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The Accuracy of Three-Dimensional Ultrasound Imaging in Detection of Lip and Palate Clefts

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ABSTRACT

Background: Although there is a lack of robust evidence from prospective cohort studies that supporting using 3D ultrasound, it becomes widely used in the clinical practice of obstetrics. This review aimed At evaluating the evidence assessing the accuracy of 3D ultrasound, in the detection of cleft lip and palate in different populations at different trimesters. **Methods:** In July 2017, we conducted a systematic search of the databases (MEDLINE, EMBASE and Science Direct databases) as demonstrated in table 1. The titles and abstracts of the detected articles were screened to exclude irrelevantly and duplicated, in addition to articles of case reports and reviews. Finally, articles were finally included in this review and subjected to data extraction and qualitative data analysis. **Results:** The detection rates of cleft lip ± alveolar bone cleft by 3D ultrasound imaging were found very high by many of the included studies. A range of 85%-100% detection rate of cleft lip only and cleft lip with cleft alveolus was reported by many studies. The detection rate of cleft palate with or without cleft lip varied between 50%-100%. This review revealed a detection rate of cleft lip and palate in low-risk populations ranged between 80-100%, while in high-risk populations the detection rate varied widely between 50% -100%.

Conclusion: Although there is a wealth of evidence demonstrated the high accuracy of 3D imaging in the detection of cleft lip and palate, the available studies had a poor methodology with a high risk of bias in their findings.

Keywords: Accuracy, Ultrasound, Cleft, Lip, Palate, Three-dimensional.

INTRODUCTION

The prenatal screening of congenital anomalies becomes a major research area in obstetrics. Ultrasound has been used as an important tool for prenatal detection of congenital anomalies including facial clefting [(1)]. Facial clefts resulted from the failed fusion of yaw arch maxillofacial and nasal processes in the embryogenesis stage. The cleft lip plus or minus cleft palate are the most common facial clefts, which could occur as an isolated anomaly or associated with other global anomalies and syndromes [(2)]. Cleft lip and palate incidence have reported reaching 2.19/ 1000 live births in the central province of Saudi Arabia, which is a higher incidence when compared to other countries such the UK where incidence rate was 182/1000 live births [(3, 4)].

When using ultrasound, the detection rate of these clefts differed greatly according to the skills of the operator and the design of the study. It ranges from as low as 13% in a prospective study conducted by **Stoll *et al.*** [(5)] to as high as 90% in a retrospective study conducted by **Benacerraf *et al.*** [(6)]. Proper prenatal screening associated with early detection of facial clefts, especially in a low-risk population, can improve the management plan. Recently, the three-dimensional (3D) ultrasound imaging techniques have introduced to the prenatal screening methods [(7)]. The benefits of using 3D ultrasound imaging include the provision of depth and volume, which explore more details than those available in two-dimensional (2D) ultrasound imaging [(8)]. There is a current belief that 3D ultrasound is a time-saving technique that can play an important role the future. However, it is not obvious what is the clinical significance of the additional data provided by 3D ultrasound imaging. Although there is a lack of robust evidence from prospective cohort studies that supporting using 3D ultrasound, it becomes widely used in the clinical practice of obstetrics [(7)]. The main problem occurs when using 3D ultrasound is the deviation from the initial plane, which can reduce the quality of the images. In addition to the problem of acoustic shadowing, that may also occur in 2D ultrasound [(9)]. Recently, it becomes possible to update the 3D image at a rate of 24/second which leads to living view of the 3D volumes or what is known as 4D ultrasound imaging [(10)].

This review aimed at evaluating the evidence assessing the accuracy of 3D ultrasound, in the detection of cleft lip and palate in different populations at different trimesters.

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METHODS

In July 2017, we conducted a systematic search of the databases (MEDLINE, EMBASE and Science Direct databases) as demonstrated in table 1. The title and abstract of the detected articles were screened to exclude irrelevantly and duplicated, in addition to articles of case reports and reviews. The full texts were retrieved for 23 articles and furthermore, 9 articles were excluded from review because of inconsistent outcomes or unclear objectives. Since the number of articles aimed to assess the accuracy of 3D ultrasound imaging was small, no strict inclusion criteria were applied in this review. Only publications before 1990 were excluded since the ultrasound techniques before 1990 were incomparable with the recent techniques. Fourteen articles were finally included in this review and subjected to data extraction (table 2. The data were extracted for the outcomes such as study design, sample size, calibration methods, gestational age, detection rates for cleft lip and palates by 3D and 2D ultrasound imaging. This information was subjected to in-depth analysis and the risk of bias was assessed to evaluate the accuracy of 3D ultrasound imaging. The study was done after approval of the ethical board of King Abdulaziz University and written informed consent were obtained from study participants.

RESULTS

Fourteen studies were included in this review, in which 10 of them were prospective cohort studies [11-21], 3 were retrospective studies [21-23], and one was mixed of prospective and retrospective approaches [24]. The samples of fetuses were selected either from high-risk populations as in 11 studies [11, 13-15, 17-22, 24] or from low-risk populations as in 3 studies [12, 16, 23].

The gestational ages of fetuses included in these studies were different, where some studies included the fetuses only in the second trimester [12, 16, 18]. However, the majority of the studies included fetuses in the second and third trimester as in [11, 13-15, 17, 19-23].

All the studies mainly aimed to detect the accuracy of diagnosis made by 3D ultrasound imaging, however, 5 studies compared the accuracy of 3D ultrasound imaging to that of 2D imaging [13, 14, 16, 20, 21]. In regard to the main outcomes of this review, the detection rates of cleft lip ± alveolar bone cleft were found very high by many of the studies included in this review. About 100% detection rate of cleft lip reported by [14, 16, 17, 19, 20]. Slightly fewer detection rates of 95% and 85% were reported for cleft lip only and cleft lip with cleft alveolus respectively [15]. Moreover, the detection rates of palatal clefts were widely different across the included studies. Some studies reported 100% detection rate of cleft palates [14, 16-19, 24], while it was 90% for cleft lip and palate detected by **Sommerlad *et al.*** [15], **Johnson *et al*.**, [20] found a detection rate of 86% for cleft lip and palate, while a detection rate of 78% for primary palate cleft found by Martinez-Ten and his colleagues in 2012 [24], and the detection rate for isolated cleft palate was found 50% by **Gindes *et al***. [22]. The comparisons of the accuracy of 3D ultrasound and 2D ultrasound were conducted by 5 studies [13, 14, 16, 20, 21]. All of them found the much higher accuracy of 3D ultrasound when compared to 2D ultrasound, except **Kurjak *et al.*** [13] who found the slightly higher sensitivity of 2D ultrasound but lower specificity than 3D technique.

The calibration of the ultrasound scan images was reported by 8 of included studies, however, it was not conducted in a proper way [12, 14, 16, 18-20, 22, 24]. Only one examiner reviewed the imaging findings [19, 20], while tow reviewers examine the ultrasound images [12, 14, 16, 18, 22], and three reviewers in [24]. No study reported kappa statistics to demonstrate the agreement percentage between recruited reviewers.

Table (1): Summary of search results

Search Engine	Search Terms	Limits activated	Papers
PubMed	(three-dimensional OR 3dimensional OR 3D) AND (ultrasound OR screening OR sonography) AND (prenatal OR fetal OR fetus) AND (cleft OR lip OR palate)	All fields searched, All years, English language	148
Science Direct	(three-dimensional ultrasound OR 3-dimensional ultrasound OR 3D ultrasound OR screening OR sonography)) AND (cleft OR lip OR palate)	Titles, abstracts, keywords searched, All years, Medicine and Dentistry, English language	237
Total	Titles and Abstracts examined Papers excluded Full texts retrieved		**385** **362** **23**
	Papers included in the review		**14**

Table (2): Summary of findings of Sensitivity (detection rate) in 3D ultrasound

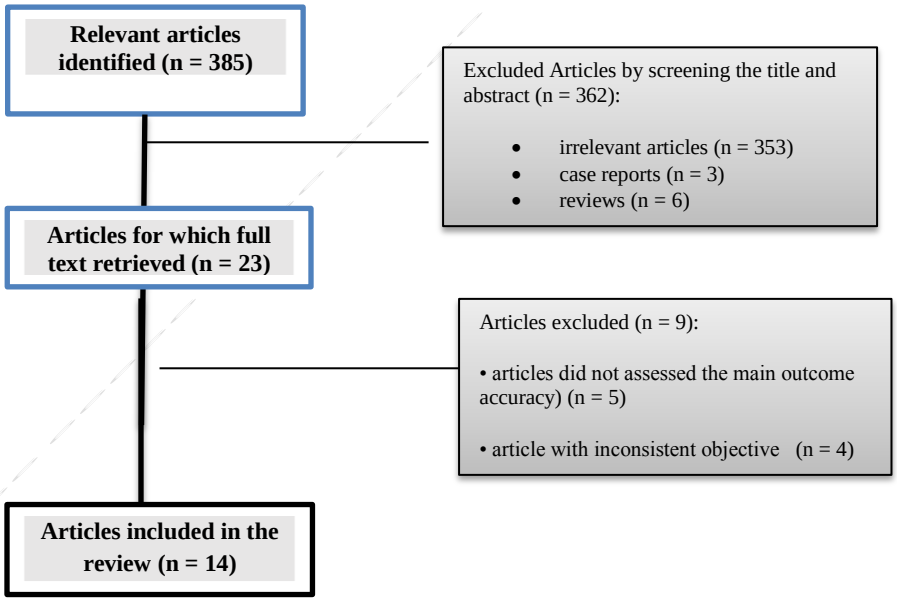
Reference	Study design	Sample size	Calibration	etection of	Gestational Age (weeks)	Sensitivity (detection rate) in 3D ultrasound				
						All clefts	Cleft lip only	cleft lip with cleft alveolus	cleft lip and cleft palatine he, without cleft alveolus	cleft lip with cleft alveolus and palatine bone
Johnson *et al.* [20]	Prospectiv e study	31 fetuses of high-risk population	One examiner eview either 2D or 3D	Location f cleft only	(15-35) mean 24.8 weeks	Not-eported	The location 100% accurate	Not-reported	Not-reported	(86%) of 22 cleft palates were detected or suspected
Bäumler *et al.* [19]	Prospectiv e study	81 cases \of high-risk population	The same examiners eview either 2D or 3D	Location f cleft only	23–29 weeks	77/79 (97%)	15/15 (100%)	3/5 (60%)	No cases	9 (100%)
Xu HX *et al.* [21]	Retrospecti ve study	4 fetuses of high-risk population	Not reported	diagnosis	Mean age was 29.7 weeks range, 16–42)	2/4 (50%)	Not-reported	Not-reported	Not-reported	-reported
Sommerlad *et al.* [15]	Prospectiv e study	124 cases of high-risk population	Not reported	diagnosis	20–34 weeks	Not-reported	116/122 (95%),	87/103 (84.5%),	Cleft secondary hard palate 61/68 (89.7%),	
Martinez-Ten *et al.* [24]	7 cases (3 cases included retrospectively and 4 prospectively) of high risk		3D datasets were examined separately by hree operators.	Diagnosis nd quality of image	the median age was 12 range, 11–13)	Not-reported	Not-reported	Not-reported	the primary palate was detected in 7/9 cases (77.8%). Clefts of the secondary palate were confirmed in 6/6 (100%)	
Mittermayer *et al.* [14]	Prospectiv e study	18 of high-isk population	examination performed by two of the authors	diagnosis	(mean 23.6± 4.5 weeks).		15/15 (100%) of cases were correctly detected		12/12 (100%) who were affected with a cleft primary Palate detected	
Faure *et al.* [12]	prospectiv e study	87 fetuses of a low-risk population	Tow observer vith significant difference between them	diagnosis	**21–25** weeks of gestation	Not-reported	Not-reported	Not-reported	The frequency of detection of the uvula and of the velum for each observer varied between 80% and 90%	
Tonni *et al.* [16]	Prospectiv e study	1856 of low-pulation	Reviewed by 2 graphers	diagnosis	**18 to 23** ks	the detection rate of 100% of cleft lip and palate				
Zajicek *et al.* [18]	A rospective study	49 (43 r routine n, and 6 ere of the opulation)	Examination ormed by two operators	diagnosis	Mean age **1.2** weeks	2/2 (Tow fetuses with soft and hard palate cleft were identified correctly) 100%				
Kurjak *et al.* [13]	A rospective study	15 cases of high-risk population	Not reported	diagnosis	(12 – 40) ks	10/11 (91%) (with one ative)	ot-reported	Not-reported	Not-reported	Not-reported
Ulm *et al.* [17]	Prospectiv e study	17 fetus of population	Not reported	diagnosis	Mean 23 31 weeks)	17/17 (100%)	1/1	Not-reported	Not-reported	16/16
Gindes *et al.* [22]	Retrospecti ve study	(57 cases- 7 termination = 50) of high-risk pregnancies	2D and 3D images reviewed by two experienced examiners	diagnosis	Mean =27 weeks –40 weeks)	Not-ted	Not-reported		(only palatal cleft evaluated in ensitivity of detection of palatal clefts were 71.4%, The detection rate for isolated late is 50% (2/4 cases were diagnosed)	
Rotten *et al.* [23]	Retrospecti ve study	96 cases Of low-risk ulation	Not reported	Diagnosis y of cleft	The mean was 28.2 ± 4.1	84/96 (88%)	In eight cases (8.3%), the sonographic examination underestimated the severity of the cleft. Conversely, sonography overestimated the severity of the cleft in four cases (4.2%).			
Campbell *et al.* [11]	Prospectiv e study	8 cases In high-risk ulation	Not reported	Diagnosis	20-31 weeks	6/8 (75%)	ot-reported	Not-reported	Not reported	Not-reported

Table (3): Summary of findings of Comparison to 2D (if available)

Reference	Study design	Sample size	Calibration	Detection of	Gestational Age (weeks)	Comparison to 2D (if available)				
						All clefts	Cleft lip only	cleft lip with cleft alveolus	cleft lip and cleft palatine bone, without cleft alveolus	cleft lip with cleft alveolus and palatine bone
Johnson *et al.* [20]	Prospective study	31 fetuses of high-risk population	One examiner review either 2D or 3D	Location of cleft only	(15-35) (mean 24.8 weeks	Not-reported	Location was accurate in (93%)	Not-reported	Not-reported	(41%) were detected
Bäumler *et al.* [19]	Prospective study	81 cases \of high-risk population	The same examiners review either 2D or 3D	Location of cleft only	23–29 weeks	Not-reported	Not-reported	Not-reported	Not-reported	Not-reported
Xu HX *et al.* [21]	Retrospective study	4 fetuses of high-risk population	Not reported	diagnosis	Mean age was 29.7 weeks (range, 16–42)	0/4 (0%)	Not-reported	Not-reported	Not-reported	Not-reported
Sommerlad *et al.* [15]	Prospective study	124 cases of high-risk population	Not reported	diagnosis	20–34 weeks	Not-reported	Not-reported	Not-reported	Not-reported	Not-reported
Martinez-Ten *et al.* [24]	7 cases (3 cases included retrospectively and 4 prospectively) of high risk		3D datasets were examined separately by three operators.	Diagnosis and quality of image	the median age was 12 (range, 11–13)	Not-reported	Not-reported	Not-reported	Not-reported	Not-reported
Mittermayer *et al.* [14]	Prospective study	18 of high-risk population	examination performed by two of the authors	diagnosis	(mean 23.6± 4.5 weeks).	Not-reported	13 cleft lips (80%) were correctly detected		7/12 (58%) of cases with a cleft primary Palate correctly identified	
Faure *et al.* [12]	prospective study	87 fetuses of a low-risk population	Tow observer with significant difference between them	diagnosis	**21–25** weeks of gestation	Not-reported	Not-reported	Not-reported	Not-reported	Not-reported
Tonni *et al.* [16]	Prospective study	1856 of low-risk population	Reviewed by 2 sonographers	diagnosis	**18 to 23** weeks	They found that 3D US was more accurate than the 2D US for defining the severity of the lesions.				
Zajicek *et al.* [18]	A prospective study	49 (43 attended for routine examination, and 6 ere of the high-risk population)	Examinations were performed by two trained operators	diagnosis	Mean age was **14.6 ± 1.2** weeks	Not-reported	Not-reported	Not-reported	Not-reported	Not-reported
Kurjak *et al.* [13]	A prospective study	15 cases of high-risk population	Not reported	diagnosis	(12 – 40) weeks	11-Nov -100% (with 4 false positives)	Not-reported	Not-reported	Not-reported	Not-reported

Ulm *et al.* [17]	Prospective study	17 fetus of high-risk population	Not reported	diagnosis	Mean 23 (range 18-31 weeks)	Not-reported	Not-reported	Not-reported	Not-reported	Not-reported
Gindes *et al.* [22]	Retrospective study	(57 cases- 7 termination = 50) of high-risk pregnancies	2D and 3D images reviewed by two experienced examiners	diagnosis	Mean =27 weeks (range of 12–40 weeks)	Not-reported	Not-reported	Not-reported	Not-reported	Not-reported
Rotten *et al.* [23]	Retrospective study	96 cases Of low-risk population	Not reported	Diagnosis and severity of cleft	The mean ± SD was 28.2 ± 4.1	Not-reported	Not-reported	Not-reported	Not-reported	Not-reported
Campbell *et al.* [11]	Prospective study	8 cases In high-risk population	Not reported	Diagnosis	20-31 weeks	Not-reported	Not-reported	Not-reported	Not-reported	Not-reported

Figure (1): Flow diagram of the screening, identification and inclusion steps of the systematic review



DISCUSSION

The findings of this review demonstrated the evidence of a high accuracy of 3D ultrasound imaging in the detection of cleft lip and palate. In regard to the cleft lip with or without cleft of alveolar bone, the detection rate was high (between 85%-100%). In another hand, the detection rate of cleft palate with or without cleft lip varied between 50%-100%. This review found a detection rate of cleft lip and palate in low-risk populations ranged between 80-100%, which is much higher than the accuracy of 2D ultrasound reported by a systematic review of **Maarse *et al*.** [(25)]. He found a range of 9%-50% detection rate of 2D ultrasound in low-risk populations. These findings revealed the presence of evidence supporting the accuracy of 3D ultrasound in detection cleft lip and palate among low-risk populations. In high-risk populations, **Maarse *et al*.** [(25)] found a range of 60%-100% detection rate of cleft lip and palate, which is similar to that found in the current review. Thus, the 3D ultrasound imaging can be very helpful in detection of cleft lip and palate in low-risk populations.

Studies that compared 3D technique to 2D have not divided the cases into two intervention groups with randomization, instead they did screening by 2D then they scanned fetuses by 3D which yield net accuracy of both techniques rather than the accuracy of each technique separately. The correct methodology was to use two groups of cases (for 2D and 3D), randomly selected and to compare the findings of ultrasonic imaging with the outcomes at birth to calculate true positive, true negative, false positive, and false negative. After that, the calculations of sensitivity, specificity, positive and negative predictive values would be possible.

As no proper sample size calculation was done by any of the included studies sample sizes used in the included studies varied widely. In general, studies conducted among low-risk population recruited larger numbers of cases than those conducted among high-risk populations, particularly in the study of **Tonni *et al.*** [(16)], where 1856 women were recruited. The risk of bias among included studies was considerably high especially in other retrospective studies [(21-24)].

The gestational age was different in the included studies that could affect the detection rate of the cleft lip and palate since there is a significant difficulty in the diagnosis of the cleft lip and palate before week 20 of the pregnancy. Many authors of included studies have not correctly identified the accurate dominators for calculation of detection rate. Some used number of all live births as a dominator rather than using the actual number of newborns with lip and palate clefts. Other authors included stillbirths and deaths in the calculations, which yield invalid detection rates. Another cause for variation in the 3D accuracy was the inconsistent definition of the outcome, where some studies identified the detection rate of all facial clefts and some for the categories such as cleft lip only, cleft lip with cleft alveolus, cleft lip and palate, cleft soft palate only.

CONCLUSION

Although there is a wealth of evidence demonstrated the high accuracy of 3D imaging in the detection of cleft lip and palate, the available studies had the poor methodology with a high risk of bias in their findings. There is a great need for high-quality clinical trials to evaluate the accuracy of 3D ultrasound imaging in the detection of facial clefts.

Conflict of interest:

The author stated that there is no sponsorship provided and no conflict of interests.

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