Cleft Lip With or Without Cleft Palate: Prenatal Diagnosis, Chromosomal Abnormalities, Associated Anomalies and Postnatal Outcome in 18 Fetuses

Cem BATUKAN¹, Mahmut T. ÖZGÜN¹, Mustafa BAŞBUĞ¹, Hülya AKGÜN²
Kayseri-Turkey

OBJECTIVE: The aim of this study was to present our experience with prenatal diagnosis of cleft lip and/or palate (CL/P) and to determine the relationship between facial clefts, associated malformations and chromosomal anomalies.

STUDY DESIGN: Data of 18 fetuses with prenatally diagnosed CL/P were retrospectively analyzed. Postnatal outcome and incidence of additional malformations and chromosomal abnormalities were determined.

RESULTS: Postnatal findings confirmed that the type of cleft was median CL+P (n=3), bilateral CL+P (n=5), unilateral CL+P (n=5), unilateral CL (n=5). Eight cases were diagnosed at or before 24 weeks of gestation. Eleven fetuses (%61) had additional structural anomalies. Abnormal fetal karyotype was present in 5 fetuses (two cases with trisomy 13 and three cases with trisomy 18). All fetuses with isolated CL/P survived after surgery. Termination of pregnancy was requested in nine fetuses with additional anomalies and/or chromosomal anomalies, whereas one each of the fetuses died in utero or early neonatal period.

CONCLUSION: In pregnancies complicated with CL/P, patients should be informed about the risk of associated anomalies, chromosomal abnormalities and syndromic conditions.

(Ogyecol Obstet Reprod Med 2007;13:1 4-8)

Key Words: Cleft lip/palate, Associated anomalies, Fetus, Ultrasound, Prenatal diagnosis

Orofacial clefting represents one of the most commonly occurring congenital anomalies detectable by prenatal ultrasound. The incidence of facial clefts is approximately 1 in 500-1000 live births.¹ This anomaly is attributed to failure of nasal and maxillofacial process to fuse during embryogenesis. The cleft lip with or without cleft palate (CL/P) may be isolated without any additional anomalies or be one component of syndromes, chromosomal abnormalities or multiple congenital malformations. The rate of associated structural anomalies and syndromes for CL/P has been reported between 21-38%.²,³ However, the prevalence of fetal facial clefting changes with different stages of pregnancy, because the rate of spontaneous abortion is increased due to high incidence of chromosomal abnormalities and other fatal malformations. Some of these fetuses either die in utero or are aborted. Therefore, fetuses with prenatally identified CL/P represent significantly a different group of patients from the affected neonates.

Ultrasoundography is a valuable tool for the prenatal diagnosis of CL/P and for the assessment of its extent. Because the prognosis is directly related to associated anomalies and any underlying condition or chromosomal abnormality, it is important to determine the presence of additional malformations. Therefore, the prenatal ultrasound findings are of paramount importance for prenatal counseling and the planning of obstetric and neonatal treatment.

We report a retrospective study of prenatally diagnosed cases with CL/P at our tertiary referral center over a period of five years. The associated anomalies, abnormal karyotypes and neonatal outcome were also documented.

Material and Methods

A total of 18 fetuses with CL/P, diagnosed by prenatal ultrasound at the University of Erciyes, Faculty of Medicine Hospital, Department of Obstetrics and Gynecology, between January 2001 and December 2006, were included in this retrospective analysis.

All ultrasound examinations were performed transabdominally by either one of three operators (MB, CB, MTO) using a 3.5-MHz linear-array transducer GE Logiq 500 Pro (3.5-MHz linear-array transducer) which has 2D and Doppler facilities or a GE Voluson 730 (4.5-7.5 MHz linear-array transducer) which has 2D, 3D, 4D and Doppler facilities. The integrity of fetal lip was assessed via analysis of coronal, axial and sagittal view of the face. The fetal primary palate was evaluated using the axial image planes through the upper lip and anterior tooth-bearing alveolar ridge; especially, the tooth germs were evaluated for continuity. The 3D ultrasound exam-
ination was performed using a GE Voluson 730 by one of the authors (MB), which included acquisition of the fetal face images with the use of both the multiplanar imaging and surface rendered views. Volume images were obtained of the fetal face in the axial, coronal and sagittal planes. The coronal, profile, and axial views were reviewed alongside the volume-rendered images. The nature of the CL/P and associated anomalies were documented during ultrasonography.

The parents were counseled about the increased risk of chromosomal abnormality associated with CL/P and karyotyping was performed either by prenatal invasive tests or via postnatal blood or skin fibroblast culture in all cases.

The outcome data concerning the presence or absence of a CL/P and/or any other structural and chromosomal abnormalities were determined by a variety of methods, including a review of autopsy reports, postnatal chart reviews and contact with the families.

As this was a descriptive study, data were shown as mean ± standard deviation (min-max) and n(%).

Results

This report included 18 cases of prenatally diagnosed CL/P. Mean gestational age at the time of diagnosis was 25.7±7.3 weeks (15-40). A total of 8 (44%) cases were diagnosed at 24 weeks of gestation or earlier, whereas the remaining 10 cases were diagnosed beyond 24 weeks. The patient characteristics, type of clefts, associated anomalies, fetal karyotypes, pregnancy outcomes and indication of the referral were summarized in Table 1.

Table 1. Patient characteristics, type of CL/P, associated anomalies, pregnancy outcome and indication for the referral

<table>
<thead>
<tr>
<th>Case</th>
<th>Maternal age (Years)</th>
<th>GA at diagnosis (weeks)</th>
<th>Karyotype</th>
<th>Type of cleft</th>
<th>Associated anomalies</th>
<th>Outcome</th>
<th>Indication for the referral</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>30</td>
<td>Normal</td>
<td>Median CL+P</td>
<td>Holoprosencephaly</td>
<td>IUD</td>
<td>CNS anomaly</td>
</tr>
<tr>
<td>2</td>
<td>26</td>
<td>26</td>
<td>Normal</td>
<td>Unilateral CL+P</td>
<td>Skeletal dysplasia</td>
<td>TOP</td>
<td>Other anomaly</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>34</td>
<td>Normal</td>
<td>Unilateral CL</td>
<td>Crouzon Syndrome</td>
<td>A&amp;W</td>
<td>CL/P</td>
</tr>
<tr>
<td>4</td>
<td>19</td>
<td>16</td>
<td>Normal</td>
<td>Bilateral CL+P</td>
<td>None</td>
<td>TOP</td>
<td>Other anomaly</td>
</tr>
<tr>
<td>5</td>
<td>18</td>
<td>18</td>
<td>Normal</td>
<td>Unilateral CL</td>
<td>Multiple anomaly Syndrome</td>
<td>TOP</td>
<td>Other anomaly</td>
</tr>
<tr>
<td>6</td>
<td>20</td>
<td>20</td>
<td>Normal</td>
<td>Median CL+P</td>
<td>Holoprosencephaly</td>
<td>TOP</td>
<td>Other anomaly</td>
</tr>
<tr>
<td>7</td>
<td>19</td>
<td>19</td>
<td>Trisomy 18</td>
<td>Bilateral CL+P</td>
<td>Multiple anomaly</td>
<td>TOP</td>
<td>Other anomaly</td>
</tr>
<tr>
<td>8</td>
<td>35</td>
<td>35</td>
<td>Trisomy 13</td>
<td>Bilateral CL+P</td>
<td>None</td>
<td>TOP</td>
<td>Other anomaly</td>
</tr>
<tr>
<td>9</td>
<td>29</td>
<td>29</td>
<td>Normal</td>
<td>Unilateral CL+P</td>
<td>None</td>
<td>TOP</td>
<td>Other anomaly</td>
</tr>
<tr>
<td>10</td>
<td>28</td>
<td>28</td>
<td>Normal</td>
<td>Unilateral CL</td>
<td>Multiple anomaly Syndrome</td>
<td>TOP</td>
<td>Other anomaly</td>
</tr>
<tr>
<td>11</td>
<td>19</td>
<td>15</td>
<td>Trisomy 13</td>
<td>Bilateral CL+P</td>
<td>Multiple anomaly</td>
<td>TOP</td>
<td>Other anomaly</td>
</tr>
<tr>
<td>12</td>
<td>19</td>
<td>19</td>
<td>Normal</td>
<td>Unilateral CL+P</td>
<td>None</td>
<td>TOP</td>
<td>Other anomaly</td>
</tr>
<tr>
<td>13</td>
<td>30</td>
<td>30</td>
<td>Normal</td>
<td>Unilateral CL</td>
<td>Multiple anomaly Syndrome</td>
<td>TOP</td>
<td>Other anomaly</td>
</tr>
<tr>
<td>14</td>
<td>26</td>
<td>26</td>
<td>Normal</td>
<td>Unilateral CL</td>
<td>None</td>
<td>TOP</td>
<td>Other anomaly</td>
</tr>
<tr>
<td>15</td>
<td>31</td>
<td>34</td>
<td>Normal</td>
<td>Unilateral CL+P</td>
<td>Multiple anomaly</td>
<td>TOP</td>
<td>Other anomaly</td>
</tr>
<tr>
<td>16</td>
<td>20</td>
<td>20</td>
<td>Trisomy 18</td>
<td>Median CL+P</td>
<td>None</td>
<td>A&amp;W</td>
<td>CL/P</td>
</tr>
<tr>
<td>17</td>
<td>40</td>
<td>40</td>
<td>Normal</td>
<td>Unilateral CL+P</td>
<td>Multiple anomaly</td>
<td>A&amp;W</td>
<td>CL/P</td>
</tr>
<tr>
<td>18</td>
<td>39</td>
<td>24</td>
<td>Trisomy 18</td>
<td>Bilateral CL+P</td>
<td>None</td>
<td>TOP</td>
<td>Other anomaly</td>
</tr>
</tbody>
</table>

GA, gestational age; CL, cleft lip; CL+P, cleft lip and palate; IUD, intruterine death; TOP, termination of pregnancy; A&W, Alive and well

Prenatal ultrasound revealed that seven (39%) of these 18 fetuses had isolated CL/P. In 11 fetuses additional structural anomalies, including 5 fetuses with an abnormal karyotype (two cases of trisomy 13 and three cases of trisomy 18), were apparent. The type of cleft was median CL and P (n=3), bilateral CL and P (n=5), unilateral CL and P (n=5) and unilateral CL (n=5) (Figure 1). Postnatal findings confirmed the sonographic diagnosis in all cases. Postnatal examination revealed no unrecognized anomalies in cases with prenatally diagnosed isolated CL/P.

Figure 1. Coronal view of a fetus at 28 weeks of gestation showing isolated cleft lip and palate (arrow).

The indications for referral for fetal ultrasonography included anomalies other than CL/P detected during a routine prenatal scan (n=11) and CL/P detected in referral centers and send for second opinion (n=7). All newborns with isolated CL/P (n=7) survived and subsequently underwent successful
surgical repair. In cases associated with other malformations (n=11), 9 couples opted for termination of their pregnancies, one fetus died in utero and one newborn with trisomy 13 died in the neonatal period. The overall survival rate for prenatally detected CL/P was 39%.

Three-dimensional ultrasound was performed in five cases (Figure 2), which confirmed the diagnosis made by 2D ultrasound and all these examinations revealed no additional anomalies. The remaining 13 cases were evaluated by 2D ultrasound only. Both 3D and 2D examination of the face was satisfactorily performed within a few minutes. However, 3D images had advantages over 2D images during prenatal counseling because the couples did understand the defect more realistically than with 2D images (Figure 3).

Figure 2. 3D surface rendering mode of the same fetus in figure 1.

Figure 3. Postnatal appearance of the same fetus in figure 1 and 2. Note that 3D ultrasound generated realistic images which can be very helpful when explaining the nature of the anomaly to the parents.

There were no false-positive diagnoses of CL/P in the present study. However, it was not possible to obtain postnatal information for all fetuses scanned at the referring centers, so we were unable to determine the false-negative rate of prenatal ultrasound in detecting CL/P.

Discussion

Prenatal ultrasound is a valuable tool for detecting fetal malformations and is a part of routine antenatal care in many countries. Since the first report concerning prenatal detection of CL/P by Christ and Menieger in 1981, prenatal diagnosis of CL/P has gained increasing interest. With the advent of ultrasound technology, we were able to identify major facial anomalies as early as 15 weeks (case 11), when it is ideal for the performance of karyotyping by chorionic villus sampling or amniocentesis as well as search for associated anomalies can be made. It also provides an appropriate period to discuss termination of pregnancy with the couple, when an additional major defect or abnormal karyotype is identified. Moreover, in the literature, prenatal diagnosis of CL/P has been reported even in the first trimester.

It has been well documented that CL/P is frequently associated with other fetal malformations. Fetuses with CL/P and an additional anomaly are associated with poor outcome not only in utero, but also in neonatal period. Nyberg and et al. reported that 47.5% of 40 infants with CL/P have other anomalies. In a retrospective review of 4180 patients, multiple anomalies were detected in 35% of patients with CL/P. Additionally, Chmait and coworkers reported that 35.6% of 45 fetuses with CL/P had an additional anomaly. The rate of additional malformations in our study group was 61%. This higher rate may be explained by the fact that the patient population consisted of prescreened fetuses with a suspected anomaly other than CL/P, which increases the risk that the fetus will also have a CL/P. CL/P could not be detected in 61% of our patients during routine prenatal ultrasound examination at the referring center. In this group, CL/P was identified only following recognition of other extra-facial anomalies. We speculate that some of the cases with isolated CL/P may have not been diagnosed at the referring centers; this may explain the higher rate of additional anomalies in our series.

Actually, the sensitivity of prenatal ultrasound for detecting isolated facial clefts is low and this is a worldwide problem. A multi-centre study, which included 366 isolated CL/P cases, has shown that prenatal ultrasound detected only 14% of the isolated cases. While most studies have poor antenatal detection rates, which fall between 16% and 33%, only two studies reported higher sensitivities. Pilu et al. detected antenatally 57% of 14 referred fetuses with isolated CL/P. Wayne and coworkers reported in their study that the sensitivity of antenatal detection for isolated CL/P was 75% in a routine obstetric population. However, these authors stated that they performed routine facial evaluation during a routine anomaly scan. The use of transvaginal scan may increase the sensitivity; Bronstein et al. detected 11 out of 12 affected fetuses.
using transvaginal sonography.

Another important problem with the prenatal diagnosis of CL/P is late antenatal diagnosis. In the literature, many reports include cases with CL/P diagnosed near term, as our study did.\textsuperscript{5,10,11,14,15} This may cause considerable inconvenience regarding fetal cytogenetic evaluation, prenatal counseling and discussing the option on termination of pregnancy with the couple, when an associated severe malformation or abnormal karyotype is identified. There was such a case (case 8) in our series. CL/P was diagnosed at 35 weeks of gestation and cordocentesis revealed Trisomy 13. The proband died in the early neonatal period. In this case, termination of pregnancy would have been justified when the abnormal karyotype could be diagnosed much earlier, preferably before fetal viability. Although it is obvious that meticulous scanning with transvaginal ultrasonography may contribute to an earlier diagnosis,\textsuperscript{6} it is questionable whether this form of examination would be practical in busy antenatal care units and acceptable for the patients. Furthermore, the fetal face may not be accessible with the transvaginal probe if the fetus is in breech presentation.

Approximately 350 syndromes have been linked with facial clefting.\textsuperscript{16} There were a fetus with Crouzon syndrome and another fetus with amniotic bands syndrome in our series. The empirical recurrence risk for a non-syndromic fetal CL/P is approximately 4\% if the family history is negative for an oral cleft.\textsuperscript{10} Recurrence risk for syndromic causes is specific to the diagnosis. Therefore, as CL/P associated with certain syndromes may have a higher recurrence risk, which has obviously important implications on reproductive counseling. Nyberg et al.\textsuperscript{8} and Berge et al.\textsuperscript{5} demonstrated that the type and extension of cleft correlates with fetal outcome and associated anatomical and chromosomal anomalies. Our results are in concordance with these findings. None of the fetuses with cleft lip (without cleft palate) had additional anomalies and all survived. However, the fetuses with median clefts had additional anomalies which carried a dismal prognosis. Two fetuses with median clefts had holoprosencephaly and the other had trisomy 18.

Nyberg et al.\textsuperscript{8} documented that 22\% of 40 infants with CL/P was associated with an abnormal karyotype. Chromosomal abnormalities were found in 5 (28\%) of the cases. All fetuses with an abnormal karyotype had also other additional anomalies. Our findings of trisomy 13 in two cases and trisomy 18 in three cases indicate that cytogenetic evaluation is necessary when a facial cleft antenatally diagnosed, especially when it coincides with additional malformations.

Some studies investigated the role of 3D ultrasound in the diagnosis of facial clefts. Chen et al.\textsuperscript{17} reported a series of 21 cases with CL/P. The diagnosis was certain in 72\% cases using 2D ultrasound, however the accuracy was 100\% using 3D ultrasound. Johnson et al.\textsuperscript{18} showed an increase in the number of correct diagnoses from 48\% of cases with 2D to 76\% when 3D ultrasound was used. They reported three false positives with 2D ultrasound. Our results differ in that, 2D ultrasound provided no false positive results and accurately identified palatal involvement in all cases. In a subgroup of our series we also performed 3D ultrasound examination but this technique failed to add any new information to the 2D scan. However, our experience is in accordance with previous studies that reported a high level of accuracy of 2D ultrasound. Nyberg et al.\textsuperscript{8} demonstrated a series of 65 cases with CL/P with no positives and accurately classified in 63/65 cases. Bronshein et al.\textsuperscript{6} diagnosed 11 cases out of 12 fetuses with CL/P without any false positives. Berge et al.\textsuperscript{5} reported a total of 70 fetuses with CL/P with precise diagnoses. Ghi et al.\textsuperscript{14} also failed to demonstrate an advantage of 3D ultrasound over 2D ultrasound in the diagnosis and classification of clefts in 37 fetuses with CL/P.

In conclusion, we emphasize that fetal facial examination should be an integral part of prenatal ultrasound studies. A detailed search for other anomalies should be performed, when a facial cleft is diagnosed. As the risk of chromosomal abnormalities is higher in the presence of a facial cleft, cytogenetic evaluation should be considered even in isolated cases. Knowledge of an abnormal karyotype, an associated anomaly or a syndrome is useful in planning obstetric management and during prenatal counseling. The prognosis is usually favorable when a cleft is not associated with an abnormal karyotype, a syndrome or an additional malformation. In our experience, the accuracy of conventional 2D ultrasound was very high and was not increased by the use of 3D ultrasound.

**References**


