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Pregnancy Outcomes of Patients Diagnosed As Having Cleft Lip Or/and Cleft Palate In Antenatal Screening

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ABSTRACT

To evaluate the obstetric outcomes of extra ultrasonographic anomalies in patients with cleft lip or/and cleft (CL±P) palate.

This retrospective study was conducted in a tertiary referral hospital between December 2017 and March 2021. The patients were analyzed under three groups as follows: isolated CL±P (group 1), CL±P with ultrasonographic anomalies with mild fetal and neonatal consequences (group 2), and CL±P with ultrasonographic anomalies with severe fetal and neonatal consequences (group 3).

Fourty cases were analyzed. The abnormal karyotype result (16.7%) were 46,x,t (t15;16)(q26;24), monosomy 18, trisomy 13, 46, XX, 21ps +. In the central cleft, ultrasonographic anomalies were seen in nine patients, which was statistically significantly higher than in isolated CL±P (p=0.004). Seven patients with extra ultrasonographic anomalies underwent termination, one patient with anencephaly died in utero. Preterm birth was the most common obstetric complication in all groups (n=9, 27.2%). In group 3, polyhydramnios was observed statistically significantly more frequently than in group 2 (p=0.033), and the first minute APGAR score was statistically significantly lower than in group 1 and 2 (p=0.003). The fifth minute APGAR score was statistically significantly lower and the need for the neonatal intensive care unit was statistically significantly higher than group 1 only (p=0.004 and p=0.007, respectively).

Polyhydramnios is not found in isolated cases, but only in cases with additional anomalies. Patients with CL±P with either major or minor additional ultrasonographic anomalies have worse fifth minute Apgar results and a greater need for the NICU.

Keywords: Lip; palate; cleft; fetal; obstetric

Introduction

Cleft lip or/and cleft palate (CL±P) (oral clefts) are the most common congenital craniofacial malformation (1). The prevalence of CL±P varies between countries and races in the same country. The incidence of CL±P is approximately 1.5/1000 live births (2). The causes of the CL±P are multifactorial; these major risk factors include maternal exposure to alcohol, tobacco smoke, and corticosteroids; folic acid deficiency; zinc deficiency; pregestational and gestational diabetes; gene mutations and chromosomal defects (3). According to the time of closure of the primary and secondary palate during embryogenesis, oral facials clefts are classified as only cleft lip, only cleft palate, and cleft lip with cleft palate. CL±P is cleft from front to back, only cleft palate is cleft from the uvula to the incisive foramen, which is from back to front (1, 3).

Approximately 70% of CL±P malformations are isolated, and 30% are associated with multiple congenital anomalies, syndromes, and chromosomal anomalies of unknown cause (4). Genes associated with orofacial clefts are often velocardiofacial syndrome (TBX1, COMT), CHARGE syndrome (CHD7), and Apert syndrome (FGFR2), but CL±P has been associated with nearly 500 genetic abnormalities in the Online Mendelian Inheritance in Man (OMIM) database (3, 5).

CL±P can be diagnosed in the first trimester with two-dimensional (2D) ultrasound maxillary gap and retronasal triangular images in sagittal and

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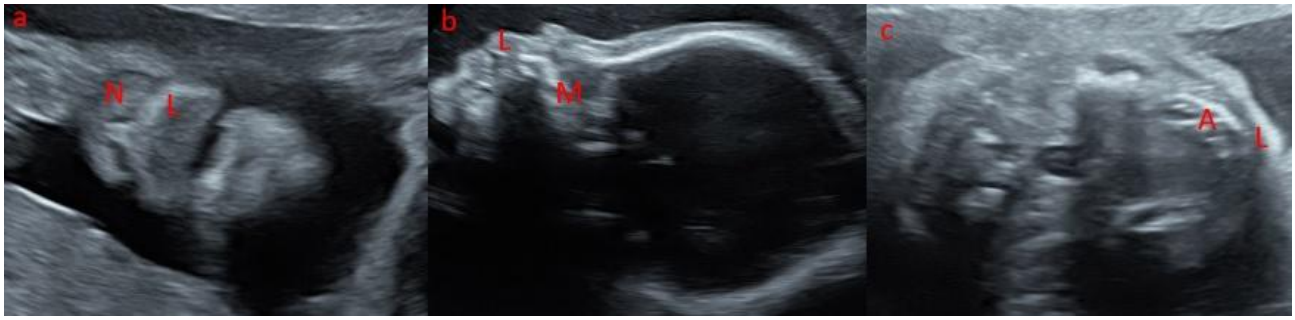

Fig. 1. Lip views with 2D ultrasound: a, coronal plane; b, sagittal plane; c, axial plane; N, nose; L, lip; M, maxillary bone; A, alveolar bone

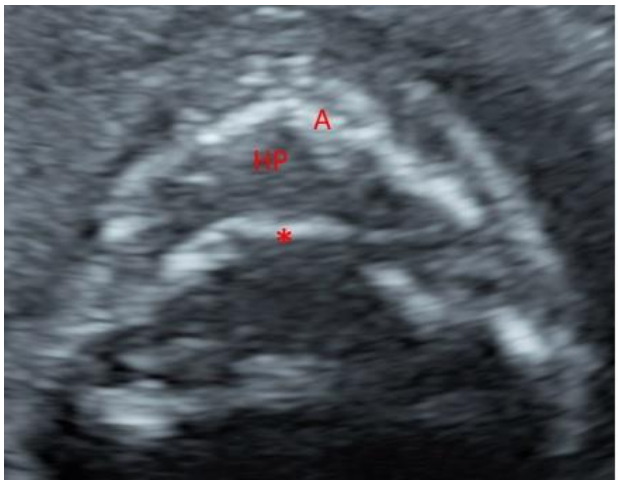

Fig. 2. Palate view with 2D ultrasound: A, alveolar bone; HP, hard palate; *, soft hard palate interface

coronal planes (6). However, prenatal diagnosis of CL±P is mostly made in the second trimester (7). It is an absolute necessity to scan the upper lip in routine second-trimester screening programs (8, 9). It is recommended to scan the palate more easily with the developing palate scanning techniques and to evaluate them in routine screening (10, 11).

In prenatal follow-up, polyhydramnios secondary to swallowing problems is seen in fetuses with CL±P. If it is shown that the outcomes of pregnancies with CL±P do not change due to polyhydramnios, 6.5% of patients have polyhydramnios (12, 13).

In prenatal diagnosis of CL±P and prenatal follow-up, invasive diagnosis options are valuable for the financial and moral preparation of the family after birth (14). Our study aimed to evaluate the clinical significance of CL±P detected during the antenatal period.

Materials and methods

This retrospective study was conducted at the perinatology clinic of the University of Health Sciences Etlik Zübeyde Hanim Gynecology Training and Research Hospital between December 2017 and March 2021. The study was approved by the Etlik Zübeyde Hanim Women's Health Application and Research Center Clinical Research Education Board (decision number: 05/21).

Each patient's age, gravidity, parity, pregnancy history, smoking history, body mass index (BMI) (kg/m^2), additional ultrasonographic findings, 75/100 g oral glucose tolerance test results, prenatal invasive diagnostic test (PIDT) results (amniocentesis or cordocentesis), week of diagnosis, pregnancy outcome (classified as abortion, termination or delivery), obstetric history, gestational week at birth, mode of delivery, delivery association, 1- and 5-minute Apgar scores, and need for neonatal intensive care unit (NICU) were evaluated. Obstetric complications: intrauterine fetal demise was accepted as fetal death after the 20th gestational week in utero (15); preterm birth as birth occurring between the 20th and 37th gestational week (16); intrauterine growth restriction as estimated fetal weight less than 10% (17); and polyhydramnios was defined as over 80 mL in a single vertical pocket or total amniotic fluid index over 240 mL (18) .

The patients were analyzed under three groups: group 1 as patients with CL±P without additional ultrasonographic findings; group 2 (minor) is CL±P with additional ultrasonographic anomalies with mild fetal and neonatal consequences; and group 3 (major) as patients with CL±P with additional ultrasonographic anomalies with severe fetal and neonatal consequences.

All fetal ultrasonographic examinations were performed using a Voluson E6 convex volumetric probe (GE Healthcare, Milwaukee, WI) and Vivid S6 ultrasound (GE Medical Systems, Horten, Norway) 4C probe, in line with the International Society of Ultrasound in Obstetrics & Gynecology

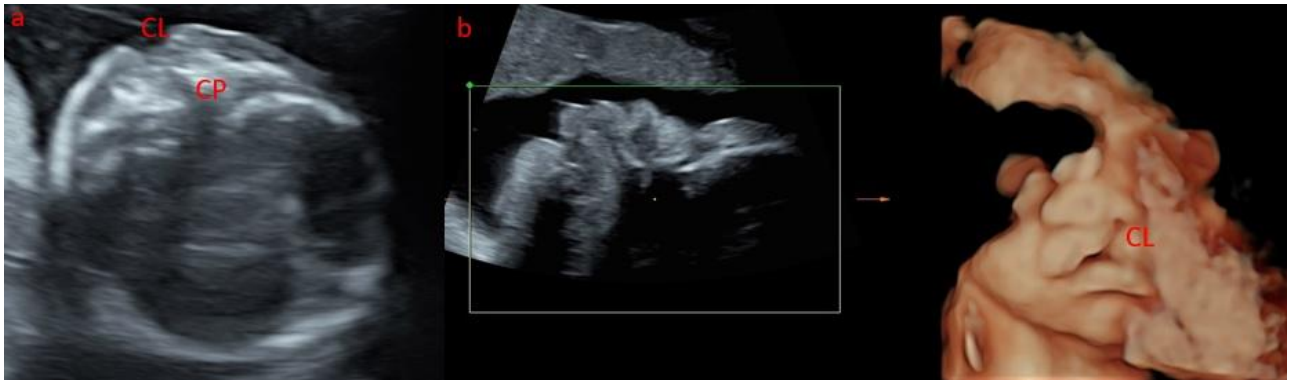

Fig. 3. Palate view with 2D ultrasound: a, axial transfers view; b, cleft lip with 3D ultrasound; CL, cleft lip; CP, cleft palate

(ISUOG) guidelines (9), by experienced perinatology specialists and the data were entered into a computer database. Lip examinations were performed using 2D ultrasound with sagittal, coronal, and axial planes or 3D ultrasound for the face (Figure 1 and 3). Palate exams were performed using 2D ultrasound with the axial transverse view (10, 11) (Figure 2 and 3).

Karyotype analysis and chromosomal microarray (a-CGH) were recommended for all patients with CL±P. CL±P, regardless of the gestational week, is not sufficient for the valid termination criteria (population planning laws) in Turkey for pregnancy (19). However, depending on the major accompanying anomalies and genetic anomalies, termination can be performed with the consent of the family and medical ethics board. The diagnosis of CL±P was confirmed by experienced perinatology specialists after termination and labor. All patients diagnosed as having CL±P are consulted by a psychologist, the department of genetics, the department of pediatrics, and the department of otolaryngology - head and neck surgery in the prenatal period. There is no department of otolaryngology - head and neck surgery in our hospital so all neonates are sent to a multidisciplinary center when the neonate is well enough for transfer. If the patient diagnosed as having CL±P dies in utero or postpartum, an autopsy is recommended to the family.

The IBM SPSS version 21.0 for Windows was used for statistical analysis. Descriptive analysis and categorical variables were defined as number and percentage, and numerical variables as median (range minimum-maximum). The Chi-square test and Fisher's exact test were used for the analysis of categorical data. The Mann-Whitney U test was used for the analysis of non-normally distributed quantitative data. The independent sample t-test was used for the analysis of normally distributed quantitative data. A value of $P < 0.05$ was accepted as the level of statistical significance.

Results

During the 3 years, a total of 40 patients, 18 (45%) with isolated and 22 (55%) with ultrasonographic abnormalities were diagnosed as having CL±P during the prenatal period. Group 1 (n=18) comprised isolated CL±P cases, group 2 (n=9) comprised cases of minor ultrasonographic abnormalities, and group 3 (n=13) comprised cases of minor ultrasonographic abnormalities. One patient (5.5%) in the isolated group was diagnosed as having cleft lip only prenatally, but a postnatal evaluation showed CL±P. One patient (4.5%) in the major ultrasonographic anomalies group was diagnosed as having CL±P prenatally, but a postnatal evaluation showed only cleft lip. According to the postpartum results in all groups, the sensitivity of prenatal ultrasound for correct diagnoses for palate was 96.3% and specificity was 92.3%. Table 1 lists the demographic and clinical data of all cases in the study groups. CL±P was statistically significantly more frequent in group 3 compared with group 2 (p=0.003).

Isolated CL±P cases were seen in 12 patients in unilateral cleft cases, which was statistically significantly higher than in the extra ultrasonographic anomaly cases (p=0.004) (Table 2). In the central cleft cases, extra ultrasonographic anomalies were seen in nine patients, which was statistically significantly higher than in the isolated CL±P group (p=0.004).

When the ultrasonographic anomalies accompanying CL±P were evaluated, the most common was central nervous system anomalies (n=9, 40.9%), followed by cardiac anomalies (n=7, 31.8%) (Table 3). A prenatal invasive diagnostic test was performed in 24 (60%) cases. Four (16.7%) had abnormal results. On fetal ultrasound,

Table 1. Demographic and Clinical Data in The Study Groups

		Isolated CL±P (n=18)	Minor (n=9)	Major (n=13)	p
Age		27.4±6.6	27.4±5.5	28.7±6.8	0.824
Gravidity		2 (1-9)	2 (1-5)	2 (1-7)	0.695
Abortus		0 (0-2)	0 (0-2)	0 (0-3)	0.372
Body mass index		25.8±3.8	28.3±4.3	26±2.6	0.156
Diagnosis week		22 (16-33)	22 (18-33)	21 (17-27)	0.853
Nationality	Turkish	16 (88.9%)	8 (88.9%)	12 (92.3%)	0.945
	Syrian	2 (11.1%)	1 (11.1%)	1 (7.7%)	
Maternal disease		2 (11.1%)	2 (22.2%)	0	0.227
Smoking		3 (16.7%)	0	3 (23.1%)	0.318
	Lip and palate	12 (66.7%)	3 (33.3%)[c]	13 (100%)[b]	0.003
Sex	Female	6 (33.3%)	4 (44.4%)	6 (46.2%)	0.736
	Male	12 (66.7%)	5 (55.6%)	7 (53.8%)	
Karyotype (n=24)	Normal	8 (88.9%)	6 (85.7%)	6 (75%)	0.73
	Abnormal	1 (11.1%)	1 (14.3%)	2 (25%)	
Termination		0[c]	1 (11.1%)	6 (46.5%)[a]	0.003

[a]Different from the isolated CL±P
[b]Different from the CL±P with minor ultrasonographic anomaly
[c]Different from the CL±P with major ultrasonographic anomaly

Table 2. Cleft Type In Study Groups

	Central cleft (%)	Unilateral cleft	Bilateral cleft	p
Isolated CL±P (n=18)	1 (1%)[b]	12 (75%)[a]	5 (35.7%)	0.004
CL±P with extra anomalies(n=22)	9 (99%)[a]	4 (25%)[b]	9 (64.3%)	0.004

[a]Different from the isolated CL±P
[b]Different from the CL±P with minor ultrasonographic anomalies
[c]Different from the CL±P with major ultrasonographic anomalies

bilateral club foot, increased nuchal fold thickness, and kyphoscoliosis were observed in the first case in which the amniocentesis result was 46,x,t(t15;16)(q26;24). The amniocentesis result of the second case was deleted short arm (p) of chromosome 18 (monosomy 18). In the ultrasound of the fetus, isolated persistent left superior vena cava and corpus callosum agenesis were observed. The third cordocentesis result was trisomy 13. Perimembronous ventricular septal defect, corpus callosum dysgenesis, and hypertelorism were observed in the ultrasound of this patient. The fourth case was isolated CL±P and the amniocentesis result was 46, XX, 21ps +.

Seven patients with extra ultrasonographic anomalies were terminated, one patient with anencephaly died in utero. Table 4 lists the fetal prenatal complications of all cases in the study groups. Preterm delivery was observed more frequently than other obstetric complications in nine cases (27.2%) of all groups. In group 3, polyhydramnios was observed statistically significantly more frequently than in group 1 (p=0.033). In group 3, the first minute APGAR score was statistically significantly lower than in group 1 and 2 but the fifth minute APGAR score was statistically significantly lower and the need for NICU was statistically significantly higher than group 1 only (p=0.004 and p=0.007, respectively) (Table 5).

Discussion

In this study, extra accompanying anomalies, chromosomal anomalies, prenatal counseling, and pregnancy outcomes in 40 cases of CL±P were evaluated. An accurate prenatal diagnosis of lip and palate anomaly is important in terms of prognosis prediction, treatment planning, and providing counseling to parents (20). Zimmerman et al. demonstrated that prenatal consultation was associated with earlier postnatal clinic appointments and a shorter time to repair in patients with CL±P (14). The clinics where

Table 3. Characteristics of CL±P cases in group 2 and 3

	Pregnancy outcome	Age	Diagnosis week	Result of PIDT	Cleft	Ultrasonographic anomalies	Sex	NICU
2 (n=9)	Termination	30	18	Normal	LP	Micrognathia, polysyndactyly[1]	Female	
		25	20	Normal	LP	Micrognathia,VSD[2]	Female	No
		35	18	Normal	LP	VSD[2]	Male	No
	Delivery	25	20	Normal	L	VSD[2]	Female	Yes
		37	22	Normal	L	Cardiac hyperechogenic focus[2]	Male	Yes
		27	24	None	L	Thick nuchal fold, pelviectasis[2]	Male	Yes
		23	22	Normal	L	Single umbilical artery[4]	Female	Yes
		21	20	46,x,t(t15;16)(q26;24)	L	Bilateral club foot, thick nuchal fold[1,4]	Male	No
		24	33	None	L	Single umbilical artery[4]	Male	Yes
3 (n=13)	Termination	29	18	Normal	LP	Anencephaly[3]	Female	
		26	21	None	LP	Alobar holoprosencephaly, hypotelorism[3]	Female	
		30	25	Normal	LP	Severe hydrops fetalis[5]	Male	
		39	24	None	LP	Lumbosacral spina bifida, rocker button on the left, VSD, aortic hypoplasia[1,2,3]	Female	
	IUFD	19	17	Normal	LP	Semilobar holoprosencephaly, exophthalmos[3]	Male	
		23	18	Normal	LP	Ventriculomegaly, omphalocele[3,6]	Male	
		23	19	None	LP	Anencephaly[1]	Male	
		34	24	None	LP	Encephalocele[1]	Female	Yes
	Delivery	25	27	Trisomy 13	LP	Perimembrenous VSD, hypertelorism, corpus callosum dysgenesis[2,3]	Male	Yes
		22	27	Normal	LP	Ventriculomegaly[3]	Male	Yes
		38	21	Normal	LP	Severe hydrops fetalis[5]	Female	Yes
		27	21	None	LP	Mega cisterna magna, vermian agenesia[3]	Female	Yes
		39	22	Monosomy 18p	LP	PLSVC, corpus callosum agenesis[2,3]	Male	Yes

[1]Skeletal system; [2] Cardiac anomalies;[3] Central nervous system anomaly; [4] Soft markers; [5] Severe hydrops fetalis; [6] Gastrointestinal system anomaly; VSD, ventricular septal defect; PLSVC, persistent left superior vena cava; L, lip; LP, lip and palate; NICU, neonatal intensive care; IUFD, intrauterine fetal demise; PIDT, preinvasive invasive diagnostic test

Table 4. Prenatal Obstetric Complications in The Study Groups

	Group 1 (n=18)	Group 2 (n=8)	Group 3 (n=7)	p
Polyhydramnios	0[c]	1 (12.5%)	3 (42.9%)a	0.013
IGR	2 (11.1%)	1 (12.5%)	1 (14.3%)	0.976
Preterm delivery	5 (27.8%)	1 (12.5%)	4 (57.1%)	0.162
IUFD	0	0	1 (14.3%)	0.147

[a]Different from the isolated CL±P
[b]Different from the CL±P with minor ultrasonographic anomalies
[c]Different from the CL±P with major ultrasonographic anomalies

Table 5. Fetal Outcomes In The Study Groups

	Group 1 (n=18)	Group 2 (n=8)	Group 3 (n=7)	p
Vaginal delivery	10 (55.6%)	1 (12.5%)	2 (28.6%)	0.094
Cesarean delivery	8 (44.4%)	7 (87.5%)	5 (71.4%)	
Birth week	38 (35-39)	37 (36-39)	34 (31-39)	0.168
APGAR 1	8 (5-9)[c]	9 (3-9)[c]	5 (0-8)[a,b]	0.003
APGAR 5	9.5 (7-10)[c]	10 (0-10)	6 (0-9)[a]	0.004
NICU	5 (27.8%)[c]	5 (62.5%)	6 (100%)[a]	0.007

[a]Different from the isolated CL±P
[b]Different from the CL±P with minor ultrasonographic anomalies
[c]Different from the CL±P with major ultrasonographic anomalies

neonatal follow-up and surgery will be performed for all life-expectancy fetuses with CL±P were determined, and their appointments were made with the consultancy we provided.

The diagnostic accuracy of 2D ultrasonography differs in detecting CL ± P in low-risk populations. Over time, the diagnostic sensitivity of CL±P has increased with the development of ultrasound devices and imaging techniques. Wayne et al. reported that the sensitivity of second-trimester ultrasonographic scans was 75% (21). Nicholls et al. reported that the detection rate was 84.6% when CL±P imaging was performed by specialist obstetricians and sonography clinics (22). Although prenatal ultrasonographic diagnosis is difficult, the rate of accurate prenatal diagnosis of palate clefts has increased with the 'equal sign view' and 'axial transfer view' imaging techniques (10, 11, 23). Secondary cleft palate is present in 90% of unilateral or bilateral lip clefts (24). Prenatal diagnosis is valuable because fetal outcomes and fetal genetic and structural anomaly rates increase with the presence of cleft palate in the fetal cleft lip (25). The prognosis of CP is worse than cleft lip because cleft palate affects neonatal nutrition, abnormal speech, hearing loss, facial development, and other functions, and surgical correction is more difficult or associated with postoperative complications (1, 3, 26). When CL was diagnosed, Bäumler et al. showed that the sensitivity for prenatal detection of CL±P was 100% and the specificity was 90% (27). In our perinatology clinic, high-risk patients are screened with more multiplane using ultrasound. If cleft lip is present or suspected, the palate is screened using an 'equal sign view' and 'axial transfer view'. Prenatal ultrasound sensitivity for accurate diagnosis of cleft palate is 96.3% and the sensitivity is 92.3% in all groups.

Olusanya et al. reported that no predisposing factors were identified for pregnant women with fetal orofacial clefts despite antenatal follow-ups (28). Gilham et al. demonstrated that offering invasive testing was not inappropriate for all patients but antenatal-specific scans to diagnose both the anatomic type of cleft and the presence or absence of associated abnormalities and counseling of patients was recommended (29). In our study, the karyotype abnormality was similar between groups, but the only karyotype anomaly in isolated CL±P, 46, XX, 21ps +, was considered a normal variant. Other karyotype anomalies were 46,x,t(t15;16)(q26;24), monosomy 18, trisomy 13, and all had accompanying structural anomalies. The rate of accompanying structural and genetic anomalies increases in oral clefts, cases with palate cleft only, and cases with CL±P (29, 30). In isolated CL±P and CL±P cases with extra anomalies, it was observed that the CL±P was proportionally more frequent. Interestingly, this

rate was higher in CL±P with major ultrasonographic anomalies than in CL±P with minor ultrasonographic anomalies; it was not different from isolated CL±P. The incidence of associated structural abnormalities varies according to the anatomic cleft type and central clefts are proportionally more prevalent in additional anomalies (29). Similarly, in our study, santal cleft was significantly more frequent in the CL±P group with extra anomalies and unilateral cleft in the isolated CL±P group.

Michel et al. showed that CL±P with associated anomalies significantly increased the risk of poor neonatal outcomes, but antenatal outcomes were not evaluated (31). Wyszynski et al. reported that low gestational age, low birth weight, low 5-minute Apgar, and increased risk for prenatal and perinatal complications in the mother in oral cleft cases, but this large population-based, case-control study included isolated cases (13). There are a limited number of studies in the literature with obstetric complications of CL±Ps, which showed no difference from the normal population, except for polyhydramnios (12, 13, 32). In our study, when all groups were considered, the most common obstetric complication was preterm labor. Although there was an expected increase in pregnancy and fetal complications due to the accompanying anomalies of patients with CL±P, there was not a significantly lower rate in pregnancy complications other than polyhydramnios in patients with isolated anomalies compared with patients with extra ultrasonographic anomalies. Interestingly, polyhydramnios was never observed in isolated CL±P cases. However, significantly increased NICU hospitalization rates and decreased fifth APGAR minutes were observed in the patient group with major anomalies. Interestingly, this difference was not observed in the groups with major and minor anomalies.

The limitations of this study are the small number of cases and its retrospective design. An additional limitation is that there is no department of otolaryngology - head and neck surgery in our hospitals. Therefore, after we transferred the neonates to another hospital, we did not know final outcome. Another limitation is that prenatal genetic results were not known because approximately half of the patients did not accept the invasive diagnostic test. The strengths of the study were that all patients were evaluated by the same experienced perinatologists and followed up regularly during the antenatal period.

The increased rate of additional anomalies in central cleft cases should be considered when performing ultrasonographic evaluations. Polyhydramnios is not found in isolated cases, but only in cases with additional anomalies. The most common obstetric complication is preterm labor. Except for polyhydramnios, there are no negative consequences of additional ultrasound findings in prenatal outcomes. However, in postnatal results, patients with CL±P with either major or minor additional anomalies have worse fifth minute Apgar results and a greater need for the NICU compared with isolated CL±P. It is important to track the antenatal follow-ups and determine whether there are any changes according to the structure of the accompanying anomaly.

Conflict of Interest: The authors declare no conflict of interest.

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