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Ultrasonographic screening for fetal rib number anomalies

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Objective: To determine associations between fetal rib number anomalies detected on ultrasonography and chromosomal anomalies and other structural anomalies, and the outcome of affected pregnancies.
Methods: All cases of fetal rib number anomalies referred to the Prenatal Diagnosis Clinic of Queen Elizabeth Hospital between 1 January 2016 and 31 December 2019 were reviewed. Fetal ribs were examined by static three-dimensional multiplanar or volume contrast ultrasonography. Genetic counselling was offered. The prenatal and postnatal records were reviewed.
Results: 21 fetuses with rib number anomalies were identified over 4 years. The most common presentation was unilateral or bilateral absence of the 12th thoracic rib (n=12, 57.1%), followed by the presence of lumbar rib (n=6, 28.6%) and the presence of cervical rib (n=3, 14.3%). Three (14.3%) fetuses were identified to have anomalies in other systems: unilateral absence of nasal bone (n=1) and minor vascular anomalies (n=2). One patient with multiple anomalies of the fetus underwent amniocentesis, and the chromosomal microarray analysis was normal. Postnatally, 13 babies had chest radiographs taken. Two were confirmed to have normal number of ribs. Prenatal and postnatal findings were consistent in 6 (46.2%) babies.
Conclusion: Fetal rib number anomalies were an isolated finding in most cases. The prognosis is good in the absence of other major anomalies. The accuracy of prenatal ultrasonography appears to be low. These findings do not support routine counting of fetal rib number in second-trimester ultrasonography.

Keywords: Ribs; Ultrasonography, prenatal

Introduction

Human ribs can have a wide range of variations in the number, length, morphology, density, and fracture. Such abnormalities can be focal or generalised. Some can be isolated; others can be part of the pathological disorders including chromosomal or genetic disorders, syndromal disorders, metabolic diseases, bone dysplasias, and maternal drug exposure[1].

Visualisation of fetal ribs by two-dimensional ultrasonography is difficult owing to the spinal curvature and rib curvature. Three-dimensional (3D) ultrasonography improves visualisation of the spine and ribs by displaying the three orthogonal planes simultaneously on the coronal plane[2]. It improves the display of complex anatomy and is less operator dependent. Visualisation of the fetal ribs on 3D ultrasonography may help in the diagnosis of chromosomal or syndromal disorders such as the short rib polydactyly syndrome[3] and agenesis of the 12th rib with trisomy 21[4].

The incidence of fetal rib number anomalies ranges from 1% to 8%[1,5-7]. Rib number anomaly is the most common type of fetal rib anomalies, with supernumerary (cervical or lumbar ribs) and missing ribs accounting for 30% and 26% of all patterns, respectively[8]. International guidelines have recommended the practice to assess the curvature of the ribs in mid-trimester structural scan[9]. However, there is no recommendation on routine counting of fetal rib number. We have observed an increasing number of referrals for isolated fetal rib number anomalies in low-risk pregnant women. This is probably related to the increasing availability and application of 3D ultrasonography. Such findings induce anxiety of many parents. The present study aims to review cases of fetal rib number anomalies detected on ultrasonography, and to determine their association with chromosomal anomalies and other structural anomalies, and the outcome of the pregnancies. The findings are useful for determining the value of routine counting of fetal rib number as a part of standard procedure and to facilitate the management and counselling of the affected pregnancies.

Methods

This retrospective review was approved by the Kowloon Central / Kowloon East Cluster Research Ethics Committee (reference number: KC/KE-20-0028/ER-3). All cases of fetal rib number anomalies referred to the Prenatal Diagnosis Clinic of Queen Elizabeth Hospital between

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1 January 2016 and 31 December 2019 were reviewed. Data recorded included the source of referral, ultrasonographic findings (feasibility of assessment, fetal rib number), results of aneuploidy screening or invasive prenatal testing, and outcome of the babies.

Women were examined by maternal fetal medicine specialists after 20 weeks' gestation using a high-resolution ultrasonographic machine (Voluson E10, GE Healthcare, Wauwatosa [WI], USA) equipped with a volumetric abdominal transducer. The fetal spine was examined when the back was facing up and in the sagittal plane. A static 3D volume was obtained with a mechanical sweep when fetal movements were minimal. Fetal rib pattern and number were assessed using multiplanar reconstruction or volume contrast imaging or both (Figure).

Ultrasonographic and systemic examinations were performed to look for other structural abnormalities. All patients with fetal rib number anomalies were offered genetic counselling. The babies who delivered in our hospital were referred for postnatal examination by paediatricians, and chest radiographs were assessed by radiologists.

Results

In 2016, 2017, 2018, and 2019, there were 8435, 7591, 7903, and 7581 antenatal bookings in our units, respectively. We identified 21 (2, 1, 9, and 9, respectively) referrals for fetal rib number anomalies (Table 1). The incidence was 0.02%, 0.01%, 0.11%, and 0.12%, respectively. All 21 cases were singleton pregnancy. 20 (95.2%) patients were referred by private doctors, because fetal rib number was not routinely counted during mid-trimester structural scans in most public hospitals. One (4.8%) patient was referred by a midwife who had been trained to perform fetal anomaly scans. The most common presentation was unilateral or bilateral absence of the 12th thoracic rib (n=12, 57.1%), followed by the presence of lumbar rib (n=6, 28.6%) and the presence of cervical rib (n=3, 14.3%).

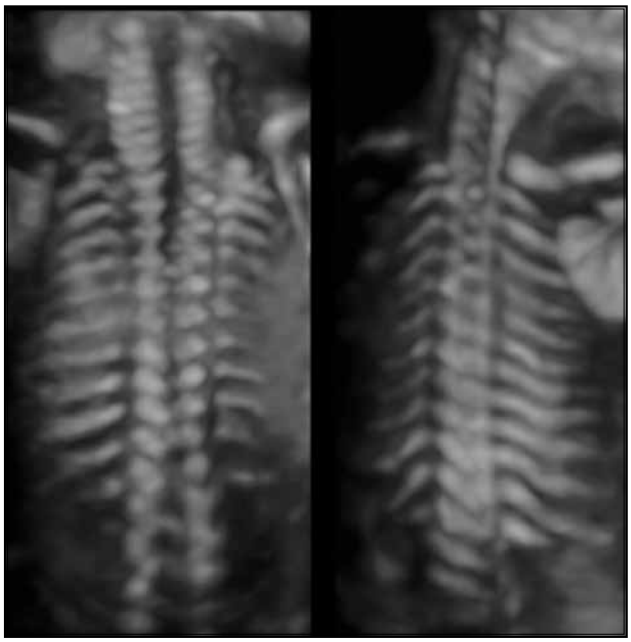

Figure. Volume contrast ultrasonographic images demonstrating normal number of ribs in a fetus

Visualisation of fetal ribs was successful in all 21 cases at 20 to 29 weeks' gestation, but visualisation was feasible in only 3 (18.8%) of 16 cases who were reassessed after 30 weeks' gestation.

Three (14.3%) fetuses were identified to have anomalies in other systems: unilateral absence of nasal bone (n=1) and minor vascular anomalies (n=2). One patient with multiple anomalies of the fetus underwent amniocentesis, and the chromosomal microarray analysis was normal. Others underwent combined first trimester screening (n=14), second trimester biochemical screening (n=1), and/or non-invasive prenatal screening (n=6) for Down syndrome. Results were all low risk.

All patients continued their pregnancies. 14 (66.7%) patients delivered in our unit with livebirths. Postnatally, 13 babies had chest radiographs taken. Only 2 were confirmed to have normal number of ribs. Prenatal and postnatal findings were consistent in 6 (46.2%) babies only. One baby with aberrant right subclavian artery and bovine aortic arch was found to have atrial septal defect; all other babies did not require further follow-up assessment.

Discussion

Ribs are developed from sclerotome cells in para-axial cells, which grow out from mesenchymal costal processes of the thoracic vertebrae[10]. The formation of ribs starts at 6 weeks' gestation and ossification takes place at 9 weeks[11]. The cells of the sclerotome are guided to their proper location by *homeobox (HOX)* gene and growth differentiation factor 11 *(GDF11)*[10]. Abnormal expression of *HOX* genes results in changing the positional identity of the vertebra[12]. This occurs more frequently at transitional zones between vertebral regions (cervico-thoracic and thoraco-lumbar boundaries), causing a change in the number of ribs[12]. Animal studies demonstrated significant effects of *GDF11* pro-peptide transgene on vertebral formation, which are likely occurring through depressing *GDF11* function and alternated locations of Hoxa-4 and Hoxa-5

Table 1. 21 cases of fetal rib number anomalies detected on ultrasonography

Maternal age, y	Rib number anomaly on ultrasonography			Pregnancy outcome	Postnatal radiography	Consistency of prenatal and postnatal imaging
	At <30 weeks' gestation	At ≥30 weeks' gestation	Other anomalies			
32	Lumbar rib, unilateral	Not visualised	No	Livebirth	Absence of 12th thoracic rib, bilateral	No
32	Absence of 12th thoracic rib, bilateral	-	No	Livebirth	Absence of 12th thoracic rib, bilateral	Yes
38	Cervical rib, unilateral	Not visualised	No	Livebirth	Cervical rib, unilateral	Yes
37	Lumbar rib, unilateral	-	No	-	-	-
34	Absence of 12th thoracic rib, unilateral	Not visualised	No	Livebirth	Normal	No
28	Absence of 12th thoracic rib, unilateral	Not visualised	No	Livebirth	Absence of 12th thoracic rib, bilateral	No
27	Absence of 12th thoracic rib, unilateral	Absence of 12th rib, bilateral	No	-	-	-
30	Absence of 12th thoracic rib, unilateral	Absence of 12th rib, unilateral	No	-	-	-
28	Absence of 12th thoracic rib, bilateral	Not visualised	Unilateral absence of nasal bone	Livebirth	Absence of 12th thoracic rib, bilateral	Yes
34	Absence of 12th thoracic rib, bilateral	Not visualised	No	-	-	-
32	Lumbar rib, bilateral	-	Aberrant right subclavian artery	-	-	-
35	Cervical rib, bilateral	Not visualised	No	Livebirth	Absence of 12th thoracic rib, bilateral	No
41	Absence of 12th thoracic rib, unilateral	Not visualised	No	Livebirth	Absence of 12th thoracic rib, unilateral	Yes
34	Cervical rib, bilateral	Not visualised	No	-	-	-
34	Lumbar rib, unilateral	Not visualised	No	Livebirth	Absence of 12th thoracic rib, unilateral	No
34	Absence of 12th thoracic rib, bilateral	-	Aberrant right subclavian artery and bovine aortic arch	Livebirth	Absence of 12th thoracic rib, bilateral	Yes
31	Lumbar rib, bilateral	Not visualised	No	Livebirth	Absence of 12th thoracic rib, unilateral	No
35	Absence of 12th thoracic rib, unilateral	-	No	-	-	-
32	Lumbar rib, bilateral	-	No	Livebirth	Normal	No
33	Absence of 12th thoracic rib, bilateral	Normal rib number	No	Livebirth	-	-
28	Absence of 12th thoracic rib, bilateral	Not visualised	No	Livebirth	Absence of 12th thoracic rib, bilateral	Yes

expression[13]. Experimental studies showed that altered expression of *Hoxa-4* and *Hoxa-5* genes result in formation of cervical ribs[13], whereas inactivation of *Hoxa-10* gene results in supernumerary lumbar ribs[14]. Over one-fifth of fetuses with cervical rib also had absent or rudimentary 12th rib, and this supports the theory of posterior homeotic shift[15]. Case reports of familial isolated cervical ribs suggest possible autosomal dominant inheritance[16,17].

The current recommendations for obtaining optimal ultrasonographic images of the ribs are based on expert opinions but are not validated by postnatal imaging. The 3D skeleton mode, multiplantar imaging, and volume contrast imaging are commonly used[5-7,18]. A small but significantly higher rate of satisfactory assessment of fetal ribs was reported at 21 to 23 weeks' gestation (97.37%-98.19%) than at 20 weeks' gestation (94.99%)[7]. The rate of fetal rib visualisation was higher at 20 to 27 weeks' gestation (100%) than at 14 to 19 weeks' gestation (82%)[19]. Minimal flexion of the fetal head is recommended[6,7]. The acquisition time is usually short (2 to 4 seconds per volume) to minimise the effect of fetal movements[5,6]. When volume contrast imaging is used, the maximum mode rendering is suggested to maximise the contrast between the bones and other tissues[5-7,18]. A thickness of volume contrast imaging of 15 to 20 mm was used in previous studies[5,18]. In multiplanar imaging, the region of interest is minimised to achieve clear and accurately rendered images[5,6]. Symmetrical appearance of ribs is preferred to compare the two sides and prevent acoustic shadowing[7,18].

Assessment of fetal ribs after 30 weeks' gestation has a low success rate. The reasons include unfavourable fetal position, lack of adequate amniotic fluid in front of the fetal spine, and relatively large fetal size resulting in difficulty to obtain an adequate volume for visualisation of the ribs. Visualisation of the first and second rib is more difficult in advanced gestation[6]. Reassessment of fetal ribs after 30 weeks' gestation does not yield additional findings to change the obstetric management.

To our knowledge, this is the first study that compares the prenatal ultrasonographic findings with the postnatal radiographic findings. Parents may not consent for postnatal radiographic examination owing to radiation exposure to their babies. In 7 of 13 babies, postnatal radiographic findings were inconsistent with prenatal ultrasonographic findings; rib numbers were underestimated or overestimated. Reasons for the inconsistency include delayed ossification of the ribs resulting in false impression of absent ribs, especially in early gestations; difficulty in identification of the first and second cervical ribs giving a false impression of absent ribs, especially in advanced gestation and when excessive flexion of the cervical spine[6]; and difficulty in identification of the correct vertebral level. It is difficult to determine the supernumerary ribs to be cervical or lumbar[7]. The correct vertebral level can be better ascertained by including the caudal or rostral end of the spine in the image, assuming that the number of vertebrae is correct. Multiple volumes may be required to visualise the entire fetal spine to determine the correct vertebral level. Gestational age should be taken into account in the interpretation of fetal rib anomalies. If the gestational age is <21 weeks, it is reasonable to repeat the scan before 30 weeks. Because of limitations of antenatal scanning, the need of postnatal radiological examination after birth should be included during antenatal counselling.

Absence of the 12th thoracic rib is the most common type of fetal rib number anomalies[5,6]. The selection against a change at the thoraco-lumbar boundary is much weaker than that against a change at cervico-thoracic one[20]. The incidence of other structural abnormalities has been estimated to be 18.2% to 46.7%[5,7,18], which is higher than the 14.3% in our study. Other associated systemic anomalies include cardiovascular, urinary tract, and neurological anomalies[5,7,18]. In our study, two of three fetuses with other anomalies had cardiovascular anomalies (aberrant right subclavian arteries). In cases of fetal rib number anomalies, a meticulous search for systemic anomalies is recommended[6]. However, the value of routine counting of fetal rib number in an otherwise structurally normal fetus is low when structural examination is routinely performed in the second-trimester ultrasonography[9].

Associations of aneuploidies or genetic syndromes with fetal rib number anomalies have been reported (Table 2)[21-30]. Around one-third of newborns with Down syndrome have 11 pairs of ribs on radiographs, and the incidence was six times higher than in those without aneuploidies[21]. Absence of the 12th thoracic rib occurs more frequently in those with free trisomy 21 (20.2%) than in those with translocation (9.1%) or mosaic trisomy 21 (0%)[4]. Significant reduction in the proliferation zones of chondrocytes results in rib aplasia in Down syndrome patients[31]. Lower than normal number of ribs is associated with trisomies 13 and 18[22]. In our study, none of the cases was found to have chromosomal abnormalities prenatally or postnatally. Our findings are consistent with more recent studies that report no associated chromosomal abnormalities[6,7]. This is probably related to the universal Down syndrome screening or non-invasive prenatal

Table 2. Associations of major fetal abnormalities with fetal rib number anomalies

Type of fetal rib number anomalies	Associated aneuploidies or genetic syndromes	Reference
11 pairs of ribs	Trisomy 21	Edwards et al[21], 1988
Reduced number of ribs	Trisomy 18, Trisomy 13	Achter et al[22], 2016; Ho et al[23], 1989
Absence of one rib	VATERL syndrome	Chen et al[24], 2012
10 pairs of ribs	Campomelic dysplasia	Basani et al[25], 2018
Absence of upper ribs	Poland syndrome	Ta et al[26], 2014
Cervical rib	Trisomy 21, Nail-patella syndrome, KBG syndrome, Simpson-Golabi- Behmel syndrome type 1	Furtado et al[27], 2011
	Monosomy X	Keeling et al[28], 1999
	Trisomy 9	Nakagawa et al[29], 2006
Lumbar ribs	Trisomy 8, Monosomy X, Cleidocranial dysplasia, Aarskog syndrome, Incontinentia pigmenti	Aly et al[30], 2016

screening, which enables early diagnosis in first or second trimester before fetal ribs can be clearly visualised. These findings suggest that routine counting of fetal rib number does not appear to have extra benefit in the diagnosis of Down syndrome in fetuses without other structural anomalies and with low-risk aneuploidy results.

Cervical rib was observed in over one-fourth of fetuses with monosomy X and hydrops and thus was considered a useful marker for evaluation of fetal hydrops. The presence of cervical rib is related to the altered function of *HOX* gene located in chromosome Xp22[28]. However, invasive prenatal testing is readily available to diagnose chromosome abnormalities in hydropic fetuses, irrespective of the presence of cervical rib. Although ossification centres of cervical ribs can be detected in radiographs earliest by 14 weeks' gestation, the timing of prenatal cervical rib detection has not been studied. This limits its value in early prenatal diagnosis. Moreover, it is technically difficult to visualise the skeleton in the neck region in the presence of nuchal oedema. It may be considered as a part of the assessment for hydropic fetuses after miscarriage or stillbirth where genetic diagnosis is not available.

Cervical ribs are regarded as markers of disadvantageous developmental events during morphogenesis that have been subjected to strong negative selection during evolution[20], and can be an independent predictor of stillbirth[27]. The prevalence of cervical ribs is almost 4 times higher in stillborn fetuses (43.1%) than liveborn infants who die in the first year of life (11.8%)[27]. The mortality rate of fetuses and neonates with cervical ribs is >70%[20]. The high incidence of major congenital anomalies in deceased fetuses and infants suggests that simple and pure presence of cervical ribs is not directly associated with fetal death, but it is related to other disadvantageous changes[20,27]. Routine prenatal screening of cervical ribs should not be used to predict fetal outcome in those without any associated anomalies.

Childhood cancer is associated with cervical rib anomalies[32,33]. *HOX* gene mutant may affect the tumour suppression and cause oncogenesis. A small but clinically significant higher prevalence of cervical ribs is reported in children with cancers, including neuroblastoma, brain tumour, leukaemia, soft tissue sarcoma, Wilms tumour, Ewing sarcoma, and germ cell tumour[32,33]. As the baseline risk of childhood cancer is very low (1.4 per 10 000 children in Hong Kong)[34], it is unlikely that cervical rib anomaly can be an effective marker for childhood malignancy.

Most patients with rib number anomalies do not have any symptoms, but clinical manifestations and complications can occur, depending on the type of anomaly. Up to 10% of individuals with a cervical rib may have thoracic outlet syndrome secondary to mechanical compression of the brachial plexus or subclavian artery by the cervical rib[35]. The type of manifestation depends on the morphology of the cervical rib, with incomplete ribs affecting only the brachial plexus and complete ribs affecting the subclavian artery as well[35]. Rare complications of thoracic syndrome include subclavian artery aneurysm[36,37] and cerebellar stroke in young patients[38,39]. Surgical removal may be required in symptomatic patients.

Most patients with isolated lumbar ribs or absent 12th thoracic ribs are asymptomatic, although pain in the

renal angle has been reported in those with lumbar ribs[40]. Presence of lumbar rib may hinder percutaneous renal biopsy through the renal angle between the 12th thoracic rib and lumbar vertebra[40]. Absence of the 12th thoracic rib may result in incorrect vertebral segment identification during lumbar intervention[41]. A rare case of lung herniation has been reported as a complication secondary to absence of multiple ribs[42].

The major limitations in the present study include the small sample size from a single centre and the retrospective nature. The true incidence of fetal rib number anomalies is underestimated because counting of fetal rib number is not routinely performed. The imaging modalities and techniques used for visualisation of fetal ribs varied with different operators and have yet to be standardised.

Conclusion

With adequate prenatal screening for aneuploidies and absence of other structural abnormalities, isolated fetal rib number anomalies have good prognosis. Detailed ultrasonographic evaluation is recommended owing to the increased risk of major structural anomalies. Invasive prenatal assessment should not be routinely offered for isolated fetal rib number anomalies with low-risk aneuploidy results and no structural abnormalities.

The value of routine counting of fetal rib number in structural scan in low-risk pregnancies remains uncertain. The low accuracy may create unnecessary anxiety to parents. Counselling should include the limitations of ultrasonographic assessment, possible complications/conditions associated with fetal rib number anomalies, the need of postnatal radiographic examination to confirm the diagnosis, and the need of systemic evaluation after birth.

Declaration

The authors have no conflict of interest to disclose.

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