European Radiology (2019) 29:5600–5606
https://doi.org/10.1007/s00330-019-06089-9

HEAD AND NECK

The prenatal diagnosis and classification of cleft palate: the role and value of magnetic resonance imaging

Weizeng Zheng[1] · Baohua Li[2] · Yu Zou[1] · Fenlan Lou[1]

Received: 2 December 2018 / Revised: 28 January 2019 / Accepted: 8 February 2019 / Published online: 18 March 2019

Abstract

Objective The aim of this study was to evaluate the value of MRI in the prenatal diagnosis and classification of cleft palate (CP).

Methods We collected 94 fetal cases that were suspected of cleft palate with or without cleft lip by prenatal ultrasound (US) and then carried out further MRI to examine the entire body of each fetus within 1 week. The diagnoses resulting from MRI and US examination were compared separately with the final diagnoses obtained from postnatal physical examination or fetal autopsy. The diagnostic accuracy between MRI and US was then determined.

Results During the follow-up period, the results for 6 fetuses (6.38%) were lost. Of the remaining 88 cases, the final diagnoses identified 23 cases of cleft lip (CL), 45 cases of unilateral cleft lip with cleft palate (UCLP), 4 cases of median cleft lip with cleft palate (MCLP), 12 cases of bilateral cleft lip with cleft palate (BCLP), 3 cases of unilateral cleft lip and cleft alveolus (CLA), and 1 case of isolated cleft palate (CPO). The total accuracy rate of US was 59.09%, while that of MRI was 92.05%. More importantly, 81 cases were accurately identified by MRI; the accuracy rate for CL, UCLP, MCLP, BCLP, CLA, and CPO was 86.96%, 95.56%, 100%, 91.67%, 66.67%, and 100%, respectively.

Conclusion Our results suggest that MRI could be a useful adjunct to US examination in the prenatal diagnosis of fetuses with cleft palate, and further demonstrates the classification and degree of involvement of the cleft palate.

Key Points

- *MRI is a useful adjunct to prenatal ultrasound.*
- *MRI has a higher accuracy rate for CP.*
- *The accurate classification of CP diagnosed by MRI can guide clinical management.*

Keywords Prenatal diagnosis · Magnetic resonance imaging · Cleft lip · Cleft palate · Classification

Abbreviations

BCLP	Bilateral cleft lip with cleft palate
CL	Cleft lip
CL/P	Cleft lip with or without cleft palate
CLA	Cleft lip and cleft alveolus
CP	Cleft palate
CPO	Isolated cleft palate
MCLP	Median cleft lip with cleft palate
UCLP	Unilateral cleft lip with cleft palate

Introduction

Cleft lip, with or without cleft palate (CL/P), is the most common congenital craniofacial anomaly and the second most common birth defect worldwide. The incidence of this condition is 0.80 to 2.69 per 1000 births [1]. Currently, the rate of occurrence ranges from 1.33 to 2.22 per 1000 births in the Chinese population [2]. As a cleft palate (CP) affects neonatal feeding, abnormal speech, hearing loss, facial development, and other functions [3], and because surgical correction is more difficult or associated with postoperative complications [4], CP has a poorer prognosis than simple

✉ Baohua Li
lbh19787@zju.edu.cn; lbh8888@163.com

[1] Department of Radiology, Women's Hospital, Zhejiang University School of Medicine, Xueshi Rd No. 1, Hangzhou Zhejiang, People's Republic of China

[2] Department of Obstetrics, Women's Hospital, Zhejiang University School of Medicine, Xueshi Rd No. 1, Hangzhou 310006 Zhejiang, People's Republic of China

cleft lip (CL) [5, 6]. Therefore, the identification of a non-invasive, rapid, and easily reproducible examination that could distinguish between cleft lip and cleft palate is of great clinical importance.

Since the lip and anterior palates have distinct developmental origins from the secondary palate, clefts of these areas can be subdivided into CL/P and isolated cleft palate (CPO) [7]. Anatomically, the palate is also divided into three parts: the anterior or primary palate (alveolar ridge), the posterior or secondary palate, and the soft palate. Therefore, there are several types of CP: cleft lip and cleft alveolus (CLA), cleft lip with cleft palate (CLP), isolated cleft palate, and cleft soft palate [8]. The orofacial cleft can be isolated, or can be part of a syndrome; in particular, median CLP (MCLP) and CPO are more common with some abnormalities, such as Pierre Robin's sequence and holoprosencephaly [9–11]. In the case of bilateral CLP (BCLP), surgery is more difficult and prognosis is poor [12]. Hence, prenatal imaging examination is very instructive for detection and classification of CP and helps preparing and management.

Currently, ultrasound (US) is extensively used for prenatal diagnosis. However, US examination can be limited by several factors including advanced gestational age, maternal obesity, oligohydramnios, complex fetal anomalies, fetal position, overlying limbs, or the technical skills of the performing operator [13]. Clefts may be unilateral or bilateral and are classified depending upon anterior and/or posterior palate involvement; such complexity is difficult to discern by prenatal US [9, 14]. Magnetic resonance imaging (MRI), as a useful adjunct to US, has been involved in the diagnosis of fetal abnormalities. However, the safety is an important issue concerning MRI, including static field exposure, gradient field switching, and radiofrequency power deposition. Although a few animal model studies have shown general deleterious embryonic effects, multiple agencies around the world have not found that MRI affected pregnant women, human fetuses, and neonates in the second and third trimesters [15–18]. The Food and Drug Administration (FDA) and other international agencies have published the specific absorption ratio (SAR) limits for whole body and local body. Strizek et al [19] found no adverse effects of exposure to 1.5-T MR imaging in utero on neonatal hearing function or birth weight percentiles.

MRI represents a valuable technique for detection of fetal facial deformities [20–22]. However, it has received only scant attention in terms of diagnostic value for patients with cleft palate with or without cleft lip.

The present study aimed to evaluate the added role of MRI in patients who were firstly diagnosed with CP with or without cleft lip by transabdominal US, and subsequently underwent in utero MRI within 1 week.

Materials and methods

Patients

The present study was approved by the Institutional Review Board, Women's Hospital, Zhejiang University School of Medicine. Informed consent was obtained from all individual participants included in the study.

Fetuses were enrolled between January 2014 and January 2018 at the Women's Hospital, Zhejiang University School of Medicine, Hangzhou, China. Fetal cases diagnosed as CP with or without CL by US were recruited when prenatal diagnostic ultrasound found that the continuity of alveolus or palatine bone was interrupted, or when ultrasound images indicated that the alveolar bone was disordered or irregular.

Transabdominal US examinations were performed by two experienced ultrasound physicians using Voluson 730D (GE) or Voluson E8 (GE) systems with a 3.5–6 MHz convex probe. No specific imaging requirements were provided, except that operators were asked to visualize the defects by three-dimensional (3D) surface rendering. All cases, examined by US, underwent MR imaging within 1 week.

All prenatal MR images were obtained with a 1.5-T unit (GE Signal HDxt) and an eight-element phased array body coil. The mothers were placed in a supine or left oblique position without sedative. After a localizing gradient echo sequence, we randomly selected single-shot fast spin echo T2-weighted imaging (SSFSE: TR/TE, 3100/90 ms; bandwidth, 32 kHz; FOV, 30 × 32 cm; matrix, 256 × 192; slice thickness, 3 to 5 mm; gap, 0 to 1 mm; NEX, 1) and fast imaging employing steady-state acquisition (FIESTA: TR/TE, 3.6/1.7 ms; bandwidth, 80 Hz; FOV, 32 × 32 cm; matrix, 256 × 224; slice thickness, 4 to 5 mm; gap, 0 to 0.5 mm; flip angle, 55°) according to fetal face position in the axial, coronal, and sagittal planes. Three-dimensional fast imaging employing steady-state acquisition (3D-FIESTA) sequence (TR/TE, 3.5 ms/minimum; slice thickness, 2 mm; FOV 35 × 35 cm; flip angle, 60°) was then used to evaluate fetal CL/P during 13–17-s breath-hold. In our study, the SAR values of all sequences were lower than 2.0 W/kg.

During fetal MRI scanning, transverse views were studied to assess the continuity of the upper lip and upper alveolar ridge and the laterality of the nasal septum, and the four anterior tooth buds were also well seen. Especially when amniotic fluid filled the fetal mouth, coronal views were particularly important for visualizing the fetal morphology: nose and nasal septum, lips, and secondary palate by visualization of the uvula and palatine process of the maxilla. In addition, sagittal views provided complementary information on the secondary palate and were used to detect the potential change on the face and neck. Sometimes we needed to scan a plane again when motion artifacts in the fetus affected image's quality. We considered that CL involved an opening in the upper lip that may

extend into the nose on axial or coronal T2-weighted imaging. When the upper lip and the primary palate were filled with hyperintense amniotic fluid or the alveolar bone was irregular, fetus was diagnosed as CLA. The secondary and/or primary palate defects were observed as amniotic fluid communicates between the oro- and nasopharynx, appearing either on the coronal images or on the sagittal images as bright signal extending upwards from the tongue, and fetus was diagnosed as CLP. Meanwhile, the continuity of the upper lip or alveolar ridge dictated that the CP was unilateral or bilateral. CPO did not typically affect the dentition found within the alveolar processes on either side of the cleft. Our main interest in 3D-FIESTA images was focused not only on evaluation of fetal facial details but also on the display of surface-rendered images. If we are not confident in whole facial deformity, volume reconstruction (VR) image had visually displayed the appearance of the cleft and face, as a complement to 2D images. It is significant for pediatric surgeons to observe the classification of CP and the extent of the defect by multiplanar reconstructions (MPR) and other forms of image post-processing.

According to this standard, all MRI images in the present study were carefully evaluated by two radiologists with proven experience in prenatal diagnosis; discrepancies were resolved by consensus.

Follow-up records

Patients were followed up by an interview at the clinic or by telephone call. Postnatal diagnosis was determined by the operating surgeon, newborn physical examination, or fetal autopsy, and compared separately with intrauterine imaging findings. All cleft types were recorded either as an isolated finding or as being associated with other structural anomalies. Of the 94 fetal cases, 6 (6.38%) were lost during follow-up.

Statistical analysis

Statistics were assessed using software packages SPSS version 22.0. The correlation of diagnosis results between US and MRI was determined by Pearson's chi-square test. Additionally, Student's t test was used to analyze the differences between the diagnosis gestational age of US and MRI. All statistical tests were two-sided, and p values 0.05 were considered statistically significant.

Results

Patient characteristics

Of the 94 cases, the mean gestational age at MRI diagnosis was 26.50 ± 3.59 weeks (range 19–39), the mean gestational age at US diagnosis was 26.06 ± 3.59 weeks (range 19–38), and there is no statistical difference in the gestational age of MRI and US ($p = 0.41$). The mean age of mothers was 29.69 ± 5.31 years (range 18–45). Moreover, for US, the gestational age at prenatal diagnosis was not significantly different between accurate diagnosis (26.35 ± 4.41 weeks) and misdiagnosis (25.64 ± 2.14 weeks) ($p = 0.39$). For MRI, the gestational age at prenatal diagnosis was not significantly different between accurate diagnosis (26.68 ± 3.79 weeks) and misdiagnosis (25.43 ± 2.07 weeks) ($p = 0.32$). These data provide that the gestational age makes no difference in missing diagnosis.

We performed data analyses in 88 patients, and systematic karyotyping was examined in 13 fetuses (13.83%); these tests did not reveal any chromosomal defects. Using US examination, there were 82 cases of unilateral CLP (UCLP), 5 cases of BCLP, and 1 case of CPO. However, in the same cases, MRI identified 21 cases of CL, 47 cases of UCLP, 4 cases of MCLP, 11 cases of BCLP, 4 cases of unilateral CLA, and 1 case of CPO, as shown in Table 1. A representative MRI photograph and a detailed diagnostic description are presented in Fig. 1. Eventually, 26 of the pregnant women decided to continue with pregnancy, while 62 pregnant women chose to induce labor.

Comparing US and MRI diagnosis

According to newborn physical examination or fetal autopsy, there were 23 diagnosed cases of CL, 45 cases of UCLP, 4 cases of MCLP, 12 cases of BCLP, 3 cases of unilateral CLA, and 1 case of CPO. The total accuracy of US was 59.09%, while that of MRI was 92.05%; the data was significantly different ($p = 3.63^{-7}$). For US examination, 23 cases of CL were misdiagnosed as CP; the accuracy of BCLP and UCLP was separately 41.67% and 100%, and CLA or MCLP deformities were not clearly diagnosed. MRI refuted 21 diagnoses of UCLP made by US examination and revised these diagnoses to CL, although 1 case was misdiagnosed and further revised by fetal autopsy. In addition, the most important factor was that the accuracy rate of CL, UCLP, MCLP, BCLP, CLA, and CPO diagnoses was 86.96%, 95.56%, 100%, 91.67%, 66.67%, and 100% by MRI, respectively. The difference in BCLP diagnosis when comparing US and MRI methodology was significant ($p = 0.03$), although there was no difference in terms of UCLP diagnosis ($p = 0.475$). Based on these results, we can confirm that MRI is an effective supplemental method for US examination. MRI showed a high diagnostic accuracy for cleft palate and, more importantly, had better diagnostic criteria for the specific classification of cleft palate. Thus, MRI can help clinicians to guide patient counseling with regard to postnatal management.

Merging other malformations

MRI could not only help in the diagnosis and classification of CL/P but also identify other fetal malformations. The final results

Table 1 Comparison of prenatal imaging and follow-up results in 88 cases of fetal CL/P

n	US diagnosis before referral for MRI	MRI diagnosis	Postnatal diagnosis	US vs MRI	Additional structural anomalies (on US* and/or MRI†)
20	UCLP	CL	CL	Misclassification on US ($n = 20$)	Missed on prenatal imaging ($n = 1$): nasal bone depression, intersecting palms, inferior orbital fissure
3	UCLP	UCLP ($n = 2$), CLA ($n = 1$)	CL	Misclassification on US and MRI ($n = 3$)	No
2	UCLP	CLA	CLA	Misclassification on US ($n = 2$)	No
1	UCLP	UCLP	CLA	Misclassification on US and MRI ($n = 1$)	No
43	UCLP	UCLP	UCLP	US findings confirmed ($n = 43$)	Tetralogy of Fallot*† ($n = 1$), twin*† ($n = 3$)
2	UCLP	CLA ($n = 1$), CL ($n = 1$)	UCLP	Misclassification on MRI ($n = 2$)	No
4	UCLP	MCLP	MCLP	Misclassification on US ($n = 4$)	Partial absence of corpus callosum†, holoprosencephaly† ($n = 1$), Dandy-Walker malformation*†, single umbilical arteries*†, cardiac single atrial and single ventricular malformations*† ($n = 1$), absence of nasal bone*†, semilobar holoprosencephaly*†, narrow intraocular distance*†, left eye dysplasia† ($n = 1$)
5	BCLP	BCLP	BCLP	US findings confirmed ($n = 5$)	Cerebellar hypoplasia*†, widened intraocular distance*† ($n = 1$), sacrococcyx teratoma*† ($n = 1$), right repetitive renal pelvis*† ($n = 1$)
6	UCLP	BCLP	BCLP	Misclassification on US ($n = 6$)	Dandy-Walker malformation† ($n = 1$), nasal malformation† ($n = 1$)
1	UCLP	UCLP	BCLP	Misclassification on US and MRI ($n = 1$)	No
1	CPO	CPO	CPO	US findings confirmed ($n = 1$)	Micrognathia† ($n = 1$)

*Detected on US. † Detected on MRI

CL cleft lip, *CP* cleft palate, *UCLP* unilateral cleft lip with cleft palate, *BCLP* bilateral cleft lip with cleft palate, *CLA* cleft lip and alveolus, *CPO* isolated cleft palate, *MCLP* median cleft lip with cleft palate, *MRI* magnetic resonance imaging, *US* ultrasound

from fetal autopsy identified 11 cases with other malformations in 88 cases of CL/P, including holoprosencephaly ($n = 3$), velocardiofacial ($n = 2$), and Pierre Robin's sequence ($n = 1$) (Table 1). There was only one severe complication with UCLP (2.22%), but we found that the rates of BCLP and MCLP complicated by deformity were 41.67% (5/12) and 75.00% (3/4), respectively. US failed to accurately diagnose such abnormal brain development in 2 fetuses. Regrettably, the deformity of 1 case with nasal bone depression and inferior orbital fissure was missed by both prenatal US and MRI; these malformations were ultimately detected by fetal autopsy. These data provide useful information with regard to detecting the presence of malformations associated with other organs for further clinical management.

Discussion

In the present study, we identified that MRI is a useful adjunct to prenatal US in the diagnosis of CL/P. For MRI or US, the gestational age at prenatal diagnosis was not significantly different between accurate diagnosis and misdiagnosis. The accurate rate of MRI diagnosis for the patients who were suspected of CP, with or without CL by US, was as much as 92.05%. Furthermore, MRI could demonstrate the classification and degree of involvement of the cleft palate.

CL/P is the most common congenital anomaly involving the face. In recent years, US has been widely used in the diagnosis of CL/P. Jean-Marc et al [23] reported that recognition rates of the presence of an anomaly of the fetal face using US can be as high as 85%. In another study, Maarse et al [24] reported a sensitivity of 88% for CL/P by ultrasound screening, but the accuracy for CP was less than 73%. Compared with US, MRI has the characteristics of the strong tissue contrast, multiplanar ability, and resolution and is less affected by human factors. Furthermore, MRI has been reported to involve in the diagnosis of fetal cleft lip and/or cleft palate [17, 21]. In our study, MRI identified 21 cases of CL and 67 cases of CP in all cases which were suspected as CP with or without CL by the US examination. The accuracy of the MRI diagnosis was 92.05%, according to postnatal physical examination or fetal autopsy. Marjanne et al [3] also reported that the positive predictive value of MRI for the involvement of CP was 96%, and that the negative predictive value was 80%.

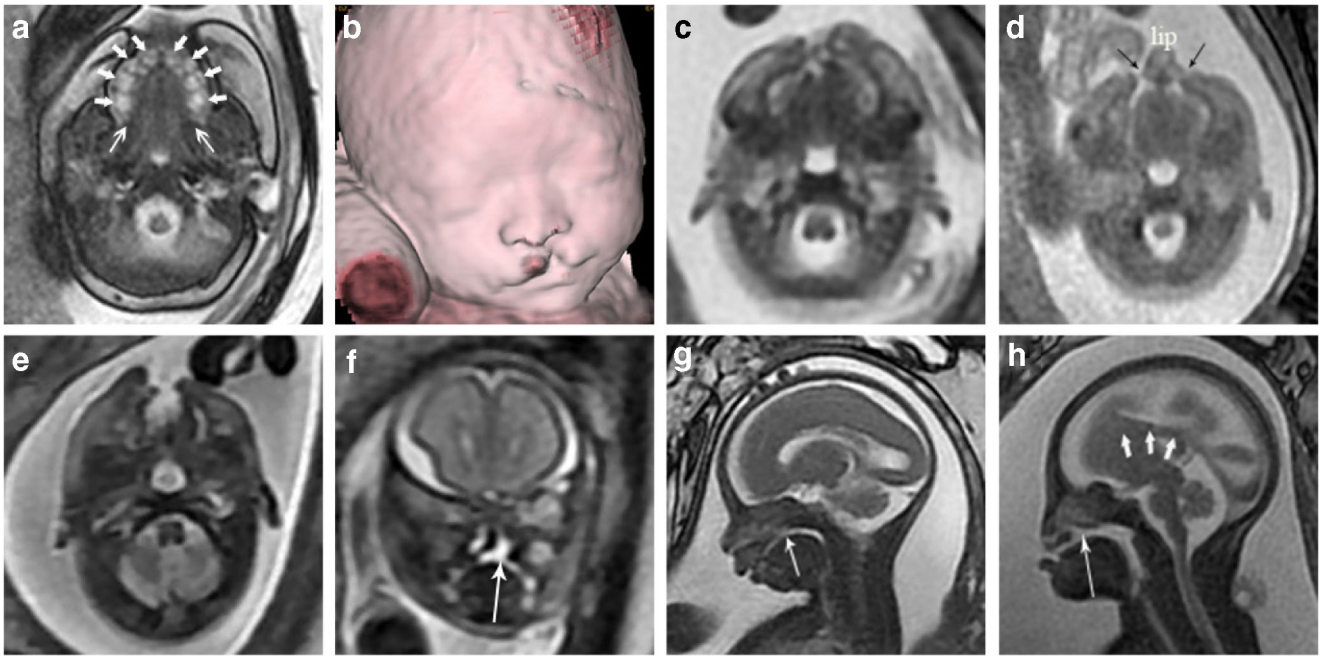

Fig. 1 MRI of different classifications of cleft lip with or without cleft palate. **a** Normal fetal upper lip and palate. Ten tooth buds are identified on maxillary transverse T2-weighted images at 37 weeks of pregnancy. In this case, the four dental buds are clearly visible on both sides, while the fifth tooth bud was only partially displayed (thin arrow). **b** The left cleft lip (CL) at 25 weeks of gestational age (GA). Volume reconstruction (VR) image clearly shows a left cleft lip. **c** Cleft lip and cleft alveolus (CLA) at 22 weeks of GA. Axial image shows that the right upper lip and tooth buds are missing in the medial alveolar ridge. **d** Bilateral cleft lip with cleft palate (BCLP) at 23 weeks of GA. The upper lip is surrounded by amniotic fluid; the black arrows show bilateral clefts. Repeated renal pelvis is not shown. **e** Unilateral cleft lip with cleft palate (UCLP) at 24 weeks of GA. Axial image shows the left lip and palate filled with hyperintense amniotic fluid. **f** UCLP, same fetus as panel **e**. The coronal T2-weighted image shows cleft palate and hyperintense fluid communicates between the oral cavity and the nasal cavity (white arrow). **g** Pierre Robin's sequence at 25 weeks of GA. The sagittal T2WI demonstrates CPO (white arrow), micro mandible dysmorphia, and retrognathia. **h** Median cleft lip with cleft palate (MCLP) with holoprosencephaly at 27 weeks of GA. The transparent compartment cavity is not shown clearly and the corpus callosum is partially absent (short arrow). On the median sagittal T2WI, MRI demonstrates dysplasia of the nasal bone and absence of the lip and palate (long arrow)

Our results, along with other previous studies, show that MRI enables us to accurately predict the occurrence of CP to guide clinical management.

We found that many previous studies lack evidence for the classification of CL/P [25, 26]. A study [27] reported that the incidence of CL, CLA, UCLP, and BCLP was 18.99%, 6.33%, 50.63%, and 24.05% within a cohort of CL/P cases. In our study, we found that 23 cases of CL were misdiagnosed as CP, the accuracy of BCLP was 41.67%, and CLA or MCLP deformities were not clearly diagnosed with US examination. Our results showed that the accuracy rate of US in CP, particularly the classification of CP, might be very poor. This demonstrates the need for us to identify better imaging modalities with which to compensate for the limitations of US.

Wang et al [13] suggested that MRI allows for a more accurate assessment of CL/P than US and particularly provides an accurate diagnosis of cleft palate, although the sample size in this study was small. Several studies [9, 28] have determined that real-time imaging allows for the rapid assessment of the palatal midline in the fetus, allowing for accurate diagnosis of secondary cleft. In our study, we used fast sequences, 3D scanning, and multiple post-processing techniques to produce more intuitive images. The diagnostic accuracy rate of CL, UCLP, MCLP, BCLP, CLA, and CPO by MRI was 86.96%, 95.56%, 100%, 91.67%, 66.67%, and 100%, respectively. Furthermore, MRI demonstrated the degree of involvement and classification of the palate and showed a strong ability to diagnose unilateral or bilateral CL/P. However, the accuracy of MRI in diagnosing CLA needs to be improved (only 66.67%). Additionally, our study collected a larger number of cases (94) than other studies, and the range of gestational weeks of the mothers was also wider (19–39). Thus, MRI could improve the processing capacity for prenatal diagnosis and provide useful information that could change patient counseling and management.

Several studies have reported that CL/P may be isolated or associated with other deformities, chromosome abnormalities, or various syndromes [10, 11, 29]. In CL/P, the incidence of associated cerebral abnormalities overlooked by ultrasound has been reported to be 4.6% [30], although fetal brain malformations were described. Prenatal US and MRI can help to identify various complications or syndromes with CL/P, such as Robin's sequence with micrognathia [31], velocardiofacial syndrome [32], and DiGeorge syndrome [33]. In addition, Stickler's

syndrome can cause CL/P, joint pain, and myopia, while Hardikar syndrome can cause CL/P, hydronephrosis, intestinal obstruction, and other symptoms. Ultrasound with Doppler flow imaging has a significant advantage for the diagnosis of congenital heart disease. However, MRI can be used as an ultrasound supplement to add useful information relating to fetal malformations and allow precise evaluation to inform further management. In all of our cases, Pierre Robin's sequence, velocardiofacial syndrome, holoprosencephaly, and other malformations were identified by prenatal imaging, postnatal physical examination, or autopsy. We found that CLA was not associated with complications, and only one case of UCLP was complicated by tetralogy of Fallot. The three main features of Pierre Robin's sequence (CPO, micrognathia, and glossoptosis) were also found. More importantly, we reported that 75% (3/4) of MCLP was significantly associated with craniocerebral malformation, such as holoprosencephaly and Dandy-Walker. The incidence of BCLP complicated by deformity was 41.67%. Therefore, these data may provide the possibility of fetal MRI in the evaluation of merging other malformations with CP.

Indeed, this study has several limitations. It is a retrospective study and is involved in a single hospital center. The bias is inevitable. Further multicenter prospective studies are needed to identify the associated factors of accurate diagnosis of MRI in CP with or without CL.

Conclusion

Our data show that prenatal US is a good means of screening for CL/P in the fetus. However, when US cannot clearly diagnose a deformity, the addition of MRI, as a good auxiliary technique, provides better accuracy. In addition, MRI can provide a basis for the specific classification of CL/P and other incorporative anomalies, and consequently provides specific assistance for perinatal follow-up and management.

Funding The authors state that this work has not received any funding.

Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Baohua Li, who is from Department of Obstetrics, Women's Hospital, Zhejiang University School of Medicine.

Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval The present study was approved by the Institutional Review Board, Women's Hospital, Zhejiang University School of Medicine.

Methodology
- retrospective
- case-control study
- performed at one institution

References

1. Vanderas AP (1987) Incidence of cleft lip, cleft palate, and cleft lip and palate among races: a review. Cleft Palate J 24:216–225
2. Wong FW, King NM (1997) A review of the rate of occurrence of cleft lip and palate in Chinese people. Hong Kong Med J 3:96–100
3. Descamps MJ, Golding SJ, Sibley J, McIntyre A, Alvey C, Goodacre T (2010) MRI for definitive in utero diagnosis of cleft palate: a useful adjunct to antenatal care? Cleft Palate Craniofac J 47:578–585
4. Ha S, Koh KS, Moon H, Jung S, Oh TS (2015) Clinical outcomes of primary palatal surgery in children with nonsyndromic cleft palate with and without lip. Biomed Res Int 2015:185459
5. Goodacre T, Swan MC (2008) Cleft lip and palate: current management. Paediatr Child Health 18:283–292
6. Christensen K, Juel K, Herskind AM, Murray JC (2004) Long term follow up study of survival associated with cleft lip and palate at birth. BMJ 328:1405
7. Mossey PA, Little J, Munger RG, Dixon MJ, Shaw WC (2009) Cleft lip and palate. Lancet 374:1773–1785
8. Allori AC, Mulliken JB, Meara JG, Shusterman S, Marcus JR (2017) Classification of cleft lip/palate: then and now. Cleft Palate Craniofac J 54:175–188
9. Dabadie A, Quarello E, Degardin N et al (2016) Added value of MRI for the prenatal diagnosis of isolated orofacial clefts and comparison with ultrasound. Diagn Interv Imaging 97:915–921
10. Marazita ML (2012) The evolution of human genetic studies of cleft lip and cleft palate. Annu Rev Genomics Hum Genet 13: 263–283
11. Mishra S, Sabhlok S, Panda PK et al (2015) Management of midline facial clefts. J Maxillofac Oral Surg 14:883–890
12. Freitas JA, Almeida AL, Soares S et al (2013) Rehabilitative treatment of cleft lip and palate: experience of the Hospital for Rehabilitation of Craniofacial Anomalies/USP (HRAC/USP)-part 4: oral rehabilitation. J Appl Oral Sci 21:284
13. Wang G, Shan R, Zhao L, Zhu X, Zhang X (2011) Fetal cleft lip with and without cleft palate: comparison between MR imaging and US for prenatal diagnosis. Eur J Radiol 79:437–442
14. Ghi T, Tani G, Savelli L, Colleoni GG, Pilu G, Bovicelli L (2003) Prenatal imaging of facial clefts by magnetic resonance imaging with emphasis on the posterior palate. Prenat Diagn 23:970–975
15. Triulzi F, Manganaro L, Volpe P (2011) Fetal magnetic resonance imaging: indications, study protocols and safety. Radiol Med 116: 337–350
16. Victoria T, Jaramillo D, Roberts TP et al (2014) Fetal magnetic resonance imaging: jumping from 1.5 to 3 tesla (preliminary experience). Pediatr Radiol 44:376–386
17. Patenaude Y, Pugash D, Lim K et al (2014) The use of magnetic resonance imaging in the obstetric patient. J Obstet Gynaecol Can 36:349–355
18. Sammet S (2016) Magnetic resonance safety. Abdom Radiol (NY) 41:444–451

19. Strizek B, Jani JC, Mucyo E et al (2015) Safety of MR imaging at 1.5 T in fetuses: a retrospective case-control study of birth weights and the effects of acoustic noise. Radiology 275:530–537
20. Smith FW, Adam AH, Phillips WP (1983) NMR imaging in pregnancy. Lancet 321:61–62
21. Benson CB, Doubilet PM (2014) The history of imaging in obstetrics. Radiology 273:S92–S110
22. Hayat TTA, Rutherford MA (2018) Neuroimaging perspectives on fetal motor behavior. Neurosci Biobehav Rev 92:390–401
23. Levaillant J-M, Nicot R, Benouaiche L, Couly G, Rotten D (2016) Prenatal diagnosis of cleft lip/palate: the surface rendered oropalatal (SROP) view of the fetal lips and palate, a tool to improve information-sharing within the orofacial team and with the parents. J Craniomaxillofac Surg 44:835–842
24. Maarse W, Pistorius L, Van Eeten W et al (2011) Prenatal ultrasound screening for orofacial clefts. Ultrasound Obstet Gynecol 38:434–439
25. Fuchs F, Burlat J, Grosjean F et al (2018) A score-based method for quality control of fetal hard palate assessment during routine second-trimester ultrasound examination. Acta Obstet Gynecol Scand 11:1300–1308
26. Burnell L, Verchere C, Pugash D, Loock C, Robertson S, Lehman A (2014) Additional post-natal diagnoses following antenatal diagnosis of isolated cleft lip+/− palate. Arch Dis Child Fetal Neonatal Ed 99:F286–F290
27. Bäumler M, Faure JM, Bigorre M et al (2011) Accuracy of prenatal three-dimensional ultrasound in the diagnosis of cleft hard palate when cleft lip is present. Ultrasound Obstet Gynecol 38:440–444
28. Kazan-Tannus JF, Levine D, McKenzie C et al (2005) Real-time magnetic resonance imaging aids prenatal diagnosis of isolated cleft palate. J Ultrasound Med 24:1533–1540
29. Sommerlad M, Patel N, Vijayalakshmi B et al (2010) Detection of lip, alveolar ridge and hard palate abnormalities using two-dimensional ultrasound enhanced with the three-dimensional reverse-face view. Ultrasound Obstet Gynecol 36:596–600
30. de Milly MN, Alison M, Arthurs O et al (2013) Is fetal cerebral MRI worthwhile in antenatally diagnosed isolated cleft lip with or without palate? Prenat Diagn 33:273–278
31. Pilu G, Romero R, Reece EA, Jeanty P, Hobbins JC (1986) The prenatal diagnosis of Robin anomalad. Am J Obstet Gynecol 154: 630–632
32. Pacella E, Malvasi A, Tinelli A et al (2010) Stickler syndrome in Pierre-Robin sequence prenatal ultrasonographic diagnosis and postnatal therapy: two cases report. Eur Rev Med Pharmacol Sci 14:1051–1054
33. Kobrynski LJ, Sullivan KE (2007) Velocardiofacial syndrome, DiGeorge syndrome: the chromosome 22q11. 2 deletion syndromes. Lancet 370:1443–1452