ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Cleft Lip and Palate: Prenatal Diagnosis, Genetic Testing, and Pregnancy Outcomes in a Tertiary Referral Center

Fenda Lábio-Palatina: Diagnóstico Pré-Natal, Estudo Genético e Desfechos da Gravidez num Centro Terciário de Referência

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Acta Med Port 2026 Jan;39(1):33-40 ▪ https://doi.org/10.20344/amp.23371

ABSTRACT

Introduction: Orofacial clefts are common congenital malformations that may occur in isolation or as part of a syndrome. Early prenatal diagnosis provides crucial information for parental counseling, delivery planning, and multidisciplinary neonatal care. This study aimed to review orofacial cleft cases diagnosed during the prenatal period and to assess the relationship between cleft type, associated anomalies, genetic findings and pregnancy outcomes.

Methods: This retrospective study included all fetuses with a prenatal diagnosis of cleft lip and/or cleft palate who received obstetric care at the Unidade Local de Saúde São João between January 2014 and December 2023. Data collected included baseline maternal characteristics, fetal sex, gestational age at diagnosis, associated anomalies, genetic and pathological evaluation and pregnancy outcomes.

Results: Forty-eight fetuses were included. Prenatal diagnosis was most often made in the second trimester (77.1%), while all first-trimester diagnoses were associated with additional anomalies. Overall, 20 fetuses (41.7%) had syndromic or non-isolated clefts, accounting for all chromosomal and genetic abnormalities. In isolated cases (58.3%), genetic testing consistently yielded normal results, with only two of them receiving a genetic diagnosis postnatally. Eighteen pregnancies were terminated, mostly in cases with associated anomalies.

Conclusion: In this single-center retrospective case series, chromosomal and genetic abnormalities were only detected in fetuses with syndromic clefts or additional anomalies. Among isolated cases, genetic testing was uniformly normal. These results reinforce that prenatal genetic testing may be most valuable when syndromic features or a strong family history are present, rather than as a routine in isolated clefts. Further multicenter studies are needed to support this approach and define standardized protocols.

Keywords: Cleft Lip; Cleft Palate; Congenital Abnormalities/diagnosis; Genetic Testing; Pregnancy Outcome; Prenatal Diagnosis

RESUMO

Introdução: As fendas lábio-palatinas são malformações congénitas frequentes que podem ocorrer isoladamente ou em associação com outras malformações. O diagnóstico pré-natal precoce é fundamental para o aconselhamento parental, planeamento do parto e organização de cuidados neonatais multidisciplinares. O objectivo deste estudo foi rever os casos de fenda lábio-palatina diagnosticados no período pré-natal e avaliar a relação entre o tipo de fenda, malformações associadas, achados genéticos e desfechos da gravidez.

Métodos: Este estudo retrospetivo incluiu todos os fetos com diagnóstico pré-natal de fenda labial e/ou palatina acompanhados na Unidade Local de Saúde São João entre janeiro de 2014 e dezembro de 2023. Foram recolhidos os dados relativos a características maternas, sexo fetal, idade gestacional ao diagnóstico, malformações associadas, testes genéticos e estudo anatomopatológico e desfechos da gravidez.

Resultados: Foram incluídos 48 fetos. O diagnóstico pré-natal foi realizado maioritariamente no segundo trimestre (77,1%), sendo que todos os diagnósticos no primeiro trimestre estavam associados a outras anomalias. No total, 20 fetos (41,7%) apresentavam fendas sindrómicas ou não isoladas, correspondendo a todos os casos com alterações cromossómicas ou genéticas neste estudo. Nos casos de fenda isolada (58,3%), os testes genéticos foram sempre normais, tendo-se identificado apenas duas anomalias adicionais no período pós-natal. Dezoito gravidezes foram interrompidas, essencialmente nos casos com malformações associadas.

Conclusão: Nesta série de casos retrospetiva, as alterações cromossómicas e genéticas foram identificadas apenas nos casos de fendas sindrómicas ou com malformações adicionais. Nos casos isolados, os testes genéticos foram invariavelmente normais. Estes resultados reforçam que a realização de testes genéticos pré-natais pode ser mais útil quando existem malformações associadas ou história familiar relevante. São necessários estudos multicêntricos para validar esta abordagem e definir protocolos estandardizados.

Palavras-chave: Anomalias Congenitas/diagnóstico; Diagnóstico Prenatal; Fenda Labial; Fenda Palatina; Resultado da Gravidez; Testes Genéticos

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Recebido/*Received*: 20/05/2025 - **Aceite/*Accepted*:** 14/10/2025 - **Publicado *Online*/*Published Online*:** 19/12/2025 - **Publicado/*Published*:** 02/01/2026

KEY MESSAGES

- Most orofacial clefts were diagnosed during the second trimester.
- Syndromic cases were diagnosed earlier.
- Genetic alterations were found only in syndromic cases.
- Isolated clefts had a high prenatal-postnatal diagnostic concordance.
- Genetic testing should be reserved for syndromic or familial cases.

INTRODUCTION

Orofacial clefts, which include cleft lip (CL), without or with cleft palate (CLP) or cleft palate alone (CP), are one of the most common congenital malformations, affecting approximately 1 to 2.2/1000 live births.[1] These anomalies result from failure in the fusion of the nasal and maxillofacial processes between the 6th and 8th week of embryogenesis.[2]

Earlier prenatal diagnosis of orofacial clefts can be achieved by targeted examination of the retronasal triangle and the maxillary gap during the 1st trimester ultrasound.[3] However, isolated findings are often only identified during the 2nd or 3rd trimester.

Most orofacial clefts are sporadic and multifactorial. Chromosomal abnormalities, such as trisomies 13 and 18, and monogenic disorders, account for most syndromic cases. In non-syndromic familial cases, monogenic causes are responsible for up to 10%,[4] typically showing autosomal dominant inheritance with reduced penetrance and variable expressivity.[5] The most common associated anomalies are congenital heart defects (31.1%).[6-8]

Most cases of CL and/or CP result from a complex interplay between environmental and genetic factors during the initial weeks of pregnancy. Maternal age, drugs (e.g. antiepileptic agents or corticosteroids), smoking and alcohol consumption during pregnancy, obesity, diabetes *mellitus*, and folate deficiency are among the environmental factors that can impact fetal development and increase the risk of facial cleft.[9] Polymorphisms inherited from either parent can also contribute to that outcome or increase an individual's susceptibility.[10]

The newborn prognosis depends on the presence of associated malformations, which is determined by the accuracy of prenatal diagnosis. The prenatal diagnosis of orofacial cleft plays a central role in preparing families and optimizing neonatal care (e.g., chosen location for labor, an adequate multidisciplinary team, and organized surgical teams for timely interventions) to improve postnatal outcomes.

The aim of this study was to review orofacial cleft cases diagnosed during the prenatal period and to assess the relationship between cleft type, associated anomalies, genetic findings and pregnancy outcomes.

METHODS

This retrospective case series included all fetuses with prenatal diagnosis of CL and/or CP managed at a tertiary university hospital in Porto (Unidade Local de Saúde São João) between January 2014 and December 2023.

All the cases with an antenatal suspicion of CL and/or CP were included; cases could be diagnosed in our center or referred from other centers at any gestational age.

Cases were identified through a search on a dedicated departmental electronic database with cases prospectively collected, weekly updated, and created in our prenatal diagnosis clinic. Additional data were retrieved from hospital-based electronic records, including: Obscare® – Virtual Care (Porto, Portugal) and SClínico® – SPMS (Lisbon, Portugal). Ultrasound data were obtained from the ASTRAIA® software. Following a review of the medical records, the collected data included maternal characteristics (age, gravidity, parity, body mass index, and family history), fetal characteristics (sex, gestational age at diagnosis, presence of other fetal malformations, genetic evaluation) and pregnancy outcomes (gestational age and birth weight at delivery, termination of pregnancy) and, when applicable, pathological examination findings. When available, newborn examinations and pathology reports were reviewed to identify anomalies not detected antenatally.

Cases lost to follow-up were excluded.

This study was approved by the institutional ethics committee of Unidade Local de Saúde de São João [CES-OP-11-2025].

RESULTS

The study enrolled 48 fetuses with a CL and/or CP prenatal diagnosis (Table 1).

Gestational age at diagnosis

These anomalies were diagnosed at different stages of pregnancy (Table 1). Ten cases (20.8%) were identified in the first trimester, 37 cases (77.1%) in the second trimester, and one case (2.1%) in the third trimester. All fetuses diagnosed in the first trimester had additional malformations.

Syndromic/non-isolated clefts

A total of 20 fetuses (41.7%) were found to have other structural anomalies on ultrasound, and all chromosomal anomalies or genetic variants were identified within this

group. Among these cases, two had CP, while the remaining cases involved CLP. Regarding laterality, 12 presented with unilateral clefts, five with bilateral clefts, and three with midline clefts – representing all the midline clefts in this study.

Chromosomal abnormalities (n = 12): Trisomy 13 was identified in eight fetuses and trisomy 18 in four, accounting for 60.0% of cases with additional anomalies and 25.0% of all cases.

Non-trisomic cases (n = 8): In the eight non-trisomic cases, cardiac malformations were present in all, while central nervous system anomalies, skeletal defects, and abdominal wall anomalies were each observed in one case. Targeted or advanced genetic testing revealed:

Table 1 – Clinical characteristics of the study groups

Patients' Characteristics	Associated malformations n (%)	Isolated orofacial cleft n (%)	Total cases
Number of cases	20 (41.7%)	28 (58.3%)	48
General			
Maternal age at diagnosis (years) **± SD**	34.1 ± 6.0	31.4 ± 5.7	32.5 ± 5.9
Gravidity ± SD	2.1 ± 1.4	2.5 ± 1.7	2.3 ± 1.6
Parity ± SD	0.7 ± 0.9	1.1 ± 1.4	0.9 ± 1.2
Body mass index (kg/m^2) **± SD**	24.2 ± 4.2	26.5 ± 6.2	25.6 ± 5.5
Family history	0	9 (32.1%)	9 (18.8%)
Fetal sex			
Male	10 (50.0%)	19 (67.9%)	29 (60.4%)
Female	10 (50.0%)	9 (32.1%)	19 (39.6%)
Time of ultrasound diagnosis			
1st trimester	10 (50.0%)	0	10 (20.8%)
2nd trimester	9 (45.0%)	28 (100%)	37 (77.1%)
3rd trimester	1 (5.0%)	0	1 (2.1%)
Type of cleft			
Cleft lip	0	6 (21.4%)	6 (12.5%)
Cleft palate	2 (10.0%)	0	2 (4.2%)
Cleft lip and palate	18 (90.0%)	22 (78.6%)	40 (83.3%)
Cleft laterality			
Unilateral	12 (60.0%)	20 (71.4%)	32 (72.9%)
Bilateral	5 (25.0%)	8 (28.6%)	13 (27.1%)
Midline	3 (15.0%)	0	3 (6.25%)
Genetic testing			
QF-PCR	20 (100%)	22 (78.6%)	42 (87.5%)
Karyotype	13 (65.0%)	3 (10.7%)	15 (31.3%)
Microarray analysis	7 (35.0%)	19 (67.8%)	26 (54.2%)
Orofacial cleft panel	2 (10.0%)	2 (7.1%)	4 (8.3%)
Whole exome sequencing	3 (15.0%)	0	3 (6.25%)
Not performed	0	6 (20.7%)	6 (12.5%)
Pregnancy outcome			
Medical termination of pregnancy	16 (80.0%)	2 (7.1%)	18 (37.5%)
Intrauterine fetal demise	1 (5.0%)	0	1 (2.1%)
Alive fetus	3 (15.0%)	26 (92.9%)	29 (60.4%)
Gestational age at birth (w)	38.6 ± 1.3	38.7 ± 2.2	38.7 ± 2.0
Birth weight (g ± SD)	2863 ± 344 g	3143 ± 491 g	3100 ± 468 g

- *WDPCP*-related disorder: a fetus with unilateral CLP, pre-axial polydactyly in both feet and the left hand, bilateral brachydactyly, atrioventricular septal defect, and an aberrant subclavian artery was diagnosed prenatally. Karyotype and microarray results were normal, but whole exome sequencing identified a pathogenic *WDPCP* variant, confirmed postnatally (Table 2, case 14).
- Pathogenic variant in the *ABCA4* gene: a fetus with bilateral CLP, cardiomyopathy and early growth restriction had a heterozygous pathogenic variant in the *ABCA4* gene identified on a targeted gene panel (Table 2, case 16).
- Pathogenic variant in the X-linked *STAG2* gene: a male fetus with a small trabecular ventricular sept defect (VSD) as the sole finding (Table 2, case 20) was found to have a *de novo* pathogenic variant in the X-linked *STAG2* gene, leading to pregnancy termination. The postmortem pathological study confirmed the diagnosis of complete bilateral CLP and VSD, and additionally, identified a thoracic hemivertebra and minor anomalies in the lower limbs.
- Wiedemann-Steiner syndrome: this case involved a pregnant woman with epilepsy, treated with clobazam and carbamazepine. The prenatal ultrasound revealed CP, corpus callosum agenesis, and Fallot's tetralogy. Prenatal genetic testing (QF-PCR and microarray) was normal, but the postnatal evaluation was consistent with Wiedemann-Steiner syndrome, which was confirmed by genetic testing (Table 2, case 15).

Pregnancy outcomes: among the 20 fetuses with additional anomalies, 16 pregnancies were medically terminated, including eight in the first trimester. Of the four ongoing pregnancies, one fetus affected by trisomy 13 experienced fetal demise at 37 weeks of gestation.

Isolated clefts

Of the 28 fetuses (58.3%) diagnosed with isolated orofacial clefts, all were detected in the second trimester, between 19 and 23 weeks of gestation.

Regarding maternal and family history, nine cases (32.1%) had a family history of facial clefts. Folic acid supplementation was reported in three women before conception, in 15 during the first trimester, while three did not take folic acid; data were unavailable for seven cases. Maternal age ≥ 35 years was observed in nine cases (32.1%), and maternal obesity (BMI ≥ 30 kg/m^2) was present in ten cases (35.7%).

With respect to subtype distribution, 22 fetuses (78.6%) had cleft lip and palate (CLP), including 14 unilateral and eight bilateral cases, while six fetuses (21.4%) presented with unilateral cleft lip (CL) only. Of the 28 fetuses, 19 were male (67.8%) and nine female (32.1%).

Genetic testing was performed in 22/28 cases. In 19 cases (67.9%), QF-PCR followed by microarray analysis yielded normal results. A targeted gene panel was conducted in two pregnancies, both with negative findings, while in three cases only a karyotype was performed, also without abnormalities.

Pregnancy outcomes were favorable in most cases: 26 pregnancies continued to term. Two pregnancies were electively terminated upon parental request, and in both cases histopathological analysis confirmed unilateral or bilateral CLP without additional anomalies.

DISCUSSION

Orofacial clefts are a significant category of fetal malformations due to their diagnostic, therapeutic, and prognostic complexities. This highlights the critical role of prenatal diagnosis in ensuring timely referral and appropriate management of orofacial clefts by a multidisciplinary healthcare team.

Time of diagnosis

In this study, the gestational age at diagnosis ranged from 11 to 34 weeks, with most of the diagnoses occurring during the second trimester ultrasound. However, when other structural malformations were simultaneously present with orofacial cleft, the diagnostic yield of ultrasound in the first trimester was markedly higher, reaching 50.0%.

Although prenatal diagnosis is often established during the second trimester, some ultrasound signs can predict orofacial clefts as early as 11 to 13 weeks of gestation,[11-13] with higher reliability at 13 to 14 weeks.[14] During this period, the main ultrasound features described in the literature that may suggest an underlying cleft lip and palate include: an abnormal configuration of the retronasal triangle in both the coronal and midsagittal views, a maxillary gap, absence of the superimposed-line sign, and a palatine-maxillary diameter below the 5th percentile.[13,15-17] For bilateral clefts, assessment of the integrity of the fetal profile is crucial.

In the second trimester, the main findings were the discontinuity in the soft tissues of the upper lip, with or without discontinuity of the alveolar ridge, in a coronal and axial plane, respectively. Color Doppler ultrasonography can also be helpful, especially in detecting fetal hard palate clefts.[12]

For high-risk populations, three-dimensional ultrasound significantly enhances diagnostic sensitivity, with the added benefit of allowing parents to clearly visualize the specific type of malformation.[15,18,19]

Associated anomalies

In our cohort, 41.7% of fetuses with orofacial cleft had

Table 2 – Description of the cases with ultrasound diagnosis of orofacial cleft and associated malformations. For each case, gestational age at diagnosis, genetic diagnosis (when established), and pregnancy outcomes are also included.

Case	Cleft malformation description and associated findings	Gestational age at diagnosis (weeks)	Genetic testing	Outcome
1	Unilateral cleft lip and palate, fetal growth restriction, hypoplastic kidneys, overlapping fingers	21	Trisomy 18	TOP (22w)
2	Bilateral cleft lip and palate, brachycephaly, corpus callosum agenesis, microphthalmia, micrognathia, hypotelorism, diaphragmatic hernia, interventricular communication, polydactyly, hypospadias	13	Trisomy 13	IUFD at term (37w)
3	Midline cleft lip and palate, holoprosencephaly, omphalocele	12	Trisomy 13	TOP (12w)
4	Bilateral cleft lip and palate, choroid plexus cysts, absent stomach, renal duplication, closed hands with overlapping fingers	21	Trisomy 18	TOP (22w)
5	Cleft palate, omphalocele, pericardial effusion, atrioventricular septal defect, syndactyly	13	Trisomy 18	TOP (14w)
6	Medline cleft lip and palate, holoprosencephaly	12	Trisomy 18	TOP (12w)
7	Unilateral cleft lip and palate, holoprosencephaly, omphalocele, large and hyperechogenic kidneys, skin edema, polydactyly	13	Trisomy 13	TOP (13w)
8	Unilateral cleft lip and palate, fetal hydrops, complex cardiomyopathy	13	Trisomy 13	TOP (13w)
9	Unilateral cleft lip and palate, holoprosencephaly, omphalocele, hypoplastic left heart	12	Trisomy 13	TOP (13w)
10	Unilateral cleft lip and palate, holoprosencephaly, hypotelorism, complex cardiomyopathy, single umbilical artery	11	Trisomy 13	TOP (12w)
11	Unilateral cleft lip and palate, omphalocele, hypoplastic left heart, single umbilical artery	11	Normal karyotype	TOP (14w)
12	Unilateral cleft lip and palate, Dandy-Walker malformation, bilateral ureteral stenosis, overlapping fingers, single umbilical artery	18	Trisomy 13	TOP (18w)
13	Midline cleft lip and palate, double-outlet left ventricle	16	Normal QF-PCR and microarray	TOP (18w)
14	Unilateral cleft lip and palate, atrioventricular communication, polydactyly, brachydactyly	20	Normal QF-PCR and microarray. *WDPCP*-related disorder (prenatal exome)	Alive
15	Cleft palate, corpus callosum agenesis, bilateral ventriculomegaly, Fallot tetralogy/double-outlet right ventricle, retrognathia	35	Wiedemann-Steiner syndrome, heterozygous pathogenic variant in *KMT2A* (postnatal exome)	Alive
16	Bilateral cleft lip and palate, fetal growth restriction, cardiomyopathy	24	Normal QF-PCR and microarray, heterozygous pathogenic variant in *ABCA4* (cleft panel)	Alive
17	Unilateral cleft lip and palate, abdominal cyst, complex cardiomyopathy, single umbilical artery	12	Normal QF-PCR and microarray	TOP (16w)
18	Unilateral cleft lip and palate, atrioventricular communication, distended jugular lymphatic sacs	16	Normal QF-PCR and microarray	TOP (17w)
19	Bilateral cleft lip and palate, cerebellar hypoplasia, hyperechoic kidneys; disproportion of the cardiac chambers, with predominance of the right chambers.	16	Trisomy 13	TOP (20w)
20	Bilateral cleft lip and palate, small trabecular ventricular septal defect	21	Normal QF-PCR and microarray, *de novo* pathogenic variant in *STAG2* (prenatal exome)	TOP (24w)

TOP: termination of pregnancy; IUFD: intrauterine fetal demise; w: weeks

associated anomalies. All cases presented with CLP, except for two cases involving CP alone.

Previous studies have reported non-isolated clefts in around 30%,[1,2] with a wide range of associated anomalies.[20,21] For example, in a case series of 45 fetuses with orofacial clefts, 35.6% of these cases also had additional anomalies.[2] Another multicenter study of 35 924 non-selected pregnancies, identified 62 cases of orofacial clefts, 39% of which had associated defects.[22]

Sixty percent (12/20) were trisomies (T13 and T18), a trend consistent with the literature, where trisomies are most prevalent in cases of CLP and CP.[22]

Among our eight non-trisomic cases, the most frequent anomalies were in the cardiovascular system, followed by the musculoskeletal and central nervous systems. According to the literature, excluding trisomies, the anomalies most commonly associated with CL and/or CP involve the cardiovascular, musculoskeletal, and central nervous systems.[23]

Genetic testing: yield and interpretation

In our study, all genetic findings were confined to syndromic cases, with all isolated cleft cases yielding consistently normal results. Our findings are consistent with the literature, emphasizing a higher frequency of genetic diagnosis in non-isolated orofacial clefts.[23,24]

Trisomies were the most frequent diagnosis (60%). In the remaining cases, the etiology was not diagnosed prenatally using karyotyping and/or microarray. However, whole exome sequencing (WES) was performed in three fetuses with additional anomalies and provided a definitive diagnosis in all: WDPCP-related disorder (Table 2, case 14), an *ABCA4*-related disorder (Table 2, case 16), and Wiedemann-Steiner syndrome caused by a *KMT2A* pathogenic variant (Table 2, case 15). Recent literature, however, suggests a more modest diagnostic yield of WES in prenatal cohorts. For example, Basha *et al* reported a yield of around 10% in familial non-syndromic clefts.[4]

In one case, a heterozygous pathogenic variant in the *ABCA4* gene, typically associated with Stargardt disease, was identified using a target gene panel. However, recent literature suggests that polymorphisms in this gene may increase susceptibility to CL and/or CP. These associations, primarily derived from genome-wide association studies, should be interpreted cautiously (Table 2, case 16).[25,26]

Only one case received a postnatal diagnosis: Wiedemann-Steiner syndrome, identified via exome sequencing (Table 2, case 15). This syndrome has been reported in 3% of cases with submucous cleft palate.[27] However, the potential clefting effect of anti-epileptic drugs taken during pregnancy should also be considered.[28] A future episignature study could help differentiate the influence of these two factors.

In most cases of suspected isolated orofacial clefts, QF-PCR and microarray were primarily offered, all yielding normal results. The three cases that underwent only karyotype analysis were referred to our center after the chromosomal study, at or after 25 weeks of gestation. Six cases chose not to undergo prenatal genetic testing. Further genetic analysis using specific panels for clefts was conducted in two cases, based on individual clinical decisions, and exome sequencing was not performed. Among all the genetic tests performed no significant abnormalities were found.

These results raise several important questions regarding prenatal genetic testing. How extensive should prenatal genetic testing be, especially in cases of isolated orofacial cleft? In isolated cases, particularly if unilateral, would it not be more relevant to complete genetic testing (panel or exome) in the postnatal period, tailoring the study based on additional findings or family history? This approach may be crucial for developing more universal and consistent genetic testing strategies[5] that both ensure the quality of prenatal diagnosis and address complex and often challenging outcomes of genetic testing.

Genetic testing in isolated orofacial cleft also presents significant ethical dilemmas. Nearly all cases yield normal results,[5,29] which can delay decision-making beyond the legal time frame for pregnancy termination in Portugal (24 weeks of gestation). Notably, genetic testing, particularly targeted NGS panels or whole-exome sequencing (WES), can take several weeks to complete. Consequently, even if a relevant genetic alteration is identified, it might be reported after the optimal time frame. Additionally, many findings may lack clear prognostic value, as many variants associated with isolated orofacial clefts often exhibit incomplete penetrance and clinical heterogeneity.[29] This suggests that limiting prenatal genetic testing to syndromic cases or those with a strong family history may be a more appropriate approach.

Pregnancy outcomes

In our series, 18 out of a total of 48 cases resulted in the termination of pregnancy, with only two cases involving an isolated orofacial cleft.

In the 28 cases of presumed isolated facial cleft, additional malformations were detected postnatally in two cases. In the first case, the postnatal evaluation revealed left macroglossia (lymphatic malformation), and in the second case, hypospadias were identified. This corresponds to a 7.1% rate of undiagnosed anomalies in cases with CL and/or CP, which is much lower than the 35.5% reported in the literature.[2]

During childhood, one child was diagnosed with autism spectrum disorder. Before the diagnosis, both microarray

and cleft panel analyses were performed, yielding normal results, and the family was waiting for a genetics consultation.

In another case, a newborn presented with asymmetrical macroglossia, prompting microarray analysis, which also returned normal results.

Parental impact and conselling

Diagnosing an orofacial cleft during prenatal ultrasound can indeed have a profound emotional impact on the parents, often becoming a heavy burden. This emotional strain is intensified by the understanding that prenatal evaluation may not always detect all associated anomalies, making it challenging to predict the full extent of the prognosis. As a result, the decision to continue or terminate the pregnancy becomes more difficult and emotionally charged. However, based on our case series, we found that ensuring an excellent prenatal diagnosis can significantly reduce the percentage of cases with postnatal diagnoses of additional anomalies. This highlights the importance of comprehensive and accurate prenatal screening, as it can provide more clarity for parents and better guide decision-making during such a difficult time. The benefits of prenatal diagnosis extend far beyond the detection of an orofacial cleft, playing a crucial role in providing parents with the necessary information to understand their options and plan for postnatal care. This early communication allows parents to prepare emotionally and practically, improving their adherence to recommended treatments and interventions, which ultimately benefits the child's well-being.

A multidisciplinary team – including obstetricians, geneticists, neonatologists/pediatricians, pediatrics and plastic surgeons, stomatologists, otolaryngologists, physiatrists, speech therapists, nutritionists, and psychologists – is essential for the comprehensive management of orofacial malformations. This collaborative approach ensures the best possible outcomes for both the child and the parents, addressing the physical, emotional, and social aspects of care.

Limitations

We acknowledge some limitations in our study, such as its retrospective nature and the lack of assessment of postnatal cases of orofacial cleft without a prenatal diagnosis, mainly clefts of the secondary palate.

CONCLUSION

This retrospective case series highlights the importance of an accurate prenatal diagnosis of orofacial clefts, which was most often achieved in the second trimester but could be established earlier in the presence of associated anomalies. Syndromic cases accounted for all genetic abnormalities and had a markedly higher rate of termination, whereas isolated clefts were usually carried to term with favorable neonatal outcomes. Genetic testing in isolated clefts consistently yielded normal results, reinforcing that prenatal genetic testing may be most valuable when additional anomalies or a strong family history are present. These findings underscore the need for multicenter studies to establish consistent and universal strategies for genetic testing and counseling in pregnancies complicated by orofacial clefts.

ACKNOWLEDGMENTS

During the preparation of this work, the authors used OpenAI's ChatGPT-4 to improve readability and language. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

AUTHOR CONTRIBUTIONS

HD, RO, TC, MMo: Study conception and design, data acquisition, analysis and interpretation, writing and critical review of the manuscript.

DFR, MHC, SG: Data acquisition, analysis and interpretation, critical review of the manuscript.

ACB, MMa, CPM: Critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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