17.4 per thousand, which is quite above the average of Turkey. This result is caused by the fact that our hospital is the referral hospital in the region.

Anencephaly is characterized by the outward exposure of cranial neural tube and a defect open in the calvarium. It is one of the three major neural tube defects. The other two defects are encephalocele and spina bifida. Anencephaly is a severe congenital defect incompatible with life. Babies born live usually dies within hours, or rarely may live a few days or a few weeks. In our study including 35 cases, mean maternal age was 27.7±7.4. There were 7 cases below 20-year-old and 8 cases above 35-year-old.

With the current ultrasonography technology, it is possible to identify almost all anencephaly cases. In the last decade, some papers have been published reporting that anencephaly diagnosis can be established as of 10 weeks of gestation. Anencephaly diagnosis can be established by identifying the lack of cranial dome. However, since current brain tissue may be in variable amounts, it may be difficult to establish this diagnosis in the first trimester in particular.

In our study, mean week of gestation during diagnosis was 17±4.6 weeks. Eight cases (22.9%) were diagnosed in the first trimester, 24 cases (68.6%) were identified in the second trimester, and 3 cases (8.6%) were diagnosed in the third trimester. The reason for diagnosing most of the patients during the second trimester in our study can be associated to the fact that many of the cases (57.1%) live in small residential areas such as villages and districts. We believe that the diagnosis delayed due to the difficulties during first trimester for reaching a center capable of conducting prenatal screening. In a study carried out in Brazil, mean week of gestation during diagnosis was found as 21.3 weeks. This result is consistent with the results of our study.

In the studies carried out, the rate of fetuses with anomalies coexisting with anencephaly was provided in a wide range. Tan et al. reported the rate as 9.4% while David et al. reported it as 84%. In another study conducted in India, the rate of coexisting anomaly in 20 patients with anencephaly was reported as 80%. In our study, we found coexisting anomaly in 23 (65.7%) of 35 cases with anencephaly. It was found in various studies that anencephaly is more common among female fetuses. In conformity with the literature, 22 (62.9%) fetuses were female and 13 (37.1%) fetuses were male in our study. About 40–50% of cases with anencephaly have polyhydramnios, and oligohydramnios is observed rarely. In the analysis of 30 cases with anencephaly, Kurjak et al. reported that polyhydramnios did not develop before 25 weeks. We found polyhydramnios in 14.3% (n=5) of our cases, amniotic fluid was within normal ranges in 85.7% (n=30) of them. Five cases with polyhydramnios were at 25 weeks of gestation or above.

In our study, the most common anomalies coexisting with anencephaly were spina bifida (craniospinal rachischisis in 10 cases, thoracolumbar spina bifida in 2

<table>
<thead>
<tr>
<th>Anomaly</th>
<th>n</th>
<th>%</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spina bifida</td>
<td>12</td>
<td>34.3</td>
<td>Craniospinal rachischisis in 10 cases</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Thoracolumbar spina bifida in 2 cases</td>
</tr>
<tr>
<td>Iniencephaly</td>
<td>2</td>
<td>5.7</td>
<td></td>
</tr>
<tr>
<td>Skeletal deformity</td>
<td>4</td>
<td>11.4</td>
<td>Pes equinovarus in 4 cases</td>
</tr>
<tr>
<td>Cleft palate/lip</td>
<td>2</td>
<td>5.7</td>
<td>Cleft palate in 1 case</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cleft lip in 1 case</td>
</tr>
<tr>
<td>Gastrointestinal anomalies</td>
<td>3</td>
<td>8.5</td>
<td>Omphalocele in 2 cases</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gastroschisis in 1 case</td>
</tr>
</tbody>
</table>
cases), pes equinovarus (4 cases), cleft palate/lip (2 cases), iniencephaly (2 cases) and gastrointestinal anomalies (3 cases). Craniospinal rachischisis is the most severe form of spina bifida, and it is observed more in anencephalic fetuses compared to general population. In the study of Gole et al., spina bifida was observed in 9 of 20 anencephalic cases, and while 8 of them had cervical craniorachischisis, only one case had lumbar spina bifida. Similarly, we identified spina bifida in 12 of 35 cases in our study; of these cases, 10 cases had craniospinal rachischisis and 2 cases had lumbar spina bifida (Figs. 1a and b).

Among our cases, 4 (11.4%) cases had pes equinovarus as skeletal deformity. David et al. reported the anencephaly + skeletal deformity incidence as 1.7%, Gole et al. reported as 35%, and Tan et al. reported as 20%. In our study, 2 (5.7%) cases had iniencephaly. Iniencephaly is characterized with the distinct dorsiflexion of the head and cervical rachischisis. The head is on

![Image](image_url)

**Fig. 1.** Anencephaly case (a) with spina bifida (arrow) in lumbar area. The anencephaly (arrow) case (b) with craniospinal rachischisis. Craniospinal rachischisis is observed in the case with iniencephaly (c). The case (d) with iniencephaly and omphalocele (arrow).
extreme dorsiflexion due to the lack of foramen magnum and cervical vertebra. Extreme lordosis of cervical spine causes the face to look upward (star observer) (Fig. 1c). Forty-eight percent of the fetuses with encephalocoe have coexisting anomalies such as anencephaly, holoprosen-
cephaly, vermian agenesis, cleft palate and lip, abdominal wall defects, anal atresia, and diaphragmatic hernia. In our study, one case with encephalocoe had anencephaly and omphalocele additionally (Fig. 1d).

Two cases in our study had cleft palate/lip as facial anomalies. In the studies conducted, cleft palate and lip was reported as facial anomaly in addition to the anencephaly. As gastrointestinal anomalies, two cases had omphalocele, and one case had gastroschisis. We found no genital anomaly in our cases. While Nielsen et al. and Golalipour et al. reported no genital anomaly in fetuses with anencephaly, Gole et al. reported hypospadias in two anencephalic male cases.

Conclusion

Anencephaly develops due to the incomplete closing of rostral neural tube; however, its etiology is still controversial. Many studies have been conducted to understand the association between anencephaly and neural tube defects. However, the genetic association of neural tube defects could not be fully explained. In anencephaly which is the most common type of neural tube defects, there is an additional anomaly coexisting with anencephaly. In our study, the anomalies coexisting with anencephaly are spina bifida, pes equinovarus, intercnephalocoe, omphalocele, gastroschisis, and cleft palate/lip.

Conflicts of Interest: No conflicts declared.

References

Questionnaire on mouth and dental health during pregnancy: myths and facts

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²Perinatology Clinic, Kanuni Sultan Süleyman Training and Research Hospital, Istanbul, Turkey
³Gynecology and Obstetrics Clinic, Kanuni Sultan Süleyman Training and Research Hospital, Istanbul, Turkey

Abstract

Objective: The aim of the study is to assess the opinions of gynecologists and obstetricians in Turkey about oral hygiene, odontotherapy, periodontal diseases and their perinatal impacts during pregnancy.

Method: A questionnaire consisting of 20 closed-ended questions was prepared for gynecologists and obstetricians, and 217 gynecologists and obstetricians from various hospitals in Turkey who accepted to participate in the questionnaire were included in the study. The questionnaire was applied in a standard way to the participants and the names of some participants were not revealed upon their requests.

Results: According to the data obtained from the study, 90.8% of the participants believed that the pregnancy increased gingival inflammation. Similarly, a large number of physicians (79.3%) stated that there was a relationship between prenatal outcomes and oral and dental health. Most of the participants believed that dental scaling (86.6%), dental extraction (81.6%), filling (82.6%) and periapical radiography (80.2%) practices are safe, and the rates of trust in root canal treatment and panoramic radiography were 64.5% and 53.5%, respectively. While 73.3% of the participants recommended dental check-up before pregnancy to their patients who were planning pregnancy, 36.1% of the participants recommended dental check-up to their pregnant patients in the first prenatal visit.

Conclusion: Gynecologists and obstetricians should have more confidence that both diagnostic and therapeutic procedures in the dentistry are safe during pregnancy, and should inform the patients they follow up properly. It should be kept in mind that having a good oral health before pregnancy and also to maintain it during the pregnancy will have a positive impact on gestational outcomes.

Keywords: Pregnancy, oral hygiene, periodontal disease, dental treatment, gestational outcomes.

Özet: Gebelikte ağız ve diş sağlığı konusunda doğru ve yanlış bildiklerimiz: Anket çalışması

Amaç: Çalışmanın amacı Türkiye’deki Kadın Hastalıkları ve Doğum uzmanlarının gebelikte ağız hijyeninin, diş tedavi tayininde, periodontal hastalıktan ve perinatal etkilerini degerlendirmektedir.


Bulgular: Çalışmadan elde edilen verilere göre katılımcıların %90.8’si gebeliktegingival inflamasyonu arttığını duydu. Benzer olarak katılımcıların büyük çoğunun (%79.3) ağız ve diş sağlığı ile prenatal sonuçların arasında ilişki olduğunu bildirdiler. Çalışmaya katılımcıların büyük çoğunun (%73.3) diş temizliği, dolgu ve tek diş radyografi (periapikal radyografi) uygulamalarının srasıyla %86.6, %81.6, %82.6 ve 80.2 oranlarında güvenli olduğu düşündüğünü, kanal tedavisi ve panoramik radyografi uygulaması srasında %64.5 ve %53.5 oranında kaldı. Katılımcıların %73.3’ü gebelik planlayan hastaların gebelik öncesinde diş hekimiyi muayenesi öneriyordu, gebe hastalarına ilk prenatal vizitte diş hekimiyi muayenesini öneren, gebe hastaları ilk prenatal vizitte diş hekimiyi muayenesine öneren katılmcı oranı %36.1 olarak saptandı.

Sonuç: Diş hekimliğinde hem tansal işlemlerin hem de tedavi girişimlerinin gebelikli olduğu konusunda Kadın Hastalıkları ve Doğum uzmanları daha fazla güvene sahip olmalı ve takip etkileri hastaları doğru bilgilendirmelidirler. İyı bir sağlık için gebelikten önce çalışılmasını ve gebelikle de sürdürülebilmesinin, gebelik sonuçlarına olumlu etki yapacağını akla tutulmalıdır.

Anahtar sözcükler: Gebelik, ağız hijyenı, periodontal hastalık, diş tedavisi, gebelik sonuçları.
Introduction

Complex physiological and hormonal changes occur during pregnancy which is a unique period in the life of women. Estrogen and progesterone hormones increasing during pregnancy cause the increase of gingival vascularization and the suppression of immune response. Many physiological changes occur during the adaptation of body to the pregnancy. In terms of the oral changes, it is seen that salivation and pH level do not change during pregnancy.\(^1\) It was also shown that some microorganism species (Prevotella) increase in the mouth.\(^2\) These increasing microorganisms increase the possibility of gingival bleeding and cause gingival inflammation to worsen; however, there is no finding to assert that pregnancy cause or accelerate tooth decay.\(^3,4\)

During pregnancy, various diseases and lesions may occur in the mouth. Benign gingival lesions which are also known as pyogenic granuloma or gestational epulis are seen in approximately 5% of the pregnancies.\(^4\) Ptyalism is a rare complication characterized by nausea and loss of saliva in a significant amount such as 1–2 l/day. In the gestational gingivitis, gingivae are hyperemic and become very sensitive to bleed even during tooth brushing. Gestational gingivitis typically recovers during postpartum period.\(^5\) Gestational gingivitis and periodontitis are the most common oral diseases observed during pregnancy.\(^6\)

There are some studies reporting that the presence of maternal periodontitis is a risk factor for preterm labor and low birth weight.\(^7,8\) In this sense, both dentists and obstetricians should have current knowledge on oral hygiene, oral diseases and treatments during standard prenatal care of pregnant women and they also should show the ultimate attention.

In this study, we aimed to assess the opinions of obstetricians through a questionnaire on oral hygiene, oral treatments and their impacts on perinatal outcomes in frequently encountered cases during daily practices of dentistry.

Methods

A total of 217 volunteer gynecologists and obstetricians from various hospitals in Turkey were included in this cross-sectional questionnaire study. The questionnaire including 20 closed-ended questions were applied to the participants as a standard and names of some participants were not revealed upon their requests. In the first part, there were questions evaluating the demographic information of the physicians including name (optional), age, sex, expertise period, the institution they work and their expertise field. In the second part, the questions “Do you believe that pregnancy increases the possibility of gingival inflammation?” “Do you believe that there is a relationship between oral and dental health and perinatal outcomes?” and “Do you believe that periodontal diseases can cause preterm labor and/or deliveries with low birth weight?” were asked to the physicians.

In the third part, the question “Among dental scaling, dental extraction, filling, root canal treatment, periapical radiography and panoramic radiography, which one(s) do you believe to be safe during pregnancy?” was asked. The fourth and last part included following questions:

- “Do you recommend dental check-up before pregnancy to your patients who were planning pregnancy?”
- “Do you recommend dental check-up to your pregnant patients in the first prenatal visit?”
- “Do you recommend your pregnant patients to postpone their dental check-up to postpartum period?”
- “Do you believe that it is safe to use local anesthetics including vasoconstrictor during pregnancy?”
- “Which trimester do you believe is the safest period for dental treatments during pregnancy?”

The participants were informed about the aim and the content of the study first, and then they were included in the study on a volunteer basis. The study was initiated with the decision of the ethics committee of the related hospital (no. 9322, dated 2015/2).

All questionnaire forms received from the participants were coded and analyzed in the electronic environment. The responses obtained were evaluated by descriptive statistics (frequency, percentage, and mean±standard deviation). The difference among the groups was assessed by chi-square test at p<0.05 significance level.

Results

A majority of 217 gynecologists and obstetricians who participated in the study were between 31- and 40-year-old (56.3%), working at the training and research hospital of the ministry of health (62.2%) and had a professional expertise between 0 and 10 years (65%). Thirteen participants had sub-branch expertise on
Perinatology and 6 of them had sub-branch expertise on Gynecological Oncology. A majority of the participants were in the age group of 31–40 (56.3%) and 50.7% of the participants were women. Male–female ratio among the participants was similar. Those who accepted to participate in the study answered all the questions in the questionnaire. The demographic characteristics of the participants are shown in the Table 1.

In the second part of the questionnaire, participants were asked questions assessing the relationship between perinatal outcomes and oral health and diseases. According to the data obtained from the study, 90.8% of the participants believed that the pregnancy increased gingival inflammation. Similarly, a large number of physicians (79.3%) stated that there was a relationship between prenatal outcomes and oral and dental health. For the question if the presence of periodontal diseases could be a risk factor for preterm labor and/or delivery with low birth weight, 78.8% of the participants replied that it could be risk factor.

The third part of the questionnaire includes questions about the reliability of diagnosis and treatment methods used frequently in the daily dentistry practices in terms of pregnancy. Most of the participants believed that dental scaling (86.6%), dental extraction (81.6%), filling (82.6%) and periapical radiography (80.2%) practices are safe, the rates of trust in root canal treatment and panoramic radiography were 64.5% and 53.5%, respectively (Fig. 1). The difference between these two groups was statistically significant (p<0.001, chi-square test).

In the fourth and last part of the questionnaire, the participants were asked questions about their recommendations on dental check-ups during pregnancy, on local anesthetics and on the safest trimester for procedures. While 73.3% of the participants recommended dental check-up before pregnancy to their patients who were planning pregnancy, 36.1% of the participants recommended dental check-up to their pregnant patients in the first prenatal visit. Almost all of the participants (90.3%) agreed that dental check-up should not be postponed during pregnancy. The results of the study showed that the participants had suspicions on the reliability of using local anesthetics including vasoconstrictor during pregnancy. Only 65% of the participants thought that they are safe. Finally, 68.7% of the participants stated that the second trimester is safer for dental treatments during pregnancy while 23% of them considered third trimester is safer. The questions and the analysis of responses for the fourth part of the questionnaire are shown in Table 2.

The participants were regrouped according to their sex (male: 105; female: 109) and the responses were reanalyzed. While 87.6% (92/105) of the male physicians replied negatively to the question for postponing dental check-up to the postpartum period, 95.4% (104/109) of the female physicians replied negatively to the same question, and this difference was found to be statistically significant (p<0.05). No significant difference was found among the responses for other questions.

**Table 1.** The demographic data of the physicians who participated in the study.

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (year)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤30</td>
<td>30</td>
<td>13.8</td>
</tr>
<tr>
<td>31–40</td>
<td>122</td>
<td>56.3</td>
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<tr>
<td>41–50</td>
<td>42</td>
<td>19.3</td>
</tr>
<tr>
<td>≥51</td>
<td>23</td>
<td>10.6</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>107</td>
<td>49.3</td>
</tr>
<tr>
<td>Female</td>
<td>110</td>
<td>50.7</td>
</tr>
<tr>
<td><strong>Institution</strong></td>
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<td></td>
</tr>
<tr>
<td>Private Hospital</td>
<td>15</td>
<td>6.9</td>
</tr>
<tr>
<td>State Hospital</td>
<td>46</td>
<td>21.2</td>
</tr>
<tr>
<td>University Hospital</td>
<td>21</td>
<td>9.7</td>
</tr>
<tr>
<td>Training and Research Hospital</td>
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<td>62.2</td>
</tr>
<tr>
<td><strong>Expertise (year)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–10</td>
<td>141</td>
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</tr>
<tr>
<td>10–20</td>
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<tr>
<td>&gt;30</td>
<td>5</td>
<td>2.3</td>
</tr>
</tbody>
</table>

**Fig. 1.** Opinions of the participants on the reliability of most common daily practices of dentistry (DC: dental scaling; DE: dental extraction; PA: periapical radiography; RCT: root canal treatment).
Questionnaire on mouth and dental health during pregnancy

Discussion

It was shown that the number of some oral microorganisms increases with the impact of steroid hormones increasing during pregnancy.\cite{12,13} Due to these increasing microorganisms, the tendency of gingiva to bleed increases and may cause severe inflammation even on low plaque levels. Considering the responses of the participants, it is seen that almost all of them (90.8%) stated the increase of gingival inflammation during pregnancy. In the studies carried out on this matter, it was reported that the presence of maternal periodontitis is a risk factor for preterm labor and low birth weight, and therefore perinatal outcomes may be worsened.\cite{8,9} Since preterm labor and the complications developing secondary to preterm labor are among the leading factors responsible for newborn morbidity and mortality, this matter is of vital importance. Also, periodontal diseases in various forms were found in about 40% of pregnant women.\cite{10} There are also other studies not asserting that the presence of periodontal diseases increases poor perinatal outcomes.\cite{11,12} In the study of Agueda et al. it was reported that the relationship between periodontal diseases and perinatal outcomes is controversial.\cite{13}

In the literature review of Shah et al., it was concluded that periodontal disease treatment during pregnancy improved perinatal outcomes in terms of preterm labor and delivery with low birth weight.\cite{14} On the contrary, Michalowicz et al. reported that the rates of preterm labor, low birth weight and growth retardation did not change with periodontal treatment.\cite{15} Although it is not fully clarified in the current literature, the presence of periodontal disease is considered as a risk factor for preterm labor and low birth weight, but it is also thought that the treatment carried out during pregnancy do not affect the outcomes significantly. According to the analysis of the questions on this matter, 79.3% of the participants believe that there is a relationship between perinatal outcomes and oral and dental health while almost same rate of the participants (78.8%) believe that it may be associated with preterm labor and/or low birth weight. Although the relationship between periodontal disease and perinatal outcomes is controversial, regular oral care and dental check-up should be recommended all women who are pregnant and planning to be pregnant.

In the third part of the study, the participants were asked to respond to the questions for the reliability of diagnosis and treatment methods frequently used in daily dentistry practice. As it is understood that a majority of the participants agree as a result of the analysis of the results, dental scaling, dental extraction and filling procedures can be carried out safely during pregnancy.\cite{16} However, the concerns of physicians about the reliability of root canal treatment were reflected to the questionnaire results significantly. Almost one third (35.5%) of the participants reported that the root canal treatment during pregnancy is not safe. On the basis of these results, it was concluded that the female obstetricians should update their knowledge on root canal treatment.

Similarly, the concerns of physicians about panoramic radiography were found out from the questionnaire results. It was shown in the studies carried out on radiation exposure during pregnancy that there was no increase in the congenital anomalies in pregnant women who were exposed to X-ray exposure less than the dose of 5–10 cGy (1 Gy = 100 cGy).\cite{17,18} Dental radiographic procedures covering entire mouth provides 0.0008 cGy.
radiation exposure.\[^{16}\] In periapical and panoramic radiographies, radiation exposure is one third of the exposure provided in full mouth radiographies.\[^{16}\] Diagnostic radiographies are significant examinations for the diagnosis and treatment of dental conditions and they are considered to be safe during pregnancy.\[^{19-22}\]

The radiation dose in the radiographies used in dentistry is quite lower than the dose which is potentially harmful. FDA does not recommend making any change in the radiography use due to the pregnancy.\[^{24,26}\] In the daily standard practice, the abdominal region and the neck of pregnant woman can be protected during procedure. American College of Obstetricians and Gynecologists (ACOG) reports that the diagnosis and treatment procedures including radiographies used for oral and dental pathologies and local anesthetics (with or without epinephrine) are safe to use during pregnancy.\[^{4}\] It was seen in the questionnaire results that almost half of the participants (46.5\%) do not trust panoramic radiography and 19.8\% of them do not trust periapical radiography, where this distrust is wrong. By increasing the knowledge of physicians on these matters, the concerns of patients can be resolved in daily practice and the procedures can be carried out more easily.

In the analysis of our questionnaire data, it was seen that 73.3\% of the participants recommend their patients to have a dental check-up before pregnancy, only 36.1\% of them recommended dental check-up during the first prenatal visit during pregnancy. Among the reasons for recommending dental check-up during first prenatal visit at such a low rate can be considered that the physicians do not have sufficient knowledge on this matter, have no chance due to the busy schedule or consider it as unimportant. In the 2013 statement of ACOG committee,\[^{4}\] it was stated that regular dental care is the key for good oral health and well-being. Since female obstetricians are those admitted most frequently among general healthcare professions, it is believed that this is a unique opportunity throughout the life of women to highlight the significance of good oral hygiene and dental care. ACOG recommends dental check-up regularly and at first prenatal visit.\[^{4}\]

The concern among physicians against local anesthetics is also another significant point of the study. Forty-five percent of the participants are against the use of local anesthetics during pregnancy. This rate inconsistent with scientific facts is remarkable. Use of local anesthetics at appropriate amounts and with proper techniques is safe during pregnancy.\[^{14,21}\] According to FDA, the pregnancy category of local anesthetics (lidocaine %2, prilocaine) used by dentists during daily practices is B. The pregnancy category of mepivacaine %3, bupivacaine and articaine is C.\[^{24}\] These local anesthetics can be combined with vasoconstrictor agents. The pregnancy category of epinephrine used as a vasoconstrictor is B. Adding epinephrine to local anesthetics has the potential to decrease uteroplacental blood flow theoretically in case of intravascular injection.\[^{21}\] On the other hand, epinephrine in 1/100,000 concentration used dentistry is safe at the effective lowest dose with the proper technique.\[^{22,25}\]

Traditionally, dental treatments are avoided during first trimester; however, there is no sufficient evidence on this matter.\[^{26}\] It should be remembered that any emergency dental treatment can be carried out regardless of the trimester.\[^{27}\] Wasyliko et al. reported that the most ideal period for dental treatments is the beginning of the second trimester (14–20 weeks).\[^{28}\] According to the results of our study consistent with the literature, a majority of the participants (68.7\%) reported that the most ideal period for treatments which cannot be postponed is the second trimester. Based on these data, all elective treatments planned to perform during pregnancy should be postponed to postpartum period.\[^{25}\]

**Conclusion**

Oral health is a significant part of general health and its significance increases during pregnancy. Routine checks for oral health should be maintained during pregnancy as before the pregnancy. The patients who do not have dental check-ups or have them irregularly should be directed to a dentist at the first prenatal visit. While postponing elective dental treatments to postpartum period, emergency dental treatments can be safely carried out during pregnancy. Although we did not have a wide population, the questionnaire results show that female obstetricians should update and improve their knowledge about oral and dental health. The patients should be informed that both diagnostic and treatment procedures are safe during pregnancy, and dentists and obstetricians should work on this matter in concordance with each other. It should be remembered that a good oral health may improve general health and affects gestational outcomes positively as well.

**Conflicts of Interest:** No conflicts declared.
References
Cytokines and C-reactive protein in moderate and severe preeclampsia

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Abstract

Objective: Studying the production of pro-inflammatory (IL-1β, IL-8) and anti-inflammatory (IL-10) cytokines, CRP and tumor necrosis factor (TNF) in moderate and severe preeclampsia in third trimester of pregnancy.

Methods: Fifty women with pregnancies complicated by preeclampsia and 50 women with normotensive pregnancy were evaluated in the third trimester of pregnancy. Levels of IL-1β, IL-8, IL-10, and TNF-α were measured by using a solid-phase enzyme immunoassay. Statistical data processing was done using the application program SPSS for Windows 13.0. Descriptive methods (mean, median, min and max) were used in order to describe the distribution of analyzed variables.

Results: In severe preeclampsia IL-10 had a downward trend, IL-8, IL-10, and TNF-α were measured by using a solid-phase enzyme immunoassay. Statistical data processing was done using the application program SPSS for Windows 13.0. Descriptive methods (mean, median, min and max) were used in order to describe the distribution of analyzed variables.

Conclusion: Analyzing cytokines in third trimester of pregnancy complicated with preeclampsia is useful. Moderate phase can be considered a critical stage in preeclampsia that comes to most functional strain homeostatic system.

Keywords: Cytokines, c-reactive protein, preeclampsia.

Introduction

Preeclampsia is a multi-factorial syndrome that occurs in the second half of pregnancy; it manifests with a triad of symptoms: swelling, proteinuria and hypertension, and in severe cases, convulsions and coma. Despite the success in the study of the pathogenesis and etiology of preeclampsia, there is no single theory explaining the causes and the mechanism of its development; both being important for its diagnosis and prevention. It is believed that preeclampsia is caused by neurogenic, hormonal, genetic and immunological factors. Preeclampsia is considered a failure of body’s adaptive mechanisms.
Compared to normal pregnancy, increased inflammatory responses are reported and immune deviation toward T helper type 1 (Th1) in pregnancy with established preeclampsia. Roberts was one of the first who suggested that mediators released in preeclampsia are responsible for the endothelial damage. Injured endothelium initiates a dysfunctional cascade of coagulation, vasoconstriction and intravascular fluid redistribution; it results in the clinical syndrome of preeclampsia.

Numerous studies showed that the balance of cytokines had importance in the regulation of pregnancy. Diagnostic and prognostic significance of breaches in the immune balance during preeclampsia has not yet been determined.

Pro-inflammatory cytokines, such as IL-2, IL-8, TNF are increased in the blood, in leukocytes during preeclampsia (PE). Elevated concentrations of TNF-α have been observed in the blood of women with PE.

Compared to the increased level of pro-inflammatory cytokines, the blood level of some anti-inflammatory cytokines, as IL-4 and IL-10 are decreased in patients with PE.

The purpose of this study was to evaluate the pro-inflammatory TNF-α, IL-1β, IL-8, and anti-inflammatory IL-10 cytokines and C-reactive protein (CRP) in moderate and severe preeclampsia, compared to normotensive pregnancies in the third trimester.

**Methods**

This study was designed as a prospective single-center study of pregnant women in their third trimester. Inclusion criteria were singleton pregnancy (between 28 and 40 weeks of gestation) and reproductive age. Exclusion criteria were acute and chronic genital and extra genital diseases (essential hypertension, heart failure, diabetes, morbid obesity, immunodeficiency, systemic diseases, chronic infectious diseases, genetic pathology). All patients signed the informed consent for the inclusion in the study. The study was approved by the Ethical Committee of our clinic.

Fifty patients with moderate or severe preeclampsia and 50 with normal pregnancy were included in this study. Patients were divided into two groups: those complicated by varying degrees of preeclampsia in the third trimester of gestation, and normotensive patients without threatening signs of hypertension and preeclampsia (control group).

The severity of preeclampsia was determined according to the definition of the World Health Organization, Handbook for guideline development, Geneva, 2010. Moderate or severe preeclampsia was diagnosed on the criteria for classification at the time of collection of maternal serum.

The level of IL-1β, TNF, IL-8, and IL-10 was determined through a commercial test. Cytokine level in the serum was measured by the "sandwich" method of solid-phase enzyme immunoassay using double antibody. Recombinant cytokines as part of the test – whale were used as a standard for comparison. The detection was done by "Victor" immunoassay analytics. According the standard samples titration, calibration graphs were made for each cytokine, as determined by their level in the range of detected concentrations (1–2000 pg/ml).

Data were analyzed using SPSS Statistics for Windows, version 13.0 (SPSS Inc., Chicago, IL, USA). Data are presented as means and percentages, standard deviations, and minimal and maximal values. The Mann-Whitney U test was used to evaluate between-group differences in results. A value p <0.05 was considered statistically significant.

**Results**

Our analysis showed that in pregnancy complicated by preeclampsia, cytokine levels essentially change compared with the respective levels in physiological pregnancy. Even a lighter form of preeclampsia shows directional change, i.e., elevated levels of pro- and anti-inflammatory cytokines, with the exception of IL-10 that has a downward trend in severe preeclampsia.

Table 1 shows statistical analysis of difference in age and gestational age. The difference in average age among pregnant women with medium and severe preeclampsia (29.9±4.7 versus 34.2±3.85) was statistically significant (p=0.004). Pregnant women from the examined groups differ slightly in terms of average length of gestational age, which ranges from 34.4±3.6 weeks in the group with severe PE, and 35.5±3.4 weeks in the group with symptoms of moderate PE (Fig. 1).

With regards to the distribution by ethnicity, Albanians were often represented with 56% in the group with preeclampsia, or 44% with symptoms of medium, and 68% with symptoms of severe PE (Table 1). Pregnant Albanians in 68% dominated the normoten-
sive pregnant group. The average BMI (kg/m²) in the group of pregnant women with preeclampsia was 34.33±4.5 kg/m², and is insignificantly (p=0.09) higher than average body mass in the control group, with a value of 32.8±3.8 kg/m². However, the examined difference in the average body mass index (BMI) among pregnant women with moderate and severe PE, and normotensive pregnant, was statistically significant (p=0.026), due to significantly higher average index in pregnant women with severe PE versus normotensive pregnant women (35.57±4.1 kg/m² versus 32.88±3.8 kg/m², p=0.025) (Table 1).

Pregnant women with preeclampsia and healthy pregnant women had a slightly (p=0.7) different values of IL-8 in serum, whereas pregnant women with moderate and those with severe preeclampsia had insignificant higher values than the control group (p=0.17). The

<table>
<thead>
<tr>
<th>Variable</th>
<th>Groups</th>
<th>All PE (n=50)</th>
<th>Moderate PE (mPE) (n=25)</th>
<th>Severe PE (sPE) (n=25)</th>
<th>Control (c) (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong> Mean±SD</td>
<td></td>
<td>32.06±4.8</td>
<td>29.9±4.7</td>
<td>34.2±3.85</td>
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<tr>
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<tr>
<td><strong>Gestational week</strong> Mean±SD</td>
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<td>34.99±3.5</td>
<td>35.5±3.4</td>
<td>34.4±3.6</td>
<td>34.8±3.6</td>
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<td>All PE/c t=0.2 p=0.8</td>
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<tr>
<td>mPE/sPE/c F=0.6 p=0.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ethnicity</strong> n(%)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macedonian</td>
<td></td>
<td>18 (36%)</td>
<td>10 (40%)</td>
<td>8 (32%)</td>
<td>15 (30%)</td>
</tr>
<tr>
<td>Albanian</td>
<td></td>
<td>28 (56%)</td>
<td>11 (44%)</td>
<td>17 (68%)</td>
<td>34 (68%)</td>
</tr>
<tr>
<td>Romanian</td>
<td></td>
<td>4 (8%)</td>
<td>4 (16%)</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
<tr>
<td><strong>BMI</strong> Mean±SD</td>
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<tr>
<td>mPE/sPE/c F=3.8 p=0.026</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All PE: all preeclampsia groups; BMI: body mass index; SD: standard deviation

![Fig. 1. Mean levels of age (year), gestational week and BMI in moderate, severe preeclampsia and control group (BMI: body mass index; PE: preeclampsia).]
average values, the lowest and highest serum values of IL-8 in the analyzed groups are shown in Table 2.

Statistical analysis did not confirm significant difference in the serum values of IL-10 among pregnant women with moderate preeclampsia and healthy pregnant women (p=0.5), but highly significant (p<0.01) difference among moderate preeclampsia/severe preeclampsia/control group was due to the lower values of this interleukin in severe preeclampsia group, comparing moderate preeclampsia in relation to the control, and due to the highly significant lower values when comparing control in relation to moderate preeclampsia group (Table 2). Average concentrations of IL-10 in serum amounted to 23.2±40.7 pg/ml in group of preeclampsia, 45.5±48.4 pg/ml in the group of moderate preeclampsia, and 0.8±0.4 pg/ml in the group with severe preeclampsia. In normotensive group, average serum concentration of IL-10 was 4.2±6.7 pg/ml.

Patients with preeclampsia had significantly (p=0.02) higher serum concentrations of IL-1β compared to normotensive, owing to the highly significant (p<0.01) higher concentrations in the group of severe preeclampsia versus control group, while the difference observed in moderate form of preeclampsia and control group was statistically insignificant (p=0.5) (Table 2). The difference between the two subgroups of preeclampsia was statistically significant (p=0.04). The lowest average value of IL-1β was 1.8±7.4 pg/ml, as recorded in the control group, with similar average values observed in the group with moderate preeclampsia, while the highest average value in the group with severe preeclampsia measured 11.3±35.7 pg/ml.

Mean levels of IL-8, IL-10 and IL-1β in patients with moderate and severe preeclampsia and control group are presented in Fig. 2.

Both subgroups insignificantly (p=0.7) differed in terms of CRP values (Table 3). Significant difference (p<0.01) was confirmed among pregnant women with PE, and pregnant women with moderate and severe PE in relation to healthy pregnant women. The average values of CRP in group of PE with severe range was recorded at around 12 mg/L, while in the group of healthy pregnant women an average of 4.7±4.6 mg/L was recorded (Fig. 3).

Results of the analyzed differences between groups in terms of TNF-α values show that the serum of pregnant women in the group with secondary symptoms expressed in PE records such significantly higher values in pregnant women with PE compared with the control group (p=0.012) (Table 3). TNF-α had an average value of 146.3±254.3 in the group of pregnant with PE, 206.6±300.9 in the group with moderate PE, and 86.1±184.3 in the group with severe PE, whereas the lowest average value of 58.3±243.4 was identified in the normotensive group.

Table 2. Comparative values (pg/ml) of IL-8, IL-10 and IL-1β in moderate, severe preeclampsia, and control groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Groups</th>
<th>All PE n=50</th>
<th>Moderate PE (mPE) n=25</th>
<th>Severe PE (sPE) n=25</th>
<th>Control (c) n=50</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-8</td>
<td>Mean±SD</td>
<td>46.4±117.2</td>
<td>57.1±93.6</td>
<td>35.7±138</td>
<td>13.6±33.1</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>6.31</td>
<td>8.11</td>
<td>5.99</td>
<td>6.03</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>2.39–697</td>
<td>3.05–259</td>
<td>2.39–697</td>
<td>1.2–237</td>
</tr>
<tr>
<td>All PE/c Z=0.4 p=0.7</td>
<td>mPE/sPE/c H=3.6 p=0.17</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-10</td>
<td>Mean±SD</td>
<td>23.2±40.7</td>
<td>45.5±48.4</td>
<td>0.8±0.4</td>
<td>4.2±6.7</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>1.36</td>
<td>27.28</td>
<td>0.75</td>
<td>1.47</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>0.2–164</td>
<td>0.56–164</td>
<td>0.2–2.12</td>
<td>0.44–26.28</td>
</tr>
<tr>
<td>All PE/c Z=0.6 p=0.5</td>
<td>mPE/sPE/c H=37.68 p&lt;0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-1β</td>
<td>Mean±SD</td>
<td>6.6±25.7</td>
<td>1.9±4.9</td>
<td>11.3±35.7</td>
<td>1.8±7.4</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>0.78</td>
<td>0.67</td>
<td>0.95</td>
<td>0.665</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>0.42–131</td>
<td>0.42–24.67</td>
<td>0.49–131</td>
<td>0.13–53</td>
</tr>
<tr>
<td>All PE/c Z=2.3 p=0.02</td>
<td>mPE/sPE/c H=9.8 p&lt;0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All PE: all preeclampsia groups; BMI: body mass index; SD: standard deviation
Discussion

Results of this research showed that the most of the changes in the concentration of pro-inflammatory cytokines are seen in moderate preeclampsia. In moderate preeclampsia there is increased synthesis of these cytokines and the level of IL-10 and IL-8 reaches maximum values. In severe preeclampsia the level of pro-inflammatory cytokines remained elevated or did not differ from the values characteristic of physiological pregnancy. Thus, the study showed that, according to the cytokine profile, levels of pro-inflammatory cytokines in pregnancies complicated by preeclampsia did not only increase, but they also amended the ratio of opposite pools coinciding with the results of other studies.

However, changes in the level of cytokines determined by the degree of preeclampsia did not differ in our study from the dynamics identified in studies of other authors. Thus, many researchers argue that the concentration of IL-1β significantly rises with the increasing severity of preeclampsia and reaches maximum values during severe preeclampsia. An analo-

Table 3. Comparative values of CRP and TNF-α in moderate, severe preeclampsia, and control groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Groups</th>
<th>All PE (n=50)</th>
<th>Moderate (mPE) n=25</th>
<th>Severe PE (sPE) n=25</th>
<th>Control (c) n=50</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td>Mean±SD</td>
<td>12.5±8.5</td>
<td>12.8±7.3</td>
<td>12.2±9.6</td>
<td>4.7±4.6</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>2.6</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>0.1–35.1</td>
<td>0.1–29</td>
<td>0.9–35.1</td>
<td>0.1–15.9</td>
</tr>
<tr>
<td></td>
<td>All PE/c Z=4.9 p&lt;0.01 mPE/c p&lt;0.01 H=24.8 p&lt;0.01</td>
<td>12.5±8.5</td>
<td>12.8±7.3</td>
<td>12.2±9.6</td>
<td>4.7±4.6</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Mean±SD</td>
<td>146.3±254.3</td>
<td>206.6±300.9</td>
<td>86.1±184.3</td>
<td>58.3±243.4</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>31.15</td>
<td>46.33</td>
<td>22.07</td>
<td>19.14</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>5.41–954.8</td>
<td>5.41–954.8</td>
<td>6.98–896</td>
<td>6.27–1743</td>
</tr>
<tr>
<td></td>
<td>All PE/c Z=1.6 p=0.1 mPE/c p=0.048 H=6.1 p=0.012</td>
<td>146.3±254.3</td>
<td>206.6±300.9</td>
<td>86.1±184.3</td>
<td>58.3±243.4</td>
</tr>
</tbody>
</table>

All PE: all preeclampsia groups; BMI: body mass index; CRP: C-reactive protein; TNF: tumor necrosis factor
gous situation was the change in the concentration of other pro-inflammatory cytokines (IL-6 and TNF-α), which increased with the worsening of the disease.\textsuperscript{[27]}

They are both important mediators of the inflammatory and immune responses. These cytokines produce wide variety of effects on numerous cell types, including induction and suppression of the production of other cytokines, and many other factors including prostaglandins, platelet-activation factor and nitric oxide.\textsuperscript{[28]}

Some authors emphasize the increased synthesis of IL-2 in the third trimester of pregnancy complicated by preeclampsia, and significantly increase the proportions of TNF-α/IL-4 and IL-2/IL-4.\textsuperscript{[29]} Based on the data obtained, they are coming to a conclusion about the prevalence of Th1 immune response in this pathology. A comparison of changes in cytokine profile with increasing severity of preeclampsia allow us to determine the levels of compensation of this pathological condition which reflect the degree of implementation and functional reserve of various mechanisms to maintain homeostasis.\textsuperscript{[30]} The first phase of the changes seen in mild preeclampsia increases when creating of all studied cytokines except IL-4 and IL-10. The second phase the IL-1β and TNF-α starts to decrease ceding place to further increments in the level of IL-8 and IL-6, which suppress the inflammatory reaction and act as antagonists of IL-1β and TNF-α. During that period, the limiting role of IL-10 weakens and it is manifested through reduced levels when compared to values in normal pregnancy, giving testimony to the weakened compensatory mechanisms. The third phase, which can be called decompensated, characterized by the absence of significant differences in the level of IL-1β and IL-6, is comparable to the same level during normal pregnancy. This happens in the background of increased concentrations of other pro-inflammatory cytokines and reduced levels of the anti-inflammatory cytokines IL-4 and IL-10.

Statistical analysis confirmed a significant difference in average age between pregnant women with moderate and severe preeclampsia. Maternal age at the extremes (<20 and >40 years) has been identified as a risk factor for preeclampsia.\textsuperscript{[31]} Maternal age (>35 years) is also associated with an increased risk for preeclampsia. Similar risk factors were observed in our study, where the elderly (>30 years), women are at greater risk for preeclampsia, both classified as moderate or severe preeclampsia.

CRP is a marker of tissue damage and inflammation. Maternal levels of CRP are elevated in overt preeclampsia, but there is still a debate about its usefulness as a predictive marker for preeclampsia during the first and second trimester of pregnancy. Similar findings have been made in a number of studies. Chunfang et al.\textsuperscript{[11]} have reported that women with BMI ≤25 kg/m\textsuperscript{2} and elevated CRP were associated with a 2.5 fold increased risk of
preeclampsia, but no similar association was observed in overweight women. Wolf et al.\textsuperscript{10} have reported that the first trimester CRP levels were significantly higher among women who developed preeclampsia.

In connection with the changes that the anti-inflammatory cytokine concentrations in severe preeclampsia caused in the opposite direction, moderate phase can be considered a critical stage in the complicated pregnancy that comes to most functional strain homeostatic system.

**Conclusion**

With increasing severity of the pathological process, the impact of regulatory factors that limit the systemic effect is reduced.

At a certain stage of this process there is a significant decrease in concentration of IL-4 and IL 10 in blood serum in women with severe preeclampsia, compared with other indicators in moderate preeclampsia that are increased. This is a major pathogenetic difference of severe preeclampsia and normal pregnancy.

**Conflicts of Interest:** No conflicts declared

**References**


Pregnancy and puerperium during lactation

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Abstract
As the lactation period extends, the chance that they still breastfeed when they get pregnant increases. The studies show that there is no increase in the risk of miscarriage, preterm labor and intrauterine growth retardation. On the other hand, when pregnant woman maintains lactation, it seems that birth weight to be born decreases. No guidelines has been found in the literature showing the daily calorie, protein, vitamin and mineral needs of lactating pregnant women; however, it should be taken into consideration that energy, protein, vitamin, mineral and water needs of pregnant women who also lactate increase. Although the data in the literature indicates that lactating during pregnancy is safe, available studies cannot prove that lactation during pregnancy is either harmful or useful for mother/fetus/baby.

Keywords: Lactation, pregnancy, maternal health, miscarriage risk, early labor.

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able amount of new pregnant women in the clinics who have a child below 2-year-old they are breastfeeding. Pregnancy, delivery and puerperium are the periods that women are in close contact with healthcare professionals. Therefore, efficient presentation of healthcare services during these periods is significant.

According to various studies, women who have training about lactation before delivery are more tended to breastfeed their babies during the first 6 months and to continue lactating afterwards compared to other mothers.\textsuperscript{[3,4]} It is very critical to inform mother for the continuation or discontinuation of lactation when a breastfeeding woman gets pregnant. We need to have up-to-date information and clear opinions on this matter. Does lactation affect fertility negatively? Should the lactation be discontinued after conception? Does lactation during pregnancy increase abortion or preterm labor risk? What will happen after delivery? Is it possible to breastfeed two siblings at the same time, one being newborn and other being nursing infant? What should we recommend mothers and their families?

**Lactation and Subfertility**

Prolactin hormone secreted in the anterior pituitary enables milk production. Prolactin hormone increases gradually beginning from the 5 weeks of gestation up to delivery and reaches its maximum level at the end of pregnancy which is 200–400 ng/ml from 10–25 ng/ml.\textsuperscript{[5]} Prolactin level decreases approximately to 50% of term level in the first postpartum period.\textsuperscript{[5]} However, during each breastfeeding, hypothalamus is stimulated through the nerves on nipple. The secretion of prolactin hormone increases 10–20 times within an hour and milk is produced.\textsuperscript{[6]} While prolactin hormone enables milk production, it also suppresses follicle stimulating hormone (FSH) and luteinising hormone (LH), keeps estrogen levels low and ovulation is suppressed by preventing follicle development. This hypothesis explains the prevention of fertility by lactation.

Women who feed their babies only with lactation and do not menstruate are not expected to get pregnant within first 6 months during postpartum period. This can be considered as the contraception method during postpartum period. This method called as lactational amenorrhea is a method that can be used when certain conditions are met until an effective contraception method is chosen. Under these conditions, menstruation should not have started yet and baby is only fed by breast milk.\textsuperscript{[6]} If both conditions are available, lactational amenorrhea becomes efficient about 98–99.5%.\textsuperscript{[6]}

The efficacy of lactational amenorrhea method is directly associated with the lactation duration and frequency. The studies have showed that feeding the baby with only breast milk (full lactation) extends the duration of lactational amenorrhea compared to partial lactation and prevents the return of postpartum fertility.\textsuperscript{[7,9]} Feeding baby with only breast milk means that there is only 4-hour interval between two breastfeeding activities during the day at the most and 6-hour interval during the night at the most, baby does not receive any liquid or solid nutritional supplements\textsuperscript{[10]} and lactation duration is at least 4–5 minutes.\textsuperscript{[10]} Lactation frequency decreases with the nutritional supplements after first 6 months as well as the milk amount produced, and therefore the body becomes ready for a new pregnancy. Lactational amenorrhea method is effective in the first sixth months after delivery. Afterwards, the couples should prefer another contraception method.

**Lactation and Fertility**

Conception during lactation period and discontinuing lactation is a common case in the world.\textsuperscript{[11,12]} Conception during lactation period has been common for ages in societies with low socioeconomical levels and in developing countries where lactation takes long and effective contraception methods are restricted.\textsuperscript{[13]} For instance, 25% of the women on gestational follow-up in Egypt got pregnant during lactation period.\textsuperscript{[14]} We know that half of the pregnancies in Guatemala\textsuperscript{[15]} occurred during lactation periods, and that 70% of the pregnant women in some poor regions of India\textsuperscript{[11]} were already breastfeeding. On the other hand, no data has been found in the literature about the rate of pregnancies during lactation in the developed countries.\textsuperscript{[13]}

**Lactation During Pregnancy and Tandem Nursing: Do-Or-Die?**

When lactating mother gets pregnant and decides to continue lactating during the pregnancy, following questions cross clinician’s mind: the nutritional needs of mother will change. What should I recommend about nutrition to a lactating woman who gets preg-
nant? Do the development and growth of fetus and nursling slow down? Does the amount/quality/taste of milk change? Will abortion or preterm labor be triggered?

Nutritional Needs

Recommended dietary allowance increases during pregnancy and lactation periods. Depending on the age of mother who lactates or gestational age, this increase is roughly 34.6% for energy and 54% for protein.\(^{14}\) Lactation requires more nutrition than pregnancy; during lactation, carbohydrate need increases 61.5% and protein need increases 54.3%.\(^{16}\) Vitamin and trace element needs does not increase for some individuals (biotin, potassium and chloride needs) while it may double for some individuals (i.e. vitamins A and C).\(^{17–19}\) After delivery, women should complete the deficiencies of their bodies until next pregnancy and delivery. As the needs for energy, vitamin, mineral and protein increase during lactation, the duration between the end of lactation and next pregnancy is more significant than the “duration between pregnancies”. The minimum period without pregnancy and lactation is still controversial.

Although there are no guidelines for daily dietary need of lactating mother for each trimester, it is clear that lactating mother should be nourished better than other pregnant women and increase her protein/energy/vitamin/mineral/water supplement. It can be easily predicted that the nourishment needs of lactating pregnant woman will reach the maximum level at third trimester in which fetus has the fastest growth rate. Also, when lactation is continued more than one year, the energy and fat content of milk is statistically and significantly higher than the milk women who have been lactating for a short time.\(^{20}\) The study carried out in Philippines\(^{21}\) compared lactating and non-lactating women and found no difference in terms of total weight gain during pregnancy but observed that lactating pregnant women gained weight faster significantly at third trimester. In this study, mean lactation period during pregnancy was 11.9±0.35 weeks in women who got pregnant during lactation. On the other hand, weight gain of those continuing lactation on the third trimester was affected negatively.\(^{21}\) According to this study, it is seen that the pregnant women who lactate only in the beginning of the pregnancy make up the difference by rapid weight gaining through the end of pregnancy; however, those who lactate throughout the whole pregnancy seem to gain less weight eventually. The study comparing 45 women lactating during pregnancy and 120 women not lactating during pregnancy found that lactating pregnant women gained less weight.\(^{22}\)

Institute of Medicine (USA) recommends lactating women to nourish with a diet including various vegetables, fruits and grains rich in calcium and protein.\(^{23}\) Although it is easy to meet calorie need as foods rich in fat and sugar are consumed much in developed countries, vitamin and mineral deficiencies should be paid attention in both developed and developing countries. During the pregnancy, women should take 150 kcal/day at the first trimester, and 300 kcal/day at the second and third trimesters in addition to normal nourishment.\(^{24}\) During the period when baby is fed only with breast milk, mothers consume 628 kcal/day additionally due to milk production.\(^{25}\) It is not recommended to receive such calories by additional foods, a little lower amount of calories can be received since the body of mother stores fat for postpartum period during a normal pregnancy.\(^{25}\)

In another study comparing lactating and non-lactating women, it was found that women who lactate consume an additional 580 kcal daily (2460 kcal vs. 1880 kcal).\(^{24}\)

Increasing blood production in order to tolerate growing fetus and increasing blood volume of mother during pregnancy and the loss during delivery also increases the need for iron. While required iron support is daily 30–60 mg elementary iron for women not lactating during pregnancy,\(^{27}\) it is 9 mg/day after 19-year-old during lactation where mother is not pregnant, and 10 mg/day during 14–18-year-old.\(^{28}\) When the support of iron and non-availability of iron support during pregnancy were compared, it was found that preterm labor, low birth weight, maternal anemia and iron deficiency were higher in those who were not provided iron support.\(^{27}\) The significance of iron for both fetuses\(^{20}\) and mental development of babies\(^{29}\) and also the role in gestational diseases such as preeclampsia and intruterine growth retardation\(^{30}\) are known. The most common vitamin/mineral deficiency in developed and developing countries is iron deficiency.\(^{31}\) Ayrim et al. found a significant decrease in hemoglobin values of women lactating during pregnancy compared to those not lactating during pregnancy.\(^{24}\) Consequently, providing iron support to lactating pregnant women is significant for fetus, mother and nursling.
Since folic acid elimination through urine increases during pregnancy and there are high amount of cells with rapid division in the body of pregnant woman, the need for folic acid of pregnant women increases.\textsuperscript{27} Neural tube is closed on day 28 and even pregnancy may not be identified yet in such a short period of time. After pregnancy is identified, folic acid support will not be beneficial for neural tube development but for meeting the needs of mother.\textsuperscript{27} World Health Organization recommends to take 400 µg folic acid daily during pregnancy.\textsuperscript{27} During lactation, it is recommended to take 500 µg folic acid daily.\textsuperscript{17}

Increasing calcium need during pregnancy is met by the increase of calcium absorption from gastrointestinal system.\textsuperscript{12} Calcium release from bones also helps to meet the increasing need during pregnancy.\textsuperscript{12} Therefore, additional calcium support is not required during pregnancy.\textsuperscript{34} Pregnant women are recommended to take 1200 mg/day calcium through foods.\textsuperscript{16} In societies with insufficient consumption of foods rich in calcium, it is recommended to provide 1.5–2 g elementary calcium support daily from 20 weeks of gestation up to delivery.\textsuperscript{11} It is seen that the greatest source for calcium transfer to milk during lactation period is skeletal system, renal reabsorption also provides calcium in small amounts.\textsuperscript{12} It is understood that the calcium taken by food is the greatest source during pregnancy while the calcium stored in the body is the greatest source during lactation.\textsuperscript{13} It is clear that the calcium need of woman who undertook a pregnancy and started to lactate, then gets pregnant and continues to lactate is high; however, there is no detailed information on the exact amount of daily calcium support for a lactating pregnant woman.

Vitamin A has a significant role for cell division, development of fetal organs and skeletal system, vision and immune system. While vitamin A supplement is not recommended in the routine pregnancy follow-up, vitamin A supplement during pregnancy and postpartum period in countries, where vitamin A deficiency is a significant public health issue, is recommended to protect both fetus during pregnancy and the baby during lactation against vitamin A deficiency.\textsuperscript{16} The recommendation is to take 800 µg retinol daily together with foods during pregnancy; however, since vitamin A is available in foods which are not easily accessible such as vegetable, fruit, meat and dairy products in low-income countries, pharmacological support is required in such countries.\textsuperscript{34} The supplement for vitamin A is maximum 10,000 IU daily or 25,000 IU weekly for at least 12 weeks during pregnancy.\textsuperscript{36} The babies born with low amount of vitamin A reserve and breast milk should include sufficient amount of vitamin A to nourish babies. Yet, vitamin A supplement is not recommended for puerperant women; postpartum vitamin A supplement does not affect maternal and fetal mortality and morbidity.\textsuperscript{17} In developed and developing countries, further studies are required to determine whether women who are lactating during pregnancy or not, and the amount if required.

During the pregnancy, 3 lt/day water is required while 3.8 lt/day water is required during the lactation period.\textsuperscript{39} Although there is no clear data for the need of daily water amount for lactating pregnant women, they need to drink more water than regular amount in order to increase milk production and to meet the need increased during pregnancy.

**Growth and Development of Fetus When Breastfed**

No study has been found in the literature focused on determining if lactation during pregnancy increases to deliver baby small for gestational age or the rate of in utero growth retardation. On the other hand, the studies in the literature have reported different results. A study in the past found that the children of lactating mother were 57 g lighter than the children of non-lactating mother, which is statistically not a significant difference.\textsuperscript{11,12} A study carried out in Turkey in 2013 included 61 women who got pregnant again within 2 years after the delivery; in this study, lactating and non-lactating pregnant women were compared and it was found that the birth weight was statistically and significantly lower in the lactating pregnant women than the other group (p=0.006).\textsuperscript{38} In another study, overlapping of lactation and pregnancy was not found to be associated with delivering baby small for gestational age.\textsuperscript{19}

**Growth and Development of Baby When Lactating Mother Gets Pregnant**

When lactating women get pregnant, it is hard to understand if the development of nursing is delayed. Besides, even such a case is identified, no causation can be interpreted between lactation or quality/content of milk and development. With the new pregnancy, the attention and time spared for the baby will decrease. There are a few
studies in the literature investigating the effects of lactation during pregnancy on pediatric health. Devecioglu et al. presented two cases in their studies in which one case found out in the postpartum third month that she was pregnant while the other case found out in the postpartum 15th month, and they continued lactation both during pregnancy and after the delivery. Both babies of both women were regularly followed up in the same clinic, and since developments of four babies in the first 6-month follow-ups were normal, it was considered normal to feed them with only breast milk. The first child of first mother was 25-month-old and the mother was continuing to lactate when we were preparing the paper. Second mother discontinued to lactate the first child when the child was 26-year-old. Growth and development of both children of both mother had regular progress according to their ages. Bohler et al. found that the growth rates of children which were discontinued to breastfeed during pregnancy were lower than those never breastfed or continued to be breastfed during pregnancy. This matter remains unclear since the development of older child does not only depend on breastfeeding.

**Does the Amount/Quality/Taste of Milk Change?**

As the lactation frequency decreases, the sodium and protein concentrations of the milk increase while glucose, lactose and potassium concentrations decrease. These changes occur depending on the decrease of lactation rate. In the beginning of the pregnancy, independent from the lactation rate, same changes occur (sodium and protein concentrations increase, and glucose, lactose and potassium concentrations decrease). It is seen that milk production decreases in the beginning of the pregnancy by resisting to the stimulus created by lactation. These changes in the breast milk during pregnancy would change the taste of milk. These changes may create problems for nursing, the baby may decrease to suck milk, does not want breast milk or continue to suck breast milk as before. Besides, it is known that the taste of breast milk change and the baby tastes different milk every time.

**Relationship Between Lactation and Abortion**

The opinion that lactation may cause abortion is based on the idea that two hormones are considered to be dangerous: prolactin and oxytocin. Hirahara et al. found that the pregnancy rates of patients with hyperprolactinemia are higher when treated with bromocriptine than those not treated with bromocriptine. Bromocriptine inhibits prolactin production and decreases the prolactin level. When prolactin reaches normal levels, ovulation and then fertilization may occur. Hirahara et al. also found that prolactin levels were higher in the early periods of pregnancy in patients who had miscarriage. It is understood through these two data that prolactin increase occurring during lactation may increase the risk of spontaneous pregnancy loss during the first trimester. The second problem is the increase of oxytocin release from hypothalamus as the nursing sucks nipple. Oxytocin enables the release of milk by the contraction of myoepithelial cells of breast and also triggers uterine contractions. While this effect is beneficial for hemodynamics by decreasing uterine hemorrhage during postpartum, is it harmful by causing abortion when conception occurs? Oxytocin release by lactation seems that it does not cause any risk in pregnant women for 3 reasons. First of all, the oxytocin receptors in myometrium and sensitivity of uterus to oxytocin increases in the late periods of pregnancy and especially during delivery, and the amount of oxytocin receptors decreases rapidly after delivery. There is resistance before and after delivery relative to oxytocin. Secondly, oxytocin release decreases over time in response to nipple stimulation; oxytocin release occurring with lactation after months following delivery is not as strong as those during the first postpartum days. And thirdly, it was found that the oxytocin increase in pregnant women was not as high as in other groups when the increase rate of oxytocin after nipple stimulation was investigated in pregnant women, postpartum lactating women and women with normal cycles. Although prolactin and oxytocin levels higher in lactating women than normal pregnant women seem to increase abortion risk in the first trimester, the three studies we have found no relationship between lactation and early gestational losses. Ishii compared 110 lactating pregnant women with 774 non-lactating pregnant women and found similar abortion rates between two groups. Vitzthum et al. investigated the abortion cases before 7 weeks of gestation as early gestational losses and did not find any increase in lactation and rates of abortions. Ayrim et al. found no increase in the risk of threatened abortion in lactating pregnant women.
abortion cases in the group of lactating women while the other group had no abortion. This difference is not statistically significant; however, the low population of the groups should also be considered.[38]

The Relationship between Lactation and Preterm Labor

Oxytocin is one of the pharmacological methods used for labor induction. It is thought that not only oxytocin by IV but also oxytocin secreted with nipple stimulation causes labor induction. On the other hand, no case was found in the literature which had early labor as a result of oxytocin secretion due to lactation. The studies in the literature compared the gestational outcomes of lactating and non-lactating women and found no relationship in terms of preterm labor.[22,38]

Personal Decision

The data found in the literature can neither prove that lactation during pregnancy is harmful nor completely safe for mother/fetus/baby. Therefore, pregnant women should be warned that it may not be safe although there is no strong data to recommend discontinuing the lactation after conception. The age of nursing is also important when informing lactating pregnant women; the need of a 7-month-old baby for breast milk is not same as a 24-month-old baby. Whether the mother has additional diseases or not, dietary habits of mother, access to diet rich in calcium and protein together with mineral and vitamin supplement, obstetric amnnesia of pregnant woman (presence of previous abortion/preterm labor history), progress of pregnancy and whether fetus has sufficient growth or not in ultrasound follow-up are the issues to consider when making a decision.

The decision to continue or discontinue lactation during pregnancy should be a personal decision to be made by mother according to the information she gets. If it is decided to discontinue lactation, this process may not be always very fast and easy. Also, according to a study, it was found that 39% of pregnant women continued to lactate but did not inform their gynecologists and obstetricians.[11] Due to these two reasons, lactating pregnant women should be recommended to pay attention their diets and to consume plenty of water, and they should be informed about tandem nursing.

Conflicts of Interest: No conflicts declared.

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16. Food and Nutrition Board, Institute of Medicine, National Academies. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids.


Abstract
This guideline, based on the report\textsuperscript{1} of Perinatal Thyroid Workshop – 2015 which was prepared in the Perinatal Thyroid Workshop held in Afyonkarahisar, Turkey on November 8–9, 2013 with the participation of the academicians who are the members of the Turkish Perinatal Society and work at universities and training and research hospitals in Turkey, and published in the Issue 2, Volume 23 of the Perinatal Journal on August 2015, aims to provide guidance in clinical practices related with thyroid during pregnancy.

Keywords: Pregnancy, perinatal, thyroid.

Guideline for the assessment of thyroid during pregnancy
Perinatal Thyroid Study Group
Türk Perinatoloji Derneği, İstanbul

Hypothyroidism During Pregnancy
Since the association of overt hypothyroidism with poor gestational outcomes was proven, maternal hypothyroidism should be avoided by initiating treatment as soon as identified during pregnancy.

It is known that subclinical hypothyroidism is more common than overt hypothyroidism.

The association between subclinical hypothyroidism and poor gestational outcomes are controversial. While cohort studies showed the association of subclinical hypothyroidism and poor gestational outcomes, randomized controlled studies showed no such association. On the other hand, there is uncertainty in the potential benefits of treatment with oral L-thyroxine for pregnant women with subclinical hypothyroidism.

Since maternal oral L-thyroxine intake cannot treat fetal hypothyroidism in the intrauterine life, it is scientifically not right to say that L-thyroxine treatment of a mother would also treat the possible hypothyroidism in fetus.

Hyperthyroidism During Pregnancy
While overt hyperthyroidism has many reasons, it occurs during pregnancy mostly associated with Graves’ disease. Hyperthyroidism during pregnancy may cause abortion of mother, hypertension associated with pregnancy, preterm labor, anemia, arrhythmias and coronary failure in more advanced cases and thyroid crisis. Therefore, the treatment is initiated immediately as soon as it is detected during pregnancy, and it is aimed to keep mother in mild hyperthyroidism.

The medication mostly preferred in the treatment is propylthiouracil (PTU) since it passes through placenta at minimal rates (PTU).

Hyperthyroidism during pregnancy is the hyperthyroidism which is seen more common than Graves’
disease and associated with human chorionic gonadotropin (hCG). Hyperthyroidism associated with hCG courses slighter than Graves’ disease. hCG-dependent hyperthyroidism is temporary and does not require treatment.

There is no evidence showing that subclinical hyperthyroidism treatment has positive impact on the pregnancy progress, and treatment of subclinical hyperthyroidism is not recommended since treatment may have potential side effects on fetus.

Iodine Insufficiency During Pregnancy
In Turkey, scientific data seem insufficient for now to suggest routine iodine support for all pregnant women during antenatal care. However, large-scale and society-based studies are required immediately to determine iodine sufficiency prevalence in Turkey.

If the region that pregnant women live is known to have severe iodine insufficiency, iodine supplement should be recommended certainly during antenatal period.

Mild-medium iodine insufficiency during pregnancy was shown to have short- and long-term negative impacts on neurological, behavioral and learning abilities. However, the cause-effect relationship has not been established fully yet.

Should Thyroid Diseases be Screened During Pregnancy?
The benefit of the screening for thyroid dysfunction in the pregnant population has been proved to determine clinical hypothyroidism and to initiate treatment early. This screening should be carried out before conception preferably or in the onset of the pregnancy if possible.

The benefit of screening to determine subclinical hypothyroidism has not been proven; because there is no data available showing the benefits of subsequent thyroxine treatment.

Screening at the onset of pregnancy just requires the measurement of TSH levels. The tests to be carried out for free or total T4 are only required when there is a change in TSH.

Similarly, anti-thyroid antibodies during pregnancy are not recommended to use for routine screening since there is no evidence to make a recommendation in favor of or against screening.

Due to the changes in thyroid physiology during pregnancy, it is very significant to highlight that interpreting thyroid hormone test results during pregnancy is more different.

For that reason, we recommend that each laboratory should calculate percentile values of their own gestational study population for each trimester separately and report the studied results through percentile values.

Considering the current literature, guides and expert opinions generally, it is seen that screening all pregnant women with TSH in the first trimester is not convenient. Screening with TSH should be carried out for risky cases.

Pregnant Women Recommended for TSH Screening during Early Pregnancy

- Thyroid dysfunction / surgery underwent (since hypothyroid development rate is 33% after lobectomy)
- Thyroid disease history in the family
- Goiter presence
- Thyroid antibody positivity, especially thyroid peroxidase auto-antibodies (TPOAb increases hypothyroidism risk, and the probability increased 40% in those with TPOAb positivity compared to TPOAb negativity)
- Presence of clinical hypothyroidism findings/symptoms
- Type I diabetes (since hypothyroidism rate increases to 16%)
- Miscarriage and preterm labor
- Presence of vitiligo, adrenal failure, hypoparathyroidism, atrophic gastritis, pernicious anemia, systemic sclerosis, SLE, Sjögren’s syndrome associated with autoimmune thyroid dysfunction
- Infertility presence (Although overt and subclinical hypothyroidism rates are as wide as 1–43%)
- Those who underwent head-neck irradiation (since hypothyroidism prevalence is 67% in the 8-year follow-up)
- Morbid obeses whose BMI (body mass index) is >40 (since hypothyroidism was found as 13–19.5%)
• Women over 35 years (The rate of serum TSH value be ≥5 increases together with the age)
• Amiodarone treatment applications (14–18% hyperthyroidism-hypothyroidism)
• Lithium use (6–52 hypothyroidism)
• Exposure to iodinized contrast agents (until 6 weeks before pregnancy, thyroid dysfunction in 20% cases)
• Living in regions with medium level of iodine insufficiency

Lower and upper limit values for serum TSH
- 0.1 – 2.5 mU/L for the first trimester
- 0.2 – 3.0 mU/L for the second trimester
- 0.3 – 3.0 mU/L for the third trimester

Management
As in non-pregnant women, high TSH blood levels make established primary hypothyroidism diagnosis in pregnant women. In the first trimester of pregnancy, there is no sufficient evidence to support a routine screening with only thyroid auto-antibodies, so it is not recommended.

In the current literature, it is not clarified which is the best screening strategy among screening only TSH, only anti-TPO antibody or anti-TPO antibody together with TSH.

TSH >2.5–10.0 mU/L together with normal free T4 level: Subclinical hypothyroidism
TSH >2.5–10.0 mU/L together with low free T4 level: Clinical (overt) hypothyroidism
TSH ≥10.0 mU/L, without considering free T4 level: Clinical (overt) hypothyroidism

However, it should be careful when interpreting free T4 levels during pregnancy, and ranges specific to trimester determined by each laboratory should be referred, or instead, in second and third trimesters, new reference ranges obtained by multiplying gestational total T4 reference ranges by 1.5 can be used. Free T4 index can also be used as an alternative reference value to be used during pregnancy. Free T4 index can also be used during pregnancy as a different alternative reference value.

Since the association of overt hypothyroidism with poor gestational outcomes was proven, maternal hypothyroidism should be avoided by initiating treatment as soon as identified during pregnancy.

All pregnant women newly diagnosed with overt hypothyroidism should be treated with thyroid hormone (thyroxine, T4). T4 dose should be adjusted as keeping TSH below 2.5 mIU/L in first trimester and below 3 mIU/L in second and third trimesters (or within TSH ranges specific to trimester). Thyroid function tests should be evaluated within 30–40 days after the onset of treatment and once every 4–6 weeks subsequently.

When using levothyroxine to treat cases with hypothyroidism associated with any reason, it is not required to include routine iodine supplement additionally.

Since there is no study for the gestational outcomes of euthyroid pregnant women with positive TG-antibody, it is not recommended to treat such patients with levothyroxine.

If hypothyroidism diagnosis is established before pregnancy, T4 dose should be arranged as keeping TSH below 2.5 mIU/L in the preconceptional period.

After delivery, the dose administered during pregnancy of most of the hypothyroid women should be decreased to pregestational dose.

As we do not have sufficient evidence about its activities and due to the inconsistencies in free T4 measurement, it is currently not recommended to treat isolated hypothyroxinemia.

If there is more demand for thyroid during pregnancy and evidences are available showing that euthyroid women, which have autoimmune thyroid disease at the early periods of gestation, have more risk for subclinical hypothyroidism or overt hypothyroidism in the advanced weeks of gestation, it is required to monitorize TSH once every 4-6 weeks in these women.

Although current literature data are limited, gestational loss is higher in first trimester pregnant women whose thyroid antibody is negative and TSH value is between 2.5 and 5 mIU/L compared to first trimester pregnant women whose TSH value is below 2.5 mIU/L. However, since the efficiency of treatment cannot be suggested, levothyroxine treatment is controversial. Studies evaluating treatment efficiency are required for these cases.
Considering the current literature, guides and expert opinions generally, it is seen that screening all pregnant women with TSH in the first trimester is not convenient. **Screening with TSH should be carried out for risky cases.**

Since maternal oral L-thyroxine intake cannot treat fetal hypothyroidism in the intrauterine life, it is scientifically not right to say that L-thyroxine treatment of a mother due to any thyroid dysfunction would also treat the possible hypothyroidism in fetus.

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

**Reference**

Dear Editor,

Due to World Breastfeeding Week, it is planned to support and encourage breastfeeding and to protect breastfeeding women between August 1 and 7, 2015. World Alliance for Breastfeeding Action (WABA) is a global network of individuals and organizations endeavoring to highlight the significance of breast-milk and to make breastfeeding widespread. WABA has announced its goals for 2015. The most important two goals are to support women being able to breastfeed in workplace and to encourage governments to establish laws protecting mothers.

Since 2001, World Health Organization has been recommending exclusive breastfeeding up to 6 months of age, with continued breastfeeding along with appropriate complementary foods up to two years of age or beyond.[1] Most of the mothers want to breastfeed for a long time for the purposes of feeding their babies, protecting them against infections and having the emotional satisfaction of breastfeeding. Turkish Population and Health Survey 2013 showed that 33.9% of 20–23-month-old babies were breastfed and the mean lactation period for all children born within three years before 2013 was 16.7 months.[2] According to the data of the same survey, 18% of the deliveries in Turkey occurred less than 24 months after the previous delivery.[3] According to these data, we should observe a considerable amount of pregnant women in the clinics who have a child below 2-year-old they are breastfeeding. It is very critical to inform mothers for the continuation or discontinuation of lactation when a breastfeeding woman gets pregnant. In Turkey, women tend to discontinue lactation when they get pregnant. Atar Güler et al. found that 26 of 102 pregnant women, whose pregnancy interval (the period between previous delivery and the onset of following pregnancy) is less than 24 months, discontinued lactation due to the pregnancy.[4] At this point, gynecologists and obstetricians may support the discontinuation of lactation due to the concern that lactation during pregnancy may have risks for fetus and/or mother. However, the studies show that miscarriage[5, 6] and preterm labor[7] risks do not increase in pregnancies during lactation. In cases where pregnancy coincides with lactation, it is unclear if continuation of lactation causes the fetal growth to slow down. When birth weights of babies delivered by women continuing lactation during pregnancy were compared with those delivered by women discontinued lactation during pregnancy, a study carried out on 505 pregnant women found no statistically significant difference[8] while another study carried out on 61 pregnant women found statistically significant difference.[9] No guide has been found in the literature showing the daily needs of lactating pregnant women for calories, protein, vitamin and mineral.

On the other hand, it should be taken into account that energy, protein, vitamin, mineral and water needs of both pregnant and lactating women increase. Although the data in the literature indicates that lactating during pregnancy is safe, current studies cannot prove that lactation during pregnancy is either harmful or useful for mother/fetus/baby. Today, where there are many efforts to make breastfeeding widespread and to extend lactation period, it is possible that we come across mothers more frequently who prefer to continue lactation during pregnancy. Therefore, gynecologists and obstetricians should have up-to-date knowledge about the outcomes of lactation in cases where pregnancy and lactation coincide.

Conflicts of Interest: No conflicts declared.
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Let's meet where the continents meet
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