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Review Article

Modern Practice for Accurate Prenatal Detection of Cleft Lip & Cleft Palate; Literature Review

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Abstract

Introduction: Orofacial clefts, including cleft lip and/or palate are prevalent congenital anomalies forming between the 4th and 12th week of gestation which show varying incidences worldwide. Orofacial clefts can be syndromic or non-syndromic with both environmental and genetic factors increasing the risk of developing these structural defects. Management involves a multidisciplinary team to addresses structural, functional, cosmetic and psychological aspects of these defects which require early and accurate diagnosis during gestation. This literature review aims to identify imaging techniques and modalities including 2D, 3D and MRI to accurately diagnose cleft lip and palate.

Method: A qualitative narrative form of literature review was carried out using PubMed, ScienceDirect and Cochrane library. Published articles between January 2010 and March 2024 were reviewed. PRISMA flow chart was used to display selection process. Methodology quality of each study was assessed using the Newcastle-Ottawa scale for cohort studies and QUADAS-2 scale for diagnostic studies.

Results: 21 studies met the eligibility criteria to be included in this literature review with 12 studies being diagnostic and 9 observational studies. 17 studies utilized 2D ultrasound with 9 studies comparing 2D ultrasound to 3D ultrasound and 7 studies comparing ultrasound with MRI. Some studies proposed novel techniques using 2D Ultrasound. Overall, studies suggested that the combined use of 2D US with 3D or MRI may improve diagnostic accuracy of detecting orofacial cleft prenatally.

Conclusion: 2D ultrasound is the initial imaging modality used for imaging during early gestation however high risk pregnancies require referral to tertiary centres for evaluation suing 3D ultrasound and MRI for accurate diagnosis of orofacial clefts.

Keywords: Cleft Lip; Cleft Palate; Gestational; Pregnancy; 2D Ultrasound; 3D Ultrasound; MRI.

Abbreviations

OC: Orofacial

CL: Cleft Lip

CP: Cleft Palate

CLP: Cleft Lip and Palate

US: Ultrasound

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MRI: Magnetic Resonance Imaging

SLS: Superimposed Line Sign

CLA: Cleft Lip and Alveolus

RNT: Retronasal Triangle

Introduction

Orofacial clefts (OC) rank among the most prevalent congenital anomalies affecting the face and are the second most common type of birth defect. They include cleft lip (CL), cleft palate (CP) or cleft lip and palate (CLP) and typically form between the 4th and 12th weeks of gestation [1]. The occurrence of cleft lip and palate varies significantly worldwide with incidence rates of 1 in 700. Orofacial clefts are most frequently observed in Japan and South American populations with lower incidence being observed in South Africa. The World Health Organisation (WHO) noted that the overall incidence of orofacial clefts was 3.4 –22.9 per 10,000 births for cleft lip and/ or palate and 1.3 – 25.3 per 10,000 for isolated cleft palate [2]. Male patients were noted to have a higher incidence for cleft lip and palate with a male to female ratio being 1.81 to 1 however females were noted to have a higher incidence for cleft palate. This may be because in females the palatine shelves fuse at a later stage [3].

The palate is divided into the primary and secondary palate with the primary palate including the lips, mandible and nasal bone while the secondary palate includes both hard and soft palates. The severity of the cleft defect can range from partial to complete involvement of the lip, jaw and palate and can be unilateral or bilateral. The aetiology of cleft lip and palate is complex and multifactorial. Environmental exposure and genetics play a major role in developing craniofacial abnormalities.

Cleft lip and palate can be classified as syndromic or non-syndromic with 70% of all cases of cleft lip and/or palate and 50% of isolated cleft palate are considered as non-syndromic. The remaining 30% and 50% respectively are linked to a number of syndromes which include Mendelian syndromes, Pierre Robin sequence, Van Der Woude syndrome amongst others [4]. Non-syndromic cleft lip and palate have been associated with gene and chromosomal mutations. Studies have confirmed that IRF6, VAX1 gene are involved in the development of these defects [5]. Increasing maternal age and maternal exposure to smoking has been linked to an increased risk of developing cleft lip and palate. Smoking has been linked to genetic defects in the IRF6 gene and gene deletions in glutathione S-transferase-θ1 which increase the risk of developing orofacial clefts. Maternal alcohol consumption especially binge drinking, and low folate levels have also been identified as risk factors. Maternal occupational exposure to teratogens such as pesticides, solvents, lead or radiation have been associated with development of cleft lip and palate [4].

Patients born with orofacial clefts require a multidisciplinary patient-centred approach encompassing a number of specialities including plastic surgeons, dental surgeons, otorhinologists, speech and language therapists, cleft nurse, midwives, psychologist and paediatrician. The primary aim of these specialist is to improve the patient's quality of life and reduce the impact of the pathology by addressing the structural, functional and aesthetic aspects of the structural deformity as well as provide psychological support to both the patient and parents. These patients then require coordinated long term follow up appointments under skeletal maturity is reached [6].

Orofacial clefts were first identified by 2D ultrasonography in 1981. Over the past 43 years ultrasound imaging has become universally available with improvement in resolution, equipment, software and technique. The introduction of 3D ultrasound has led to better quality images of the palate and improved views however was noted to be more time consuming and requires higher operator skill [7]. In addition to ultrasound (US), foetal magnetic resonance imaging (MRI) has been able to detect a number of congenital abnormalities and may be able to delineate the anatomy of posterior palate more accurately [8].

Given the considerable incidence and lifelong impact of orofacial clefts it is critical to accurately diagnose cleft lip and/or palate prenatally to allow adequate timing for appropriate management. This literature review aims to identify imaging techniques and modalities including 2D, 3D and MRI to accurately diagnose cleft lip and palate.

Aim: To identify imaging modalities and techniques that enhance diagnostic accuracy of antenatal cleft lip and palate.

Methodology

A qualitative, narrative form of literature review was carried out using Preferred Reporting Items for Systemic Reviews and Meta-Analysis (PRISMA) statement which was agreed upon before conducting this literature search. The aim of this literature review was to identify imaging modalities which enhance diagnostic accuracy of prenatal detection of cleft lip and palate as well as compare these imaging techniques with identification of cleft lip and/or palate throughout different phases of pregnancy.

PICO Question

The objective of this literature review was designed according to the Population Intervention Comparison and Outcome (PICO) question which was adapted to qualitative research (Table 1).

Search protocol

A detailed search strategy was developed and modified for different databases taking into considering varying syntax rules and vocabulary. A search was of the following databases

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Table 1: Shows detailed structure for PICO question

	Keywords	Alternative question
Population	Pregnant women who have undergone prenatal screening in the global population and progressed with live births or termination of pregnancy	Gestational, mother/s
Intervention	Use of imaging techniques such as 2D US,3D US, 4D US, Foetal MRI	Sonography, Ultrasonography, Magnetic Resonance Imaging
Comparison	Comparing detection of cleft lip and palate using 2D with 3D,4D US and foetal MRI.	
Outcome	Have 3D, 4D US and Foetal MRI improved prenatal detection of cleft lip and/or palate compared to 2D ultrasound	

was carried out: PubMed, ScienceDirect and Cochrane library. Reference lists were also screened to identify any studies which met inclusion criteria but were not found in the database search. The literature search aimed to identify any relevant information which met the literature review criteria which had been published till the end of March 2024.

Inclusion and Exclusion Criteria

This literature search included literature which was published in the English language from January 2010 to March 2024. It included cohort studies, diagnostic studies, case-controlled studies, randomised control studies. Patients who were reviewed were evaluated throughout their gestational period and studies included evaluation of cleft lip, cleft palate, cleft lip and palate, unilateral or bilateral clefts of the alveolar palate. Finally, studies included the use of either 2-dimensional, 3-Dimensional, 4-Dimensional ultrasonography or Foetal Magnetic resonance imaging.

Exclusion criteria for this literature review were studies which were in any other language other than English language, published before January 2010 or after March 2024, duplicate articles, systemic reviews or metanalysis, studies in which the focus was a prenatal syndrome associated with cleft lip and palate and studies which did not meet the inclusion criteria.

Search strategy

A manual search was carried out and adapted according to the database used. Keywords were identified and the search was improved using Boolean operators ("OR" and "AND"). A search was conducted using all possible combination of terms using the following keywords; Gestational OR Prenatal, Cleft lip AND/OR Cleft palate AND/OR 2dimensional ultrasound, 3-dimensional ultrasound, 4-dimensional ultrasound OR Sonography OR Magnetic resonance imaging. The data search was carried out on 5th April 2024. Articles were then exported to Refworks Proquest LLC.

Data was search for relevant articles was carried out with the following combination of words;

(Gestational OR prenatal) AND (cleft lip AND/OR palate) AND (ultrasound OR ultrasonography OR Magnetic Resonance Imaging).

Data selection

The study selection involved manually identifying and eliminating duplicate articles found in databases which was performed by 1 author. The author was not blinded to the outcome of study, authors or institutions. Article title, abstract and full text were analysed to assess whether studies where eligible for review according to the inclusion and exclusion criteria. From a total of 6062 articles, 901 were collected from PubMed, 32 from Cochrane library and 5122 from Science Direct. A total of 4811 duplicates were identified and removed. 980 articles were excluded as their title did not fit the scope of the study. A review of the abstract of 271 articles was performed and 239 articles were excluded. 32 articles were retrieved, and full text was reviewed. 11 studies were excluded as they were systemic reviews or meta-analysis, diagnosis was aimed at other pathology, studies targeted prenatal syndromes, or the study focused on a different study outcome. 21 articles were included in the literature review. Figure 1 shows the PRISMA algorithm:

Data for selected studies was extracted and tabulated. For each article the following criteria were noted; Primary author, year of publication, type of study design, sample number, diagnostic imaging used during the study (2D US, 3D US, 4D US, MRI), gestational age, degree of cleft involvement (CL, CLA, CLP) and quality of methodology used. Quality assessment was then performed using the QUADAS-2 scale for observation diagnostic studies and the Newcastle-Ottawa for observational cohort studies. PRISMA checklist has been included and may be found on page 37 to 39.

Results

Study characteristics

In this literature review a total of 21 studies were included. Of these studies, 12 studies were diagnostic studies [8-19] whilst the remaining 9 were observational cohort studies [20-28]. From these 9 studies, 2 studies were retrospective [21,28], 1 was mixed [26] and the remaining 6 were prospective studies.

All 21 studies confirmed the diagnoses of CL, CLA, CLP, CP postnatally or postmortem. 17 studies utilized 2D ultrasound but only 1 study [9] performed 2D ultrasound as

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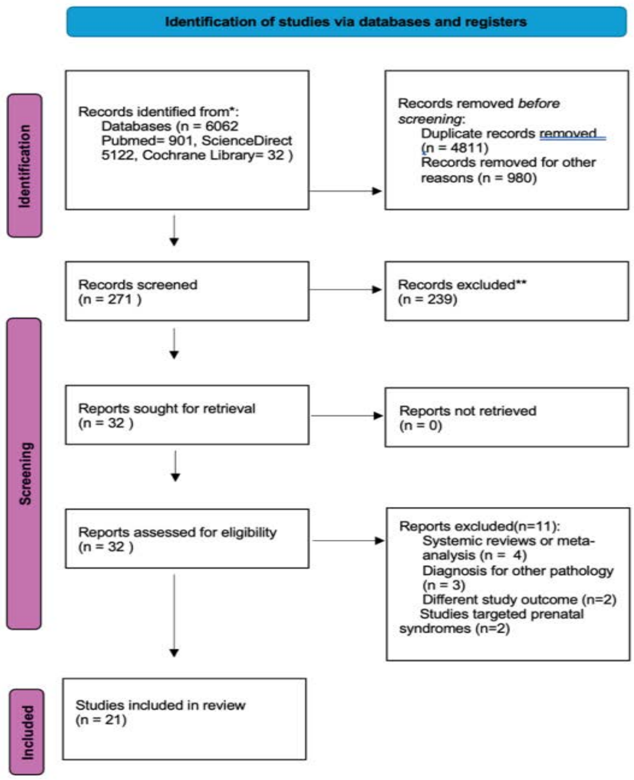

Figure 1: PRISMA 2020 flow diagram for new systemic reviews which included reaches of databases and registers

a second line investigation. The remaining 16 studies [8,10-12,14-23,25,27] included 2D ultrasound as part of their routine US screening during pregnancy. 9 studies [12,14-16,18,19,23,25,27] compared the use of routine 2D US with 3D ultrasound and confirmed diagnoses with gold standard postnatal diagnosis. A total of 7 studies included the use of foetal MRI for diagnosis of orofacial clefts. 1 study [14] combined all 2D US, 3D, MRI and compared results with postnatal / postmortem findings and another study [28] compared sensitivity of detection of CP between early and late gestation. The remaining 5 studies [8,9,11,20,21] compared 2D and MRI with postnatal/postmortem findings. 4 studies [15,17,19,25] suggested 4 novel markers for detection of CP. Table 2 shows a summary of the methodology, individuals included in each study, imaging modality, weeks of gestation and structural involvement noted.

Qualitative analysis

Most of the studies included in this literature review focused on detection of isolated cleft lip, isolated cleft palate, cleft lip and palate and cleft lip & alveolus. Cleft lip and palate were assessed to see if they were unilateral or bilateral [8–12,14,16,19–23,27]. In 8 studies [13,15,17–19,24-26] the main objective of these projects was to assess improved imaging detection of the secondary palate using 2D US, 3D US and MRI.

Our literature review involved several studies which included routine ultrasound screening. Maarse et al,.(2011) [22] performed 2D US in low and high risk groups and noted that the overall sensitivity for detection of CL, CLP and CP was 88%. CL detection had a sensitvity of 81% in low risk groups and 100% in high risk groups while CLP showed a sensitivity of 91% in low risk groups and a sensitivity of 100% in high risk groups. The overall sensitivity of 2D US in the second trimester was 88% however on further evaluation decreased to 65% in low-risk groups and 62.5% in high-risk groups as no cases of isolated CP were detected by 2D US.

Lakshmy et al., (2017) [25] noted that all cases of CP were diagnosed using 2D US in 3 views (sagittal view of the palatine line, coronal view of RNT and axial view of the maxilla) during the first trimester. Zheng et al.,(2018) [10] assessed the sensitivity and specificity of different views of the maxilla using 2D US during the 1st trimester to detect CLP and noted that axial views of the maxilla showed a sensitivity of 100% and specificity of 100% which was higher than that of the coronal view of the RNT and sagittal views of the palate where sensitivity was noted to be 75% and 50% and specificity 96.5% and 93.4% respectively. It was also noted that axial views had an obtaining rate of 95.2% which was the highest of all 3 views. Weissbach et al, (2024) [17] performed a hard palate sweep during 2D US throughout pregnancy and were able to detect CP in 75% of cases.

Wu et al., (2020) [23] followed this study and noted that using 2D US and obtaining 4 different views of the foetal face sagittal view of the palatine line, axial view of the maxilla, coronal view of the RNT, coronal view of the lip) and 3D US had a sensitivity and specificity of 100% during the first trimester. The study also noted that sagittal and coronal views of RNT identified all cases of OC however axial views, coronal views of the lip and 3D US had lower sensitivity with 93.3%, 66.7% and 73.3% respectively. Ramos et al. (2010) [26] using their technique of modified ‘flipped face view’ noted that sensitivity and specificity of 3D US for detection of the secondary cleft palate was variable. Sensitivity ranged between 33 to 63% whilst specificity ranged between 84 to 97%. Shao et al., (2024) [18] followed suit compared 3D us with 2D three section US which including central sagittal section of the face, axial skeleton of the superior alveolar process and coronal section of the posterior triangle of the face during the first trimester to detect CP. This study noted that 3D US detected 85% of CP and three phase 2D US detected 81% of CP therefore no statistical significance was noted. From the 3 views on 2D US selected for this study the coronal section of the posterior nasal triangle was able to detect 81% of cases of CP compared to the low rates of detection by central sagittal detection of the face and axial section of the superior alveolar process which detected CP in 52.3% and 66% respectfully.

Sommerland et al., (2010) [27] noted that using 2D and 3D “reverse face view” had a sensitivity for detection of CL

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Table 2: Shows methodology, study type, population studies, imaging performed and structural defect identified

	Study design	Number of patient reviewed in study	Type of diagnostic test	Weeks of gestation	Structural involvement	Methedology quality
Wang et al,. 2011(5)	Diagnostic study	12	2D US, MRI	28 +/- 4 weeks	CL,CLP	Moderate
Baumler et al,. (2011)(7)	Diagnostic study	79	2D US, 3D US	2D 22-25 weeks 3D 23-29 weeks	CL, CLP, CP, CLA	High
Tonni et al,.(2013)	Diagnostic study	150	2D US, 3D US	11-13 weeks	CLP	High
Zajicek et al,. (2013) (12)	Diagnostic study	49	3D US	12-16 weeks	CP	Moderate
Dabadie et al., (1) 2016	Diagnostic study	22	2D US, MRI	2D US 24-34 weeks MRI 27-34 weeks	CL, CP, CLP, CLA	High
Zheng et al,. (2018)	Diagnostic study	2879	2D US	Conception - 12 weeks	CL,CP,CLP	Low
Zheng et al,. 2019(4)	Diagnostic study	88	2D US, 3D US, MRI	2D US 26.06 +/- 3.59 weeks MRI 26.50+/- 3.59 weeks	CL, CLP, CLA, CP	High
Lakshymy et al(2019) (15)	Diagnostic	9576	2DUS, 3D US	12-20 weeks	CLP	High
Ji et al,. (2021) (16)	Diagnostic study	103	2D,3D, 4D US	18.3 - 31.7 weeks	CL, CLA, CLP	High
Gai et al,. 2022(8)	Diagnostric study	2D US 110, 286	2D US, MRI	2D US 25+/-4 weeks	CL, CLP, CP	High
Sheo et al,.(2024)	Diagnostic study	21	2D US, 3D US	11 - 13 weeks	CP	High
Weissbach et al,.(2024) (17)	Diagnostic study	676	2D US	13 - 40 weeks	CP	High
Mailath-Pokorney et al,. 2010 (21)	Cohort study	34	2D, MRI	2D US 24 +/- 8 weeks MRI 26 +/- 7 weeks	CL, CLA, CLP, CP, unilateral, bilateral	Moderate
Ramos et al,. (2010) (26)	Cohort study	92	3D US	12-36 WEEKS	CP	Moderate
Sommerlad et al,.(2010) (27)	Cohort study	124	2D US , 3D US	20-34 WEEKS	CL, CLA, CLP	High
Maarse et al,. (2011)(22)	Cohort	38, 760	2D US,	18-23 weeks	CL, CLP, CP	High
Martinez et al (2011) (24)	Cohort study	240	3D US	11-13 weeks	CLP	High
Lakshmy et al,. (2017) (25)	Cohort Study	2014	2D US, 3D US	11-13 weeks	CLP	High
Leifer-Narin et al,. (2019) (28)	Cohort study	42	MRI	<> 24 weeks	CL,CP.CLP	High
Tian et al,. 2018 (20)	Cohort Study	71	2D US, MRI	Not specified	CL, CLA, CLP, CP	High
Wu et al,. (2020)(23)	Cohort	2944	2D US	11-13 weeks	CP, CLP	High

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of 95%, 84.5% for CLA and 89.7% for CLP. Martinez et al., (2011) [24] also noted a high detection rate of CLP when performing offline analysis of the foetal face using 3D US to characterize the primary and secondary palate. Zajicek et al., (2013) [13] aimed to evaluate the secondary palate during the first trimester using axial 3D US however the soft palate was adequately visualised in only 34% of cases and hard palate in 26% of cases. Tonni et al. (2013) [19] also incorporated the use of 3D US to reformat the RNT and was able to detect all cases of CLP found in the study population. Baumler et al., (2011) [12] performed axial 3D US in patient with CL diagnosed with 2D US in the second trimester and noted a sensitivity of 100% and specificity of 90%. Lakshmy et al., (2019) [15] ventured to describe a novel sign referred to as absence of the "superimposed-line" sign on 2D US during the first trimester to detect defects of the secondary palate. Sensitivity for facial cleft was noted to be 60.7% and for cleft of the secondary palate 89.5%. Specificity was 99.8% with a positive predictive value of 43.6% and negative predictive value of 99.9%. Ji et al., (2022) [16] worked on applying the use of 3D US with reformatting technique (4D US) to detect OC. This study noted that CL showed a 95% diagnostic accuracy however 3D US detected 92% of CLA and 91.8% of CLP whilst 2D US detected 80% of CLA and 6.12% of CLP.

A number of studies have been conducted comparing significant increase in sensitivity and specificity between 2D US and foetal MRI. Mailath-Pokorney et al., (2010) [21] and Wang et al., (2011) [11] compared 2D US and MRI during the third trimester. 2D US only identified 41.2% CL and 45.5% of CP whilst MRI successfully identified100% and 91% of CP respectfully. Zheng et al., (2019) [14] supported the above results however noting further improvements are required in the detection of CLA. Dabadie et al., (2016) [9] noted that 2D US and MRI were consistent on 91% of cases during imaging performed between the second and third trimester. Two cases in this study were misdiagnosed. Tian et al., (2018) [20] showed that CL had a sensitivity of 100% for both 2D US and MRI however for CP 2D US showed a sensitivity of 77.5% and specificity of 58% while MRI had a sensitivity and specificity of 100%. Gai et al., (2022) [8] further supported the value of MRI with a sensitive for detection of OC of 89.90%. MRI was also an effective imaging technique to distinguish between the different severity of clefts.

Leifer-Narin et al., (2019) [28] went on to assess diagnostic accuracy of foetal MRI in early and late gestation. The authors noted that early gestation was identified before 24 weeks gestation and late gestation after 24 weeks gestation. This study noted that sensitivity for MRI for CP was 100% in early gestation and 86.7% in late gestation. Specificity was 100% for both gestational ages. Positive predictive value was noted as 100% for each gestation period. Negative predictive value was noted 100% for early and 77.5% for late gestation. On the other hand, when comparing with US, sensitivity for CP was 22.2% in early gestation and 26.7% in late gestation while specificity was 90.9% and 100% respectfully. Positive predictive value in early gestation was 66.7% versus 100% in late gestation while negative predictive value in early gestation was noted 58.8% and negative predictive value was 38.9%. This study therefore concluded that foetal MRI was highly accurate throughout gestation. Table 3 summarizes the sensitivity, specificity, positive and negative predictive value of 2D,3D US and MRI.

Table 3: Summary of 2D US, 3D US and MRI for diagnosis of CL,CLP,CP,CLA

	Type of diagnostic Test	***Sensitivity***	***Specifiticy***	***Positive predictive value***	***Negative predictive value***
Maarse el at,. (2011)(10)	2D US	Overall low risk group 65%			
		Overall high risk group 62.5%			
Zheng et al.,(2018) (10)	2D US	CLP Axial views of maxilla 100%, Coronal views of RNT 75%, Sagital views of the palate 50%	CLP Axial view 100%, Coronal views 96.55, Sagital 93.4%		
Baumler et al,. (2011) (12)	2D, 3D US	100%	90%	97%	100%
Ramos et al,. (2010) (26)	3D US	33-63%	84-97%		
Wu et al.,(2020) (23)	2D US, 3D US	Sagital & coronal view of RNT 100%, Axial views 93.3%, Coronal view of the lip 66.7%, 3D US 73.3%			
Sommerlad et al,.(2010) (17)	2D US, 3D US	Accuracy of 3D reverse face diagnosis of the CL,CLA,CLP CL: 95%	CL: 92.3% Cleft alveolar ridge: 92.8% CP: 84.4%		
		Cleft alveolar ridge: 84.5%			
		CP: 89.7%			
Lakshymy et al(2019) (15)	2D US, 3D US	60.7% in facial clefts 89.5% in detecting cleft of secondary palate	OC (99.8%)	43.60%	99.90%

Tian et al,. 2018 (20)	2D US, MRI	CL 2D US & MRI 100% CP 2D US 77.5% MRI 100%	CP 2DUS 95% MRI 100%		
Gai et al.,(2022)	2D US, MRI	2DUS 81.85% MRI 89.90%	2DUS 99.95% MRI 99.95%	2D US 80.14% MRI 95.65	2DUS 99.95 MRI 99.88
Leifer-Narin et al,. (2019) (28)	MRI	CP Early GA US: 22.2% MRI 100% Late GA US 26.7% MRI 100%	CP Early GA US: 90.9% MRI 100% Late GA US 100% MRI 90.9%	CP Early GA US: 66.7% MRI 100% Late GA US 100% MRI 91.7%	CP Early GA US: 58.8% MRI 100% Late GA US 38.9% MRI 100%

Quality Control

Quality of study methodology for observational diagnostic studies was performed using the QUADAS-2 scale. A total of 12 studies were noted to be diagnostic observational studies. Of the 12 studies, 3 exhibited a moderate to high risk of bias in the selection. This was attributed to the inclusion of foetuses with previously suspected or diagnosed orofacial clefts or as a result of non-random samples. Zheng et al (2018) [10] was the only study to have a high probability of bias. This was because the index test & reference standard was unclear as the study did not specify blinding. There were also patients who were lost to follow up. Two studies, Wang et al (2011) and Zajicek et al (2013) [11,13] were noted to have moderate bias. For Wang et al (2011) [11] this was due to lack of blinding in the index test and change in diagnoses between prenatal and post-natal examination. For Zajicek el al (2013) selection bias was noted and risk of bias was introduced in the index test. The remaining 8 studies had a low probability of bias. Table 4 illustrates the QUADAS-2 score;

The remaining 9 studies [20–28] included in this literature review were observation cohort studies and were assessed with the Newcastle-Ottawa scale. Two studies [22,23] achieved a score of 9/9. Whilst 2 studies [24,28] scored 8/9 and 1 study 24 scored 7/9. Two studies scored [20,21] scored 6/9 and 1 study scored 5/9 [26]. 6 of the 9 studies included were noted to have a low risk of bias as they scored above or equal to 7. Those studies scoring 5/9 and 6/6 were considered having a moderate risk of bias. The findings of the Newcastle-Ottawa Scale are summarised in Table 5.

Discussion

Embryology

Cleft lip and cleft palate are commonly associated together because of their clinical presentation however these structures have distinctly different embryological development. Facial morphology is established between the 4th and 10th week of gestation. During the 5th week of gestation neural crest cells differentiate to form a special ectomesenchyme which migrates to form the 5 facial prominences surrounding the oral cavity. The 5 structures are the frontonasal prominence, the paired maxillary prominences and the paired mandibular prominences. The frontonasal prominence develops in the midline over the brain forming the nasal placodes which invaginate and create nasal pits dividing the frontonasal prominence into the medial and lateral nasal processes. The median processes fuse to form the midline of the nose, medial upper lip, philtrum, incisor teeth and primary palate during the 6th week of gestation. The lateral processes form the nasal alae and alar base. The maxillary processes grow forward to merge with the medial nasal processes leading to the formation of the lateral upper lip, majority of the maxilla and secondary palate. The mandibular prominence will then give rise to the mandible and lower lip. Therefore, the primary palate is the part of the palate located ventrally to the foramen incivisum and the secondary palate is the part of the palate located dorsally to the foramen incisivum. Fusion of facial cushions occurs cranio-caudally between the 4th and 6th week of gestation and failure of fusion will result in orofacial clefts. Palatogenesis occurs between the 5th and 12th week of gestation from the primary and secondary palate. As mentioned previously, the primary palate forms from the medial nasal prominences during the 6th week gestation. The secondary palate is formed from neural crest mesenchyme within the maxillary primordia. It serves as a dividing wall between the nasal and oral cavity and goes on to form the hard and soft palate. The secondary palate occurs through two outgrowths referred to as the palatine shelves which grow vertically on either side of the tongue. During the 8th week of gestation these structures then rotate to a horizontal position as the mandible develops and the tongue descends. The palatal shelves undergo intramembranous ossification forming the palatine process of the maxilla and palatine bone. The palatal shelves approximate in the midline, forming a midline epithelial seam which degenerates leaving a mesenchymal confluence between the palatal shelves. Fusion occurs posterior to the foramen incisivum and extends posteriorly to close off the palate. Simultaneously, the nasal septum and primary palate undergo fusion. The hard palate is then formed by extension of bone from the palatine processes of the maxilla and palatine bone. The dorsal aspects however do not undergo ossification and extend posteriorly to form the soft palate [29]. Therefore, clefts of the secondary palate develop by a failure of fusion of the palatine processes. Facial development is complex and involves development of a number of small structures which poses diagnostic challenges when assessing foetuses during the initial weeks of pregnancy [24].

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Table 4: Shows QUADAS-2 assessment for observational diagnostic studies.

Study	**Risk of bias**				**Applicability**			**Total**
Author title	***Patient selection***	***Index test***	***Reference Standard***	***Flow and Timing***	***Patient selection***	***Index test***	***Reference standard***	
Dabadie et al., 2016 (9)	☹	☺	☺	☺	☺	☺	☺	*Low probability*
Gai et al,. 2022 (8)	☺	☺	☺	☺	☺	☺	☺	*Low probability*
Zheng et al,. 2019 (14)	☺	☺	☺	☺	☺	☺	☺	*Low probability*
Wang et al,. 2011(11)	☺	☹	☹	☺	☺	☺	☺	*Moderate probability*
Baumler et al,. (2011) (12)	☺	☺	☺	☺	☺	☺	☺	*Low probability*
Zajicek et al,. (2013)(12)	☹	?	☺	?	☺	☺	☺	*Moderate probability*
Zheng et al,. (2018)(10)	☹	?	?	?	☺	☺	☺	*High probability*
Lakshymy et al(2019)(15)	☺	☺	☺	☺	☺	☺	☺	*Low probability*
Ji et al,. (2021)(16)	☺	☺	☺	☺	☺	☺	☺	*Low probability*
Weissbach et al,.(2024)	☺	☺	☺	☺	☺	☺	☺	*Low probability*
Sheo et al,.(2024)(18)	☺	?	☺	☺	☺	☺	☺	*Low probability*
Tonni et al,. (2013)(19)	☺	☺	☺	☺	☺	☺	☺	*Low probability*
☺ *Low bias*								
☹ *High bias*								
? *Unclear bias*								

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Table 5: Shows Newcastle Ottawa scale for observational cohort studies

Study	Selection				Comparabiliy		Exposure			Total
	1	2	3	4	5a	5b	6	7	8	
Tian et al,. 2018 (20)	*	*	*					*	*	*06 OF 09*
Mailath-Pokorney et al,. 2010(21)	*		*		*		*	*	*	*06 OF 09*
Maarse et al,. (2010)(22)	*	*	*	*	*	*	*	*	*	*09 OF 09*
Wu et al,. (2020)(23)	*	*	*	*	*	*	*	*	*	*09 OF 09*
Martinez et al (2011)(24)		*	*	*	*		*	*	*	*07 OF 09*
Lakshmy et al.,(2017)(25)	*	*	*	*	*		*	*	*	*08 OF 09*
Ramos et al,. (2010)(26)		*	*		*			*	*	*05 OF 09*
Sommerlad et al,.(2010)(27)	*	*	*		*			*	*	*07 of 09*
Leifer-Narin et al,. (2019)(28)	*	*	*	*	*		*	*	*	*08 of 09*

Imaging

During the 1950s, obstetric ultrasound imaging became part of routine antenatal care practice. Ultrasound imaging is a non-invasive diagnostic, cost-effective tool which provides invaluable information for expecting parents such as foetal viability, gestational age, foetal growth and examining foetal anomalies, making it a gold standard diagnostic tool for facial malformations. However imaging of midline structures prior to 15 weeks gestation may prove to be difficult and inaccurate as foetal size is too small and foetal head position may be difficult to assess [24]. Ultrasonography however has several limitations such as maternal obesity, gestational age, foetal head position, soft tissue visualisation, amniotic fluid volume and operator dependence which may all contribute to decreased detection rates of orofacial clefts. A significant factor affecting sensitivity of US for accurate diagnoses of orofacial clefts are acoustic shadows which are cast from palatine bone [11].

In 1999, the Eurofetus study noted that cleft lip and palate showed low rates of detection using traditional transabdominal 2D Ultrasonography in early gestation with 25% of CL/CLA, 22% of CLP and 1.4% of cleft palate being detected before 24 weeks gestation [30]. Maarse et al., (2011) [22] sought to evaluate sensitivity and specificity of 2D US. This study had a large study population and noted the overall sensitivity of 2D US in the second trimester was 88% however isolated cases of CP were not detected. The large sample size may have led to a significant improvement in the test's predictive capacity [22]. It is important to note that systemic screening using 2D US required at least two scans.

Novel 2D US markers and techniques such the 'Superimposed Line Sign'(SLS) introduced by Lakshmy et al (2019) [15] and 'Hard Palate Sweep' introduced by Weissbach et al.,(2024) [17] have been suggested to evaluate the clefts of the secondary palate. Lakshmy et al suggested evaluating the Vomero maxillary junction in the midsagittal plane. In this view the secondary palate shows a double echogenic line at the distal 2/3 of the maxillary line. The shorter line representing the vomer bone being superimposed on the longer line of the secondary palate. Absence of the superimposed sign due to absence of the longer line representing the secondary palate suggests CP. In Weissbach et al(2024)17 performed a full hard palate sweep with the foetus laying the in the supine position holding the head upright and extended. Obtaining this position could increase scanning time however it was noted to reduced shadowing artifacts. Both studies intended on suggesting a quick, easy and feasible method for evaluation of the hard palate and both studies were performed in the first trimester leading to an early indication of cleft palate incentivizing referral to a tertiary centre for further evaluation. Weissbach et al (2024) [17] implemented their technique throughout pregnancy however Lakshmy et al (2020) [15] suggested the optimal timing for detecting SLS was between 13 to 17 weeks of gestation as after the 24th week of gestation as the superimposed lines fuse and appear as a single line. Both studies included a large subject population and showed high intra and inter operator agreement. Lakshmy et al (2020) noted a 89.5% sensitivity in detection of CP whilst Weissbach et al (2024) noted a sensitivity of 75%. Moreover, Lakshmy et al (2020) were also able to detect the degree of extension of the cleft within the secondary palate.

Despite the ongoing improvement with 2D US for diagnosis of cleft lip and palate many centres have advocated the use of 3D US as an adjunct to 2D US. The "reverse face" described by Campbell et al (2005) [31], "flipped faced" view described by Platt et al (2006) and "oblique view" described by Faure et al(2007) [24] all aimed to better identify the secondary palate. Over the past years 14 years various studies with different modalities have been performed to adequately assess the use of 3D US. Ramos et al (2010) [26] assessed the use of a modified "flipped face view" to assess the secondary palate whilst Sommerland et al (2010) [27] assessed the use of "reverse face view". Both studies were performed during the second and third trimester however both studies had a relatively small sample size with 92 and 124 participants respectively. Ramos at al noted a 33-63%

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sensitivity and specificity of 84 to 95%. Authors attributed the low sensitivity with this view to decrease foetal movements, shadowing by foetal limbs and tongue position. On the other hand, Sommerland et al 27 carried the largest cohort study for 3D-Reverse face view at the time and noted an improved CP was detection of 89.7%. This study was also able to classify the degree of clefting and noted a 95% sensitivity for CL and 84.5% sensitivity for CLA. The improved results from this study were likely due to decreased maxillary shadowing producing improved views of the mouth, nasal cavity and tongue. Baumler et al (2011) [12] followed these two studies by suggesting 3D axial ultrasound to assess for CP in those foetus with diagnosed CL on 2D US during the second and third trimester. The authors successfully diagnosed and categorized 77/79 foetuses. This technique was noted to have a sensitivity of 100% and specificity of 90%. Using this technique 2 cases were diagnosed as CLP prenatally however postnatally were noted to be CLA. The authors noted that the error may have been due to shadowing obscuring visualisation of the palatine bone. Martinez et al [24] in the same year as Baumler et al went on to examine the foetal face and secondary palate using 3D offline analysis in the axial plane during the first trimester. Similar to the previously mentioned study, this study showed a high detection of CLP. The authors of this study and Wu et al (2020) [23] noted that during the first trimester the secondary palate is flat and non-ossified which decreased shadowing from neighbouring facial structures. This technique was also able to identify median clefts by noting that in such cases the lateral components of the retronasal triangle are widely separated and the horizontal aspect is absent. Zajicek et al (2013) [13] noted that 3D US in axial views to evaluate the secondary palate with focus on soft palate in the first trimester yielded low results with identification of the hard palate in 26% and soft palate in 34%. This study noted that it might be easier to visualise the soft palate compared to the hard palate using 3D US however this study assessed only 49 foetuses and therefore larger scale studies should be performed to support this evidence.

Given the variability in these results, some researchers have sought to assess orofacial clefts using multiple views through both 2D and 3D ultrasound. Lakshmy et al. (2017) [25], Zheng et al. (2018) [10], Wu et al. (2020) [23], and Shao et al. (2024) [18] have combined multiple views using 2D ultrasound and 3D ultrasound to enhance the evaluation of orofacial clefts during the first trimester. The first three mentioned studies had a large study population and focused on diagnosis of CL, CLP, CP however the study carried out by Shao et al(2024), only included 21 foetuses and focused on detection of isolated CP. Lakshmy et al (2017) performed 2D US during nuchal translucency assessment and aimed to obtained 3 views; sagittal view to assess an intact palatine line, axial view to assess the continuity of the maxilla and the coronal view to assess the if the base of retronasal triangle was complete. This study focused on identifying bony landmarks and as a result of this soft palate defects may have been overlooked. Lakshmy et al were also able to classify the degree of clefting seen on each view. These findings can be found tabulated in the table 6 below as noted in the published article.

Table 6: Shows characteristic features noted on 3D US as noted by Lakshmy et al (2017) [25]

Plane	Unilateral CP	Bilateral CP involving the secondary palate	Bilateral CP involving the premaxilla and intact secondary palate	Median
Midsagittal	Intact palate line	Interrupted palatal line with proximal portion formed by the premaxillary protrusion and posterior position formed by the vomer bone	Proximal portion of the palate line formed by the premaxillary protrusion and posterior portion of the palatine line intact	Absence of proximal portion of palatal line and posterior portion of line formed by vomer bone
Axial	Unilateral defect seen in alveolar ridge	Bilateral defect on both sides of premaxillary protrusion seen in alveolar ridge vomer bone seen through defect caudal to alveolar ridge	Bilateral defect on both sides of premaxillary protrusion seen in alveolar ridge non visualisation of the vomer bone	Defect in midline in alveolar ridge
Coronal	Base of retronasal triangle has unilateral defect	Base of retronasal triangle absent if cleft extends to secondary palate	Retronasal triangle intact in clefts involving premaxilla alone	Base of retronasal triangle deficient in midline

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Following 2D US, 3D US was performed and on post-natal examination sensitivity for detection of facial clefts was noted at 60.7% and 89.5% in detecting clefts of the secondary palate. Zheng et al (2018) [10] supported this study and noted axial views of the maxilla for detecting CLP had a sensitivity of 100% while the sensitivity with coronal views of the RNT was 75% and sagittal views of the palate was 50%. The authors also noted adequate views were obtained in 95.2%, 93.8% and 98.2% respectively and therefore implementation of these views using 2D US is feasible. Wu et al (2020) [23] found contrasting results and noted midsagittal and coronal views of the RNT had a 100% sensitivity while axial views of the maxilla had sensitivity of 93.3% which is significantly different compared to the 100% sensitivity noted by the previous author. Sensitivity using coronal views remained low at 66.7 %. Shao et al (2024) [18] focused on evaluating isolated CP using 2D 3 sectional imaging followed up by 3D US and noted that 2D three phase US was able to accurately diagnose 81% of CP whilst 3D US diagnosed 85.7% of cases. Of note, 2D coronal section of the retro nasal triangle was able to obtain an 81% detection rate whilst, axial view of the superior alveolar process detected 66.6% of cases as opposed to 52.3% in the central sagittal section. This study concluded was using 2D US for detection of CP requires multiple views, but this suggested method requires further evaluation with a larger study population.

Ji et al (2021) [16] looked at the clinical value of using 3D US with reformatting technique in patients suspected of having orofacial clefts following 2D US. The study used 4D software, OMNIVIEW, to allow examination of multiple datasets which can review multiple views simultaneously. Omniview simplifies examination and increases diagnostic accuracy. Ji et al (2021) noted that CLP showed higher detection rates compared to 2D US however there were no significant results for detection of CLA.

Obtaining adequate imaging of the secondary palate can prove problematic for a number of experienced ultra sonographers however clear views of the palate are mandatory to ensure its structural integrity. Two studies performed by Fuchs et al (2018) [32] and Faure et al (2020) [33] proposed a simple score based system to identify anatomical landmarks of the palate. Both studies visualised the foetal hard palate using 2D ultrasonography in the axial transverse anatomical view during the second trimester. Fuchs et al (2018) [32] identified major and minor criteria with major criteria being the identification of the palatine bone horizontal plate and presence of two pterygoid process while the minor criteria identification of the complete maxilla with alveolar ridge, axis of isonation. Each major criteria was allocated 2 points whilst minor criteria were allocated 1 point. Images were then scored from 0 to 6. A satisfactory image was an image scoring 4 or more. The authors in this study noted a good inter and intra-reviewer agreement with 86.7% of scores being identical. This scoring method was reproducible and reliable. Faure et al (2020) [33] on the other hand identified the maxilla and the pterygoid processes and noted that a score of 3 or above was adequate. Both scoring systems focused on identification of bony structure and may miss defects of the soft palate.

Several studies have promoted the use of foetal MRI for diagnoses of orofacial clefts, with particular focus on the assessment of the palate. MRI provides a high resolution and does not expose the foetus to ionizing radiation. It allows review of multiple images through one examination which is an advantage over ultrasonography. Foetal MRI is not affected by maternal factors such as maternal obesity, oligohydramnios, stage of pregnancy or foetal head position. One of the main advantages of MRI is that it is not affected by interferences of bony structures which makes it advantageous compared to US. MRI runs on consistent protocols and sequences and therefore the images produced are consistent and reproducible. Wang et al (2011) [11] and Mailath-Pokorney et al (2010) [21] compared 2D US and MRI during the second trimester. Mailath-Pokorney et al (2010) [21] were able to successfully diagnose 100% of cases of CP at 19 weeks' gestation however Wang et al (2011) [11] obtained a 91% successful detection rate of CP and argued that the optimal gestational age for Foetal MRI was at 28 weeks' gestation as the larger foetal size will restrict movement and reduce artifacts. Gai et al (2022) [8] noted a diagnostic accuracy of 89.5% with foetal MRI however noted that optimal gestational age for the study was at 30 weeks gestation. Mailath-Pokornery and Wang et al, noted that the secondary palate can be best visualised with using the axial and coronal sections this is because of hyperintense amniotic fluid may be seen filling the orofacial defect may be seen on T2 weighted images. Wang et al also noted that using the coronal views any abnormality in nasal development can be observed, whilst sagittal views can detect the presence of bilateral defect of the lip and palate by assessing for premaxillary protrusion. Both studies agreed the presence of any defect in the alveolus can be seen when assessing the semicircular alveolar ridge. Tian et al (2019) [20] also noted a sensitivity of 100% for detection and classification of clefts compared to 2D which noted a sensitivity of 77.5%. Tian et al also proposed signs on MRI images which may aid in the detection of orofacial clefts. Axial images were used to adequately assess the alveolar process. The authors noted that in normal development of the hard palate an "inverted T-sign' can be seen on the coronal view which represents fusion of the hard palate bilaterally with the septum. In cases of unilateral CL, a "L sign" may be seen as the nasal septum does not fuse with the hard palate whilst in bilateral CLP a "U sign" can be observed. The authors also noted that in cases of isolated CP a "Notch sign" can be seen in the area where in normal soft palate a horizontal line is observed.

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Zheng et al (2019) [14] and Leifer Narin et al (2019) [28] noted that gestational age for performing MRI was not significant and it can be safely performed during early (<24 weeks) and late (>24 weeks) gestations. MRI was also able to detect further developmental abnormalities which may have an impact on the pre and post-natal care.

MRI is an attractive diagnostic technique as they instil confidence in accurate diagnoses and provide reassurance to expecting patients. In view of this one might argue that foetal MRI could be used as a standard technique for evaluation of orofacial clefts however it may be considered that that MRI is an expensive imaging modality, and it requires a trained radiologist to interpret imaging. Dabadie et al proposed a list of criteria which should be met during antenatal screening using 2D US which included detailed analysis of the extension of the cleft, potential premaxillary hypoplasia and detection of frequently associated malformation (orbits, lower maxilla and ears and limbs). If any abnormalities were noted foetal MRI was considered.

Continuous advancements in 2D, 3D and MRI will enhance the accuracy and detection rates of orofacial clefts. Of the three imaging modalities, 2D US has the lowest rates of detection especially when involvement of the palate is noted. 3D US has been reliable in diagnosing cleft lip and palate however remains limited in cases of isolated cleft palate [27]. Foetal MRI provides improve diagnostic accuracy as it can visualise the entire palate. The recent advancements in artificial intelligence with the application of computer vision techniques such as deep learning algorithms allows extraction of meaningful data from images which may allow identification of facial anomalies on images during early gestation [34].

Only 21 studies were eligible for inclusion in this literature review with some studies only evaluating a small population which may not have been representative of the actual population of patients with cleft lip and palate. The review focused on studies which evaluated non-syndromic patients and excluded studies which focused on syndromic patients which may have contributed greatly to the number of studies included. The review focused on a literature search of 3 databases and included no registries. Differences in methodological design, search criteria and quality measurement tools caused difficulty in drawing up conclusions.

Conclusion

2D ultrasound remains the imaging tool used for screening during early gestation as it is easily accessible, non-invasive and an effective tool for initial evaluation however in high risk pregnancies or suspected cases of orofacial clefts referral to tertiary centre is advised for further evaluation using 3D US and MRI. This literature review notes that there are increasing novel techniques for evaluating the palate using 2D US during the first trimester however there is improved diagnostic accuracy for orofacial clefts during the second trimester as facial structures are more developed and easier to visualise. The combination of 2D US with 3D US or MRI has improved diagnostic accuracy and can provide a reliable diagnosis. Orofacial clefts have a significant effect on the psychological well being of both the parent/s and child therefore early and accurate diagnosis is necessary to allow time for appropriate counselling, surgical planning and to prepare for any challenges which may arise.

Consent for publication: Not applicable.

Data availability

This data has not been published or submitted for publication elsewhere

Conflict of interest

The authors of this article did not have any conflicting interest financial or otherwise which may influence the final outcome of this paper. No funding was provided for this paper.

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