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Prenatal diagnosis of fetal urinary system anomalies

Ezgi Hürcan, Alper Biler, Atalay Ekin, Gökhan Tosun, Cüneyt Eftal Taner

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Abstract

Objective: The aim of this study is to determine concurrent structural and chromosomal anomalies in the cases found to have fetal urinary system anomaly.

Methods: The pregnant women established with the diagnosis of fetal urinary system anomaly in our clinic between 2010 and 2015 were included in the study. Age, week of gestation, gravida, parity, number of abortion, anomaly type, presence of concurrent anomaly, prenatal diagnosis method and fetal karyotype results of the pregnant women were recorded. Urinary system anomalies were categorized in sub-groups which were renal agenesis, pyelectasis, multicystic dysplastic kidney, polycystic kidney and megacystis.

Results: Pylectasis was the most common fetal urinary system anomaly. In terms of other concurrent anomalies, the central nervous system anomaly was the most common anomaly seen in 17 (28.3%) pregnant women. The most common concurrent urinary system anomalies seen with additional anomalies were unilateral pylectasis (91.7%), unilateral renal agenesis (75%), bilateral multicystic dysplastic kidney (66.7%), and bilateral pylectasis (62.5%). Anhydramnios developed in 5 (8.3%) cases. When karyotype results were assessed, it was seen that one (1.7%) case had triploidy, and 16 (26.6%) cases had trisomy. Of the cases with trisomy as karyotype, 3 (17.6%) had isolated urinary system anomaly and other 14 (82.4%) had additional anomaly. The difference between the cases whose karyotype results were normal, and trisomy and the cases with additional anomaly was statistically significant (p=0.040).

Conclusion: The concurrent structural and chromosomal anomalies should be determined in the management of pregnancies with fetal urinary system anomaly diagnosed during prenatal period.

Keywords: Fetal urinary system anomaly, karyotype, pylectasis, trisomy.

ÖZET: Fetal üriner sistem anomalilerinin prenatal tanısı

AMAÇ: Çalışmanın amacı fetal üriner sistem anomalisi saptanan otların eşlik eden yapısal ve kromozomal anomalileri belirlemektir.


BULGULAR: En sık görülen fetal üriner sistem anomalisi pylectazi idi. Eşlik eden diğer anomaliler iklendenden 17 (%28,3) gebe ile santral sinir sistemi anomalisi en fazla karşılaştırılan anomalidi. Ek anomalilerle ile en sık birlikte görülen diğer anomaliler ise: unilateral pylectazi (%91,7), unilateral renal agenezi (%75), bilateral multikistik displastik börek (%66,7) ve bilateral pylectazi (%62,5). Beş (%8,3) olguda anhidramnios gelişti. Karyotip sonuçlarını değerlendirildiğinde bir (%1,7) olguda trisomi ve 16 (%26,6) olguda trizomi mevcuttu. Karyotip trizomi olan otların 3’si (%17,6) izole üriner sistem anomalisi saptandı ve diğer 14 (%82,4) hastada ek anomali mevcuttu. Karyotip sonucu normal ve trizomi olan otlar ile ek anomali arasındaki fark istatistiksel olarak anlamlı (p=0,040).

SONUÇ: Prenatal dönemde tanılan fetal üriner sistem anomalileri, karyotip, pylectazi ve trizomi.

Anahtar sözcükler: Fetal üriner sistem anomalisi, karyotip, pylectazi, trizomi.

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Introduction

Congenital urinary system anomalies include various levels of structural and functional malformations such as kidney, collecting ducts, bladder and urethra, and its incidence is approximately between 0.3 and 1.6 per 1000 births. They consist of 15–20% of all anomalies during prenatal period.

Many structures forming the fetal urinary system develop between 10 and 20 weeks of gestation, and most of these anomalies can be diagnosed by ultrasonography during this period. The most common urinary system anomalies are obstructive pathologies. However, they contain a wide spectrum between mild asymptomatic malformations and severe pathologies with high mortality.

The common findings of urinary system anomalies during antenatal period are oligohydramnios, and the distinct changes in kidney, ureter or bladder morphology. While some of the forms are seen together with the syndromes accompanied by multi-organ anomalies, most of the cases are non-syndromic. Although it has been shown in sporadic cases and some animal models that some genes play a role in the developmental defects of urinary system, it is still controversial for determining which has the main role. Multiple genes play a role in the development of urinary system pathologies as in many congenital anomalies. Environmental factors also affect the development of embryo and fetus.

Urinary system anomalies may affect not only the current system but also other fetal functions. For example, some anomalies in this group may lead to oligohydramnios and therefore fetal pulmonary hypoplasia and extremity contractures. While most of the uriological abnormalities are progressive, functional reversion can be possible by treatment methods carried out during intrauterine or postnatal period.

In our study, we aimed to assess the frequency of chromosomal anomaly in cases found to have urinary system anomaly, its association with other system anomalies, and their impacts on karyotype results.

Methods

In this study, we retrospectively evaluated 60 cases which were found to have fetal urinary system anomaly during fetal anomaly screening and routine obstetric ultrasound examination and underwent karyotyping for prenatal diagnosis at the Gynecology and Obstetrics Clinic of Tepecik Training and Research Hospital, Health Sciences University between January 1, 2010 and December 31, 2015. For genetic diagnosis purpose, the cases underwent chorionic villus sampling (CVS), amniocentesis or cordocentesis. Approval of ethics committee required for the study was obtained from the Local Ethics Committee of Tepecik Training and Research Hospital with the number 30.09.2015/1.

Age, week of gestation, gravida, parity, number of abortion, anomaly type, presence of concurrent anomaly, prenatal diagnosis method and fetal karyotype results of the pregnant women found to have fetal urinary system anomaly were recorded. Urinary system anomalies were categorized in sub-groups which were renal agenesis, pyelectasis, multicystic dysplastic kidney, polycystic kidney and megacystis. For pyelectasis diagnosis, the threshold for renal anterior-posterior diameter was determined 4 mm for up to 32 weeks of gestation and 7 mm for 33 weeks of gestation and above.

For prenatal diagnosis, all families were provided genetic consultancy before the karyotyping procedure. Written and oral information about the technique of karyotyping procedure and possible complications were given and informed consents were obtained. The procedures were done together with ultrasonography. Local anesthesia was not applied during any procedure, and antibiotic prophylaxis was performed for all patients after the procedure. For CVS procedure, chorion frondosum was entered by using 18 gauge needle through double-need technique and then the stylet was removed. Afterwards, sampling needle was inserted. After it was fixed to the needle tip of 20 ml injector containing heparinized culture medium, aspiration was conducted by forward and backward movements. In the amniocentesis procedure, 22 gauge spinal needle was used to enter into amniotic cavity where there was no fetal structure and cord. Amniotic fluid was aspirated by means of 10 ml injector by applying slight negative pressure, and 1 ml was collected per week of gestation. In order to prevent contamination, separate injectors were used and first 2–3 ml of fluid was discarded. In the cordocentesis procedure, 20 gauge spinal needle was used and umbilical vein was entered on 1–2 cm away from the entrance point of cord into placenta. About 1–5 ml blood sample was collected by heparinized injector. The pregnant women...
who had normal karyotype results and no significant anomaly were followed up by ultrasonography until delivery. The fetuses who had fatal chromosomal or structural anomaly were evaluated by the perinatology council of our clinic and the family was offered the option for terminating the pregnancy.

All statistical analyses of the data were done by using SPSS software, version 17.0 (SPSS, Inc., Chicago, IL, USA). Conformity of the numerical variables to normal distribution was evaluated by Shapiro-Wilk test. The categorical variables were determined by frequency and percentage while numerical variables were determined by mean and standard deviation or median and minimum-maximum values. The correlation between two categorical variables was investigated by chi-square test. Two independent mean values were compared by Student’s-t test while two independent median values were compared by Mann-Whitney U test. The study was evaluated within 95% confidence interval. The value p<0.05 was considered statistically significant.

Results

The study group consisted of 60 pregnant women who were found to have fetal urinary system anomaly and underwent karyotyping. The demographic characteristics of the cases are shown in Table 1.

Pyelectasis was the most common one among urinary system anomalies (Table 2). While fetal pyelectasis was observed in 28 (46.7%) pregnant women, 12 (20%) of them was unilateral and 16 (26.7%) of them were bilateral. Of the other pregnant women, 8 (13.3%) had unilateral multicystic dysplastic kidney, 6 (10%) had bilateral multicystic dysplastic kidney, 4 (6.7%) had unilateral renal agenesis, 2 (3.3%) had bilateral renal agenesis, 2 (3.3%) had polycystic kidney and 6 (18.3%) had megacystis. In terms of other anomalies accompanying urinary system anomalies, the central nervous system was the most common anomaly seen in 17 (28.3%) pregnant women (Table 2). Thirteen (21.7%) pregnant women had fetal hyperechogenic intestine, 12 (20%) cases had cardiovascular system anomaly, 4 (6.7%) cases had facial anomaly, 5 (8.3%) cases had extremity anomalies, 4 (6.7%) cases had single umbilical artery, 2 (3.3%) cases had anterior abdominal wall defect, one (1.7%) case had diaphragmatic hernia, and one (1.7%) case hydrops. In addition, the most common concurrent urinary system anomalies seen with additional anomalies were unilateral-

| Table 1. The demographic data of the pregnant women who participated in the study. |
| Age (Mean, SD) | 28.4 | 5.7 |
| Age (n, %) |  |  |
| <35 | 51 | 85 |
| ≥35 | 9 | 15 |
| Week of gestation (Mean, SD) | 22.1 | 6.1 |
| Week of gestation (n, %) |  |  |
| <22 weeks | 23 | 38.3 |
| >22 weeks | 37 | 61.7 |
| Gravida (Median, min-max) | 2 | 1–5 |
| Gravida (n, %) |  |  |
| 1 | 20 | 33.3 |
| 2 | 19 | 31.7 |
| 3 | 12 | 20 |
| 4 | 6 | 10 |
| 5 | 3 | 5 |
| Parity (Median, min-max) | 1 | 0–3 |
| Parity (n, %) |  |  |
| 0 | 25 | 41.7 |
| 1 | 23 | 38.3 |
| 2 | 9 | 15 |
| 3 | 3 | 5 |
| Abortion (Median, min-max) | 0 | 0–3 |
| Abortion (n, %) |  |  |
| 0 | 43 | 71.7 |
| 1 | 12 | 20 |
| 2 | 3 | 5 |
| 3 | 2 | 3.3 |

Table 2. Urinary system anomalies and concurrent anomaly types.

<table>
<thead>
<tr>
<th>Urinary system anomalies</th>
<th>n</th>
<th>%</th>
<th>Additional anomaly (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral renal agenesis</td>
<td>4</td>
<td>6.7</td>
<td>75</td>
</tr>
<tr>
<td>Bilateral renal agenesis</td>
<td>2</td>
<td>3.3</td>
<td>50</td>
</tr>
<tr>
<td>Unilateral pyelectasis</td>
<td>12</td>
<td>20</td>
<td>91.7</td>
</tr>
<tr>
<td>Bilateral pyelectasis</td>
<td>16</td>
<td>26.7</td>
<td>62.5</td>
</tr>
<tr>
<td>Unilateral MCDK</td>
<td>8</td>
<td>13.3</td>
<td>37.5</td>
</tr>
<tr>
<td>Bilateral MCDK</td>
<td>6</td>
<td>10</td>
<td>66.7</td>
</tr>
<tr>
<td>PKD</td>
<td>2</td>
<td>3.3</td>
<td>0</td>
</tr>
<tr>
<td>Megacystis</td>
<td>6</td>
<td>10</td>
<td>27.3</td>
</tr>
<tr>
<td>Additional anomalies</td>
<td>37</td>
<td>61.7</td>
<td></td>
</tr>
<tr>
<td>CNS</td>
<td>17</td>
<td>28.3</td>
<td></td>
</tr>
<tr>
<td>CVS</td>
<td>12</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Facial</td>
<td>4</td>
<td>6.7</td>
<td></td>
</tr>
<tr>
<td>Anterior abdominal wall defect</td>
<td>2</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>Extremity</td>
<td>5</td>
<td>8.3</td>
<td></td>
</tr>
<tr>
<td>Diaphragmatic hernia</td>
<td>1</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>Hyperechogenic intestine</td>
<td>13</td>
<td>21.7</td>
<td></td>
</tr>
<tr>
<td>Single umbilical artery</td>
<td>4</td>
<td>6.7</td>
<td></td>
</tr>
</tbody>
</table>

CNS: central nervous system; CVS: cardiovascular system; MCDK: multicystic dysplastic kidney; PKD: polycystic kidney disease
al pyelectasis (91.7%), unilateral renal agenesis (75%), bilateral multicystic dysplastic kidney (66.7%), and bilateral pyelectasis (62.5%) (Table 2). Anhydramnios developed in 5 (8.3%) cases in addition to other organ anomalies.

Amniocentesis procedure was carried out on 47 cases between 16 and 20 weeks of gestation, cordocentesis procedure was carried out on 6 cases between 20 and 28 weeks of gestation, and CVS procedure was carried out on 5 cases between 11 and 14 weeks of gestation. In two cases which were decided for termination by the perinatology council due to the fetal conditions which were found to have fatal urinary system anomaly, karyotype was determined through abortion material after the termination procedure. Karyotype results were evaluated to be normal in 41 (70.7%) cases. In one patient, karyotype result was reported as maternal contamination. Triploidy was found in one case, and all other karyotype anomalies were trisomies, and 16 (26.6%) cases had trisomy (Table 3).

The maternal age was <35 years in 92.7% of the cases with normal karyotype results. The karyotype result was trisomy in 6 (66.7%) out of 9 patients who were 35 years old and older. The correlation between age and normal and trisomy groups was statistically significant (p=0.014) (Table 4). No significant correlation was found between karyotype results and all urinary system anomalies. In the majority of the cases found to have trisomy by karyotype results, multiple anomalies were observed. Of the cases with trisomy as karyotype, 3 (17.6%) had isolated urinary system anomaly and other 14 (82.4%) had additional anomaly. The difference between the cases whose karyotype results were normal and trisomy and the cases with additional anomaly was statistically significant (p=0.040) (Table 4).

**Discussion**

Congenital urinary system anomalies are the malformations which have a broad spectrum and can be seen in 0.3–1.6 cases per 1000 deliveries.11 Although most of them are sporadic and isolated, they also can be seen the part of a syndrome. Urinary system anomalies are genetically heterogeneous complex developmental anomalies which may display various phenotypic characteristics. However, single gene diseases also may lead to congenital anomaly in kidney and urinary system; similar conditions can also be observed in family history. Congenital

---

**Table 3.** Karyotype results of fetal urinary system anomalies.

<table>
<thead>
<tr>
<th>Karyotyping technique</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC</td>
<td>47</td>
<td>78.3</td>
</tr>
<tr>
<td>CC</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>CVS</td>
<td>5</td>
<td>8.3</td>
</tr>
<tr>
<td>Abortion material</td>
<td>2</td>
<td>3.3</td>
</tr>
<tr>
<td>Karyotype material</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>41</td>
<td>69.5</td>
</tr>
<tr>
<td>69XXX</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Trisomy 13</td>
<td>2</td>
<td>3.4</td>
</tr>
<tr>
<td>Trisomy 16</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>4</td>
<td>6.8</td>
</tr>
<tr>
<td>Trisomy 21</td>
<td>10</td>
<td>17</td>
</tr>
</tbody>
</table>

AC: amniocentesis; CC: cordocentesis; CVS: chorionic villus sampling

---

**Table 4.** Distribution of fetal urinary system anomalies according to karyotype results.

<table>
<thead>
<tr>
<th>Age</th>
<th>Normal (n, %)</th>
<th>Trisomy (n, %)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35</td>
<td>38 (92.7)</td>
<td>11 (64.7)</td>
<td>0.014</td>
</tr>
<tr>
<td>≥35</td>
<td>3 (7.3)</td>
<td>6 (35.3)</td>
<td></td>
</tr>
<tr>
<td>Week of gestation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;22</td>
<td>13 (31.7)</td>
<td>8 (47.1)</td>
<td>0.268</td>
</tr>
<tr>
<td>≥22</td>
<td>28 (68.3)</td>
<td>9 (52.9)</td>
<td></td>
</tr>
<tr>
<td>Gravida</td>
<td></td>
<td></td>
<td>0.114</td>
</tr>
<tr>
<td>Primigravida</td>
<td>16 (39)</td>
<td>3 (17.6)</td>
<td></td>
</tr>
<tr>
<td>Multigravida</td>
<td>25 (61)</td>
<td>14 (82.4)</td>
<td></td>
</tr>
<tr>
<td>Abortion</td>
<td></td>
<td></td>
<td>0.067</td>
</tr>
<tr>
<td>Not available</td>
<td>32 (78)</td>
<td>9 (52.9)</td>
<td></td>
</tr>
<tr>
<td>Available</td>
<td>9 (22)</td>
<td>8 (47.1)</td>
<td></td>
</tr>
<tr>
<td>Unilateral renal agenesis</td>
<td>3 (7.3)</td>
<td>1 (5.9)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Bilateral renal agenesis</td>
<td>0 (0)</td>
<td>2 (11.8)</td>
<td>0.082</td>
</tr>
<tr>
<td>Unilateral pyelectasis</td>
<td>6 (14.6)</td>
<td>5 (29.4)</td>
<td>0.270</td>
</tr>
<tr>
<td>Bilateral pyelectasis</td>
<td>12 (29.3)</td>
<td>4 (23.5)</td>
<td>0.755</td>
</tr>
<tr>
<td>Unilateral MCDK</td>
<td>8 (19.5)</td>
<td>0 (0)</td>
<td>0.090</td>
</tr>
<tr>
<td>Bilateral MCDK</td>
<td>6 (14.6)</td>
<td>0 (0)</td>
<td>0.166</td>
</tr>
<tr>
<td>PKD</td>
<td>1 (2.4)</td>
<td>0 (0)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Megacystis</td>
<td>9 (22)</td>
<td>2 (11.8)</td>
<td>0.480</td>
</tr>
<tr>
<td>Additional anomaly</td>
<td></td>
<td></td>
<td>0.040</td>
</tr>
<tr>
<td>Not available</td>
<td>19 (46.3)</td>
<td>3 (17.6)</td>
<td></td>
</tr>
<tr>
<td>Available</td>
<td>22 (53.7)</td>
<td>14 (82.4)</td>
<td></td>
</tr>
<tr>
<td>CVS</td>
<td>10 (24.4)</td>
<td>6 (35.3)</td>
<td>0.520</td>
</tr>
<tr>
<td>Facial</td>
<td>3 (7.3)</td>
<td>9 (52.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anterior abdominal wall defect</td>
<td>1 (2.4)</td>
<td>1 (5.9)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Extremity</td>
<td>3 (7.3)</td>
<td>2 (11.8)</td>
<td>0.624</td>
</tr>
<tr>
<td>Diaphragmatic hernia</td>
<td>1 (2.4)</td>
<td>0 (0)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Diaphragmatic hernia</td>
<td>6 (14.6)</td>
<td>7 (41.2)</td>
<td>0.040</td>
</tr>
<tr>
<td>Single umbilical artery</td>
<td>3 (7.3)</td>
<td>1 (5.9)</td>
<td>&gt;0.999</td>
</tr>
</tbody>
</table>

CNS: central nervous system; CVS: cardiovascular system; MCDK: multicystic dysplastic kidney; PKD: polycystic kidney disease
anomalies of renal and urinary systems may cause hypertension and renal failure, and it is accounted for 30–50% of end-stage renal failure in children.\(^{[5,7]}\) Therefore, the early diagnosis of urinary system malformations are very important in terms of fetal prognosis and postnatal problems. While the diagnosis of urinary system anomalies is easy (89% success rate for diagnosis), we could establish diagnosis at over 20 weeks of gestation in 61.7% of the cases in our study.\(^{[8]}\) The patients in this group referred to the hospital at a late period and did not undergo regular follow-up previously.

Pyelectasis was the most commonly diagnosed urinary system anomaly in our study (46.7%). Twelve (20%) patients had unilateral pylectasis and 16 (26.7%) patients had bilateral pylectasis. In many studies, pylectasis is the most common anomaly among urinary system anomalies.\(^{[2,5,9]}\) In the cases found to have urinary system anomaly, the risk of chromosome anomaly increases especially in the presence of additional anomalies. Although isolated pylectasis is “soft marker” for Down syndrome, it is not an indication alone for chromosomal analysis. On the other hand, it should be remembered that it increases the risk of age-related anomaly for 1.5 times, and prenatal consultancy of pregnant women should be carried out accordingly. In cases where additional anomaly is not observed in the ultrasonography, it is usually a common view that chromosomal analysis is not required. In their study, Bornstein et al. reviewed 671 cases which were found to have pylectasis between 1995 and 2004, and they found major trisomies in 35 (5.22%) cases.\(^{[10]}\) In the same study, the ages of 133 (19.8%) cases were above 35 years. In this study, they did not observe isolated pylectasis as a major marker for trisomies; however, they found that trisomy risk increased in fetuses which had additional sonographic findings together with pylectasis or had abnormalities in their maternal serum markers. Observing another sonographic marker in addition to pylectasis increases trisomy risk for 8 times. With more than one concurrent anomaly, the risk increases for 62 times.\(^{[10]}\) The authors highlighted that evaluating chromosomal anomaly risk together with maternal age and/or maternal serum markers in cases with pylectasis would yield more accurate results.\(^{[10]}\)

In our study, unilateral pylectasis was the group in which additional anomalies were the most concurrent, and the prevalence of additional anomaly was 91.6% in this patient group. Also, pylectasis was the most common urinary system anomaly among the fetuses with chromosomal anomaly. Although isolated pylectasis cases were rare in our study group and therefore it was not a significant data in terms of chromosomal analysis in this group, observing high rates of concurrent structural and chromosomal anomalies is concordant with the literature when we evaluated all cases with pylectasis.\(^{[11,12]}\)

In the literature, chromosomal defect rate has been reported 21% in cases with rare fetal megacystis.\(^{[13]}\) While trisomy 13 is the most common among concurrent chromosomal anomalies, triploidy is quite rare.\(^{[14]}\) Sebire et al. carried out chromosomal analysis on the cases with fetal megacystis and found chromosomal anomaly in 3 out of 15 cases.\(^{[15]}\) In their prospective study where Favre et al. reviewed 5240 cases in France between 1992 and 1998 and found megacystis in 16 cases between 11 and 15 weeks of gestation, the authors showed the correlation between megacystis and chromosomal anomalies. While chromosomal anomaly is not found in cases with isolated megacystis, it was found in four cases with concurrent additional anomaly.\(^{[11]}\) Two of them had trisomy 13, one had trisomy 21, and one had trisomy 18. In this study, it was shown that aneuploidy (25%) was accompanying megacystis at a high rate as well as other structural anomalies, particularly intestinal malformations (33%).\(^{[13]}\) In our study, we found chromosomal anomaly only in 2 (18.1%) out of 11 cases who had megacystis.

Of 14 (23.3%) patients established with the diagnosis of multicystic dysplastic kidney, 8 (13.3%) were unilateral and 6 (10%) were bilateral. De La Vega and Torres reviewed 117 cases with congenital renal anomalies between 2001 and 2004, and found that the rate of multicystic dysplastic kidney was 17.9%.\(^{[16]}\) In a recent study, the rate of multicystic dysplastic kidney has been reported 23.8%.\(^{[12]}\) Also, bilateral renal agenesis was 12.8% in the study of De La Vega and Torres while it was 3.3% in our patient group.\(^{[10]}\)

In our study, there were 37 (61.7%) fetuses which had other structural anomalies together with urinary system anomalies. In the study of Batukan et al., 23.6% of 165 fetuses with urinary system anomaly had also other structural anomalies.\(^{[5]}\) In our study group, the high rate of concurrent anomalies can be due to the fact that our institution is a reference unit for prenatal diagnosis. On the other hand, some urinary system anomalies can be unnoticed during ultrasonography when
oligohydramnios is not present and therefore the patients are not referred to our clinic.

The prevalence of cardiac anomaly is usually high in fetuses with chromosomal anomaly, and while aneuploidy prevalence is 16% in the presence of isolated cardiac anomaly, it increases to 66% when there are other anomalies accompanying to cardiac anomaly.[2,3]

Therefore, chromosomal anomaly should be recommended due to the high aneuploidy risk for pregnant women who are found to have cardiac anomaly. In our study, we found trisomies in 75% of the cases with cardiac anomalies accompanying to urinary system anomalies.

Conclusion

In conclusion, urinary system anomalies are approximately one fourth of all congenital anomalies. Congenital urinary system malformations with a broad spectrum differ greatly in terms of etiological reasons. Additional structural anomalies may accompany urinary system anomalies at a high rate; and while they negatively affect the prognosis on one hand, they cause the incidence of chromosomal anomaly to increase on the other hand. As a result, fatal and severe malformation can be observed. Urinary system anomalies which are isolated or have a good fetal prognosis may cause urinary infection, hypertension and various levels of renal failure during childhood. Prenatal diagnosis is very important to identify these anomalies which may cause poor outcomes during fetal period or childhood.

Conflicts of Interest: No conflicts declared.

References

Investigation of toxoplasma, cytomegalovirus and rubella seroprevalence in pregnant women admitted to our hospital

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Abstract

Objective: The aim of the study is to evaluate serologically the positivity of toxoplasma, rubella and cytomegalovirus (CMV) infections in pregnant women who admitted to the Gynecology and Obstetrics Clinic of a Training and Research Hospital, and to investigate the necessity of the screening for the current region.

Methods: Serological results of pregnant women who were between 18 and 45 years old, at their first trimesters and admitted to the Gynecology and Obstetrics Clinic of Kayseri Training and Research Hospital between January 1, 2017 and January 1, 2018 were evaluated retrospectively in terms of Toxoplasma gondii, CMV and rubella infections. Anti-toxoplasma IgM, anti-toxoplasma IgG, anti-CMV IgM, anti-CMV IgG, anti-rubella IgM and anti-rubella IgG results of the pregnant women were evaluated. The serum samples collected from the patients were centrifuged for 15 minutes at 10,000 rpm and analyzed by ELISA method.

Results: The records of a total of 10,200 patients were accessed. We found in our study that anti-CMV IgM positivity was 0.2% and anti-CMV IgG positivity was 98.2%, anti-toxoplasma IgM positivity was 1% and anti-toxoplasma IgG positivity was 28.9%, anti-rubella IgM positivity was 0.59% and anti-rubella IgG positivity was 97.3%.

Conclusion: The results of our study are consistent with many seroprevalence studies carried out in Turkey. Considering the high seronegativity rates of toxoplasma, rubella and cytomegalovirus (CMV) infections in pregnant women of the high rate of CMV IgG seroprevalence in the pregnant women of the current region, we recommend the investigation of the immune condition of pregnant women in the first gestational visit in terms of toxoplasma, and providing necessary health training if the results are seronegative. It should be the primary purpose to make individuals immune before the reproductive period by maintaining vaccination programs for rubella and rubella (kızamıkçık) and cytomegalovirus (CMV) gruș fenksiyonların serolojik olarak pozitifliği değerlendirerek mevcut bölge için taramanın gerekliliğini araştırırmaktır.

Keywords: Cytomegalovirus, rubella, Toxoplasma gondii, TORCH seroprevalence.

ÖzET: Hastanemize başvuran gebelerde toksoplazma, sitomegalovirus ve rubella seroprevalansının araştırılması

Amaç: Çalışmanın amacı bir Eğitim ve Araştırma Hastanesi Kadın Hastalıkları ve Doğum Kliniğine başvuran gebelerde toksoplazma, rubella (kızamıkçık) ve sitomegalovirus (CMV) gruș fenksiyonlarının serolojik olarak pozitifliği değerlendirerek mevcut bölge için taramanın gerekliliğini araştırırmaktır.

YÖNTEM: Çalışma, Kayseri Eğitim ve Araştırma Hastanesi Kadın Hastalıkları ve Doğum Kliniğinde, 01/01/2017-01/01/2018 tarihleri arasında başvuran, 18-45 yaş aralıında ve birinci trimesterinde bulunan gebelerin Toxoplasma gondii, CMV ve rubella enfeksiyonlarının açısından serolojik sonuçlarının retrospektif olarak değerlendirilmesiyle yapıldı. Gebelerin anti-toxoplasma IgM, anti-toxoplasma IgG, anti-CMV IgM, anti-CMV IgG, anti-rubella IgM ve anti-rubella IgG sonuçları değerlendirildi. Hastalardan alınan serum örnekleri 10.000 rpm hızında 15 dakika santrifüj edildikten sonra ELISA yöntemi ile analiz edildi.

BULGAR: Toplam 10.200 hasta bilgisine ulaştık. Çalışmamızda anti-CMV IgM pozitifliği %0.2 ve anti-CMV IgG pozitifliği %98.2; anti-toxoplasma IgM pozitifliği %1 ve anti-toxoplasma IgG pozitifliği %28.9; anti-rubella IgM pozitifliği %0.59 ve anti-rubella IgG pozitifliği %97.3 olarak tespit ettiğimiz bu sonuçlar, Türkiye genelinde yapılan pek çok seroprevalans çalışması ile uyumluydur. Bölgenin toksoplazmaya salsağın seronegatif orananın göz önüne alınması, gebelik takibi ve gebelikteki gebeliğin toksoplazma ve rubella enfeksiyonlarının önlenmesi için gerekli olduğu düşünülmektedir.

Sonuç: Çalışmanının sonuçları, Türkiye genelinde yapılan pek çok seroprevalans çalışması ile uyumluydur. Bölgenin toksoplazmaya salsağın seronegatif orananın göz önüne alınması, gebelik takibi ve gebelikteki gebeliğin toksoplazma ve rubella enfeksiyonlarının önlenmesi için gerekli olduğu düşünülmektedir.

Anahtar sözcükler: TORCH seroprevalansı, Toxoplasma gondii, rubella, sitomegalovirus.
Introduction
Since the infections of *Toxoplasma gondii*, cytomegalovirus (CMV) and rubella groups have a clinical impact on fetus similar to the gestational primary infections, they should be evaluated together during pregnancy.\(^1\) Although current infections are often undergone symptomatically, they may cause perinatal morbidity and mortality by resulting in fetal congenital malformations particularly during the first trimester of pregnancy.\(^2\)

The routine screening of this group of infections during pregnancy is still controversial while there are studies arguing to perform the screening according to the seropositivity rate especially on the site of infection.\(^1,3,4\) It is known that seropositivity varies according to the regions in many studies performed in different regions of Turkey, and that it is given particular importance among different countries.

The aim of this study is to evaluate serologically the positivity of *Toxoplasma gondii*, CMV and rubella infections in the Gynecology and Obstetrics Clinic of Kayseri Training and Research Hospital, which is a tertiary center and receives approximately 12,000 new pregnant women annually, and to investigate the necessity of the screening for the current region.

Methods
In this study, the serological results of pregnant women who were between 18 and 45 years old, at their first trimesters and admitted to the Gynecology and Obstetrics Clinic of Kayseri Training and Research Hospital between January 1, 2017 and January 1, 2018 were evaluated retrospectively in terms of *Toxoplasma gondii*, CMV and rubella infections. The approval of ethic committee of Erciyes University was obtained for the study, and all steps of the study were performed in accordance with Helsinki Declaration.

Anti-toxoplasma IgM, anti-toxoplasma IgG, anti-CMV IgM, anti-CMV IgG, anti-rubella IgM and anti-rubella IgG results of the pregnant women were evaluated. The serum samples collected from the patients were centrifuged for 15 minutes at 10,000 rpm and analyzed by ELISA test. While <0.5 was considered index negative and ≥0.6 U/ml index positive for toxoplasma IgM, and <1.6 was index negative and ≥3.0 U/ml was index positive for toxoplasma IgG; <1.2 U/ml was index negative and ≥1.6 U/ml was index positive for rubella IgM, and <5 U/ml was index negative and ≥10 U/ml was index positive for rubella IgG; <0.85 U/ml was index negative and ≥1 U/ml was index positive for CMV IgM, and <6 U/ml was index negative and ≥6 U/ml was index positive for CMV IgG.

Results
The records of a total of 10,200 patients were accessed. In the study, the mean age of the pregnant women was 25.4±4.1 (range: 18 to 45) years, and the mean number of pregnancy was 2.1±1.3. We found in our study that anti-CMV IgM positivity was 0.2% and anti-CMV IgG positivity was 98.2%, anti-toxoplasma IgM positivity was 1% and anti-toxoplasma IgG positivity was 28.9%, anti-rubella IgM positivity was 0.59% and anti-rubella IgG positivity was 97.3%. The results of anti-toxoplasma IgM, anti-toxoplasma IgG, anti-CMV IgM, anti-CMV IgG, anti-rubella IgM and anti-rubella IgG of the pregnant women evaluated in the study are shown in Table 1.

<table>
<thead>
<tr>
<th></th>
<th>Number of negative patients n (%)</th>
<th>Number of positive patients n (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-toxoplasma IgM</td>
<td>10,098 (99%)</td>
<td>102 (1%)</td>
<td>10,200</td>
</tr>
<tr>
<td>Anti-toxoplasma IgG</td>
<td>7253 (71.1%)</td>
<td>2947 (28.9%)</td>
<td>10,200</td>
</tr>
<tr>
<td>Anti-rubella IgM</td>
<td>10,139 (99.41%)</td>
<td>61 (0.59%)</td>
<td>10,200</td>
</tr>
<tr>
<td>Anti-rubella IgG</td>
<td>276 (2.7%)</td>
<td>9924 (97.3%)</td>
<td>10,200</td>
</tr>
<tr>
<td>Anti-CMV IgM</td>
<td>10,180 (99.8%)</td>
<td>20 (0.2%)</td>
<td>10,200</td>
</tr>
<tr>
<td>Anti-CMV IgG</td>
<td>183 (1.8%)</td>
<td>10,017 (98.2%)</td>
<td>10,200</td>
</tr>
</tbody>
</table>
Discussion

In our study, we investigated serologically the positivity of Toxoplasma gondii, CMV and rubella infections of pregnant women who admitted to the Gynecology and Obstetrics Clinic of Kayseri Training and Research Hospital between 2017 and 2018 during the trimester of their pregnancies. In our study, anti-CMV IgM positivity was 0.2% while anti-CMV IgG positivity was 98.2%. In similar studies carried out in Turkey, CMV IgG seropositivity was found between 84% and 98%. Our result is consistent with other regions. As known, prevalence of gestational primary CMV infection varies depending on the geographical region, ethnic origin and socioeconomical status. There are also different studies reporting the incidence of primary CMV infection between 0.7% and 4% among seronegative pregnant women.[6]

CMV is the most common congenital infection complicating 0.2-2.2% of all newborns. In up-to-date study bulletins, it is estimated that the annual cost to treat permanent dysfunctions and complications caused by CMV infection is more than 1.86 billion USD in the USA. Although routine screening is not recommended for primary CMV infection, routine screening of pregnant women during their first trimester periods can be recommended considering the fact that the risk of fetal transmission is about 30–40% in the presence of CMV infection.

In our study, we found anti-toxoplasma IgM positivity 1% and anti-toxoplasma IgG positivity 28.9%. In similar studies carried out in Turkey, anti-toxoplasma IgG seropositivity was found between 28% and 60%. Our result is consistent with other regions. While the vertical transmission rate of Toxoplasma gondii is 10–15% during the first trimester, it is 25% during the second trimester, and more than 60% during the third trimester. The severity of fetal infection depends on the week of gestation at transmission time, and the severity of the disease will increase as the fetus is infected earlier.[11,12]

According to the up-to-date study bulletins, routine screening is not recommended for pregnant women in terms of Toxoplasma gondii infection, and it is recommended to limit the screening with women whose immune systems are weak or who are positive for human immunodeficiency virus (HIV). The results of our study show that the rate of anti-Toxoplasma gondii IgG negativity is 71.1% (7253 pregnant women) for the last year, and it can be said that all these pregnant women are under risk in terms of Toxoplasma gondii infection. We believe that screening pregnant women in terms of Toxoplasma gondii infection should not be planned for all cases but should be planned according to the seroprevalence values both among the countries and in relatively smaller regions.

In our study, anti-rubella IgM positivity was 0.59% and anti-rubella IgG positivity was 97.3%. In similar studies carried out in Turkey, anti-rubella IgG seropositivity was found between 90% and 99%. Our result is consistent with other regions. While rubella is a mild viral infection seen typically during childhood, primary infection developing during pregnancy results in with congenital rubella syndrome.[9] When analyzing the results of our study, we saw that the majority of the pregnant women were immune to rubella infection. It should be the primary purpose to make individuals immune before the reproductive period by maintaining vaccination programs for rubella infection which is an approach of higher priority than the gestational screening to prevent congenital rubella syndrome.

Conclusion

Although the routine screenings of Toxoplasma gondii, rubella and CMV infections are not recommended during the pregnancy, it is controversial around the world. The results of our study are consistent with many seroprevalence studies carried out in Turkey.

Considering the high seronegativity rates of toxoplasma found for our region, we recommend the investigation of the immune condition of pregnant woman in the first gestational visit in terms of toxoplasma, and providing necessary health training if the results are seronegative. It should be the primary purpose to make individuals immune before the reproductive period by maintaining vaccination programs for rubella infection which is an approach of higher priority than the gestational screening to prevent congenital rubella syndrome. Considering the high rate of CMV IgG seroprevalence in the pregnant women of our region, routine serological screening seems unnecessary.

Conflicts of Interest: No conflicts declared.
References


The prediction of preterm birth threat by uterocervical angle

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Abstract

Objective: Preterm birth is the most significant reason for newborn mortality and morbidity, and it is possible to achieve positive neonatal outcomes by early diagnosis and treatment. In our study, we aimed to investigate the efficiency of uterocervical angle (UCA) measurement for the prediction of preterm birth.

Methods: A total of 82 singleton pregnant women who admitted to our emergency maternity ward with pain complaint between 24 and 34 weeks of gestation were included in this prospective empirical study. Age, last menstrual period, week of gestation, gravidity, parity, abortion, preterm labor history, previous cervical surgery, body mass index, presence of chronic disease, and smoking habit of each pregnant woman were investigated, their Bishop scores were calculated, and cervical length and UCA measurements were performed by transvaginal ultrasound examination under optimal conditions. The patients were discharged after observation, examination and treatment processes. After the delivery, the week of gestation, delivery type, newborn’s birth weight, sex and the need for intensive care unit were investigated.

Results: Among the etiological factors, only the multiparity and abortion history were found significantly high in pregnant women who had preterm delivery. The cut-off value for UCA measurements was determined 80.5°. The rate of UCA >80.5° in women who delivered before 37 weeks of gestation was found 75%, and it was significantly higher than the term cases (p=0.007). For this value, it was found that UCA sensitivity was 75%, selectivity was 58%, positive prediction value was 53% and negative prediction value was 77%.

Conclusion: In consideration of our findings, uterocervical angle measurement over 80.5° poses a high risk for deliveries before 37 weeks of gestation, and it provides a higher diagnostic performance than cervical length measurement and Bishop scoring.

Keywords: Cervical length, preterm birth threat, uterocervical angle.

Özet: Uteroservikal açının erken doğum tehdidinde önüşü

Amaç: Preterm doğum yenidoğan mortalite ve morbiditesinin en önemli sebebi olup erken tanı ve tedavi ile olumlu neonatal sonuçlara ulaşmak mümkündür. Çalışmamızda preterm doğum öngörüsünde uterocervikal açı (UCA) ölçümünün etkinliğini incelemeyi amaçladık.


Bulgular: Etiyolojik faktörlerden yalnız multiparite ve abortus öyküsü preterm doğum yapan gebelerde anıltı olarak yüksek bulundu. UCA ölçümleri için kesit noktası 80.5° olarak belirlendi. 37. gebelik haftasi öncesi doğum yapan kadınlarda UCA’nın >80.5° olma oranı %75 bulundu ve term doğum yapanlara göre analitik olarak yüksek bulundu (p=0.007). Bu nokta için UCA dai değer %75, seçiciğ %58, pozitif kestirim değeri %53 ve negatif kestirim değeri %77 bulundu.

Sonuç: Bulgularımızda 80.5°’nin üzerinde uterocervikal açı rolü 37 hafta öncesi doğumlar için yüksek bir risk öngörmektedir ve servikal uzunluk ölçümleri ve Bishop skorlamasından daha yüksek bir tanış performans ortaya koymaktadır.

Anahtar sözcükler: Uteroservikal açı, erken doğum tehdidi, servikal uzunluk.
Introduction

Preterm birth is the most significant reason determining perinatal mortality and morbidity of fetus without any anomaly.[1] Apart from congenital malformations, pre-maturity accounts for 75–90% of newborn deaths.[2] According to the data of World Health Organization (WHO), approximately 15 million babies are born preterm (<37 weeks of gestation) every year, and this is equal to one in 10 live births. In living newborns, the risk of sequel associated with prematurity is high.[2] Every year, approximately one million children die due to the preterm birth complications, and most of the surviving children have visual and hearing problems and maintain their lives with mental or physical disabilities.[1]

Measuring cervical length by ultrasonography has become a routine practice today as an objective and non-invasive method to evaluate the preterm labor. With this method, apart from cervix length, it is possible to do structural and functional evaluations such as condition and appearance of internal os (i.e. its funneling), cervical dilatation together with membrane herniation, and cervical responses to uterine contractions and fundal pressure. Either necessarily or unnecessarily, the treatments of many pregnant women who admit emergency maternity units are carried out without distinguishing false/ineffective or actual/effective contractions. Our aim in this study is to report differences between patients admitted to emergency clinic who undergo actual labor and those undergo false labor by uterocervical angle (UCA) measurement aside from cervix length, and preterm labors carried out in association with it and related gestational outcomes.

Methods

The format of our study was planned as prospective empirical study and the ethics committee approval no. 26817412 dated 19.07.2016 was obtained.

The inclusion criteria for singleton live pregnancy cases who admitted to the emergency maternity clinic of our hospital between July 2016 and January 2017 with pain/contraction complaints and who were between 24 and 34 weeks of gestation were as below:

- Two and more regular uterine contractions in 10 minutes
- Labor not being on active phase (dilatation <4 cm, effacement <80%)
- No history of cervical cerclage in previous weeks of gestation

In the cases of chorioamnionitis, ablato placenta, fetal distress, presence of fetal anomaly, placenta previa condition or the conditions requiring maternal and fetal emergency cases, the patients were excluded from the study.

After the initial examination and contraction treatment and tocolysis at the emergency maternity unit, the patients were hospitalized in our perinatology clinic or they were followed up through the polyclinic after discharging them when they contractions ended.

Accordingly, 82 cases were included in the study in the related period. Following the medical and obstetric histories of the patients meeting the criteria, cervical dilatation, effacement, position, viscosity and the level of the incoming part of fetus were evaluated for Bishop score during gynecological examination. The pregnant women were evaluated by transvaginal sonography on lithotomy position when the bladder was empty. To ensure the standardization, all measurements were carried out by the same physician (OB). The cervical length measurement was done through sagittal plane of cervix, in a section where also internal os, external os, cervical canal and endocervical mucosa could be displayed, by enlarging the image as covering 3/4 of the screen. Also, in cases where the length between internal os and external os was not on a single line, the measurement was done as linear sections and total cervical length was obtained. The measurement was carried out three times, and the shortest length with the best image quality was recorded for each pregnant woman.

Uterocervical angle is the angle measured on the triangle which is between the anterior uterine segment and cervical canal. For this, certain straight lines should be obtained; first straight line was drawn through endocervical canal between internal os and external os. The first line drawn between internal os and external os was considered a straight line even though cervical canal was curved. The second line was drawn ideally 3 cm from internal os through anterior uterine segment. In this way, the angle obtained between two straight lines was considered as UCA (Fig. 1). In shape changes (Y- or U-like shape changes) corresponding to the early periods of funneling or the dilatation, cervical canal measurement between them was also considered as first straight line. The line drawn from the innermost point of cervical canal to anterior uterine segment was considered as the second straight line and the angle was measured (Fig. 2).
After the initial examination and contraction treatment and tocolysis at the emergency maternity unit, the patients were hospitalized and monitored in our perinatology clinic of our hospital. Depending on the ending of contractions, the patients were discharged and followed up through the polyclinic and their follow-up data were completed upon the delivery. Accordingly, the pregnant women were assessed in 2 groups which were those delivered before (study group) and after (control group) 37 weeks of gestation. Delivery type, week of gestation during delivery, newborns’ birth weight, sex, newborns’ need for intensive care unit and betamethasone doses of all pregnant women who delivered were evaluated according to their own groups.

For statistical analysis, IBM SPSS Statistics 22 (IBM SPSS, Istanbul, Turkey) was used. Conformity of the study parameters to normal distribution was evaluated by Shapiro-Wilk test. For comparing descriptive statistical methods (mean, standard deviation, frequency) when evaluating study data, Student t test was used in the two-group comparison of parameters displaying normal distribution, and Mann-Whitney U test was used in the two-group comparison of parameters not displaying normal distribution. For the comparison of qualitative data, chi-square test, Yates’ correction for continuity and Fisher’s exact chi-square were used. ROC curve was used to evaluate diagnostic performance levels of uterocervical angle measurements to distinguish those undergoing preterm labor. The significance level was considered p<0.05.

Results

In line with the method followed, a study group consisting of 32 pregnant women who were hospitalized and treated and delivered at <37 weeks of gestation and a control group consisting of 50 pregnant women who delivered ≥37 weeks of gestation were established.

It was found that gravida, parity, abortion and normal delivery numbers in pregnant women, whose weeks of gestation during delivery were <37, were higher than the pregnant women who were in the control group and whose weeks of gestation during delivery were ≥37, and this difference was statistically significant (p<0.05 and p<0.001) (Table 1). There was no statistically significant difference in terms of age, body mass index (BMI), preterm labor history, smoking habit among both groups and between the patients who found to have hypertension and gestational diabetes.

As expected, newborns’ birth weight and newborns’ need for intensive care unit were higher in patients who underwent preterm labor. The data on the delivery weeks, birth weights, delivery types and postnatal outcomes are presented in Table 2.
No statistical difference was found in Bishop scores and the measurements carried out on cervical lengths, with threshold values which were considered 20 and 25 mm, respectively, of patients who underwent preterm labor. In our study, the sensitivity, selectivity, positive prediction value and negative prediction value of cervical lengths measured less than 20 mm were calculated 6.25%, 94%, 40% and 61%, respectively, for preterm labor. In this regard, there was no statistical difference between those who underwent preterm labor among the pregnant women who delivered at <37 and ≥37 weeks of gestation (Table 3).

The rate of uterocervical angle above 80.5° was calculated 75% in the preterm labor group (<37 weeks of gestation) while it was 42% in those who delivered at ≥37 weeks of gestation, which was high and statistically significant (p=0.007) (Table 3). The cut-off value (threshold value) was found 80.5° for uterocervical angle measurements depending on the preterm labor incidence. For this value, it was found that the sensitivity was 75%, selectivity was 58%, positive prediction value was 53.3% and negative prediction value was 77.3%. The area under the ROC curve obtained was 67%, and this area under curve was statistically significant (AUC=0.655, 95% CI=0.532–

### Table 1. The distribution of the demographic characteristics of pregnant women in the groups according to their weeks of gestation (<37 and ≥37).

<table>
<thead>
<tr>
<th>Week of gestation during delivery</th>
<th>≥37 weeks (n=50)</th>
<th>&lt;37 weeks (n=32)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>26.93±6.40</td>
<td>25.88±4.67</td>
<td>ns¹</td>
</tr>
<tr>
<td>Gravida (n)</td>
<td>2.04±1.29</td>
<td>3.03±1.62</td>
<td>0.003*²</td>
</tr>
<tr>
<td>Parity (n)</td>
<td>0.68±0.94</td>
<td>1.47±1.19</td>
<td>0.001*²</td>
</tr>
<tr>
<td>Abortion (n)</td>
<td>0.20±0.57</td>
<td>0.56±0.84</td>
<td>0.023†²</td>
</tr>
<tr>
<td>NSD (n)</td>
<td>0.36±0.72</td>
<td>1.06±1.22</td>
<td>0.002*²</td>
</tr>
<tr>
<td>C/S (n)</td>
<td>0.26±0.63</td>
<td>0.38±0.66</td>
<td>ns²</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.35±3.77</td>
<td>27.12±4.70</td>
<td>ns¹</td>
</tr>
<tr>
<td>Preterm labor history, n (%)</td>
<td>1 (2%)</td>
<td>2 (6.3%)</td>
<td>ns³</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>6 (12%)</td>
<td>5 (15.6%)</td>
<td>ns³</td>
</tr>
<tr>
<td>Cases with hypertension, n (%)</td>
<td>1 (2%)</td>
<td>2 (6.3%)</td>
<td>ns³</td>
</tr>
<tr>
<td>Cases with gestational diabetes, n (%)</td>
<td>1 (2%)</td>
<td>3 (9.4%)</td>
<td>ns³</td>
</tr>
</tbody>
</table>

¹Student’s t-test; ²Mann-Whitney U test; ³Chi-square test, Yates’ correction for continuity and Fisher’s exact chi-square tests; *p<0.01; †p<0.05. ns: not significant; C/S: cesarean section; BMI: body mass index

### Table 2. The data on women and newborns according to the weeks of gestation during delivery.

<table>
<thead>
<tr>
<th>Week of gestation during delivery</th>
<th>≥37 weeks (n=50)</th>
<th>&lt;37 weeks (n=32)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delivery week (week)</td>
<td></td>
<td></td>
<td>0.001**³</td>
</tr>
<tr>
<td>Newborn’s birth weight (g)</td>
<td>38.34±1.09</td>
<td>34.25±1.84</td>
<td></td>
</tr>
<tr>
<td>Delivery type n (%)</td>
<td></td>
<td></td>
<td>0.001**³</td>
</tr>
<tr>
<td>NSD</td>
<td>33 (66%)</td>
<td>18 (56.3%)</td>
<td>ns²</td>
</tr>
<tr>
<td>C/S</td>
<td>17 (34%)</td>
<td>14 (43.8%)</td>
<td></td>
</tr>
<tr>
<td>Newborn’s intensive care unit need, n (%)</td>
<td></td>
<td></td>
<td>0.015†²</td>
</tr>
<tr>
<td>N/A</td>
<td>4 (8%)</td>
<td>10 (31.3%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>40 (80%)</td>
<td>19 (59.4%)</td>
<td>ns²</td>
</tr>
<tr>
<td>2</td>
<td>1 (2%)</td>
<td>2 (6.3%)</td>
<td></td>
</tr>
<tr>
<td>Betamethasone dose, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>23 (59%)</td>
<td>16 (41%)</td>
<td>ns²</td>
</tr>
<tr>
<td>Male</td>
<td>27 (62.8%)</td>
<td>16 (37.2%)</td>
<td></td>
</tr>
</tbody>
</table>

¹Student’s t-test; ²Chi-square test, Yates’ correction for continuity and Fisher’s exact chi-square tests; *p<0.01; †p<0.05. ns: not significant; C/S: cesarean section; NSD: normal spontaneous delivery
0.777, p=0.019; p<0.05) (Fig. 3). This indicates that the probability of uterocervical angle being above 80.5° cut-off value in the measurements carried out in pregnant women who deliver before 37 weeks of gestation is statistically significant.

Discussion

Although there have been important developments in the prognosis of preterm newborns with the newborn intensive care techniques developed in the last two decades, no decrease has been achieved in the preterm labor rates. There are studies showing that the risk of repeating preterm labor is increased in pregnancies with preterm labor history. In their study carried out to determine risk factors in preterm labors, Foix-L’Helias et al. reported the risk of preterm labor history (Odds Ratio: OR) as 4.5. Similarly, El-Bastawissi et al. reported OR as 6 in the pregnant women with preterm labor history. In our study, we found no difference between the groups in terms of obstetric history; 2% of pregnant women who delivered at ≥37 weeks of gestation and 6.3% of pregnant women who underwent preterm labor had preterm labor history; however, there was no statistically significant difference (p=0.557).

While there are many studies reporting that smoking increases preterm labor risk, Anders and Day expressed in their studies that smoking is accounted for 15% of preterm labors. In our study, only 11 (13.4%) out of 82 cases were smokers, and we found that smoking was not statistically significant between the groups (p=0.743).

There are studies reporting that maternal age is the most important factor among the socio-demographical factors in the preterm labor etiology, and that preterm labor rates prominently increase among the pregnancies before 20 years old. Moreover, various risk scoring systems including the maternal age have been developed accordingly. The most known of these systems is Creasy risk scoring system, and mother is scored with 2 points if maternal age is under 20-year-old and above 40-year-old, and with 4 points if maternal age is under 18-year-old. In our data, the mean age of term labor cases was 26.93 years and it was 25.88 for those who underwent

<table>
<thead>
<tr>
<th>Table 3. Cervical lengths and uterocervical angles according to the delivery week.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week of gestation during delivery</strong></td>
</tr>
<tr>
<td><strong>≥37 weeks (n=50)</strong></td>
</tr>
<tr>
<td>Mean week of gestation during examination (weeks)</td>
</tr>
<tr>
<td>Bishop score</td>
</tr>
<tr>
<td>Mean cervical length during examination (mm)</td>
</tr>
<tr>
<td>Cervical length (&lt;20 mm)</td>
</tr>
<tr>
<td>Cervical length (&gt;20 mm)</td>
</tr>
<tr>
<td>Cervical length (&lt;2 mm)</td>
</tr>
<tr>
<td>Cervical length (&gt;25 mm)</td>
</tr>
<tr>
<td>Mean uterocervical angle during examination (°)</td>
</tr>
<tr>
<td>Uterocervical angle (°)</td>
</tr>
<tr>
<td>&lt;80.5°</td>
</tr>
<tr>
<td>&gt;80.5°</td>
</tr>
</tbody>
</table>

\(^1\)Mann-Whitney U test; *p<0.01. ns: not significant
preterm labor; however, we found no statistically significant difference (p=0.436).

In a study investigating the association between obesity and preterm labor, it was found in women with different body weights that preterm labor rate was 0.17% in those with BMI=18.5–25, 0.21% in those with BMI=25–30, 0.27% in those with BMI=30–35, and 0.52% in those with BMI >40, and it was highlighted that preterm labor rates increase as BMI increases.[16] On the other hand, Goldenberg et al. stated that low BMI significantly increases preterm labor risk in the preterm labor etiology.[17] Body mass indexes of pregnant women in our study vary between 18 and 40 kg/m², and the mean and median of BMI are 27.38±3.84 and 28 kg/m², respectively. In our study, the mean BMI was 27.12 in pregnant women who underwent preterm labor, and 27.35 in those who delivered at ≥37 weeks; we found statistically no significant difference between the groups (p=0.807).

Cervical length measurement is one of the leading methods used commonly to predict preterm birth. In the study of Tsoi et al. consisting of 216 singleton pregnancy cases associated with preterm birth, the authors reported that only one (0.6%) of 173 cases whose cervical lengths were 15 mm and higher underwent preterm labor, 16 (37.2%) of 43 pregnant women whose cervical lengths were less than 15 mm delivered within a week.[18] In the risk prediction study for preterm birth consisting of 730 cases, Tongsong et al. reported that the cut-off value of cervical length was 35 mm. The sensitivity of this cut-off value was 65.9±5.1% and selectivity was 62.4±5.2%. In this related study, cervical length was found <35 mm in 2/3 of the patients who underwent preterm labor.[19] The cervix lengths of the patients in our study vary between 10 and 48 mm, and the mean and median values were 34.16±7.08 and 36 mm, respectively. While the cervical lengths of 9.4% of pregnant women who delivered before 37 weeks of gestation were less than 25 mm, only 6.3% of them had cervical lengths less than 20 mm. The sensitivity, selectivity, positive prediction value and negative prediction value of cervical lengths less than 20 mm were calculated 6.25%, 94%, 40% and 61%, respectively, for preterm labor. In consideration of the data of our study, we concluded that cervical length is not a sufficient method to predict preterm birth. Similarly, Bishop scores which are a subjective examination finding varied between 0 and 8, and it was found 1.38±2.34 and 1.31±1.20 in the control and study groups, respectively, which were not significant in terms preterm birth (p=0.195).

On the other hand, we observed differences in the weeks of gestation and cervical angles among the groups in association with gravidia, parity, abortion and vaginal delivery histories in our study. While there is no difference between the study and control groups in terms of cervix lengths, different cervical angles are remarkable and questionable. It is clear that there will be changes in the cervix structure of multiparous women together with previous deliveries; we refer it "multiparous dilatation" in the gynecological examinations. In this regards, uterocervical angle can be considered as a sonographic reflection of uterocervical sub-segment maturation in particular, although the change continues during the pregnancy. Cervical length in multiparous patients and these changes in the uterocervical angle are also expressed in the literature.[20,21]

Uterocervical angle measurement was first investigated by Dziadosz et al. as a tool in the prediction of preterm birth.[22] They performed cervical imaging by transvaginal ultrasound in 972 singleton pregnant women who admitted between 16 and 24 weeks of gestation. It was found that the cases with UCA >95° underwent significantly more preterm labors before 37 weeks of gestation (sensitivity 80%; p<0.001; negative prediction value 95%), and the cases with UCA>105° underwent more deliveries before 34 weeks of gestation (sensitivity 81%; p<0.001; negative prediction value 99%). A secondary result obtained in the same study was that cervical length (<25 mm) is significant for the prediction of preterm birth. However, since sensitivity is 62% and negative prediction value is 95% in preterm births before 37 weeks of gestation and sensitivity is 63% and negative prediction value is 97% in preterm births before 34 weeks of gestation, it has been concluded that UCA measurement is more successful than cervical length measurement for the prediction of preterm birth. These data are also supported by similar studies.[21,23,24]

In our study, UCA measurements varied between 50 and 150° in 82 patients who admitted to the emergency maternity clinic between 24 and 34 weeks of gestation, the mean value was 88.91° and we calculated threshold value 80.5° for uterocervical angle measurements depending on the preterm birth (<37 weeks) incidence. For this value, the sensitivity was 75%, selectivity was 58%, positive prediction value was 53.3% and negative prediction value was 77.3%. The area under the ROC curve obtained was 67%, and this area under curve was statistically significant (AUC=0.655, 95% CI=0.532–
The prediction of preterm birth threat by uterocervical angle

The rate (75%) of uterocervical angle being more than 80.5° in women whose weeks of gestation are below 37 during delivery higher than the rate of those whose weeks of gestation are 37 and above, and it is statistically significant (p<0.01). These data are also similar to the results of the study of Dziadosz et al. UCA measurement in the prediction of preterm birth is an important method with higher sensitivity, higher positive prediction value and lower negative prediction value than cervical length measurement.

Conclusion

Today, preterm birth continues to be the most serious reason for newborn mortality and morbidity. With its results, our study, which we prepared to understand etiological factors, develop early diagnostic methods and tools, and to contribute raising healthier individuals by taking diagnostic precautions, has shown that uterocervical angle measurement is an important method for the prediction of preterm birth. It is important and necessary to do further investigations on this matter in terms of developing diagnosis and treatment methods and achieving positive results.

Conflicts of Interest: No conflicts declared.

References

Investigation of fetal magnetic resonance imaging indications

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²Gynecology and Obstetrics Clinic, Isparta State Hospital, Isparta, Turkey
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Abstract

Objective: Although ultrasonography is the preferred screening method for examining fetal anatomy, fetal magnetic resonance imaging (MRI) has been used more widely upon the advancements in rapid screening techniques. MRI provides a better tissue contrast, and unlike sonography, it is not affected significantly by maternal obesity, fetal position, oligohydramnios, or bone artifacts. Fetal MRI is usually indicated for confirming uncertain sonographic findings, or for the further evaluation of fetal malformations. Our purpose is to investigate fetal MRI indications preferred by the clinicians in our tertiary center.

Methods: We retrospectively evaluated 112 cases which underwent fetal MRI during a three-year period. We classified fetal lesions according to the organ systems, and determined the reasons why clinicians employed this method and the preferred indications.

Results: Of 112 fetuses which required fetal MRI examination, 68 had intracranial anomalies, 23 had maternal obesity, 8 had intra-abdominal anomaly, 5 had intrathoracic anomalies, 4 had spinal cord anomaly, 1 had neck anomaly, 1 had genitourinary anomaly and 2 had other anomalies.

Conclusion: Intracranial pathology was the major indication for fetal MRI examination, as ventriculomegaly was the most frequently observed sub-group. We found additional findings changing the perinatal management in three (8.3%) of the cases which underwent further examination with MRI due to ventriculomegaly.

Keywords: Fetal, indication, magnetic resonance imaging.

Özet: Fetal manyetik rezonans görüntüleme endikasyonlarının incelenmesi

Amaç: Fetal anatomiyi değerlendirirken ultrasonografi tereci edilen tarama yöntemleri olmasına rağmen, hızlı tarama tekniklerinin gelişmesiyle fetal manyetik rezonans görüntüleme (MRG) giderek daha fazla kullanılmaktadır. MRG, daha iyi doku kontrastı sağlar ve ultrasonografiden farklı olarak, maternal obezite, fetal pozisyon, oligohidramnios veya bone artefaktilerden önemli ölçüde etkilenmez. Fetal MRG genellikle kesin olmayan ultrasonografik bulgular teyit etmek veya fetal malformasyonların iliçleri değerlendirilirlerinde endikedir. Amacımız, üçüncü basamak merkezimizde klinisyenler tarafından tercih edilen fetal MRG endikasyonlarını incelemektir.


Bulgular: Fetal MRG ile incelenen 112 fetüsünde, 68’inde intrakraniyel anomaliler, 23’inde maternal obezite, 8’inde intra-abdominal anomaliler, 5’inde intrathoracik anomaliler, 4’inde spinal cord anomaliler, 1’inde cilt anomaliler, 1’inde genitourinary anomaliler ve 2’inde diğer anomaliler idi.

Sonuç: Intrakraniyal patoloji, en sıklıkla tarama yöntemleri olmasına rağmen, hızlı tarama tekniklerinin gelişmesiyle fetal manyetik rezonans görüntüleme endikasyon belirlemesi için tercih edilen endikasyonlar arasında sıklıkla görüldü. Ultrasonografik bulguların前置degisimi ile fetal MRG ile ilgili olarak üç (8.3%) olguda perinatal yönetiminde değişiklik yapıldı.

Anahtar sözcükler: Endikasyon, fetal, manyetik rezonans görüntüleme.

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Introduction

Ultrasonography (USG) is a preferred primary screening method compared to other modalities in terms of characteristics such as being cheaper, having no harmful impact on mother and fetus and enabling real-time imaging. However, it has some restrictions such as narrow field of view, fetal position dependency, decreased image quality in case of maternal obesity and oligohydramnios as well as difficulty in imaging intracranial structures due to the ossification during advanced weeks of gestation. Therefore, when ultrasonography findings are uncertain or incomplete or when sufficient imaging cannot be achieved, magnetic resonance imaging (MRI) can provide a better perinatal consultancy and may play a substantial role in terms of management.

Today, with the development of ultra-fast MRI techniques and minimization of fetal movement artifacts, fetal MRI has become a more common practice. MRI provides a better tissue contrast and multiplane imaging opportunity, and unlike sonography, it is not affected significantly by maternal obesity, fetal position, oligohydramnios, or bone artifacts.

Fetal MRI is usually indicated for confirming uncertain sonographic findings, or for the further evaluation of fetal malformations. In this study, our aim is to investigate MRI indications preferred during antenatal period by the clinicians in our tertiary center.

Methods

Fetal MRI cases, which were referred to the Department of Gynecology and Obstetrics at Süleyman Demirel University during 17–35 weeks of gestation due to different indications between 2014 and 2018, were retrospectively investigated in the medical database. The demographics, prenatal ultrasound findings, and prenatal and postnatal MRI results of a total of 112 cases were recorded.

All sonographic examinations were performed by the clinicians, who had experience on obstetric sonography, by using Voluson 730 and E6 ultrasonography device (General Electric, Tiefenbach, Austria) with 2–7 mHz convex abdominal probe.

MRI examinations were done on supine or left-side decubitus position without maternal-fetal sedation and contrast substance but using phased-array body spiral according to the week of gestation by 1.5 Tesla MRI device (Magnetom Avento; Siemens Medical Solutions, Erlangen, Germany). The interpretations were done by the same radiologist who was experienced on fetal MRI.

Fetal lesions were classified according to the organ systems. Sonography and MRI results were analyzed in terms of conformity or inconsistencies. The reasons of clinicians for employing this modality and preferred indications were determined.

Results

The mean gestational age of the cases was 26.2 (range: 17 to 35) weeks. Of 112 fetuses which required fetal MRI examination, 68 (60.7%) cases had intracranial anomalies, 23 (20.5%) cases had maternal obesity, 8 (7.1%) cases had intrabdominal anomaly, 5 (4.4%) cases had intrathoracic anomalies, 4 (3.5%) cases had spinal cord anomaly, 1 (0.8%) case had neck anomaly, 1 (0.8%) case had genitourinary anomaly and 2 (1.7%) cases had other anomalies (Fig. 1). Intracranial pathology was the major indication for fetal MRI examination, as ventriculomegaly was found to be the most frequently observed sub-group.

Intracranial anomalies

Of 68 patients, 36 (53%) were planned for the further evaluation of ventriculomegaly found sonographically. Seventeen cases referred to this modality for the evaluation of posterior fossa anomalies (mega cisterna magna, cerebellar hypoplasia/atrophy, Dandy-Walker malfor-
mation) (Fig. 2), 9 cases for the further evaluation of cavum septi pellucidi and corpus callosum anomalies, 2 cases for the evaluation of intracranial calcification and one case for the evaluation of suspected space occupying formation, and remaining 3 cases for the evaluation of macrocephalus/dolichocephalic development (Fig. 3).

Of 68 cases, fetal MRI findings were found to be correlated with USG in 42 cases, and the findings in addition to antenatal sonography were found in 3 cases. Gyral anomalies (lissencephalia and polygyria) which could not be found by sonography in two cases and corpus callosum agenesis in one case were established by fetal MRI (Fig. 4).

In terms of postnatal results, additional imaging was performed for the confirmation of 26 cases which were established normal by MRI; 8 out of 16 cases who were found to have isolated mild ventriculomegaly were established normal in the postnatal imaging. Ten of 42 cases were recommended termination, and the termination was carried out in five cases; one of them was the case with corpus callosum agenesis which could not be found in the prenatal sonography but established by MRI. The case found to have lissencephalia was recommended termination, but the family decided to continue the pregnancy. Distal trisomy 15q syndrome was diagnosed in the case which was evaluated due to dolichocephaly and mild ventriculomegaly and found to have also polygyria in fetal MRI; however, the family was not

![Fig. 2. In the fetus with Dandy-Walker malformation, wide posterior fossa and cerebellar vermian agenesis (arrow) in (a) sagittal and (b) transaxial sections.](image)

![Fig. 3. The distribution of the indications associated with intracranial reasons.](image)
recommended termination due to the advanced week of gestation.

**Intrathoracic anomalies**

This method was employed for the pulmonary volume evaluation due to the congenital diaphragmatic hernia in 3 out of 5 cases and for the suspected pulmonary sequestration confirmed by MRI in two cases. While termination was carried out in one of the cases with diaphragmatic hernia due to the poor prognostic factors confirmed by MRI, follow-up was decided in other two cases after informing family.

In three cases with intraabdominal anomalies, the cyst/mass suspected in different locations within fetal abdomen during sonographic examination could not be confirmed by MRI. In one case, this modality was referred in terms of gastroschisis/ruptured omphalocele distinction for the further evaluation of abdominal anterior wall defect and the case was determined to have gastroschisis. Fetal MRI was requested in four cases, in terms of tracheoesophageal fistula/atresia examination in cases with polyhydramnios whose stomach was imaged as small/could not be imaged by sonography, and when esophageal atresia was found in one of these cases, consultation and operation planning were carried out with pediatric surgery clinic during prenatal period.

In two of the four cases with spinal cord anomalies, this modality was employed in order to determine the width of neural tube defect observed in the sonography for prognosis purposes and for the mass suspicion in remaining two cases, while diastematomyelia was found in one of these cases. This modality was used in one case with neck anomalies, due to the suspected fetal goiter which could not be confirmed by MRI. Fetal MRI was requested for renal evaluation in one case with oligohydramnios as well as urogenital tract anomalies, and polycystic kidney was found (Fig. 5). This case was lost with intrauterine loss in the further weeks.

**Other indications**

MRI was requested in 23 cases when it was considered that sonography was insufficient for fetal evaluation due to maternal obesity. Elevated alpha-feto protein (AFP) was found in the eight of these cases during the triple screening test, but fetal dorsal evaluation was insufficient. Ventriculomegaly was observed in one of 23 cases,
but no anomaly was found in other cases during fetal MRI. MRI method was referred in one case found to have placenta previa in order to evaluate placental adhesion anomalies (Fig. 6) as well as for the further evaluation in one case observed to have wide amniotic sheet.

Discussion

Although ultrasonography is always the basis of antenatal imaging, fetal MRI has becoming a significant complementary method for prenatal diagnosis. Unlike X-ray and computed tomography screenings, MRI does not use ionizing radiation. Many studies even including pregnant MRI technicians have shown that MRI is safe and does not have adverse clinical effects.\textsuperscript{[6–8]} Although the safety of MRI has been still investigated, there is no evidence that it has harmful effects on human embryos or fetuses.\textsuperscript{[9–11]} However, in practice, it is preferred to

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig5}
\caption{MRI image consistent with bilateral polycystic kidney.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig6}
\caption{The view consistent with focal invasion area (arrow) in the case with placenta previa (a and b).}
\end{figure}
wait until second trimester due to cautious approach in terms of teratogenicity, low signal-to-noise ratio in younger fetuses, increased fetal movement and insufficient organ development for evaluation. It is avoided to use intravenous contrast substance since there is no proven safety level. In our center, the earliest examination was done at 17 weeks, and fetal MRI method was not employed for any case during first trimester.

Fetal MRI is used primarily to confirm the presence of an anomaly suspected sonographically. In addition to the characterization of the anomaly, it may provide additional findings which are not found by ultrasonography. Fetal MRI indications may vary among centers due to various factors such as regional differences in perinatal management, experience of physician and technician, presence of appropriate device and access to fetal surgery. In some centers, fetal MRI is used even in the presence of normal ultrasound when it is considered that fetus is under great risk.

Suspicious central nervous system anomalies, brain anomalies in particular, are the most common indications for fetal MRI. Ventriculomegaly, posterior fossa and corpus callosum anomalies have been determined as the most common three indications for fetal cerebral MRI. In our study, intracranial pathology was the major indication for fetal MRI examination, as ventriculomegaly was the most frequently observed sub-group.

In a significant number of fetuses found to have ventriculomegaly may have a concomitant structural or chromosomal abnormality. Since those with isolated ventriculomegaly have a better neurodevelopmental result, presence or absence of a concomitant anomaly has an important impact on the prognosis. Although ventriculomegaly can be seen better by ultrasound, concomitant anomalies cannot be observed by sonographic examination. It is considered that the additional benefit of fetal MRI compared to USG can be observed in two different areas; first one is that additional diagnostic data are obtained without making any change in the treatment plan of pregnancy, and second one is that the additional diagnostic data obtained by MRI leads to changes on further approach for pregnancy. For example, Rossi and Prefumo confirmed USG findings by MRI in 65.4% of the cases while they obtained additional findings in 22.1% of the fetuses. In as high as 30% of the cases, MRI and sonography were highly different from each other, and this difference led to change in perinatal management. The disagreement was observed mostly on midline anomalies. In the study of Amini et al., the authors confirmed sonography results by MRI in 55% of the cases without any additional finding, found additional findings in 35% of the cases which did not change perinatal management, and they found additional findings in 10% of the cases which changed gestational approach. The pregnancies were terminated in these cases in the light of new data. In our study, we found additional anomalies in 3 of 36 cases which underwent fetal MRI due to ventriculomegaly, and MRI contributed to the consultancy for fetal prognosis. While we offered the termination option in two of these cases, we ruled out this option in other case due to the advanced week of gestation, but planned the postnatal management of newborn during prenatal period in consultation with related departments.

In corpus callosum and posterior fossa anomalies, the multiplane characteristics of MRI enable the detailed evaluation of these structures, and it is also beneficial to identify concomitant anomalies which are important for the prognosis. Pulmonary hypoplasia in fetuses with congenital diaphragmatic hernia is the most important factor affecting neonatal mortality and morbidity. As we preferred in our clinic, pulmonary volume measurements by fetal MRI contributes to the perinatal management via neonatal survival prediction. In the study of Lee et al. where the authors investigated the congenital diaphragmatic hernia by total pulmonary volume obtained via fetal MRI, they reported that the survival rate was 90% in the patients with total pulmonary volume higher than 40 mL, and 35% in those with less than 20 mL. A significant relationship has been observed between total pulmonary volume and need for extracorporeal membrane oxygenation. In one of the three cases with diaphragmatic hernia in our study, we planned termination in the light of the data we obtained by MRI, and we decided to follow up other three cases considering the good prognosis.

Despite the significant technical improvements in obstetric ultrasonography, there are difficulties encountered for the fetal sonography in this patient group due to the negative impacts of maternal obesity on the dispersion of sound waves. The previous studies have focused on the difficulties for obtaining sufficient images for the evaluation of cardiac and cerebrospinal fluids in particular. It is suggested to use complementary imaging modalities such as fetal MRI in order to overcome the negative impacts of obesity on the obstetric imaging.
In our center, we referred to fetal MRI method for the evaluation of abdominal anterior wall and fetal dorsal imaging in 23 cases for which fetal sonography was insufficient due to obesity and AFP values used particularly for the screening of neural tube defect were high. MRI is not superior to fetal echocardiography for the evaluation of fetal cardiac structures. Therefore, its additional contribution for this patient group is controversial.[3] We found no patient which underwent MRI examination due to cardiac anomaly.

**Conclusion**

In conclusion, fetal MRI has been used more widely for proper perinatal management and consultancy in cases where sonography is insufficient. More availability of MRI devices, increased expertise in this field and further advancements in MRI technology will lead to more common use of this modality in the perinatology field. However, unnecessary use of fetal MRI is associated with the anxiety of patient and increased cost burden. The collaboration of clinicians, who play a role in the obstetric management, with radiologists is beneficial for the selection of proper indications and the prevention of unnecessary practices.

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

**References**

The predictive value of total leukocyte count and leukocyte differential for severe preeclampsia

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Abstract

Objective: We aimed to evaluate the leukocyte, neutrophil, lymphocyte, monocyte counts and the neutrophil/lymphocyte ratio, platelet/lymphocyte ratio levels in pregnant women with preeclampsia (PE) compared with matched normal pregnant women and to assess whether there is a relation between severity of preeclampsia and these hematological parameters.

Methods: A retrospective, descriptive, cross-sectional study was performed in 186 women: 72 healthy pregnant women and 114 women with PE (severe group: n=41) and without severe clinical features group (mild PE, n=73). The clinical and hemodynamic status and the laboratory parameters of patients were obtained from medical records. The predictive value of total leukocyte and neutrophil count, MPV, NLR and PLR for the severity of preeclampsia was assessed by using a receiver operator characteristic-area under the curve (ROC-AUC).

Results: There were no significant differences between patients with PE and healthy pregnant women with regard to maternal age; however, patients with PE exhibited significantly higher blood pressure and proteinuria levels and significantly lower gestational age at delivery. Median leukocyte count was found to be significantly higher in mild and severe preeclampsia compared to healthy pregnant women (9450/μL) and significantly higher in severe PE (12,100/μL) than in mild PE (11,450/μL). Median neutrophil and lymphocyte counts were significantly higher in severe PE group than healthy pregnant women. Leukocyte count was found to be related to the presence of severe preeclampsia at admission to hospital (OR: 1.0002, 95% CI: 1.0001–1.0003; p=0.0001). The total leukocyte count had a poor predictive value for severe preeclampsia with an ROC-AUC of 0.696 (p=0.0001; the sensitivity and specificity were 65.9% and 65.5%, respectively). The maximum sensitivity and specificity cut-off point was found to be 0.191 (pointed specificity of leukocytes 10,890/μL). ROC-AUC of the neutrophil count, MPV, NLR and PLR for severe preeclampsia were 0.632, 0.564, 0.534 and 0.588, respectively.

Conclusion: Leukocyte count is significantly increased in women with preeclampsia compared to healthy pregnant women. The predictive value of total leukocyte count for severe preeclampsia is poor. The neutrophil count, MPV, NLR and PLR have poor predictive value for severe preeclampsia.

Keywords: Preeclampsia, leukocyte, leukocyte differentials, complete blood count, pregnancy.

Özet: Toplam lökosit sayısının ve lökosit değer farkının şiddetli preekzamplsiye yönelik kestirim değeri

Amaç: Çalışmamızda, eşlenen normal gebelerle karşılaştırarak preeklampsi (PE) gebelerde lökosit, nötrofil, lenfosit, monosit sayılardan nötrofil/lenfosit oranlı, trombosit/lenfosit oran ve seviyelerini inceleyerek ve preeklamspinin şiddetini kestirerek hemomatiolog parametrelerine bir ilişki olup olmadığını değerlendirmeyi amaçladık.

Yöntem: Retrospektif, tanımlayıcılı, kesitsel çalışmamız 186 kadının üzerinde gerçekleştirdilmiş olup, bunların 72’si sağlıklı ve 114’ü ise preeklampsi ile ilgili grup (n=41) ve şiddetli klinik özellikleri olan grup (hafif PE, n=73) hastaların klinik ve hemodinamik durumu ve laboratuvar parametreleri tibi bir kayıtlardan alındı. Toplam lökosit ve nötrofil sayısı, MPV, NLR ve PLR’nin preeklamsipsi şiddetine yönelik kestirim değerini, karar veriminin etkinliğini -egri altındaki alan (ROC-AUC) kullanarak değerlendirildi.

Bulgular: Preeklampsi hastaları ile sağlıklı gebeler arasında maternal yaş bakımından anlamlı fark yoktu; ancak PE hastaları anlamlı derecede daha yüksek kan basıncı ve proteinür seviyeleri ve iğden emissions anlamlı derecede daha düşük gebelik yaşına sahipti. Medyan nötrofil, lenfosit sayılardan sağlıklı gebelerle karşılaştırıldığında hafif ve şiddetli preeklampsi olgularında anlamlı derecede (9450/μL) ve şiddetli PE olgularında (12,100/μL) hafif PE olgularından (11,450/μL) anlamlı derecede daha yüksekti. Medyan nötrofil ve lenfosit sayılardan, sağlıklı gebelere kıyaslarken şiddetli PE grubunda anlamlı derecede daha yüksekti. Lökosit sayısının, hastaneyeye başvurunun esnasında şiddetli preeklampsi varlığında ileriкли kışlığı olduğu bulundu (Risik Oranı: 1.0002, %950.1: 1.0001–1.0003; p=0.0001). Toplam lökosit sayısı, 0.696’lık ROC-AUC ile şiddetli preeklampsi için düşük kestirim değerine sahipti (p=0.0001; dayanıklılık ve özgüllük srasıyla %65.9 ve %65.5 idi). Maksimum duyarlılık ve özgüllük eşik değeri 0.191 olarak bulundu (tam lökosit sayısı: 10,890/μL). Nötrofil sayısı, MPV, NLR ve PLR nin şiddetli preeklampsiye yönelik ROC-AUC değerleri sırasıyla 0.632, 0.564, 0.534 ve 0.588 idi.


Anahtar sözcükler: Preeklampsi, lökosit, lökosit değer farklı, tam kan sayımı, gebelik.
**Introduction**

Preeclampsia (PE) is a placental and systemic disorder characterized by a high degree of systemic inflammation, compared with normal pregnancy. It is also an important cause of maternal and perinatal morbidity and mortality. Clinical symptoms such as hypertension and proteinuria occur after 20 weeks of gestation. The pathological changes causing the symptoms are not clearly understood. However, it is supposed to begin with the failure of extravillous trophoblast cells invasion into maternal spiral arteries. This process causes placental hypoxia and triggers the increase in the lipid peroxidation, leukocyte activation and stimulation of proinflammatory cytokines. Activated leukocytes release several substances, which may affect vascular tone directly by contracting smooth muscle and indirectly by inactivating endothelium-derived relaxing factor. Interactions among the activated leukocytes, syncytiotrophoblast microvillus membrane, platelets and vascular endothelium also contribute to the vascular injury in the pregnancy-associated hypertension disorder.

Total leukocyte and leukocyte differential counts are well known inflammatory biomarkers. They have prognostic value for several inflammatory conditions. Mean platelet volume (MPV), neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) could be obtained from simplifying a complete blood count (CBC). CBC parameters as well as several acute phase reactants and activated innate immune cells have been studied in patients with PE for the prediction of disease severity and this contributes towards the understanding of the pathogenesis of PE.

Serious complications of preeclampsia including maternal, neonatal mortality are related with severity of disease. Prediction of severe preeclampsia at the first admission with an easily accessible method would optimize both the management of women with preeclampsia and the use of resources and reduce the poor consequences of disease. In this study, we aimed to investigate the predictive power of leukocyte, leukocyte differentials count, NLR and PLR levels for severe preeclampsia.

**Methods**

The study was designed as a retrospective, descriptive, cross-sectional study. The study population included 72 healthy pregnant women (control group) and 114 women with PE (preeclampsia group) admitted to the obstetrics ward at our hospital.

Patient with PE were further categorized into severe group (n=41) and without severe clinical features (mild PE) group (n=73), based on the severity of the clinical symptoms. Women who had diabetes mellitus, gestational diabetes, coagulation disorders, renal diseases, chronic hypertension, vascular complications and any fetal malformations were excluded from this study. The Institution’s medical ethics committee approved the study protocols.

The diagnosis of PE was established according to the guidelines of the American Congress of Obstetricians and Gynecologists (ACOG) (2013). High blood pressure was defined as systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg on at least two measurements at least 4 hours apart. Proteinuria was defined as a dipstick reading ≥1+. According to the guidelines of ACOG, severe PE was defined as SBP ≥160 mmHg or DBP ≥110 mmHg, thrombocytopenia (platelet count <100,000/μL), renal insufficiency (serum creatinine concentration >1.1 mg/dL), impaired liver function (elevated liver enzymes to twice of normal concentration, associated with epigastric or right upper-quadrant pain), pulmonary edema, new-onset cerebral or visual disturbance.

After admission to the hospital, close monitoring of the women with PE was performed with serial assessment of maternal symptoms and fetal movement along with serial measurements of blood pressure (BP). Women with PE having a persistent BP levels of 150 mmHg systolic or 100 mmHg diastolic or both were treated with antihypertensive medications. The intrapartum-postpartum regimen of magnesium sulphate was started in women with severe PE to prevent the development of eclampsia.

Maternal age, gestational age, laboratory findings such as CBC, aspartate transaminase (AST) and alanine transaminase (ALT) levels and the level of urinary protein with dipstick at the time of admission were obtained from patients’ medical records. Urinary protein was tested using a urine dipstick. Detectable urinary protein was defined as >1+ by dipstick and recorded as its folds. Neonatal outcomes were defined as Apgar scores at the 1st–5th min of life, birth weight, need for admission to neonatal intensive care unit (NICU) and neonatal death.
All blood samples were drawn from a brachial vein into sterile EDTA tubes. CBC was automatically analyzed (with ABBOT CELL-DYN 3700 blood count equipment) within 30 min. The number of leukocytes (1000/μL) and its differentials as neutrophils (1000/μL), lymphocytes (1000/μL) and monocytes (1000/μL) and platelets (1000/μL) were recorded. NLR and PLR were calculated using these parameters. Hemoglobin levels (g/dL) and MPV obtained from the patient’s whole blood count were also recorded.

Statistical analyses were performed using R Statistical Software (www.r-project.org) a free software environment for statistical computing and graphics. Baseline characteristics of the groups were presented as median, interquartile range (IQR), minimum and maximum values. The Shapiro-Wilk’s test, boxplots, PP and QQ plots were used to analyze the data distribution. Baseline characteristics, age, clinical and laboratory variables excluding spot urine proteinuria were compared by Kruskal-Wallis test and the associated p values were given. Dunn’s multiple comparison test was used after significant Kruskal-Wallis tests. Dunn’s test function in FAS package of R statistical program is used for multiple comparisons. The p-values adjusted with Holm correction were given. Spot urine proteinuria between mild and severe preeclampsia groups was compared using Mann-Whitney U test.

Correlations of proteinuria and leukocyte, neutrophil, MPV, PLR NLR were assessed by Spearman’s rank correlation test. The association between stages of preeclampsia and admission to NICU and perinatal mortality were tested using Fisher’s exact test. Receiver operating curve (ROC) analyses were construed to evaluate diagnostic performances and to determine the optimal cut-off values for leukocyte and neutrophil biomarkers in preeclampsia patients. Youden’s index (maximum sensitivity + specificity – 1) was used as an optimization criterion for cut-off values. The area under the receiver operating characteristic (ROC) curves was used to assess the discriminative ability of leukocyte and neutrophil for severe preeclampsia. Epi and verification packages were used for ROC curve estimations. The p-value produced for AUC is related to the Mann-Whitney U statistics. For all analyses, the p-value of p<0.05 was considered statistically significant.

Results

There was no significant difference in maternal age across three groups. Significant differences were noticed in the severe PE group such as increase in systolic and diastolic BPs, AST, ALT and proteinuria levels, and also decrease in gestational age at delivery. Table 1 shows the demographic and clinical data of study population and neonatal outcomes of the study groups.

The results for comparison of CBC parameters in normal pregnant controls and in women with mild and severe PE are presented in Table 1. Leukocyte count was found significantly different among the three groups. Severe PE group had the highest median leukocyte count (12,100×1000 /μL). Neutrophil and lymphocyte counts were found significantly different among the control and PE groups. There was a significant association at admission to NICU, perinatal mortality in group of PE (mild and severe) with p values of 0.031 and 0.028 respectively. Admission to NICU and mortality percentages were significantly higher for severe PE group than mild PE group. The significant differences in Table 1 were followed with pairwise comparisons and results were also presented in Table 2.

In this study, logistic regression analysis was used to identify the risk factors for the presence of severe PE during hospital admission. We found that in the reduced model, total leukocyte count has a statistically significant relationship with severe PE at the time of admission to the hospital (p<0.0001).

We also analyzed the performance of CBC parameters, MPV, NLR, and PLR in predicting the severity of PE using ROC curves and comparing with AUC. An AUC of >0.7 was considered the minimum to indicate as adequately. The performance associated with these parameters were considered from fair (0.5<AUC≤0.7) to good (0.7<AUC≤0.9).

The total leukocyte count has a poor predictive value for severe PE with an AUC of 0.696 (p=0.0001); the sensitivity and specificity were 65.9% and 65.5%, respectively. The maximum sensitivity and specificity cut-off point was at 0.191 [pointed number of leukocytes= 10,890 (1000/μL)] (Fig. 1). The neutrophil count, MPV, NLR and PLR have very fair predictive values for severe PE with AUC of 0.632, 0.564, 0.534 and 0.588, respectively (Fig. 2).
Discussion
Early detection and prediction of severe PE has gathered the attention of many researchers who have aimed to protect the mother and the baby from the detrimental effects of PE. They have performed several studies using clinical and laboratory predictors.[10] The diagnostic value of CBC parameters has been emphasized in inflammatory diseases (i.e. diabetes mellitus, coronary artery disease, ulcerative colitis and cancers).[11] These parameters are also reported as sensitive markers of inflammation.[11] However, the correlation between the severity of PE and the several complete blood count parameters has continued to be debatable.

Table 1. Characteristics of healthy pregnant, mild and severe preeclampsia groups.

<table>
<thead>
<tr>
<th></th>
<th>Healthy (n=72)</th>
<th>Mild PE (n=73)</th>
<th>Severe PE (n=41)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, year</td>
<td>29.3 (8.25)</td>
<td>30 (9)</td>
<td>27.9 (9)</td>
<td>0.1747</td>
</tr>
<tr>
<td>Gestational age, week</td>
<td>39 (1)</td>
<td>37 (4)</td>
<td>34 (6)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>110 (20)</td>
<td>160 (30)</td>
<td>160 (30)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>70 (10)</td>
<td>100 (10)</td>
<td>100 (10)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>10.5 (6.3)</td>
<td>14 (8)</td>
<td>15 (9)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>AST, U/L</td>
<td>17.5 (7.9)</td>
<td>22 (11)</td>
<td>30 (17)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Spot urine protein (+)</td>
<td>-</td>
<td>2 (1)</td>
<td>3 (1)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>11.5 (2.1)</td>
<td>12 (1.2)</td>
<td>12 (2)</td>
<td>0.066</td>
</tr>
<tr>
<td>Platelets (1×10³/μL)</td>
<td>200.5 (61.3)</td>
<td>214 (102)</td>
<td>201 (80)</td>
<td>0.218</td>
</tr>
<tr>
<td>Total leukocyte count (1×10³/μL)</td>
<td>9450 (2725)</td>
<td>11,450 (3900)</td>
<td>12,100 (5100)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Differential (1×10³/μL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>6.9 (2.97)</td>
<td>8.1 (3.70)</td>
<td>8.3 (5.80)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>1.9 (0.53)</td>
<td>2 (1)</td>
<td>2.3 (1.4)</td>
<td>0.03</td>
</tr>
<tr>
<td>Monocytes</td>
<td>0.6 (0.20)</td>
<td>0.6 (0.2)</td>
<td>0.6 (0.4)</td>
<td>0.368</td>
</tr>
<tr>
<td>MPV (fl)</td>
<td>8.85 (3.25)</td>
<td>10 (1.6)</td>
<td>10 (2)</td>
<td>0.064</td>
</tr>
<tr>
<td>NLR</td>
<td>3.7 (2.2)</td>
<td>3.72 (1.99)</td>
<td>3.94 (3.81)</td>
<td>0.689</td>
</tr>
<tr>
<td>PLR</td>
<td>106.3 (63.66)</td>
<td>102.9 (52.1)</td>
<td>98.2 (62.7)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

Continuous variables were presented as median (IQR); categorical variables were presented as number (%). ALT: alanine transaminase; AST: aspartate transaminase; DBP: diastolic blood pressure; IQR: interquartile range; MPV: mean platelet volume; NICU: neonatal intensive care unit; NLR: neutrophil-lymphocyte ratio; PE: preeclampsia; PLR: platelet-lymphocyte ratio; SBP: systolic blood pressure. *p<0.05

Table 2. Comparison of complete blood parameters among groups.

<table>
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<td>&lt;0.001*</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>1.9 (0.53)</td>
<td>2 (1)</td>
<td>2.3 (1.4)</td>
<td>0.03</td>
</tr>
<tr>
<td>Monocytes</td>
<td>0.6 (0.20)</td>
<td>0.6 (0.2)</td>
<td>0.6 (0.4)</td>
<td>0.368</td>
</tr>
<tr>
<td>MPV (fl)</td>
<td>8.85 (3.25)</td>
<td>10 (1.6)</td>
<td>10 (2)</td>
<td>0.064</td>
</tr>
<tr>
<td>NLR</td>
<td>3.7 (2.2)</td>
<td>3.72 (1.99)</td>
<td>3.94 (3.81)</td>
<td>0.689</td>
</tr>
<tr>
<td>PLR</td>
<td>106.3 (63.66)</td>
<td>102.9 (52.1)</td>
<td>98.2 (62.7)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

IQR: interquartile range; MPV: mean platelet volume; NLR: neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio. *p<0.05
In this study, we aimed to investigate the relationship between CBC parameters and the severity of PE and to determine the predictive power of each parameter of CBC for predicting the severity of disease. Our results showed that the leukocyte count was significantly increased in women with mild and severe PE compared with healthy pregnant control women. The leukocyte count for severe PE was significantly higher than that for mild PE. These findings support a study performed by Özdemirci et al. and Ozkaya et al., who reported leukocyte count above 16,000/μL is an independent predictor of severe PE. In another study, it was reported that there were statistically increased leukocyte and neutrophil counts in healthy pregnant women and women with PE compared with non-pregnant women. But these parameters could not be considered specific for PE or normal pregnancy.

Immune system is greatly affected by physiology of pregnancy and is mainly characterized by increasing activation of peripheral blood leukocytes. Preeclamptic condition is an exacerbation of this situation due to the lack of maintenance of control pathways like membrane glutathione activity as observed in normal pregnancy. The other characteristics of systemic inflammation in PE are the lack of symmetry in distribution of T lymphocyte subgroups and predominance of Th1-type immunity. Furthermore, the placental hypoxia resulting from uteroplacental arterial invasion insufficiency triggers the release of inflammatory stimuli (i.e. lipid peroxidation, leukocyte activation and increase in proinflammatory cytokine production) into the maternal circulation and contributes to systemic inflammation in PE.

In pregnant women, leukocytosis is mainly due to increase in the neutrophil count. Increase in the cortisol level triggers the mobilization of the leukocyte pool, and increase in the concentration of granulocyte-macrophage colony stimulating factor may also contribute to the increase in white blood cell count. We focused on the differential of total leukocyte count (i.e. neutrophil, lymphocyte and monocyte) and found that these leukocyte differentials were significantly increased in severe PE group as compared with healthy pregnant group. Especially there was a significant increase in neutrophil counts in severe PE compared with the control group. But, this increase was not observed in mild PE and severe PE groups. These results correlate with the study findings revealed by Canzoneri et al. Another study has demonstrated that there was an increase in neutrophil activation and production of superoxide in PE compared to normal pregnancy, and emphasized that the products of this activation play an important role in giving rise to endothelial damage and dysfunction.

We also compared the MPV, NLR and PLR between normal healthy pregnancy and preeclamptic pregnancy, but the results did not reveal any significant differences between these two groups. We found that the increase in leukocyte and neutrophil counts are associated with severity of PE. The predictive value of total leukocyte count among with PE neutrophil count, MPV, NLR and PLR were found uncorrelated for severe PE and Mihu et al. have reported significant increase in leukocyte and neutrophil count in PE pregnancy and also emphasized that these parameters were
not specific for the preeclamptic women.\textsuperscript{[27]} In several studies, NLR was reported to be significantly higher in PE than healthy pregnant women.\textsuperscript{[10,11,19,21,22]} On the other hand, opposite results were noticed about using of NLR as a marker to predict the severity of PE.\textsuperscript{[10,11,21]}

The relation between MPV and severity of PE is another debatable issue. In our study, there were no significant differences in the PE subgroups as compared with the healthy pregnant group. Some previous reports have claimed similar results as our study that PE does not affect MPV.\textsuperscript{[22,24–26]} Yavuzcan et al. have reported that there is no statistically significant difference between the PE group and control group in terms of MPV and PLR.\textsuperscript{[22]} Toptas et al. noticed that NLR and PLR are not significantly changed between these groups.\textsuperscript{[16]} However, Ozdemirci et al., reported that MPV was higher in the PE group as compared with the control subgroups\textsuperscript{[15]} and could be used as a predictive marker for severe PE.

Regarding neonatal status at birth, we found that gestational age, birth weight and Apgar score were significantly lower in severe PE group compared to mild PE and healthy pregnant groups. But, we did not compare these three groups in terms of NICU admission and neonatal mortality due to missing data in healthy pregnant group. However, these parameters were found significantly higher in severe PE group than in mild PE group. We found the demographic data correlated with the literature.\textsuperscript{[27]} and neonatal outcomes also correlated with the reviewed literature.\textsuperscript{[28,29]}

**Conclusion**

In conclusion, the idea that CBC can predict the inflammatory state and severity of PE is extremely attractive but lacks in reproducibility and validity. Further studies are needed to find powerful predictive parameters for severity of PE to reduce maternal and neonatal morbidity and mortality.

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

**References**

18. Sacks GP, Studena K, Sargent K, Redman CW. Normal pregnancy and preeclampsia both produce inflammatory changes in...


Fetal cell detection for chromosome analysis from leaking amniotic fluid in pregnancies with rupture of membranes

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Abstract

Objective: In this study, our goal was to assess the feasibility of using vaginally obtained amniotic fluid samples for prenatal chromosome analysis by fluorescence in situ hybridization (FISH) in pregnancies with ruptured amniotic membranes.

Method: Twenty-four pregnant women with known male fetal gender were retrieved for the study. All had ruptured membranes either artificially (AROM) or spontaneously (SROM) at term or at preterm gestations (PPROM). Samples from leaking amniotic fluid were collected during speculum examinations and slides were prepared for FISH using probes specific for chromosomes X and Y. Fetal cell detection rate was calculated as percentage of XY nuclei. Specimen volume, presence of mucus, presence of blood, gestational age, artificial versus spontaneous rupture of membranes and time elapsed until specimen processing were compared with regard to fetal cell detection rate.

Results: There were 12 patients with AROM (50%) and 12 with SROM (50%). Only two of those were preterm (8.3%). Six of the specimens were bloody (25%) and 16 (66.6%) were macroscopically with mucus. The proportion of male fetuses identifiable by FISH was 100% (95% CI: 86%, 100%) after exclusion of technical failures (n=4). Overall, fetal cell detection rate was 6.4%. Samples collected after AROM had borderline higher percentage of fetal cells compared with SROM after adjusting for presence of blood in the sample (p=0.07). In addition, bloody samples had a significantly higher percentage of fetal cells than those that were not bloody (p=0.01).

Conclusion: Amniotic fluid collection for prenatal chromosome analysis by interphase FISH is a feasible, non-invasive and reasonable approach on rupture of membranes patients and may be accomplished on preterm premature rupture of membranes with known male fetus pregnancies when indicated. Further studies are needed to assess the value of molecular analysis to differentiate fetal cells with higher specificity for female fetuses.

Keywords: Fluorescence in situ hybridization, membrane rupture, vaginal, pregnancy.

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Introduction

Prenatal diagnosis of a genetic disorder is valuable information at any gestational age. Many available techniques require invasive procedures such as amniocentesis, chorionic villi biopsy or cordocentesis. Although cell-free fetal DNA testing in maternal blood has reduced the need for invasive approaches significantly, it is still regarded as a good screening test for aneuploidies. Some other methods are still under investigation for their routine use as in transcervical cell sampling (TCC) by intrauterine lavage (IUL) and by mucus sampling.\[1–3\] These earlier studies reported that fetal chromosome analysis is possible through recovered trophoblasts in early gestations with intact membranes. However, after early years of 2000’s, interest in this topic has faded in the medical literature.\[2\]

Amniotic fluid contains desquamated fetal cells; they can be reached via amniocentesis when genetic, metabolic or immunologic testing of fetus is indicated. With the rupture of membranes at preterm gestations, amniotic fluid becomes available through vaginal examination, just like it is used in routine clinical practice for confirmation of membrane rupture. To the best of our knowledge, there is no data for feasibility of using vaginally obtained leaking amniotic fluid for prenatal diagnosis so far. Fetal aneuploidy analysis on amniotic fluid is accomplished by conventional karyotyping, a technique that needs rapidly dividing cells to capture as many as possible metaphase plates. Therefore, it always requires a sterile sample, since bacterial and fungal growth may inhibit fetal fibroblast culture. However, by molecular techniques such as fluorescence in situ hybridization (FISH) and quantitative-fluorescent polymerase chain reaction (QF-PCR), the need for sterile sampling and culturing can be bypassed while analyzing great number of cells/molecules in shorter period. Therefore in this study, we aimed to test the feasibility of using leaking amniotic fluid samples for fetal chromosome analysis by FISH. Primary objective was to assess the feasibility of using vaginally obtained amniotic fluid samples for prenatal chromosome analysis by FISH on ruptured amniotic membrane patients. Our secondary objective was to observe fetal cell detection rate, specimen/patient related variables and their effects on fetal cell detection rate.

Methods

Patient population

This was a two-center observational study that was conducted at Georgetown University Hospital in Washington, DC and Virginia Hospital Center in Arlington, VA, USA. The study was approved by the Institutional Review Board of Georgetown University (IRB 2008-43) and written consents were obtained from each participant. Pregnant women who came to labor and delivery clinics of these centers with complaints of ruptured membranes were evaluated for their eligibility. Inclusion criteria were male fetal gender (detected by ultrasonography or by amniocentesis/chorion villi sampling), spontaneous rupture of membranes at term (>37wks; SROM), preterm premature rupture of membranes (PPROM) at any gestational age after viability [(26+0)–(36+6)] or artificially rupture of membranes (AROM) (>37wks) at term. None of the artificial rupture of membranes was performed for the study; all had obstetric indications. All fetal genders were later confirmed by postpartum inspection of neonatal genders. Only cases with overt membrane rupture as determined by active cervical discharge and fluid pooling were recruited. Exclusion criteria were multifetal pregnancy, female fetal gender, active vaginal bleeding, recent sexual intercourse (last 7 days), premature rupture of membranes before 24 weeks, maternal age under 18 and any maternal/fetal condition that requires prompt delivery such as placental abruption, chorioamnionitis and non-reassuring fetal heart rate.

Sample collections

Samples were collected during the diagnostic speculum evaluation of PPROM or SROM or right after membranes were ruptured by the operator (in AROM cases). All diagnoses for membrane rupture were confirmed by positive inspection of pooling, nitrazine test and ferning pattern under microscope. Patients those having all of the three findings were regarded as having ruptured amniotic membranes. Sterile syringes without needle were used to aspirate the amniotic fluid accumulations on speculums. Samples were immediately transferred into a tube containing phosphate-buffered saline solution (PBS). Specimen amount, presence of mucus, presence of blood, gestational age (term vs preterm), time elapsed until specimen processing were compared with regard to fetal cell detection rate. All specimens were processed in the first 5 days of their collection.
Fluorescence in situ hybridization
Slide preparations
Slide preparations and FISH analysis for chromosomes X and Y were accomplished by using the protocols previously described in the literature. \[4\] Briefly, PBS was added to samples and centrifuged at 1000 RPM for 10 minutes. Supernatants were discarded and the precipitant cells were mixed gently. Sample mixes were dropped on a clean and dry slide. Hypotonic solution (50 mM potassium chloride) was added to each slide and incubated at 37°C for 20 minutes. Excess hypotonic was decanted and this step was repeated. Slides were then dried at 60°C for 5 minutes. After dehydration steps with ethanol series, slides were stored at -20°C until FISH procedure.

Pretreatment of slides
Slides were treated in 50% acetic acid and 50% methanol fixative solution for 10 minutes and then in 5 μl pepsin stock (10%) /HCl solution for 2.5 minutes. Formamide denaturation step was completed after another series of ethanol dehydration.

Pretreatment of probes and detection steps
For each slide a total of 20 μl hybridization mix containing 1 μl centromeric probe for each sex chromosome (X and Y) was prepared and denatured at 800°C for 10 minutes. After denaturation, probe mixes were incubated at 370°C overnight in humidifying chamber. The next day, slides were treated with formamide for stringency wash and rinsed with saline-sodium citrate (SSC) buffer. A volume of 100 μl blocking solution was added to each slides and covered with coverslips. After 30 minutes of incubation at 37°C, cover slips were removed. For each slide, 100 μl detection solution containing 1 μl avidin-FITC + 1 μl mouse anti-digoxin was added and slides were incubated at 370°C for 45 minutes.

Fluorescence microscopy
Slides that were hybridized with centromeric probes for chromosomes X and Y were analyzed under fluorescence microscope in dark room settings. For each slide (patient), 200 interphase nuclei were counted. A pattern of one green and one red signal in an interphase nucleus was recorded as male gender (XY, Fig. 1a). Nuclei with two red signals were counted as female nuclei (XX, Fig. 1b). Since maternal cell contamination (XX) was expected in all samples, male and female signal patterns were counted per slides and percentages were recorded as “fetal cell detection rate”. For example, a slide of a patient with 200 counted nuclei having XX[194]/XY[6] signals, was recorded as having 3% fetal cells in that specimen. To minimize the possible effect of signal artifacts, at least three interphase nuclei with XY signal pattern were sought per patient to call a specimen as con-

Fig. 1. FISH image of an XY nucleus carrying one red and one green signal (a) and other XX nucleus carrying two red signals (b).
Fetal cell detection for chromosome analysis from leaking amniotic fluid in pregnancies with rupture of membranes

Statistics

The proportion of male children identifiable as male by FISH was estimated with an exact 95% confidence interval. In addition, an exact one-sided binomial test was performed to test if this proportion was greater than 80%. The mean percentage of fetal cells was compared for each sample characteristic (type of membrane rupture, type of delivery, volume, presence of mucus, presence of blood, and time until processing) using t-tests and ANOVA. Linear regression was used to determine characteristics associated with percentage of fetal cells.

Results

A total of 28 pregnant women at gestational ages between 240/7 weeks and 410/7 were recruited. FISH analysis could not be done in four patients due to technical problems. Therefore remaining 24 patients were included in the final analysis. In 12 patients, samples were obtained after artificial membrane rupture (50%); the rest of the pregnancies had spontaneously ruptured membranes (50%). Only two patients were preterm (8.3%), one had PPROM at 31st weeks of gestation and the other had preterm labor with PPROM at 30th weeks of gestation. Six of the specimens were bloody (25%) and, 16 (66.6%) were with mucous macroscopically.

The proportion of male children identifiable by FISH was 100% (95% CI: 86%, 100%) (p=0.005) after exclusion of technical failures (n=4). When the percentage of fetal cells was calculated (XY signals), overall fetal cell detection rate was 6.4% (2.7–21.8%). Table 1 displays the mean percentage of fetal cells for each sample characteristic (gestational age, specimen volume, presence of mucus, presence of blood, artificial versus spontaneous rupture of membranes, time elapsed until specimens processing). Bloody samples had a significantly higher percentage of fetal cells than those that were not bloody (p=0.01). Also, samples collected after an AROM had a borderline significantly higher percentage of fetal cells than SROM (p=0.07). No other significant differences were observed in the percentage of fetal cells with regard to recorded characteristics. The final linear regression model only included type of membrane rupture and blood. The adjusted mean values and 95% confidence intervals are shown in Table 2. After adjusting for the type of membrane rupture, bloody samples had a significantly higher mean percentage of fetal cells than samples with no blood (p=0.01).

Discussion

In this study, our results indicated that fetal chromosome analysis by FISH is a feasible approach for prenatal cytogenetic diagnosis on leaking amniotic fluid in pregnancies with membrane rupture. We also observed that overall percentage for fetal cells in leaking amniotic fluid is sufficient for FISH analysis.

<p>| Table 1. Mean values and 95% confidence intervals of fetal cells by sample characteristics (n=24). |
|-------------------------------------|-----------------|------------------|------|</p>
<table>
<thead>
<tr>
<th>Type of membrane rupture</th>
<th>n</th>
<th>Mean</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AROM</td>
<td>12</td>
<td>8.3</td>
<td>(4.3, 12)</td>
<td>0.07</td>
</tr>
<tr>
<td>SROM</td>
<td>12</td>
<td>4.6</td>
<td>(3.0, 6.3)</td>
<td></td>
</tr>
<tr>
<td>Type of delivery</td>
<td>0.60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Term</td>
<td>22</td>
<td>6.7</td>
<td>(4.3, 9.0)</td>
<td></td>
</tr>
<tr>
<td>Preterm</td>
<td>2</td>
<td>4.6</td>
<td>(-6.6, 16)</td>
<td></td>
</tr>
<tr>
<td>Volume</td>
<td>0.16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 ml</td>
<td>10</td>
<td>6.2</td>
<td>(2.4, 9.9)</td>
<td></td>
</tr>
<tr>
<td>2–4 ml</td>
<td>10</td>
<td>5.1</td>
<td>(4.0, 6.2)</td>
<td></td>
</tr>
<tr>
<td>&gt;4 ml</td>
<td>4</td>
<td>11</td>
<td>(-3.1, 25)</td>
<td></td>
</tr>
<tr>
<td>Mucus</td>
<td>0.93</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>10</td>
<td>6.4</td>
<td>(3.0, 9.7)</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>14</td>
<td>6.6</td>
<td>(3.4, 9.8)</td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>13</td>
<td>4.2</td>
<td>(3.4, 4.9)</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>11</td>
<td>9.2</td>
<td>(4.9, 14)</td>
<td></td>
</tr>
<tr>
<td>Time until processing</td>
<td>0.36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;24 hours</td>
<td>17</td>
<td>4.7</td>
<td>(3.2, 6.1)</td>
<td></td>
</tr>
<tr>
<td>&lt;24 hours</td>
<td>7</td>
<td>7.2</td>
<td>(4.2, 10)</td>
<td></td>
</tr>
</tbody>
</table>

AROM: artificially rupture of membranes; SROM: spontaneous rupture of membranes

<p>| Table 2. Adjusted mean values and 95% confidence intervals estimated from the linear regression model (n=24). |
|-------------------------------------|-----------------|------------------|------|</p>
<table>
<thead>
<tr>
<th>Type of membrane rupture</th>
<th>Mean</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AROM</td>
<td>8.3</td>
<td>(5.8, 11)</td>
<td>0.07</td>
</tr>
<tr>
<td>SROM</td>
<td>5.0</td>
<td>(2.5, 7.6)</td>
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</tr>
<tr>
<td>Blood</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>4.3</td>
<td>(1.8, 6.7)</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>9.1</td>
<td>(6.4, 12)</td>
<td></td>
</tr>
</tbody>
</table>

AROM: artificially rupture of membranes; SROM: spontaneous rupture of membranes
Prenatal diagnosis to detect fetal genetic disorders is desired to make informed decisions at any time during pregnancy. While unsatisfactory sensitivity/specificity levels are inherent drawbacks for screening tests, procedure-related complications can be a problem in invasive diagnostic tests. Recent advances in testing for cell-free fetal DNA in maternal blood is considered as a good but an expensive screening test for now.\[10\] Observation of trophoblast presence in cervical canal during first trimester has inspired researchers for alternative prenatal diagnostic sampling methods.\[6–8\] Consequently, studies have demonstrated the feasibility of FISH and molecular analysis on trophoblasts obtained by two TCC sampling techniques.\[6–8\] In IUL technique, investigators were able to retrieve trophoblasts for genetic analysis by advancing a sterile flexible catheter (Pipelle) up to the point of internal cervical os, and rinsing with a small amount of sterile saline solution, and collecting it back. IUL is possible only in the first trimester and it has been tested on patients prior to their planned termination of pregnancies.\[9,10\] Other technique is cervical mucus collection (usually by cytobrush) and identification of trophoblasts under inverted microscope for prenatal genetic testing.\[3,11–13\] In a study where TCC by IUL was compared to mucus sampling in pregnant women between 7th to 12nd gestational weeks, fetal cell detection rate was 2–90% (mean 40%) and correct sex determination in male embryos was 90.2% by IUL. On the other hand, fetal cell detection rate was 1–4% and correct sex determination in male embryos was 56% by cervical mucus sampling.\[14\] Another study has used immunohistochemistry and demonstrated that trophoblasts were easily detectable by HLA-G staining in 35 out of 37 cervical mucus samples of first trimester intrauterine pregnancies.\[15\]

In this study, target population was pregnant patients with ruptured membranes. Since we did not come across a similar report in the medical literature (PubMed database), it was not possible to compare our results to others: TCC by IUL or mucus sampling methods have tested the prenatal fetal cell detection and diagnosis feasibility on patients with intact membranes in the first trimester.

One interesting finding of this study was that bloody samples had a significantly higher percentage of fetal cells than those were not bloody (p=0.01). Vaginally obtained leaking amniotic fluid may contain maternally derived cells such as leukocytes, macrophages, squamous and columnar epithelial, as well as fetal-derived cells. The reason behind this finding is not clear; however, it can be speculated that the origin of blood was more fetal than maternal. In a study where IUL was used in the first trimester, blood contamination was reported to correlate with trophoblast presence.\[16\] Although we did not test the rate of trophoblast presence in leaking amniotic fluid samples, we infer that their percentage is negligible since the shedding of trophoblasts ceases after the fusion of decidua basalis and parietalis by the end of the first trimester.\[19\] Therefore, utilizing fetal cells directly rather than trophoblasts (as in TCC and chorion villi sampling), minimizes the risk of confined placent al mosaicism.

Our results showed that, samples collected after AROM had borderline higher percentage of fetal cells compared with SROM after adjusting for presence of blood in the sample (p=0.07). This finding is justifiable since membrane rupture is imminent and collection of sample is recent in AROM. However, results also indicated that fetal cells are detectable by 100% in patients with SROM, thus eliminating the need of higher percentage of fetal cells.

In this study, specimen collection and FISH analysis steps were achieved by the same operator (corresponding author), which could be a source of bias. However, this was a feasibility study and there were no group of patients to compare each other that would necessitate blinding. Sperm contamination possibility may be another question, as addressed by previous studies that evaluated cervical mucus samples under microscope to rule out sperm cell presence.\[10\] Instead, we asked patients their last vaginal intercourse time and did not recruit if they have had intercourse recently. Besides, a haploid nucleus of a sperm cell would give only one signal, easily identifiable from fetal cells with two signals in one nucleus (red and green). We also assumed that all fetuses were non-mosaic XY males and they did not have sex chromosome aneuploidies.

In the current approach, FISH analysis alone or conventional karyotyping cannot be applied to patients with female fetal gender due to maternal cell contamination. However, this obstacle is easy to overcome by short tandem repeat (STR) analysis as it is performed in QF-PCR assays.\[16\] Maternal cell contamination should not be considered as a disadvantage; rather it was our goal to assess fetal cell (chromosome) detection rates in amniotic fluid samples contaminated with maternal cells, which was already expected. We were able to observe fetal cells
(XY carrying interphase nuclei) in all of these samples with overall cell detection rate 6.4% (2.7–21.8%), after excluding technical failures (n=4). This seems like a considerable amount of maternal cell contamination. However, for every SROM patient, detected fetal cells were more than adequate for molecular cytogenetic (FISH) and for PCR techniques that could be used in patients with female fetal gender.

As mentioned, in this study vaginally obtained leaking amniotic fluid samples were employed for fetal cell sampling. Non-invasive nature of the approach is an advantage. Clearly, it could only be applied to patients with ruptured membranes. Management of PPROM requires an assessment of risks and benefits of continued pregnancy or expeditious delivery. In certain clinical settings when prenatal diagnosis is indicated and invasive techniques are not feasible such as PPROM with oligohydramnios or PPROM and patient preference, this method might be of value.

Conclusion

Amniotic fluid collection for prenatal chromosome analysis by interphase FISH is a feasible and reasonable approach on rupture of membranes patients and may be accomplished on preterm premature rupture of membranes with known male fetus pregnancies. Future studies are needed to test the utility of molecular analysis to differentiate female fetal cells with accuracy in patients carrying female fetuses.

Conflicts of Interest: No conflicts declared.

References

Perinatal and orthopedic outcomes of patients diagnosed with pes equinovarus by mid-trimester fetal ultrasonographic imaging

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Abstract

Objective: In this study, we aimed to evaluate the perinatal and orthopedic outcomes of pregnant women diagnosed with pes equinovarus by mid-trimester fetal ultrasonographic screening in our clinic, and to compare the perinatal and neonatal outcomes of pregnant women complicated with isolated and non-isolated pes equinovarus.

Method: The pregnancy and newborn medical records of the pregnant women, who were diagnosed with pes equinovarus by mid-trimester fetal ultrasonographic screening at the Perinatology Department of İnönü University between April 1st, 2014 and January 1st, 2017 and followed up to the delivery, were reviewed retrospectively. The patients with terminated pregnancies who had congenital syndromes in addition to pes equinovarus were also included in the study.

Results: During the study period, the data of 71 patients who were prenatally diagnosed with pes equinovarus by mid-trimester fetal ultrasonographic imaging were evaluated. While bilateral pes equinovarus was found in 59.3% of the fetuses in isolated group, it was 79.4% in the non-isolated group (p=0.084). The median diagnosis week was 22 weeks in the isolated group while it was 20 weeks in the non-isolated group (p=0.041). Fetal karyotyping was performed on 37.5% of the patients in the isolated group during prenatal period while this rate was 38.4% in non-isolated group (p=0.802). The patients in the isolated group did not have aneuploidy as a result of karyotyping whereas trisomy 18 was found in three patients and 46,XX.inv(9)(p12q13) in one patient in the non-isolated group (p=0.035). In the group complicated with isolated pes equinovarus during neonatal period, 81.2% of the newborns were treated by conservative therapy (corrective casting - Ponseti’s or Kite’s method), and this rate was 27.2% in the non-isolated group. Surgical requirement was higher in the non-isolated group, and postero medial release was the most frequent operation.

Conclusion: Distinguishing the fetuses, which are diagnosed with pes equinovarus during prenatal period, as isolated and non-isolated cases has a critical significance in the prediction of neonatal outcomes. The incidence of chromosomal alteration and possibility of poor neonatal and orthopedic outcomes are higher in the non-isolated group. The results of our study will contribute to inform pregnant women properly, who are complicated with isolated and non-isolated fetal pes equinovarus during prenatal period, in terms of follow-up, treatment options and outcomes during perinatal and neonatal periods.

Keywords: Fetal ultrasonography, pregnancy, gestational outcomes, pes equinovarus.

Özet: Mid-trimester fetal ultrasonografik taramada pes ekinovarusa sahit olan hastaların perinatal ve ortopedik sonuçları

Amaç: Bu çalışmada kliniğiuzide mid-trimester fetal ultrasonografik taramada pes ekinovarus sahit olan gebelerin perinatal ve ortopedik sonuçları değerlendirildi, izole ve izole olmayan ekinovarus sahit olan gebelerin perinatal ve neonatal sonuçları karşılaştırıldığı amaçlandı.


Sonuç: Prenatal dönemde pes ekinovarus tanısı konulan fetüslere izole ve izole olmayan ayırma yapılmaması, neonatal sonuçların öngörümede kritik önem sahiptir. İzole olunan grupta kromozom değişikliklerinin görülme şıktığı, olumsuz neonatal ve ortopedik sonuçlar ile karşılaşma olasılığı daha yüksektir. Çalışmamızın sonuçları, prenatal dönemde fetüste izole ve izole olmayan ekinovarus sahit olan gebeliklerin perinatal ve neonatal dönemlerdeki izlem, tedavi seçeneği ve sonuçları açısından doğru bilgilendirilmemesineкатkıda bulunacaktır.

Anahtar sözcükler: Fetal ultrasonografi, gebelik, gebelik sonuçları, pes ekinovarus.
Perinatal and orthopedic outcomes of patients diagnosed with pes equinovarus by mid-trimester fetal ultrasonographic imaging

Introduction

Congenital pes equinovarus (PEV), also known as talipes or clubfoot, is one of the most common congenital orthopedic deformities for feet which is seen in 2–3 cases out of 1000 live births, and requires sequential therapy. PEV is seen two times more common in male fetuses than female fetuses. PEV is considered to have more than one reason, and it is characterized by adduction on the anterior side of foot, cavus on middle part, and equinism and varus (internal rotation) deformity on the posterior side. Twenty percent of the fetuses with pes equinovarus also have other symptoms, and 80% of them do not have any chromosomal disorder or any other congenital anomaly. Although various factors such as genetic reasons, vascular disorder and fetal restriction are suggested for the etiology of PEV, it has not been fully clarified yet. Conservative and surgical methods are referred in its treatment. Different rates have been reported for the success of conservative therapy alone including the serial manipulation and casting. While there are studies reporting high success rate for conservative therapy (about 90%), some other studies report low rates (about 50%). Two main methods are used most frequently as good long-term outcomes are reported. These are Ponseti’s method, which includes serial long leg casting following weekly corrective manipulations, and Kite’s method, in which splints keeping legs in dorsiflexion and mild abduction during nights are applied as well as serial manipulation and casting. Although surgical treatment modalities have been used more frequently when the biomechanics of the disease was not clear enough, surgical methods are still referred which include soft tissue releases in cases that cannot be provided sufficient recovery by conservative methods.

There is limited number of studies in the literature investigating obstetric and orthopedic outcomes of fetuses with pes equinovarus. Therefore, we aimed in our study to evaluate the perinatal and orthopedic outcomes of pregnant women diagnosed with pes equinovarus by mid-trimester fetal ultrasonographic imaging in our clinic, and to compare the perinatal and neonatal outcomes of isolated and non-isolated cases.

Methods

Approval was obtained for the study from Scientific Research and Publication Ethics Committee of Health Sciences, İnönü University (approval number of Ethics Committee: 2016/10–11). The pregnancy and newborn files of the pregnant women, who were diagnosed with pes equinovarus by mid-trimester fetal ultrasonographic imaging at the Perinatology Department of Medicine Faculty Hospital at İnönü University between April 1st, 2014 and January 1st, 2017 and followed up to the delivery, were reviewed retrospectively. The patients who had congenital syndromes in addition to pes equinovarus and chose termination of pregnancy were also included in the study. In all patients, the diagnosis of pes equinovarus was established by observing tibia and fibula on the same plane during the imaging of foot on plantar level in the fetal ultrasonographic examination at prenatal period (Fig. 1). During the study period, invasive prenatal diag-

![Fig. 1. Gray-scale ultrasonography images (a and b) where tibia and fibula are on the same plane during ultrasonographic imaging of fetal foot on plantar level.](image-url)
nosis was recommended to isolated cases and non-isolated cases which had concomitant fetal malformations. The cases with pes equinovarus developed secondary to oligohydramnios/anhydramnios, which developed due to preterm premature rupture of membranes or congenital renal anomalies, were excluded from the study. Termination option was offered in the presence of fetus with fetal chromosomal anomaly or near-fatal congenital anomaly. During the study period, the antenatal follow-ups and deliveries of pregnant women were performed in accordance with the follow-up and delivery protocols established in the Antenatal Care Management Guide and Delivery and Cesarean Section Guide of Health Ministry.\[10,11\] All newborns with pes equinovarus accompanied with isolated or congenital syndromes and born in our hospital were referred to newborn intense care unit and the Department of Orthopedics and Traumatology for examination, and the conservative therapy was initiated for these newborns within the first 3 days of life for pes equinovarus deformity (Fig. 2). Surgical treatment was conducted in cases where conservative therapy was insufficient or failed.

Inclusion criteria were (i) 18–39 years old, (ii) single live fetus, (iii) diagnosis of pes equinovarus concurrent with isolated or other anomalies in the mid-trimester fetal ultrasonographic imaging, and (iv) carrying out gestational follow-up and delivery or termination in our clinic.

Exclusion criteria were (i) multiple pregnancies and (ii) intrauterine fetal death.

For the patients included in the study, age, gravida, parity, body mass index, week of gestation for diagnosis, whether pes equinovarus is unilateral or bilateral, fetal karyotyping results, how pregnancy was ended, delivery, gestational age at delivery, birth weight, sex, neonatal intensive care unit requirement, therapy type for pes equinovarus and prognosis parameters were recorded. Statistical Package for the Social Sciences (SPSS) version 22.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. For statistical comparison of the cases, the normality distribution of the data obtained from the patients was analyzed by Shapiro-Wilk test. In isolated and non-isolated PEV groups, the data displaying normal distribution were defined as mean and standard deviation, and the data not displaying normal distribution were defined as median, minimum and maximum. While t-test was used for the data complying with normal distribution, the non-compli-
ant data were compared and analyzed by Mann-Whitney U test. The categorical variables were summarized by numbers and percentages, and Pearson’s exact chi-square and chi-square tests with correction for continuity were used for the comparisons. In all analyses, 0.05 was considered as the significance level.

Results
Of 71 patients who were diagnosed with pes equinovarus in the mid-trimester fetal ultrasonographic imaging during the study period, no fetal malformation was found in 32 (45.1%) (isolated group), and additional fetal anomaly was observed together with PEV in 39 (54.9%) (non-isolated group). Pregnancy termination was decided in 17 (43.6%) patients in the non-isolated group due to chromosomal anomaly and concurrent major fetal malformations. Flow chart for pregnant women diagnosed with pes equinovarus in the fetus in mid-trimester ultrasonographic imaging between April 1st, 2014 and January 1st, 2017 is shown in Fig. 3. When isolated PEV cases and non-isolated PEV cases were compared in terms of maternal characteristics, no statistically significant difference was found between the groups in terms of age, gravida, parity and body mass index (p=0.182, p=0.079, p=0.149, and p=0.125, respectively). When the week of gestation established with median diagnosis in the non-isolated group was compared with isolated PEV group, it was found lower which was statistically significant [20.0 (16.0–26.0) and 22 (19.0–25.0); p=0.041]. Fetal karyotyping was performed on 37.5% of the patients in the isolated group during prenatal period while this rate was 38.4% in non-isolated group (p=0.802). While no chromosomal change was found in the invasive prenatal diagnosis performed for all patients in the isolated group, trisomy 18 was found in 3 patients and 46,XX,inv(9)(p12q13) in 1 patient in the non-isolated group (p=0.053). The characteristics of pregnant women found to have isolated and non-isolated PEV are summarized in Table 1.

Fig. 3. Flow chart for pregnant women diagnosed with pes equinovarus in the fetus in the mid-trimester ultrasonographic screening between April 2014 and January 2017.
Table 1. The characteristics of the groups found to have isolated and non-isolated pes equinovarus.

<table>
<thead>
<tr>
<th></th>
<th>Isolated group (n=32)</th>
<th>Non-isolated group (n=39)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age*</td>
<td>28.34±5.64</td>
<td>30.10±5.32</td>
<td>0.182</td>
</tr>
<tr>
<td>Gravida†</td>
<td>2.0 (1.0–4.0)</td>
<td>2.0 (1.0–13.0)</td>
<td>0.079</td>
</tr>
<tr>
<td>Parity†</td>
<td>1.0 (0.0–3.0)</td>
<td>1.0 (0.0–5.0)</td>
<td>0.149</td>
</tr>
<tr>
<td>Abortion†</td>
<td>0.0 (0.0–2.0)</td>
<td>0.0 (0.0–7.0)</td>
<td>0.329</td>
</tr>
<tr>
<td>Body mass index (kg/m²)†</td>
<td>26.0 (22.0–32.0)</td>
<td>27.0 (18.4–38.0)</td>
<td>0.403</td>
</tr>
<tr>
<td>Gestational age at diagnosis†</td>
<td>22.0 (19.0–25.0)</td>
<td>20.0 (16.0–26.0)</td>
<td>0.041</td>
</tr>
<tr>
<td>Laterality‡</td>
<td></td>
<td></td>
<td>0.084</td>
</tr>
<tr>
<td>Unilateral</td>
<td>13.0 (40.7)</td>
<td>8.0 (20.6)</td>
<td></td>
</tr>
<tr>
<td>Bilateral</td>
<td>19.0 (59.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>31.0 (79.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetal karyotyping‡</td>
<td></td>
<td></td>
<td>0.802</td>
</tr>
<tr>
<td>Normal karyotyping</td>
<td>12.0 (100)</td>
<td>11.0 (73.3)</td>
<td>0.053</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td></td>
<td>3.0 (20.0)</td>
<td></td>
</tr>
<tr>
<td>46,XX,inv(9)(p12q13)</td>
<td>-</td>
<td>1.0 (6.7)</td>
<td></td>
</tr>
</tbody>
</table>

*Mean ± standard deviation; †Median (min–max); ‡n (%)

Gestational age at delivery was significantly lower in non-isolated PEV group compared to isolated group (p<0.001). When newborns’ birth weight, 1-minute and 5-minute APGAR scores and pH values of cord blood in the non-isolated PEV group were compared to isolated-PEV group, statistically significant reduction were found in all parameters (p<0.001 in all parameters). Neonatal intensive care unit need in the isolated PEV group was significantly lower compared to the newborns with non-isolated PEV (p<0.001). PEV anomaly was more common among male fetuses in both groups whereas there was no significant difference among the groups in terms of female-male ratio (p=0.332). Perinatal outcomes of the patients in isolated and non-isolated pes equinovarus groups are given in Table 2.

In the group complicated with isolated pes equinovarus during neonatal period, 81.2% of the newborns

Table 2. Delivery results of the groups found to have isolated and non-isolated pes equinovarus.

<table>
<thead>
<tr>
<th></th>
<th>Isolated group (n=32)</th>
<th>Non-isolated group (n=39)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age at delivery*</td>
<td>38.0 (34.0–39.0)</td>
<td>34.5 (25.0–39.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Delivery type†</td>
<td></td>
<td></td>
<td>0.583</td>
</tr>
<tr>
<td>Vaginal</td>
<td>17 (53.2)</td>
<td>10 (45.5)</td>
<td></td>
</tr>
<tr>
<td>Cesarean section</td>
<td>15 (46.8)</td>
<td>12 (54.5)</td>
<td></td>
</tr>
<tr>
<td>Birth weight*</td>
<td>3150.0 (1500.0–3900.0)</td>
<td>1565.0 (520.0–3600.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex†</td>
<td></td>
<td></td>
<td>0.332</td>
</tr>
<tr>
<td>Female</td>
<td>9 (28.2)</td>
<td>9 (40.9)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>23 (71.8)</td>
<td>13 (59.1)</td>
<td></td>
</tr>
<tr>
<td>1-minute APGAR score*</td>
<td>8.0 (6.0–9.0)</td>
<td>6.5 (1.0–8.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5-minute APGAR score*</td>
<td>9.0 (8.0–10.0)</td>
<td>7.5 (1.0–9.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cord pH*</td>
<td>7.33 (7.20–7.42)</td>
<td>7.20 (6.90–7.40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Newborn’s intense care unit need†</td>
<td>5 (15.6)</td>
<td>18 (81.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Median (min–max); †n (%)

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were treated by conservative therapy (corrective casting - Ponseti’s or Kite’s method), and this rate was 27.2% in the non-isolated group (p<0.001). In the conservative therapy, Ponseti’s method was used more frequently in both groups; surgical treatment need after conservative therapy was higher in non-isolated group compared to isolated PEV group which was statistically significant (18.8% and 72.8%, respectively; p<0.001). Posteromedial release operation was the most frequent practice in the newborns who needed surgery in both groups. Orthopedic treatment results of the patients during neonatal period in isolated and non-isolated pes equinovarus groups are summarized in Table 3.

Discussion
Mid-trimester fetal ultrasonographic imaging is routinely recommended for all pregnant women at prenatal care. In parallel to advanced ultrasonographic technologies, it has become possible to establish early diagnosis during prenatal period for many congenital malformations including fetal musculoskeletal deformities.\[12,13\] Also, it has been claimed that the use of 3D ultrasonography in prenatal ultrasonographic imaging has helped to establish early and accurate diagnosis for congenital malformations.\[14\] Although different rates are reported in various studies, the diagnosis rate of pes equinovarus during prenatal period is reported about 60%.\[15\] In our study, we found that median week of gestation when pes equinovarus was diagnosed was 22 weeks in isolated PEV cases and 20 weeks in non-isolated PEV cases. Similar to our study, Hartge et al. retrospectively analyzed the prenatal and postnatal results of 106 fetuses with congenital PEV and they reported median prenatal diagnosis time as 23 weeks for those who gave live births, and as 18 weeks in the group who were found to have many congenital malformations and gave stillbirth.\[16\] In the epidemiological case control study conducted in the USA, Mahan et al. found PEV diagnosis rate 62.3% at prenatal period even though there were different rates in various states. As a result of their multivariate analysis, they showed that maternal age <35 years, presence of concomitant congenital malformations and PEV anomaly being bilateral were the strongest predictors to establish PEV diagnosis at prenatal period.\[17\] In our study, we found concomitant congenital malformation in 54.9% of the patients diagnosed with PEV in mid-trimester ultrasonographic screening, and we observed that invasive prenatal diagnosis was established in 37.5% of the fetuses with isolated PEV and in 38.4% of the fetuses with non-isolated PEV. While there was no chromosomal alteration in cases with isolated PEV who underwent invasive prenatal diagnosis, we observed chromosomal alteration in 26.7% of the fetuses with concomitant malformation. While there are studies in the literature which define 46,XX,inv(9) (p12q13) chromosomal alteration observed in a patient in non-isolated patient group as a chromosomal polymorphism, which is clinically insignificant, there are also other studies associating this chromosomal alteration with fascial dysmorphism, neurodevelopmental retardation and congenital anomalies.\[18\] A recent study found that abnormal karyotype rate was 2.2% in isolated cases with fetuses diagnosed with congenital PEV and 30.3% in cases with concomitant malformations, and the study showed that the laterality of PEV anomaly is not associated with high chromosomal anomaly incidence.\[19\] On the other hand, the researchers reported that a detailed ultrasonographic imaging should be performed in order to identify concomitant malformations in fetuses diagnosed with PEV during congenital period, karyotyping should be recommended in the presence of concomitant

Table 3. Orthopedic results of the groups found to have isolated and non-isolated pes equinovarus.

<table>
<thead>
<tr>
<th></th>
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<th>Non-isolated group (n=22)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conservative therapy (Corrective casting)*</td>
<td>26 (81.2)</td>
<td>6 (27.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ponseti</td>
<td>19</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Kite</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Conservative + Surgical therapy*</td>
<td>6 (18.8)</td>
<td>16 (72.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Posteromedial release</td>
<td>4</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Posteromedial and lateral release</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Subtalar release</td>
<td>-</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Tibialis anterior tendon transfer</td>
<td>-</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

*n (%)
malformations, but it is controversial to recommend invasive prenatal diagnosis in isolated cases.\(^{[9,20]}\) Although it is important to establish PEV diagnosis on fetus at ultrasonographic imaging during prenatal period and to distinguish if the case is isolated or not, in terms of invasive prenatal diagnosis and informing the family about postnatal outcomes, the restrictions of ultrasonography also should be mentioned when counselling, and it should be stated to the family that concomitant findings can be identified during further weeks of gestation or postnatal period in about 10% of the cases established with isolated PEV diagnosis at prenatal period\(^{[21,22]}\).

While the treatment of pes equinovarus deformity during neonatal period may vary, conservative therapy is usually preferred in the beginning, and surgical option is considered when the cases do not respond to conservative therapy. In addition to conservative therapy which includes daily stretching exercises and French functional methods where physiotherapy and splints are used, Ponseti’s and Kite’s methods also can be used in which serial manipulation and casting are performed. Today, Ponseti’s method is the most frequent modality used in conservative therapy, and it is aimed to treat all foot deformities (cavus, varus, and adduction) simultaneously in this technique.\(^{[21,24]}\) In this method, manipulations performed on feet and ankles for 6–8 weeks are followed by long leg casting, where casts are replaced weekly. In more than 90% of the cases, the procedure of Achilles tenotomy is required, which is a minor surgical procedure performed by local anesthesia to fix equinism deformity completely, and this procedure is considered as a part of the routine therapy. At the end of the therapy, the patients are recommended to wear orthopedic boots for 23 hours a day for 3 months and then only during sleep times up until age of 4.\(^{[25]}\) In Kite’s method, each deformity of foot is fixed by biweekly manipulation and immobilization procedures one by one, and physicians do not proceed to next deformity until current one is fixed completely.\(^{[26]}\) In our study, we found that Ponseti’s method was the most common procedure in the conservative therapy performed on the cases diagnosed with isolated and non-isolated PEV in mid-trimester fetal ultrasonographic screening. While we found that the success rate of conservative therapy was 81.2% in cases with isolated PEV, significantly higher surgery need was observed in cases with concomitant malformations after conservative therapy. A recent study evaluating postnatal outcomes of fetuses with congenital PEV reported that at least one surgical procedure was needed during postnatal period in 32.6% of the cases.\(^{[16]}\)

Rijal et al. compared Ponseti’s and Kite’s methods in the conservative therapy of isolated PEV cases, and showed that Ponseti’s method provided a faster recovery in all deformities of PEV.\(^{[17]}\) He et al. compared Ponseti’s method with other conservative therapy options, and they reported that Ponseti’s method was safe and effective on PEV treatment and significantly decreased surgery needs compared to other methods.\(^{[28]}\)

Muscle, ligament or joint releases such as tibialis anterior tendon transfer and postero medial soft tissue release operations, and major surgical procedures such as wedge osteotomy are required in patients who do not respond to conservative therapy or develop relapse later despite the conservative therapy.\(^{[29,30]}\) In this study, we found that the fetuses found to have isolated PEV had significantly less major surgery needs than the fetuses found to have concomitant anomalies, and we observed that postero medial release operation was the most common procedure in the patients with surgery needs in both groups. Some of the long-term observational studies performed on the cases developing relapses in particular claimed that the success rate for the results of major surgery in such cases is not high, and that repeating conservative methods in these patients increases the treatment success.\(^{[11,12]}\)

Our study has some limitations which are the retrospective study design, being unable to determine the rate of detecting pes equinovarus since it was not possible to access neonatal outcomes of all patients who underwent mid-trimester fetal ultrasonographic screening, and long-term treatment results were not evaluated after conservative and/or surgical therapy.

**Conclusion**

Consequently, distinguishing the fetuses, which are diagnosed with pes equinovarus during prenatal period, as isolated and non-isolated cases has a critical significance in the prediction of neonatal outcomes. The incidence of chromosomal alterations and possibility of poor neonatal and orthopedic outcomes are higher in the non-isolated PEV cases. Success rate is higher by conservative methods in orthopedic treatment for the cases with isolated PEV, and surgery needs seem higher in non-isolated cases. The results of our study will help to inform pregnant women properly, who are diagnosed with isolated and non-isolated fetal pes equinovarus during prenatal period, in terms of follow-
up, treatment options and treatment outcomes during perinatal and neonatal periods.

Conflicts of Interest: No conflicts declared.

References


Prenatal diagnosis and follow-up of giant sacrococcygeal teratoma: a case report

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Abstract

Objective: To emphasize the favorable effect of elective and planned delivery of newborns with giant sacrococcygeal teratomas on neonatal outcomes.

Case: A 26-year-old, primigravid woman was admitted to hospital at 39 weeks of gestation because of severe polyhydramnios and a giant solid-cystic mass in the sacrococcygeal area of the fetus. A healthy newborn with a giant sacrococcygeal teratoma (25×25×20 cm) was delivered by cesarean section in elective conditions. On the second postnatal day, total excision of the mass was performed by pediatric surgeons. Histopathologic examination revealed mature cystic sacrococcygeal teratoma. The newborn was discharged with a well-developed scar tissue on 15th postnatal day.

Conclusion: Sacrococcygeal teratomas diagnosed in the prenatal period can reach very large sizes. Especially those without heart failure can reach up to the term. The planning of elective delivery in these cases is of vital importance in terms of reducing perinatal mortality and morbidity.

Keywords: Fetus, sacrococcygeal teratoma, ultrasonography.

Introduction

Although sacrococcygeal teratoma (SCT) is a rare tumor, it is an important cause of perinatal/postnatal mortality and morbidity. A multidisciplinary approach to determine the optimal time for surgical resection, to plan the mode of delivery, and to provide postnatal care and follow-up would minimize all these possible risks.¹

We aimed to present a case in which successful postnatal management of the fetus with a prenatally-diagnosed giant SCT was achieved by immediate postnatal excision of the mass.

Case Report

A 26-year-old primigravid woman was referred to our hospital from another healthcare center due to severe
polyhydramnios and a giant mass of the fetus which would possibly need pediatric surgery. The solid-cystic exogenous mass measured $25 \times 25 \times 20$ cm by ultrasound in the sacrococcygeal region (Fig. 1). The columna vertebralis was intact. Amniotic fluid index was measured as 35 cm and placentomegaly was noted. Arteriovenous shunting in the mass, fetal hydrops and fetal anemia were not detected as median cerebral artery (MCA) Doppler flow indices were within normal ranges (0.96 Mom). Fetal echocardiographic examination was normal and no other associated malformation was present. Fetal MRI was not planned because of the advanced gestational week. On the second day of admission, as the gestation was 39 weeks, cesarean section was performed because of the tumor size. 3900 g girl baby was delivered with an Apgar score of 8 at 1 minute and 9 at 5 minutes. A skin-covered giant mass with a diameter of 28 cm located at the sacrococcygeal region was observed at postpartum examination of the newborn (Fig. 2). Alpha-feto protein (AFP), beta-human choriogonadotropic hormone and carcinoembryogenic antigen levels were measured as 37,786 IU/mL, 30 mIU/mL and 3.2 ng/mL, respectively. Postnatal hemoglobin levels were 15.9 g/dl. Resection of the mass was planned as soon as possible before heart failure developed. After neonatal umbilical vein and radial artery catheterization, total excision of the mass, along with coccyx, was achieved without rupture, although it was strictly adherent to the rectum and had presacral involvement. The mass weighted 1900 g. During the 4-hour-operation, 20 ml/kg/h IV fluid and 15 ml/kg/h erythrocyte suspension were given to the neonate who, after the operation, was transferred to the neonatal intensive care unit with mechanic ventilation. Also with postoperative albumin, fresh frozen plasma and erythrocyte transfusions, the neonate went well hemodynamically at the early postoperative period. The neonate was extubated at 12th hour and discharged on the 15th day with a well-developed scar tissue overlying the operated sacral area.

Microscopically, the solid components were composed of a mixture of mature tissues including pancreatic tissue (Fig. 3a), peripheral nervous tissue (Fig. 3b), and stratified squamous epithelium (Fig. 3c). Based on these histopathological features the diagnosis was mature cystic SCT. Levels of highly elevated tumor markers in the preoperative period were decreased to normal levels in the 3rd month postoperatively. The follow-up visits were problem-free for 9 months as this paper was written.

**Discussion**

In the era of routine prenatal screening and improved fetal imaging using ultrasonography (USG) and magnetic resonance imaging (MRI), most SCTs are now diagnosed in utero. Close surveillance with serial ultrasonographic imaging and echocardiography is recommended.
so that fetal intervention or early delivery can be performed when necessary.\textsuperscript{(2)} There are some prognostic factors in the SCTs. One of them is tumor size. The tumor size being greater than 10 cm is especially high in vascular tumors, and these tumors, along with heart failure, increase the risk of fetal hydrops and intracranial fetal demise.\textsuperscript{(2)} Although the diameter of the tumor was 28 cm in our case, we did not detect any sign of heart failure. Gestational age is other prognostic factor. While the prognosis is poor among infants diagnosed before the 30th gestational week, the survival rate is very high among infants born just before term.\textsuperscript{(3)} The reason why such a large mass reaches to term without any complications is due to the absence of heart failure and additional organ anomalies, not ideal prenatal management. Anatomical location is important, too. Altman et al. described a four-stage classification system of SCTs according to their anatomical location which appears to be associated with overall prognosis, with best survival being in Type 1,\textsuperscript{(4)} as in our case. The incidence of various congenital malformations associated with SCTs range from 5\% to 26\%. Of these, anorectal and genital malformations are of prime concern.\textsuperscript{(5)} Other associated anomalies include spinal dysraphism, sacral agenesis, dislocation of the hips caused by a large tumor, and meningocele.\textsuperscript{(6)} Sivrikoz et al. presented an atypical presentation of a tethered spinal cord, associated with a SCT.\textsuperscript{(7)} Gothwal et al. reported a SCT associated with Prune Belly syndrome.\textsuperscript{(8)} Perrone et al. presented a SCT case with a large intraspinal component that was causing compression of the lower spinal cord.\textsuperscript{(9)} Due to the large tumor size, detailed examination and anatomical scanning with USG may not be possible in every case. Krekora et al. reported agenesis of the right forearm of a newborn, which had not been detected prenatally, despite many examinations.\textsuperscript{(10)}

In our case we performed prenatal and postnatal USG and postnatal MRI for detecting associated congenital malformations. No other malformations were detected.

The tumor size and location are essential for planning the mode of delivery in these cases. In the absence of obstetrical indications, vaginal delivery is acceptable for small tumors. Elective cesarean delivery is recommended for SCTs measuring more than 5 cm in diameter due to the risk for traumatic injury, rupture and subsequent hemorrhage from the tumor.\textsuperscript{(11)} Hemorrhage is

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{sacrococcygeal_teratoma.png}
\caption{Histopathological features. Microscopic view of sacrococcygeal teratoma at 400 magnifications with H&E stain. Pancreatic tissue (a), peripheral nerve tissue (b), and stratum squamous epithelium (c) are indicated with arrows, respectively.}
\end{figure}
the most common cause of neonatal mortality in patients with SCT. High-output cardiac failure, intratumoral hemorrhage and perioperative bleeding are the most common causes of early death and are all strongly associated with larger tumor sizes. Tumor rupture may be caused by uncontrolled labor or complications during delivery. Alani reported a ruptured giant SCT during cesarean section and its successful postnatal management. Advanced gestational age may be related the resistance of the rupture in a SCT. According to literature, upper vertical incision is usually preferred during cesarean section, as in our case. However, lower segment incision was performed in some patients because of the increased risk of bleeding and uterine scar rupture at the following pregnancies. Maturation of a SCT is related to fetal/neonatal prognosis. Mature teratomas are the most common and usually have excellent prognosis if completely excised. The surgical approach involves complete excision of the tumor including the coccyx in order to reduce recurrence, as in our case. Timing for tumoral resection in the postpartum period is important. Elective excision of the tumor is usually performed within the first few days of life. As recommended, resection was performed on the second postpartum day in our newborn. SCTs must be followed up with physical examination, USG, and MRI at the postpartum period.

Shortly, prenatal diagnosis has improved the perinatal management of these lesions that might benefit from fetal intervention. A comprehensive prenatal evaluation including conventional USG, Doppler USG, echocardiography and fetal MRI, is essential for adequate counseling and optimal perinatal management. Antenatal counseling helps the parents to better understand the natural history, fetal intervention, and perinatal management of these tumors. Fetal surgical debulking improves survival in cases of SCTs with cardiac decompensation. Additionally, the use of an EXIT procedure reduces the morbidity and mortality in a complicated delivery in cases with cervical and mediastinal-teratomas. Conditions amenable to intrauterine surgical treatment are rare; the mother may consider termination of pregnancy as an option. Fetal treatment can be lifesaving but it carries risks to both the infant (preterm premature rupture of the membranes, preterm delivery) and the mother. One of the prenatal therapeutic options is to occlude the feeding vessels by radiofrequency ablation, but it has not been accepted as a routine approach because of high mortality at term.

Conclusion
The aim of this paper was to present a giant mature SCT managed successfully without any pregnancy complications. A multidisciplinary approach is crucial for SCT cases in both prenatal and postnatal periods.

Conflicts of Interest: No conflicts declared.

References


Long QT syndrome diagnosed by premature atrial extrasystoles: a case report

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Introduction

Long QT syndrome (LQTS) is an inherited syndrome with an autosomal transmission.¹⁵ Prolonged QT interval on electrocardiogram (ECG), family history, symptoms of arrhythmia were used to as diagnostic criteria. LQTS is defined in neonates,¹⁶ but there are few cases reported for intrauterine period.¹⁷,¹⁸ Prenatal diagnosis of LQTS is rare, particularly in the lack of family history.¹⁹ We described a case of sporadic LQTS who presented with premature atrial extrasystoles during antenatal period.

Case Report

27-year-old primigravid woman at 29 weeks of gestation was referred to our clinic at 29 weeks of gestation due to marked fetal arrhythmia. Premature atrial extrasystoles were detected during the prenatal period. The QT interval was 500 msec in the postnatal period. So the case was diagnosed as long QT syndrome associated with premature atrial extrasystoles.

Abstract

Objective: We aimed to present a case that was prenatally diagnosed as fetal arrhythmia due to premature atrial extrasystoles but turned out to be long QT syndrome at postnatal period.

Case: A 27-year-old primigravid woman was referred to our clinic at 29 weeks of gestation due to marked fetal arrhythmia. Premature atrial extrasystoles were detected during the prenatal period. The QT interval was 500 msec in the postnatal period, So the case was diagnosed as long QT syndrome associated with premature atrial extrasystoles.

Conclusion: Premature atrial extrasystoles are easily recognized and generally presented as an isolated rhythm disorder. But the minority of cases is associated with serious arrhythmia such as long QT syndrome. This lethal condition should be considered in the differential diagnosis to predict the potential risks for the fetus and neonate.

Keywords: Fetal arrhythmia, long QT syndrome, premature atrial extrasystole.

Özet: Prematür atriyal ekstrasistoller ile tanınan uzun QT sendromu: olgu sunumu

Amaç: Prematür atriyal ekstrasistoller nedeniyle perinatal fetal aritmii olarak tanılan ancak postnatal dönemde uzun QT sendromu olduğu görülen bir olguyu sunmayız.


Anahtar sözcükler: Fetal aritmi, uzun QT sendromu, prematür atriyal ekstrasistol.
These findings were evaluated as conduction atrial bigeminy (Fig. 1). There were no evidence of congestive heart failure and structural abnormalities. The parents’ medical history was clear of any arrhythmic syndrome and their physical examination was normal. Parental QT intervals on ECG were assessed to check the possibility of the LQTS and they did not have long QT intervals (<480 msec). No additional fetal anomalies were found in the genetic sonogram. Starting from the diagnosis at 29th week the patient was followed by weekly fetal echocardiography. During the antenatal period premature atrial extrasystoles were detected without other rhythm disorders and congestive heart failure. Cesarean section was performed at 38 weeks and 2 days because of the prior cesarean section history and fetal growth restriction. A 2540 g male neonate was delivered. Echocardiography was performed after birth. A very long QT interval of 500 msec was found on ECG in the neonate (Fig. 2). As a result, the neonate was diagnosed as LQTS and followed-up due to risk of sudden infant death. He remained asymptomatic for 4 months. No medical treatment was required during postnatal period. The parents rejected any offers of genetic evaluations.

Discussion

Arrhythmias are detected in at least 2% of all pregnancies. The fetal heart should be examined carefully in the antenatal period. In our case, we described a fetus presented with premature atrial extrasystoles in utero and in whom LQTS was diagnosed in the postnatal period. Congenital LQTS is a heritable ion channel disorder that is associated with the impairment of number of genes encoding for the transmembrane sodium or potassium ion channel proteins. Mutations in six subtypes (LQT1 to LQT6) are responsible of the impairment of the ion channels leading to prolonged action potentials that are account for congenital long QT.

These mutations slow the inactivation of inward depolarizing sodium currents or cause retardation of outward repolarizing potassium currents. Long QT interval was diagnosed by using fetal magnetocardiography and fetal ECG in prenatal period. Among all cases of sudden infant death syndrome, 50% underlying risk factor is LQTS. The prognosis of LQTS is not good when detected in the prenatal period or during the first week of life. Fetal diagnosis of a prolonged QT has been recognized as early as 16 weeks of gestation. In a systematic review, 21 fetuses with LQTS were doc-
mented with significant in utero cardiac findings. 16 fetuses (76%) exhibited bradycardia ≤110 bpm; 4 of them (19%) exhibited ventricular tachycardia or tachyarrhythmia, and one case exhibited pleural effusion. Eleven fetuses (52%) exhibited atrioventricular block (AVB) in prenatal and postnatal period. 4 fetuses (19%) exhibited mild bradycardia ranging from 100 to 110 bpm and reduced baseline fetal heart rate (FHR) variability on cardiotocography. So, as result of AVB sinus bradycardia and fetal bradycardia can be seen fetuses with LQTS. Cuneo et al. detected isolated extrasystoles and AVB in 97.4% and 2.6% of the fetuses, respectively. We detected isolated premature atrial extrasystoles in our case, too. Some fetuses with LQTS show tachyarrhythmia, and one case exhibited pleural effusion. Furthermore, some patients with LQTS were presented with a FHR of 110–120 bpm; 4 of them (19%) exhibited ventricular tachycardia or tachyarrhythmia. The underlying pathologies may not be considered in differential diagnosis. With no family history of arrhythmia and syncope it may not be considered in differential diagnosis. With this case, we tried to emphasize the necessity of conducting antenatal and postnatal investigations considering the possibility of sporadic cases in pregnant women who have applied with fetal arrhythmia. Thinking of long QT syndrome as a differential diagnosis in fetal arrhythmia will help to notice the possible complications that may develop in neonate.

As a result, detection of a fetal arrhythmia is not adequate for prenatal follow-up; it is also necessary to identify the type of arrhythmia. The underlying pathologies such as the LQTS that may accompany arrhythmias should always be investigated. Especially, in sporadic cases with LQTS, prenatal diagnosis is important for both the fetus and the neonate. LQTS can be diagnosed with ECGs and genetic tests during prenatal investigations. So, the incidence of “sudden infant death syndrome” can be decreased with the help of these investigations.

**Conclusion**

The fetal echocardiography does not detect the QT interval. So, we should think about possibility of LQTS in fetal arrhythmias.

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

**References**

**Letter to the Editor** regarding “The impacts of placental localization and fetal sex on the estimation of fetal weight”

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Dear Editor,

We have read the article of Çintesun et al. with the title of “The impacts of amniotic fluid index, placental localization and fetal sex on the estimation of fetal weight” with a great interest. We would like to contribute to this article by analyzing the impacts of placental localization and fetal sex on the estimation of fetal weight in patients delivered in our clinic.

The records of the patients who delivered at the Gynecology and Obstetrics Clinic of Gülhane Training and Research Hospital between June 1 and November 15, 2017 were analyzed retrospectively. The method of measuring fetal weight and inclusion criteria were determined similar to the related study. The measurements were done by using the same ultrasonography device (SIUI, Shantou Institute of Ultrasonic Instruments Co., Ltd., Shantou, China).

A total of 257 patients were included in the study. In the statistical analyses, number, percentage, arithmetic mean and standard deviation were used for the distributions of data, and Kruskal-Wallis and Mann-Whitney U tests were used for statistical comparisons. In this study, mean age was 29.26±5.5 years, gravid median was 2, parity mean was 1, and weeks of gestation were 39.1 (range: 35 to 42). It was found in the patients that cesarean section was 39.68%, normal delivery rate was 60.31%, mean ultrasonographic estimation of fetal weight was 3261.08±4.81 g, and mean birth weight was 3338.48±4.84 g. The demographic and clinical data of the patients are shown in the **Table 1**. Similar to the study of Çintesun et al., we calculated error percentage in ultrasonographic estimation of fetal weight measurement, and considered it as “weight deficit”. Total weight deficit in all patients was -1.69%. While the deficit was -7.57% in females, it was 2.85% in males (**Table 2**). Our results are different than...
those found by Çintesun et al. We believe that the difference results from different characteristics of the population included (BMI, amniotic fluid indexes etc.), and different specialists measuring the ultrasonographic estimation of fetal weight. In terms of deficit percentages, we observed no significant difference between two sex groups in our study. This difference is greater for female fetuses. Also, as reported in the study mentioned above, we found no significant correlation between placental localization and ultrasonographic estimation of fetal weight. In terms of deficit percentages, we observed no significant difference between two sex groups in our study. This difference is greater for female fetuses. Also, as reported in the study mentioned above, we found no significant correlation between placental localization and ultrasonographic estimation of fetal weight.

In terms of weight deficit according to the placental localization, we observed no significant difference between the groups in our study. According to our results, the lowest weight deficit was in fetuses with anterior placental localization. It is anticipated in the literature that the placental localization may affect the accuracy of ultrasonographic estimation of fetal weight; however, the studies have shown that placental localization does not affect ultrasonographic estimation of fetal weight measurement.  

During gestational follow-ups, the estimation of fetal weight is the most common procedure in the daily obstetric practice. The accurate estimation of fetal weight ensures proper guidance for various matters from determining the delivery type to the skin incision during cesarean section and episiotomy length. It is reported in the literature that there are many factors affecting ultrasonographic estimation of fetal weight such as fetal presentation, amniotic fluid index, fetal sex, and maternal body mass index. In this study, we assessed the impacts of placental localization and fetal sex on ultrasonographic estimation of fetal weight. In line with the data we have obtained, we have concluded that both parameters have no impact on ultrasonographic estimation of fetal weight.

Conflicts of Interest: No conflicts declared.

References
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