Pregnancy with Facial Cleft: 20 Years of Experience at a Single Center

Marina Pekar-Zlotin MD, Natali Zilberman Sharon MD, Yaakov Melcer MD, Yael Tal-Bliman MD, Jodi Ezratty MD, Michal Feingold-Zadok MD, Ran Svirsky MD, and Ron Maymon MD

Department of Obstetrics and Gynecology, Shamir Medical Center (Assaf Harofeh), Zerifin, Israel, affiliated with Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

ABSTRACT **Background:** Fetal facial clefts are among the most common congenital anomalies detected prenatally. This finding may lead to termination of pregnancy in some cases.

Objectives: To compare a cohort of fetuses with facial clefts in which the pregnancy was terminated to the cohort of cases that were born with facial clefts. To investigate risk factors for facial clefts.

Methods: We conducted a retrospective chart review of all women with prenatal and postnatal diagnosis of facial cleft that were managed in our institute. A telephone questionnaire was conducted regarding a positive family history and/or genetic predisposition for facial clefts abnormalities.

Results: The final cohort consisted of two group. One group included 54 cases of termination of pregnancy (TOP) that were performed due to cleft lip (CL) or cleft palate (CLP); 27 women answered the telephone questionnaire. The second group comprised 99 women who delivered children with facial cleft during the same period; 60 answered the questionnaire. Only seven cases were diagnosed prenatal. Among the two groups, no correlation to family history was discovered. Of note, there was one case of three consecutive fetuses with CL in one woman, without any significant genetic findings.

Conclusions: To the best of our knowledge, this is the first study to describe an anatomical malformation posing an ethical dilemma before TOP. Primary prevention with folic acid and early sonographic detection of CL/CLP with multidisciplinary consultation should be considered.

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KEY WORDS: cleft lip (CL), cleft palate (CLP), termination of pregnancy (TOP), congenital malformation

The embryology of the lips and palate is complex and begins as early as 4 weeks after fertilization. The primary palate fuses between 4 and 6 weeks of gestation, and the secondary palate is formed between 8 and 12 weeks. Cleft lip (CL) is the result of failure of the maxillary process to fuse with the medial nasal prominence. CL is most commonly unilateral and may be associated with a cleft of the ipsilateral alveolus [1].

Fetal facial clefts are among the most common congenital anomalies recognized during the prenatal period. The prevalence of CL and cleft palate (CLP) is 1:500–1:1000 [2]. Isolated clefts are mainly a functional and aesthetic complication, with low perinatal mortality and morbidity. Complicated clefts that involve the alveolus or the palate are associated with a significantly worse prognosis, requiring a larger number of surgical corrective procedures in the postnatal period. This situation may lead to considerable morbidity, pose a substantial financial burden on families, and have social consequences [3].

Advances in medical technology and the introduction of routine prenatal scanning and screening allow for early diagnosis of various fetal abnormalities throughout the different stages of pregnancy. The early anatomy scan at 14–16 weeks of gestation can identify facial abnormalities in most cases. However, in rare examples, anomalies are seen only later in pregnancy at around 21–24 weeks gestation, thus possibly leading to late termination of pregnancy (TOP).

Considering the potentially high morbidity of facial clefts, as well as the fact that CL may be a sign of other potential underlying genetically and anatomically associated abnormalities, prenatal diagnosis is of the utmost importance for assessing prognosis and providing counseling for future parents.

There are a few known risk factors for CL/CLP. They include cigarette smoking, advanced maternal age, genetic predisposition, and socioeconomic factors. Non-syndromic CL and CLP can be commonly found in cousins. However, most cases occur with no positive family history. Studies have suggested that oxidative stress in neural crest cells may predispose the development of facial clefts. Consequently, the anti-oxidative activity of folic acid may have protective effects against the development of these anomalies [4-11].

In this study, we compared a cohort of fetuses with facial clefts undergoing pregnancy termination to the cohort of cases that were born with facial clefts. In the second group most cases were undiagnosed during pregnancy. In addition, we investigated risk factors for facial clefts. To the best of our knowledge, this study is the first cohort describing pregnancy termination due to facial clef in the English literature.

PATIENTS AND METHODS

The standard of prenatal testing in Israel is well-established and was previously described by Feldman and co-authors [13]. In short, nuchal translucency (NT) scan combined with biochemical screening, triple test, and mid-gestation anatomy scans are offered as routine screening for pregnant women. Genetic disease screening is offered according to the couple's ethnic origin. Cell free fetal DNA as well as early (14–16 weeks gestation) and third trimester anomaly scans (28–32 weeks gestation) are only performed in the private sector [12,13].

Our medical center serves as a tertiary referral center for pregnant women with suspected severe fetal abnormalities. We offer TOP via dilation and curettage (D&C) until 24 weeks of gestation [12-19].

We conducted a retrospective study by reviewing the medical charts of all women with fetuses diagnosed with CL/CLP during pregnancy and after delivery during a period of 20 years. The medical charts were reviewed for demographic and background medical information including maternal age, mode of conception, obstetric history, sonographic findings, and gestational age at the time of the diagnosis of fetal anomalies and at the time TOP was executed. Among the total cohort, those women who underwent TOP due to facial clefts as a single finding in a singleton pregnancy were identified and recorded. We also retrieved all cases of women delivering a child with a facial cleft at our institute during this period. In this study, we compared two groups: one in which a termination of pregnancy was performed due to a prenatal diagnosis of the malformations and the other in which children were born and diagnosed with facial clefts.

All cases diagnosed prenatally underwent primary consultation with a plastic surgeon and an otolaryngology specialist. The decision to terminate pregnancy or to continue the pegnancy was decided by the couple after learning the predicted prognosis of the finding, pending committee approval. Early TOPs (≤ 24 weeks gestation) are approved by an institutional committee. Whereas only a regional supreme committee is authorized to approve late TOPs occurring at gestational ages after 24 weeks [17].

We specifically excluded TOPs performed because of multisystem defects, involvement of other fetal organs, and abnormal karyotype and genetic defects.

We then subdivided the cohort of pregnancies that elected termination to two groups, early termination (< 24 weeks gestation) and late TOP (≥ 24 weeks gestation).

TELEPHONE QUESTIONNAIRE

A telephone questionnaire was conducted for all women from the two final study cohorts. The questionnaire consisted of items to determine a family history and genetic predisposition to facial cleft abnormalities. The questions included medical history, habits, use of supplements, gynecological history, use of medication during pregnancy or exposure to teratogenic agents. Relevant family history, and a history of family members with facial clefts. The relevant exams conducted during pregnancy, the week of diagnosis and TOP, and genetic work-up including chromosomal microarray analysis (CMA), were conducted.

Two-dimensional (2D) and three-dimensional (3D) ultrasound imaging scans were performed with either a 2–5 MHz curvilinear abdominal transducer or a 5–9 MHz transvaginal probe from different manufacturers. All ultrasound evaluations were conducted by ultrasound specialists from the Shamir ultrasound unit.

The study was approved by an institutional review board (Helsinki number 0104-18-ASF-52414). Statistical analyses were performed in the statistical laboratory at Tel Aviv University, Israel, using IBM Statistical Package for the Social Sciences statistics software, version 21 (SPSS, IBM Corp, Armonk, NY, USA). Continuous variables are presented as the mean ± standard deviation. Frequencies are presented as percentages. *P*-values of < 0.05 were considered statistically significant.

RESULTS

The final cohort consisted of two group. One group included 54 TOP that were performed due to CL or CLP; 27 women answered the telephone questionnaire. The second group comprised 99 women who delivered children with facial cleft during the same period; 60 answered the questionnaire.

Of the neonates born with CL/CLP, most were diagnosed postpartum. A facial cleft was suspected in only seven cases during conventional antenatal ultrasound scans. In those cases, sonographic diagnosis matched postnatal findings. Accordingly, most did not perform expanded genetic evaluation or a targeted sonographic scan. Table 1 shows the characteristics of the two groups.

A total of 3469 TOP procedures due to fetal indications were performed at our institute during the study period (1998–2017). TOP due to CL/CLP group represented 1.6% of the total performed at our institution. Forty-eight (88%) of the

Table 1. Comparison of the termination of pregnancy group and the cases that were discovered after delivery

	Aborted (n=54)	Delivered (n=99)
Age of mother, in years	31.87 ± 4.96	28.87 ± 4.9
Gravity	2 ± 1.52	2 ± 1.01
Parity	1 ± 1	1 ± 0.95
Diagnosis week	17.29 ± 3.06	Most cases undiagnosed
Termination week	18.7 ± 3.2	

cases were diagnosed before 24 weeks of gestation. Six (11%) cases were diagnosed after 24 weeks of gestation and eventually ended in late TOP. Four of the late TOPs did not undergo NT scanning, and two had a normal NT. The anomalies were discovered at the mid-gestation scan and were mostly found during the early years of our study.

We subdivided the indications for TOP in to four groups: structural malformations (47.7%), chromosomal/genetic abnormalities (43.3%), fetal infection (4.6%), and other indications (i.e., maternal indications, severe underling pathology such as early intrauterine growth restriction/oligohydramnios) (3.9%) [Figure 1A]. In addition, we subdivided the cohort based on the indication for TOP by organ system [Figure 1B]. The most common indication for TOP was multiple organ involvement and cardiopulmonary abnormalities (21% and 20%, respectively).

A total of 280 (8%) TOPs were preformed due to malformations involving the head and neck, presenting mainly as cystic hygroma. Of these 280 cases, 67 (1.9% of the total cohort) TOPs were performed because of facial malformations including CL/CLP and micrognathia. Of the 67 cases of TOP performed because of facial malformations, we excluded the following: one case of twin pregnancy and 12 cases of cleft lip or palate with additional multiple malformations or genetic abnormality. The final cohort included 54 singleton pregnancies in which TOP was conducted because of CL/CLP were the subjects of the present study [Figure 2].

TOP before 24 weeks was performed in 48 out of 54 (88%) of the cases. In 6 of the 54 cases, (11%), pregnancy termination was performed after 24 weeks of gestation. Of the 6 cases of late TOP performed, all pregnancy terminations were performed in the second trimester. The earliest TOP was performed at 13 weeks of gestational age. Postmortem findings of a fetus are presented in Figure 3.

TELEPHONE QUESTIONNAIRE

Of the 54 women included in the TOP cohort, only 27 responded to the questionnaire. Four reported a history of smoking, six regularly consumed folic acid, two reported a central nervous system (CNS) abnormality in the index pregnancy with the facial cleft, and one case had no relevant medical history. Although no positive family history was found during the telephone questionnaire, during the study period one woman presented to our department with three consecutive fetuses with facial CL/CLP. This 34-year-old gravida 4 para 1 first came to our department in 2016 with a finding of unilateral CLP on an early anatomy scan, and subsequently she opted for TOP. In 2017 she presented again with findings of fetal bilateral CL and paramaxillary agenesis with involvement of the alveolar ridge. TOP was performed. After the second TOP, she presented for a third time in a subsequent pregnancy with bilateral CLP detected during the NT ultrasound. Genetic consult, amniocentesis, and CMA during pregnancy did not reveal a genetic finding that could explain the familial tendency for CL/CLP in this case.

In the group that elected to continue the pregnancy, 60 women answered the questionnaire. In this group, no relevant medical history was reported.

Figure 1. Pregnancy termination over a 20-year period, from 5–38 weeks of gestation

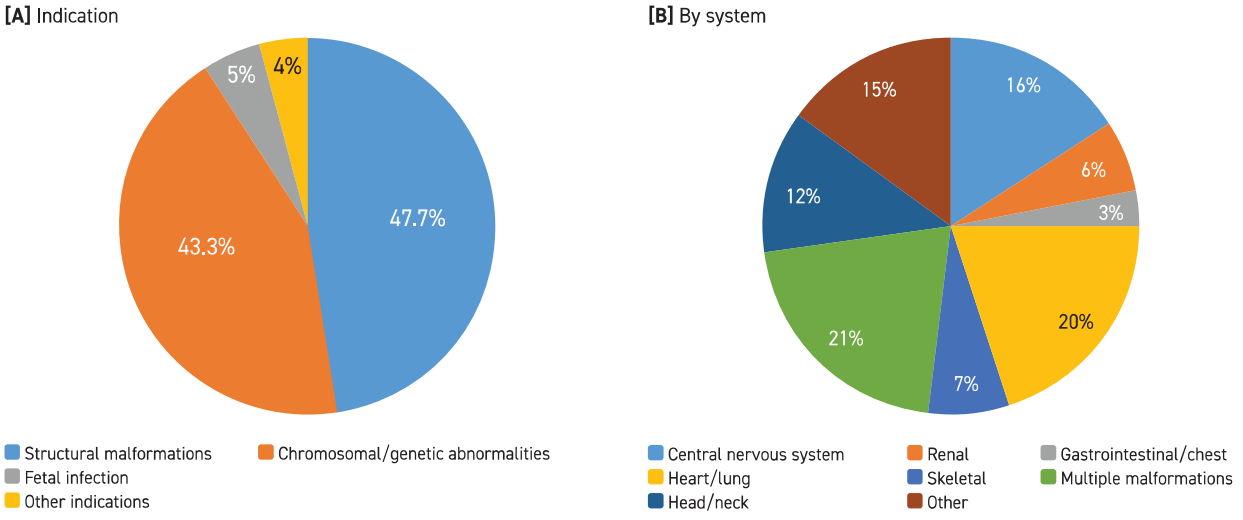


Figure 2. Flow chart showing selection process in pregnant women with singleton pregnancy who underwent TOP at our institute because of fetal facial cleft between 1998 and 2015

CL = cleft lip, CLP = cleft palate, TOP = termination of pregnancy

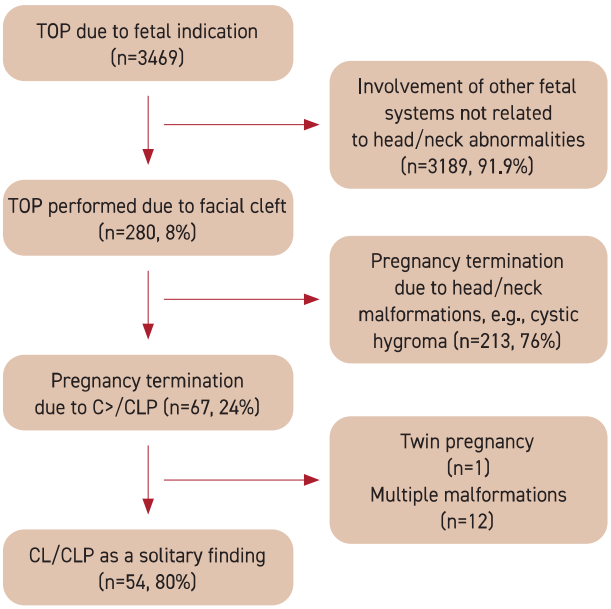
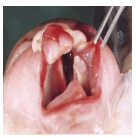
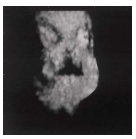


Figure 3. Representative images of cleft lip and cleft palate

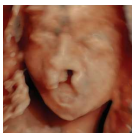
[A] Postmortem findings show cleft lip and cleft palate



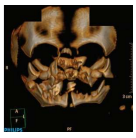
[B] 2D ultrasound shows a wide, left-sided cleft lip



[C] 3D image shows a wide, left-sided cleft lip



[D] Computed tomography scan in 3D skeletal mode showing deformation of the maxillary bone



DISCUSSION

We presented a cohort of 54 pregnancies that ended in TOP due to a solitary finding of fetal CL/CLP. In a cohort of 99 cases born with facial cleft, most were diagnosed after delivery. Recent research suggests that a diagnosis of CL/CLP can be noted as early as the first trimester. Sepulveda and colleagues [21] presented a simple algorithm for early detection of CL/CLP. They reported an even simpler technique that can facilitate the first-trimester detection of CL/CLP using the volume NT algorithm, which is a 3D sonographic algorithm that automatically detects and displays the exact midsagittal plane of the fetal head, allowing for early detection of CL [20]. Prior to this method, few studies described diagnosis if CLP in the first trimester. As technology advances and the learning curve of sonographers grows, cases of CL can now be diagnosed earlier, thus reducing the number of cases of late TOP. Sasson and co-authors [24] demonstrated the importance of prenatal diagnosis and showed that parents of children born with a CL/CLP consider a prenatal ultrasound diagnosis beneficial [24].

We included only the isolated cases of CL/CLP in our study. We excluded cases with other associated malformations and genetic abnormalities. In our previous studies [18.19], we described cases of TOP performed at our institute (a tertiary referral central for pregnancy termination) due to renal and CNS abnormalities, anomalies known to cause severe medical complications that are common indications for TOP. However, facial clefts cause mainly cosmetic complications and may propose an ethical dilemma for patients when considering TOP.

Maarse et al. [22] found that most parents reported an oral cleft as a cosmetic disability (50.6%) and only a minority (6.4%, 5/85) considered TOP. These results are consistent with our cohort. A recent study assessed opinions regarding pregnancy termination for isolated oral cleft in the Netherlands, where the number of terminations is low, and in Israel, where TOP is more prevalent. The authors found no difference in the opinions about the severity of oral cleft and the acceptability of TOP for an isolated oral cleft between the two countries [23]. Therefore, it is critical to provide future parents with optimal counseling and the option for TOP [25].

A flow chart presented in the book *Prenatal Diagnosis of Orofacial Malformations* [1] presents a case of a fetus with suspected orofacial cleft detected by prenatal ultrasound as early as 11 weeks of gestation. Cases diagnosed at 11–13 weeks during NT are considered high risk and it is recommended to perform a targeted 2D/3D ultrasound scan at 20–24 gestational weeks. Targeted scanning is recommended of the following structures: orbit, nares, ears, and brain. If multiple anomalies are detected, termination of pregnancy on patient request can be considered. If no additional structural anomalies are detected and the case is considered an isolated CL/CLP, genetic counseling and workup including karyotype and/or CMA are recommended. If abnormal results are obtained, TOP can be considered. In the case of normal genetic testing, close surveillance for the duration of the pregnancy is recommended with a multidisciplinary team including a perinatologist, plastic surgeon, otolaryngologist, and ultrasound and MRI imaging studies. In addition, in cases of non-syndromic CL/CLP, the suggested genetic workup is microarray analysis (if the diagnosis is unknown). Whole exome/genome sequencing should be considered [1].

The rare case of a woman with three consecutive fetuses diagnosed with CL/CLP led us to consider genetics as a potential cause for CL/CLP. Considering this unique case, performed a telephone questionnaire regarding familial tendency and risk factors. Unfortunately, only a small percentage of patients responded, and no significant findings were found. Future research is needed to determine genetic predisposition and risk factors among women with fetuses diagnosed with facial cleft.

Our study has some limitations. First, this retrospective cohort study was based on medical records so some cases may have been lost to follow-up. The telephone follow-up response rate was low, which could represent a bias.

Until more genetic factors and environmental hazards are discovered regarding CL/CLP, we recommend folic acid supplements to pregnant patients. We urge the primary physician to emphasize routine pregnancy workup including a detailed anomaly scan were facial clefts can be suspected and diagnosed early in pregnancy. In addition, we recommend training to the physician working in the ultrasound units targeted to early diagnosis of facial clefts. More importantly, an emphasis on secondary intervention is crucial, including early sonographic detection of the finding, as only 7/99 (7%) cases were diagnosed prenatally. In cases detected prenatally, we should use multidisciplinary consultation to provide prognosis and offer plan of treatment or TOP on patient request in severe cases.

CONCLUSIONS

Prenatal diagnosis of CL/CLP remains a diagnostic challenge despite the different imaging techniques available. Most cases born were undiagnosed prenatally in our cohort, thus not preparing the couple properly for the antenatal follow-up and treatment. The ethical aspects of TOP because of correctable malformation are challenging. We urge early detection and a good multidisciplinary approach.

Correspondence

Dr. R. Maymon
Dept. of Obstetrics and Gynecology, Shamir Medical Center (Assaf Harofeh), Zerifin 70300, Israel
Fax: (972-8) 977-9089
Email: maymonrb@bezeqint.net

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