

Diagnostic performance of two ultrasound techniques for the detection of cleft palate without cleft lip: axial-transverse and equal sign

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Abstract. – OBJECTIVE: There is no study that compares the diagnostic performance of ATV and ESV techniques in detecting cleft palate. We aimed to evaluate the diagnostic accuracy of two ultrasound techniques: axial-transverse (ATV) and “equal sign” view (ESV), in detecting fetal cleft palate without cleft lip.

PATIENTS AND METHODS: This prospective study was conducted from March 2019 to January 2022 in a tertiary referral hospital. Secondary palates were assessed with ATV and ESV by two experienced fetal medicine specialists who were blinded to each other's ultrasound findings. Final diagnosis was done according to postnatal physical examination. The sensitivity and specificity of the two techniques were calculated.

RESULTS: A total of 311 pregnancies which met the study criteria were evaluated. Postnatal physical examination showed that 13 (0.4%) neonates had cleft palate only (CPO). According to final diagnosis the sensitivity, specificity, positive predictive value and negative predictive value for ATV were 100%, 98.7%, 76.4%, 100% and 100% for ESV were 76.9%, 97.8%, 58.9% and 99%, respectively.

CONCLUSIONS: ATV in 2D ultrasound provides higher sensitivity and specificity than ESV in detecting CPO.

Key Words:

Cleft palate, Ultrasound imaging, Diagnostic imaging, Prenatal diagnosis.

in routine obstetric care. The most commonly used imaging modality for prenatal screening to detect fetal structural abnormalities is ultrasound. Although advances in the image quality of ultrasound have facilitated the diagnosis of many fetal structural anomalies, sonographic diagnosis of fetal cleft palate without fetal cleft lip [fetal cleft palate only (CPO)] remains difficult because of the acoustic shadow created by the cranial bone environment¹. In addition, the low incidence of fetal CPO has resulted in less attention being paid to ultrasonography of the palate and less experience among ultrasonographers^{2,3}. Therefore, the detection rate of fetal CPO is low. Several techniques have recently been proposed to address this problem. Equal sign view (ESV), which shows a single or bifid uvula, has been used to detect CPO. Demonstration of a normal uvula strongly suggests^{4,5} an intact hard and soft palate, but this technique does not provide information about the size of the bony defects in CPO. In addition it is difficult to detect a bifid uvula in severe cases that result in more lateralization of the uvula. Furthermore, the detection of an abnormal ESV does not mean that a cleft palate is present as bifid uvula, defined as a complete or partial branching of the uvula, which occurs in approximately 0.49-7.6% of normal individuals^{6,7}. A bifid uvula accounts for only 19.4% of cleft palates and is usually an isolated finding⁷. Recently, a promising study⁸ found higher sensitivity and specificity in the detection of CPO by using the axial-transverse (ATV) plane. In addition, this technique also allows anatomical classification of the cleft palate. This technique is based on

Introduction

Prenatal diagnosis of fetal structural abnormalities has become one of the most important tasks

transverse visualization of the hard palate at its posterior margin. However, from previous studies, we cannot affirm the superiority of one of these techniques because these techniques were not tested in the same patients. Therefore, in this study, we performed a comparative evaluation of the diagnostic performance of ATV and ESV in the same patients by two fetal medicine specialists with similar experience.

Patients and Methods

Study Design, Setting and Participants

This prospective observational study was conducted between March 2019 and January 2022 in the perinatology clinic, where 6,000 patients are cared for annually. Our clinic is a tertiary referral clinic where pregnancies with suspected or diagnosed fetal structural genetic abnormalities are screened by fetal medicine specialists who have at least eight years of experience. For prenatal screening, we follow the recommendations of the International Society of Obstetrics and Gynecology (ISUOG)⁹. Screening of the secondary palate is not part of our clinical routine. However, we screen patients for cleft palate who are at high risk for this condition due to additional fetal genetic or structural abnormalities. The decision to terminate a pregnancy is made by a perinatology council composed of three fetal medicine specialists. According to the law of our country, there is no upper limit for abortion when there is a severe genetic or structural anomaly.

During the 34-month study period, 854 pregnant patients were directed to our perinatology clinic. Of these, 349 women who were at 14 to 32 weeks' gestation and had additional fetal genetic or structural abnormalities were evaluated for the presence of CPO. Twenty-one patients were excluded because adequate images could not be obtained due to technical factors such as maternal obesity, retroverted uterus, permanent fetal lateral or prone position, or oligohydramnios. Seventeen patients with missing data or who could not be followed-up were also excluded. Thus, 311 patients were included (Figure 1). The following data were collected: Patient age, reason for referral, ultrasound findings, type of invasive tests, and genetic results. Pregnancy outcome data were also obtained from the hospital database.

Ultrasonography (USG) examination of all patients was performed with a Voluson E6 (GE Healthcare GmbH & Co. OG, Austria) by target-

ed ultrasound by two experienced fetal medicine specialists. The fetal palate was examined with an abdominal 4-8 MHz transducer. Examiner 1 (Cİ) visualized the palate with an ATV (Figure 2-3), whereas examiner 2 (ŞÇ) visualized the palate with an ESV. To avoid bias in the results, the physicians who performed both techniques were blinded to each other's results. Genetic testing, including karyotyping and microarray (a-CGH), was recommended for all patients diagnosed or suspected of having CPO. All sonographic-pathologic findings of the palate were confirmed by a pediatrician after birth. Children without postnatal confirmation of CPO were excluded from the study.

The present study was approved by the Ethics Committee of Etlik Zubeyde Hanim Maternity Hospital (Decision number: 06/15, 2021).

Application of ATV and ESV Methods

To fully visualize the palate, the fetal skull should ideally show the fetal nasal bone in the midsagittal plane. The ultrasound transducer is placed perpendicular to the secondary palate and then tilted caudally 90°. This avoids the acoustic shadow of the alveolar ridge and enables visualization of the echogenic line of the hard palate^{5,10}. To visualize the uvula, the probe is moved parallel to the caudal pole from the point where the biparietal diameter was measured. Slight movements produce a hypoechoic spatial image between the two echogenic lines, identified as the typical "equal sign", or the probe is moved in the frontal plane into the nasopharynx and the uvula is imaged in the same plane as the epiglottis⁴. The normal ATV and ESV are shown in Figures 2-4.

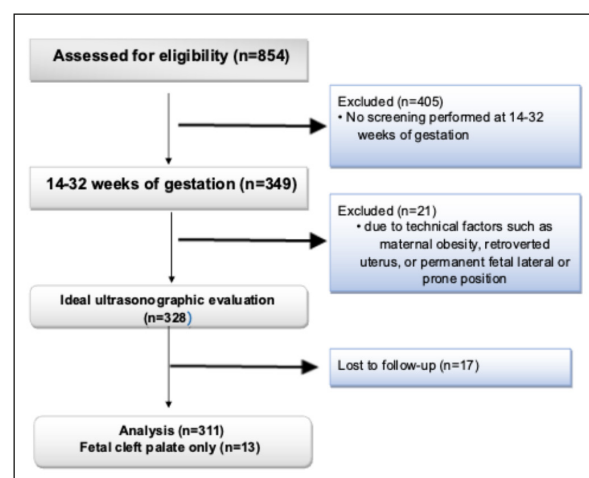


Figure 1. Flow Diagram of the study.

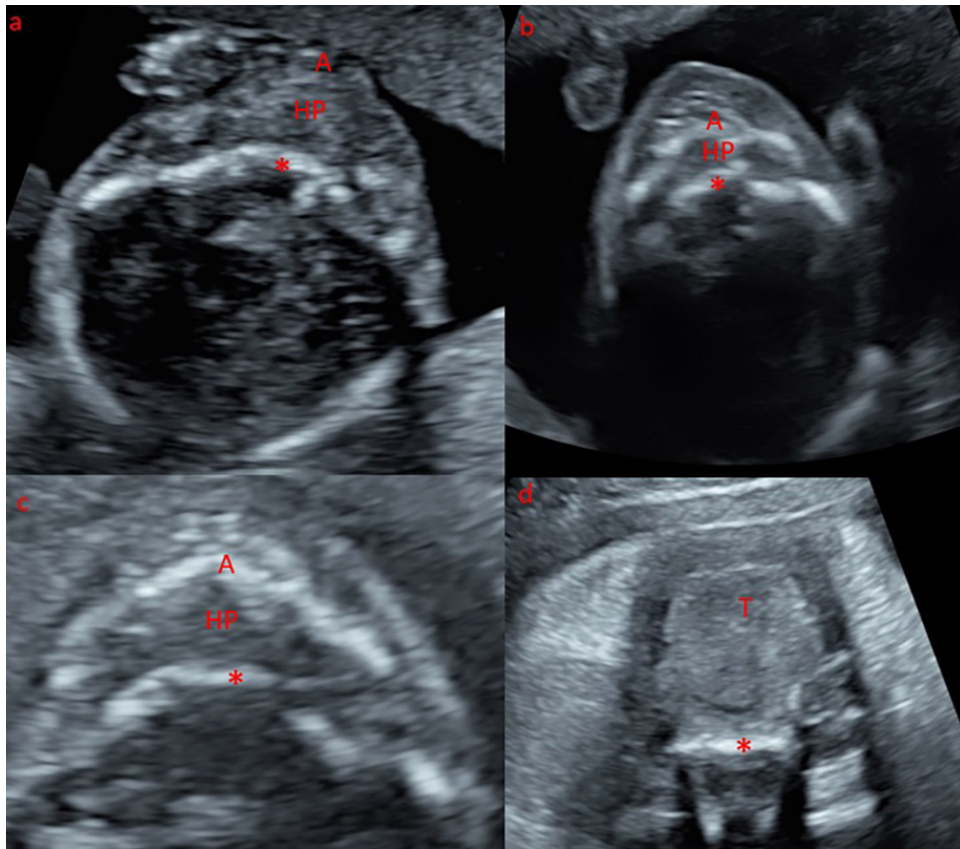


Figure 2. Normal palate as seen on the axial transverse view with 2D ultrasound. **a**, Fetus at gestational maturity (GM) = 14 weeks. **b**, Fetus at GM = 20 weeks. **c**, Fetus at GM = 30 weeks. **d**, Fetus at GM = 34 weeks. A: alveolar bone; HP: hard palate; T: tongue; *Soft hard palate interface.

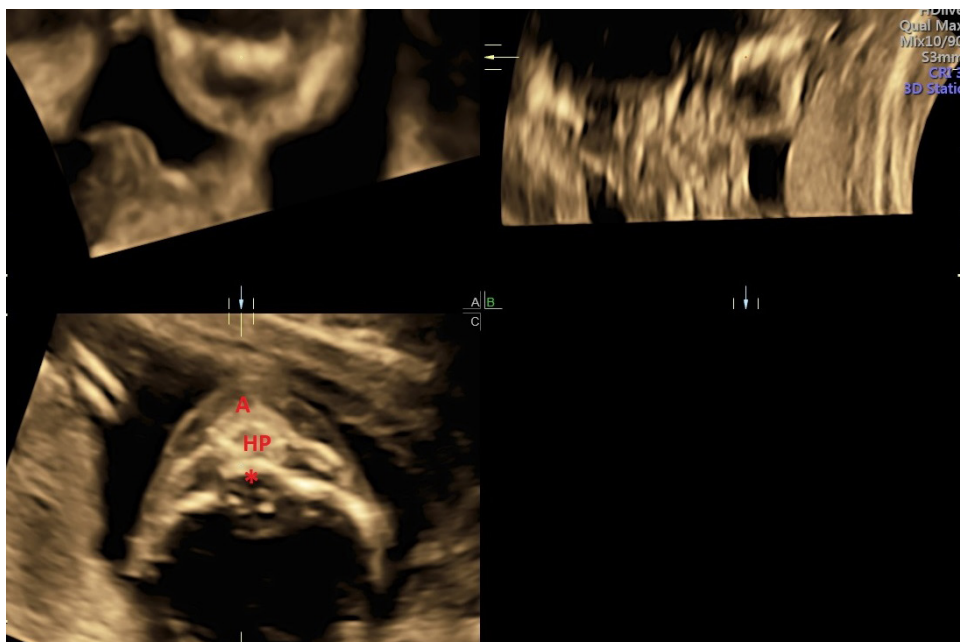


Figure 3. Normal palate as seen on the axial transverse view with 3D ultrasound. A: Alveolar bone; HP: hard palate; *Soft hard palate interface.

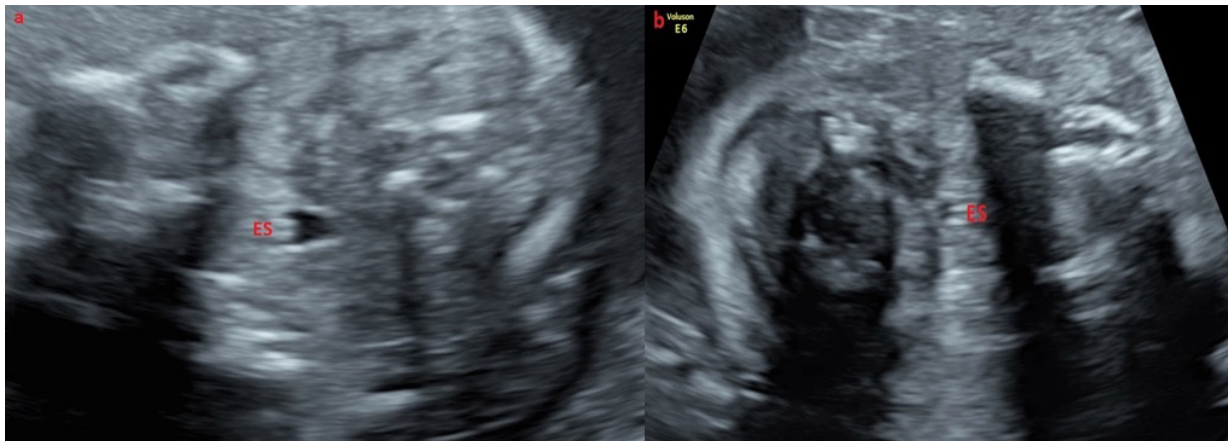


Figure 4. Normal palate as seen in the “equal sign” view on 2D USG. **a,** Fetus at GM = 22 weeks. **b,** Fetus at GM = 28 weeks. ES: equal sign.

Statistical Analysis

Statistical analysis was performed using SPSS version 26 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA). Sensitivity, specificity, positive predictive value, and negative predictive value of ATV and ESV in diagnosing isolated CP were calculated. A *p*-value lower than 0.05 was considered to be statistically significant.

Results

Thirteen of 311 fetuses that met the study criteria had CPO. Investigator 1 suspected 17 CPO on prenatal ultrasonography by the ATV method. Thirteen of them were correctly positive, while there were four false positives (Table I) (Figure 5). Using the ATV method, 13 of 13 CPO could be diagnosed, but four fetuses with intact palates were incorrectly diagnosed as CPO. Using the ESW method, 10 of 13 patients could be diagnosed as CPO, but seven

fetuses with intact palates were diagnosed as CPO. Accordingly, sensitivity, specificity, positive predictive value, and negative predictive value for ATV were 100%, 98.7%, 76.4%, and 100%, respectively, and for ESW were 76.9%, 97.8%, 58.9%, and 99%, respectively (Table I). Table II shows the clinical data of the 13 patients with CPO. Five chromosomal abnormalities or genetic syndromes were diagnosed prenatally in 13 patients. These were three 22q11 microdeletions, one case of trisomy 9, and one case of Apert syndrome (Table II). Pierre Robin sequence was diagnosed postnatally in one patient (case 7). Additional anomalies were detected in 10 of 13 patients. Pregnancy was terminated in 6 patients.

Figure 5 shows a false-positive CPO. The fetus had a choroid plexus cyst and an inlet-type ventricular septal defect. Amniocentesis revealed trisomy 18. Examiner 2 suspected that the fetus had CPO because he suspected a bifid uvula (Figure 5b). The family decided to terminate the pregnancy, and no CP was found on postnatal

Table I. Sensitivity and specificity values of axial transverse and equal sign views.

	Soft palate hard palate interface			Equals sign		
	N (311)	Value	95% CI	N (311)	Value	95% CI
Sensitivity ¹	13/13	100%	73.5-100%	10/13	76.9%	46.2-94.9%
Specificity ²	307/311	98.7%	96.8-99.5%	304/311	97.8%	95.4-99.1%
Positive predictive value	13/17	76.4%	55.1-89.6%	10/17	58.9%	39.3-75.9%
Negative predictive value	307/307	100%	99.7-100%	304/307	99%	94.4-98.5%

¹True positive (True positive + False negative). ²True negative (True negative + False positive).



Figure 5. The false-positive case as visualized with axial transverse and equal sign views. **a**, Area of suspicion for cleft palate seen with axial transverse view. **b**, Abnormal equal sign view. **c**, Fetal profile after termination because of trisomy 13. Red circle: abnormal view.

examination. A high arched palate was noted, which was thought to be the reason for the false positive CPO diagnosis.

Figure 6 shows the bifid uvula in case 9. This patient was a 23-year-old woman who was referred for a prenatal screening test that indicated high risk for trisomy 21. Ultrasonography revealed a male fetus with cerebellar hypoplasia, aberrant right subclavian artery, and CPO. Chromosomal microarray analysis revealed a 22q11 microdeletion, and the pregnancy was terminated.

Figure 7 shows the prenatal sonographic images of cases 1, 2, 9, and 6 and CPO images seen at postabortal examination. Figure 8 shows the sonographic images of a fetus with Goldenhar syndrome. The patient was a 19-year-old primipara referred for fetal micrognathia at gestational maturity (GM) = 20 weeks. Signs of Goldenhar syndrome were noted on the USG, namely an asymmetric profile, microear, micrognathia, and CPO. The family declined invasive diagnostic testing, and the male fetus was aborted.

Figure 9 shows CPO on a sagittal T2-weighted image with magnetic resonance (MR) (Case 8).

Discussion

In this study, we investigated the diagnostic accuracy of ATV and ESV in 2D ultrasound in the diagnosis of CPO. Our results showed that the sensitivity, specificity, positive predictive value, and negative predictive value for ATV were 100%, 98.7%, 76.4%, and 100%, respectively, while they were 76.9%, 97.8%, 58.9%, and 99%, respectively for ESV in detecting CPO. Currently, there are no guidelines recommending routine

palate examination for prenatal screening in the second trimester. There are two reasons for this. First, it is difficult to visualize the palate because it is acoustically shadowed by the surrounding bony environment. Second, there is no standardized CPO screening procedure. However, CPO is associated with numerous syndromes, especially when the hard palate is involved. Therefore, prenatal screening of CPO is of great benefit, especially in high-risk patients.

In the last two decades, numerous prenatal imaging techniques for the palate have been proposed. De Robertis et al¹¹ reported that retrorhinal-triangular imaging of facial clefts in the first trimester was more sensitive than maxillary imaging, but that this technique was inadequate for the diagnosis of cleft palate. In clinical practice, both ATV and ESV are well applicable after the first trimester. Wilhelm and Borgers⁴ achieved 98.4% visualization of the soft palate and/or uvula with 2D ultrasound. In addition, Fuchs et al⁵ demonstrated that it is possible to scan the hard palate in the second trimester with ATV. Later, Brusilov et al¹⁰ showed that the diagnosis of CPO can be made with ATV as early as week 14. Faure et al⁸ in their 7-year study diagnosed 43 CPO with ATV on 2D and 3D ultrasound and also classified cleft palate ultrasonographically. Frisova et al¹² recommended the use of a 2D view in the sagittal plane to visualize the palate, along with similar visualization in the axial plane by manual extrusion training of the fetal head.

Lai et al¹³ reported in their recent meta-analysis that fetal USG has a sensitivity of 87% and a specificity of 98% for detecting cleft palate in high-risk pregnancies; however, this analysis was not limited to CPO. In a prospective study of high-risk patients, Maarse et al¹⁴ examined 2,836 pregnant women with 2D and 3D ultra-

Table II. Clinical data of all cases diagnosed with cleft palates without cleft lip.

Case No.	Postnatal diagnosis	Examiner 1 prenatal diagnosis	Examiner 2 prenatal diagnosis	Age	The reason for high-risk pregnancy	Ultrasound finding	Result of Karyotype/ Microarray	Gender	Fetal outcome
1	Hard and soft palate	Cleft palate	Cleft palate	25	High risk of antenatal screening test	Double-outlet ventricle (Fallot type), vermian hypoplasia	Trisomy 9	Female	Termination
2	Hard and soft palate	Cleft palate	Normal	29	Ventriculomegaly	Bilateral club foot, cerebellar hypoplasia, tri-ventriculomegaly, micrognathia	Normal	Female	Termination
3	Hard and soft palate	Cleft palate	Cleft palate	31	Tetralogy of Fallot	Tetralogy of Fallot, micrognathia, nasal hypoplasia	Normal	Male	Termination
4	Hard and soft palate	Cleft palate	Cleft palate	30	Retrognathia	Micrognathia	Normal	Female	Delivery
5	Hard and soft palate	Cleft palate	Cleft palate	19	Micrognathia	Goldenhar syndrome (asymmetric profile, micro ear, micrognathia)	None	Male	Termination
6	Hard and soft palate	Cleft palate	Cleft palate	24	Cystic hygroma	Aberrant right subclavian artery	22q11 microdeletion	Female	Termination
7	Hard and soft palate	Cleft palate	Cleft palate	37	Drug abuse, choroid plexus cyst	Micrognathia	None	Male	Delivery
8	Hard and soft palate	Cleft palate	Cleft palate	32	High risk of antenatal screening test	Hyperechogenic intestine	None	Female	Delivery
9	Hard and soft palate	Cleft palate	Cleft palate	23	High risk of antenatal screening test	Aberrant right subclavian artery, cerebellar hypoplasia	22q11 microdeletion	Female	Delivery
10	Hard and soft palate	Cleft palate	Cleft palate	31	High risk of antenatal screening test	Thymus hypoplasia, right aortic arch, ambiguous genitalia	22q11 microdeletion	Male	Delivery
11	Hard and soft palate	Cleft palate	Cleft palate	39	High risk of antenatal screening test	Fetal pyelectasis	Normal	Female	Delivery
12	Hard and soft palate	Cleft palate	Normal	24	High risk of antenatal screening test	Normal	None	Male	Delivery
13	Hard and soft palate	Cleft palate	Normal	24	Clench hand, Malalignment VSD	Hypertelorism, syndactyly, Malalignment VSD, Craniosynostosis	Apert syndrome (FGFR2 mutation)	Male	Termination

VSD: ventricular septal defect.

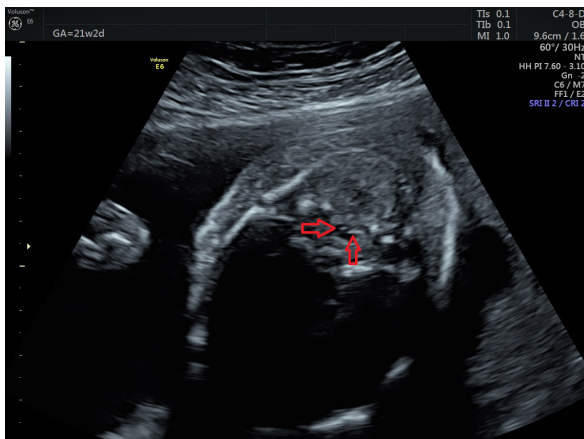


Figure 6. Bifid uvula demonstrated on coronal view (arrows).

sound and failed to detect three patients with CPO prenatally. Similarly, Dochez et al¹⁵ showed that they could make a prenatal diagnosis in only eight (40%) of 20 patients with CPO, and 87.5%

of these patients had a Pierre Robin sequence. Zheng et al¹⁶ demonstrated that the overall accuracy of USG for the diagnosis of orofacial cleft was 59.09%, and reported mixed results for the diagnostic accuracy of USG in cleft palate. Our results showed that ATV has higher specificity and sensitivity in diagnosing CPO in high-risk pregnancies. These results are consistent with the available literature¹⁴⁻¹⁶ reporting that ATV has a higher success rate in diagnosing CPO. The sensitivity and specificity of the techniques in the present study were influenced by parameters such as the study group, which included all high-risk pregnancies, and the fact that USG was performed by experienced perinatologists. False-positive cases were due to ultrasonographic assessment being performed in the wrong section of the ATV view. It is also noteworthy that despite the high practicality of ESV in clinical practice, a higher rate of false-positive cases was observed with ESV.

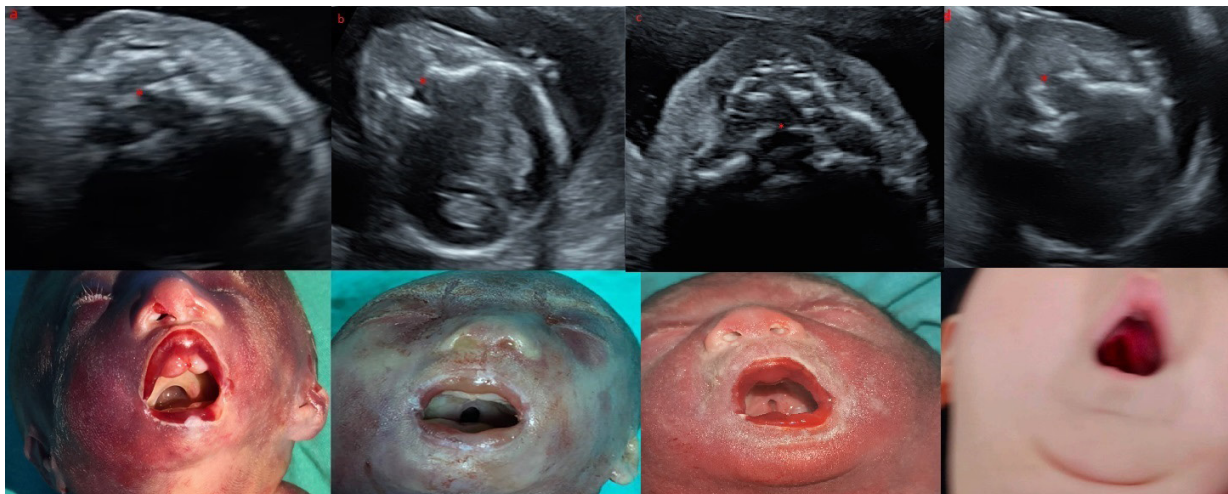


Figure 7. Prenatal ultrasound from the axial transverse view and postnatal macroscopic views of the cases with cleft palate without cleft lip. **a**, Case 1. **b**, Case 2. **c**, Case 9. **d**, Case 6. *The gap between soft-hard palate interface.

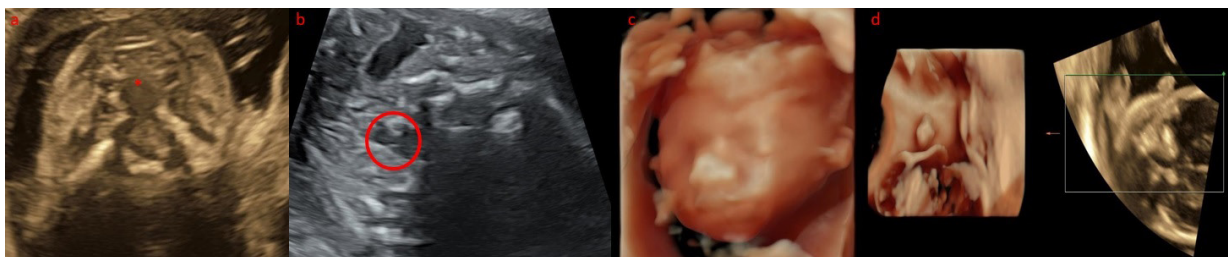


Figure 8. Fetus with Goldenhar syndrome with cleft palate and without cleft lip (Case 5). **a**, Cleft palate on axial transverse view. **b**, Abnormal equal sign view. **c**, Fetal profile as seen with 3D ultrasound. **d**, Micro ear as seen with 3D ultrasound. *The gap between soft-hard palate interface; red circle: abnormal equal sign.

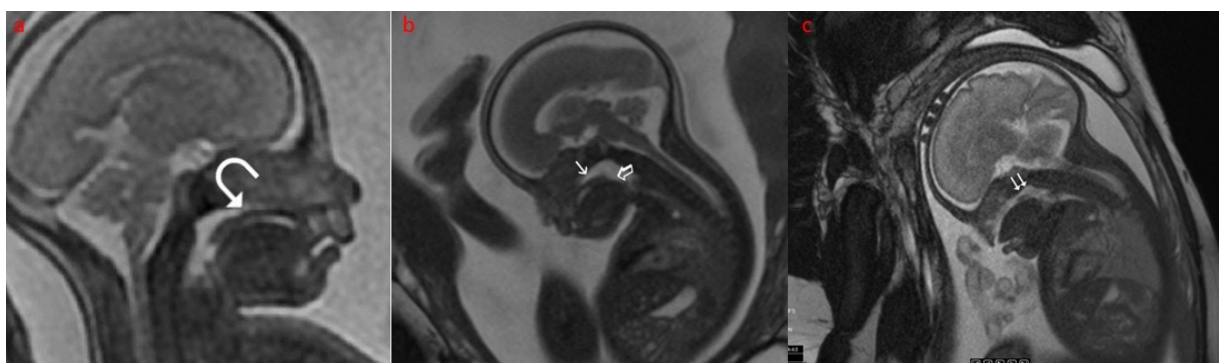


Figure 9. Normal and cleft palate views with MR. **a**, Normal soft palate (curved arrow) is seen in sagittal T2-weighted image of the fetal face. **b**, Bifid uvula (*confirmed after birth*) is seen in sagittal T2-weighted image. Compared to this image with normal soft palate in **a**, while most of the soft palate is intact (*arrow*), the most posterior part of it (*open arrow*) is missing. **c**, Cleft palate is seen in sagittal T2-weighted image. Only a small part of the soft palate is seen posteriorly (*double arrows*) (Case 7).

The diagnosis of oral clefts has significant psychological implications which also underscores the importance of prenatal diagnosis¹⁷. In addition, prenatal diagnosis aids the perinatal management such as preparation for effective airway management in cases associated with micrognathia¹⁸. Nonetheless, the strength of this study lies in the novelty of including many high-risk pregnant patients in screening for CPO. In addition, this study was designed so that the diagnostic performance of the two techniques was performed in the same pregnant population by similarly experienced ultrasonographers. In addition, there was no more than 3 days between the assessments of the two perinatologists for each case. Therefore, the influence of interobserver on the study results was minimized.

Limitations

This study has some limitations that should be mentioned. First, we found that the incidence of CPO was so high in 13 of 311 fetuses at high risk for fetal anomalies that this high incidence is not generalizable to the general pregnant population. Second, because two perinatologists were aware of the CPO study, they may have focused more on the detection of CPO than on routine prenatal fetal screening, which could influence the results of the study. Third, in this study, we did not perform 3D ultrasound to detect CPO, which is available in many centers and could increase diagnostic accuracy.

Conclusions

ATV can diagnose isolated cleft palate in patients without cleft lip with high sensitivity and

specificity. Although the “equal sign” view is a more viable option for diagnosing secondary cleft palate, its sensitivity and specificity are low compared with the axial transverse view.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contribution

Cantekin Iskender, Ozge Yucel Celik, Mevlüt Bucak, Sevki Celen: conception and design of the study; Erkan Saglam, Mujdecan Ibanoglu, Aysegul Ozturk Kaymak: acquisition of data, or analysis and interpretation of data; Tolgay Tuyan İlhan, Neval Cayonu Kahraman, Ozgur Arat, Cantekin iskender: drafting the article or making critical revisions related to relevant intellectual content of the manuscript; Elif Ergun, Sevki Celen: supervision; validation and final approval of the version of the article to be published.

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Informed Consent

Subjects followed the principle of voluntary participation and signed the study consent form.

Ethics Approval

The present study was approved by the Ethics Committee of Etlik Zubeyde Hanim Maternity Hospital (Decision number: 06/15, 2021). The privacy and safety of subjects were adequately protected in accordance with clinical study guidelines.

Availability of Data and Materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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