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Prenatal Assessment of Fetal Vertebrae and Ribs by Three-Dimensional Ultrasound and the Association with Fetal and Neonatal Outcome

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Supernumerary rib · Cervical rib · Lumbar rib · Rudimentary rib · Three-dimensional ultrasound

Abstract

Introduction: The presence of an abnormal vertebral pattern and (rudimentary) cervical ribs in particular has been associated with adverse fetal and neonatal outcomes, such as intrauterine fetal death and structural or chromosomal abnormalities. The feasibility and potential added value of prenatal assessment of the vertebral pattern and the presence of cervical ribs are currently unclear. Aims of this study were to evaluate the feasibility of prenatal assessment of the fetal vertebral pattern and cervical ribs using three-dimensional ultrasound and determine whether an abnormal vertebral pattern is associated with adverse fetal and neonatal outcome. ***Methods:*** A total of 1,138 women referred for an advanced ultrasound examination were included, and volume data sets of the spine were acquired. The vertebral pattern was reassessed on postnatal radiographic examinations, when available. Associations between adverse outcomes and abnormalities of the vertebral pattern that had at least a good agreement between prenatal and postnatal assessments were studied. ***Results:*** Agreement between prenatal and postnatal assessment of the presence of cervical ribs was poor, which also applied to assessment of the complete vertebral pattern. Moderate to fair agreement existed between prenatal and postnatal assessments of thoracic rib number. Prenatal and postnatal assessments of lumbar ribs had a very good agreement. Lumbar ribs were rare (10/768, 1.3%) and associated with female gender, but not with any other variable. ***Conclusion:*** Lumbar ribs could be assessed very well on prenatal three-dimensional ultrasound and were not associated with adverse outcomes. Prenatal and postnatal agreement between the presence of cervical ribs, number of thoracic ribs, and the vertebral pattern was insufficient.

Introduction

The presence of an abnormal vertebral pattern has been associated with adverse fetal and neonatal outcomes, such as intrauterine fetal death and structural or chromosomal abnormalities [1–5]. Variations of the

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cervical vertebral pattern in particular seem to be associated with disturbed fetal development, and most individuals with cervical ribs are not expected to reach reproductive age due to indirect selection against associated pleiotropic effects [6]. This hypothesized indirect selection against variations occurring in the cervical vertebral region can explain the striking stability of the presence of seven cervical vertebrae in nearly all mammals, regardless of the length of their neck [1, 7–9]. This selection probably occurs because disturbances of the establishment of the vertebral pattern arise at a developmental stage where they affect other developing organ systems easily [6]. The remarkably high rates of abnormalities of the vertebral pattern, including cervical ribs, in deceased fetuses and neonates with multiple structural abnormalities and in children with an anorectal malformation and/or esophageal atresia and associated abnormalities support this hypothesis [1, 10]. Prenatal assessment of the vertebral pattern using three-dimensional ultrasound seems possible [11–14], but assessment of the number of vertebrae and ribs during fetal ultrasound examinations is currently not routinely performed. Studies assessing the complete vertebral pattern, including the presence of cervical ribs, by ultrasound in a large cohort of fetuses both with and without different structural, chromosomal, or genetic anomalies, are lacking. The feasibility and potential added value of prenatal assessment of the vertebral pattern and of the presence of cervical ribs therefore remain unclear. Aims of the study were to determine whether the number of vertebrae and ribs, including the presence of cervical ribs, can be reliably assessed in the prenatal period using three-dimensional ultrasound, by comparing this prenatal assessment with postnatal radiographs, magnetic resonance imaging (MRI), or computed tomography (CT) scans, when available and to assess whether abnormalities of the vertebral pattern which have been reliably assessed prenatally are associated with an adverse fetal or neonatal outcome, such as structural, chromosomal, or genetic abnormalities or fetal or neonatal death.

Methods

Study Participants and Design

The study was a prospective single-center study, conducted at the Department of Obstetrics and Gynecology at the Erasmus University Medical Center, Rotterdam, a tertiary referral center in the Netherlands. Pregnant women who were at least 18 years old, referred for an advanced ultrasound examination in the period between May 2014 and February 2018, were included after written informed consent. Indications for referral were a suspected fetal structural abnormality or increased risk of fetal structural abnormalities due to factors such as family history, maternal diabetes, or the use of teratogenic medication. Fetuses with and without structural, chromosomal, or genetic abnormalities were included.

The ultrasound examinations were performed using Voluson E8 or E10 systems (GE Healthcare, Waukesha, WI, USA), equipped with transabdominal 1–7 MHz transducers. During the advanced ultrasound examination, volume data sets of the spine were acquired according to the study protocol (online suppl. file; for all online suppl. material, see https://doi.org/10.1159/000548341). All sonographers received instructions and were trained in obtaining the correct volume data sets of the spine. The volumes were saved, and the number of vertebrae and ribs was independently assessed by two reviewers using 4DView (version 14 Ext. 3, GE Healthcare Austria GmbH & Co OG), without knowledge of the indication of the ultrasound examination, the ultrasound findings, and fetal outcome.

The vertebral patterns were classified according to Ten Broek et al. [1] (Fig. 1). This classification system categorizes abnormalities based on the vertebral region involved and includes changes at the cervicothoracic boundary, the thoracolumbar boundary, the lumbosacral boundary, or across multiple boundaries. The seventh cervical vertebra was identified by counting downward from the first cervical vertebra in a sagittal plane. In 4DView, the sagittal, transverse, and coronal views were visualized simultaneously. When a bone-white structure was visualized separate from the ossification centers of the center or vertebral arches, it was classified as a cervical rib (Fig. 2). If the structure was less than half of the length of the first thoracic rib, it was considered a rudimentary cervical rib. Ribs on the first or last thoracic vertebra were rudimentary if their length was less than half of the adjacent thoracic rib. In case of discrepancies between the assessment of the number of vertebrae and/or ribs by both reviewers, the volumes were reassessed together and if agreement was not reached the number of vertebrae or ribs was classified as "unknown." To assess the reliability of prenatal ultrasound, the number of ribs and the vertebral pattern were studied by a single experienced radiologist (MD) on postnatal radiographs, MRI, or CT scans, when available. The radiologist was blinded to the outcome of the prenatal assessment of the vertebral pattern. Agreement between prenatal and

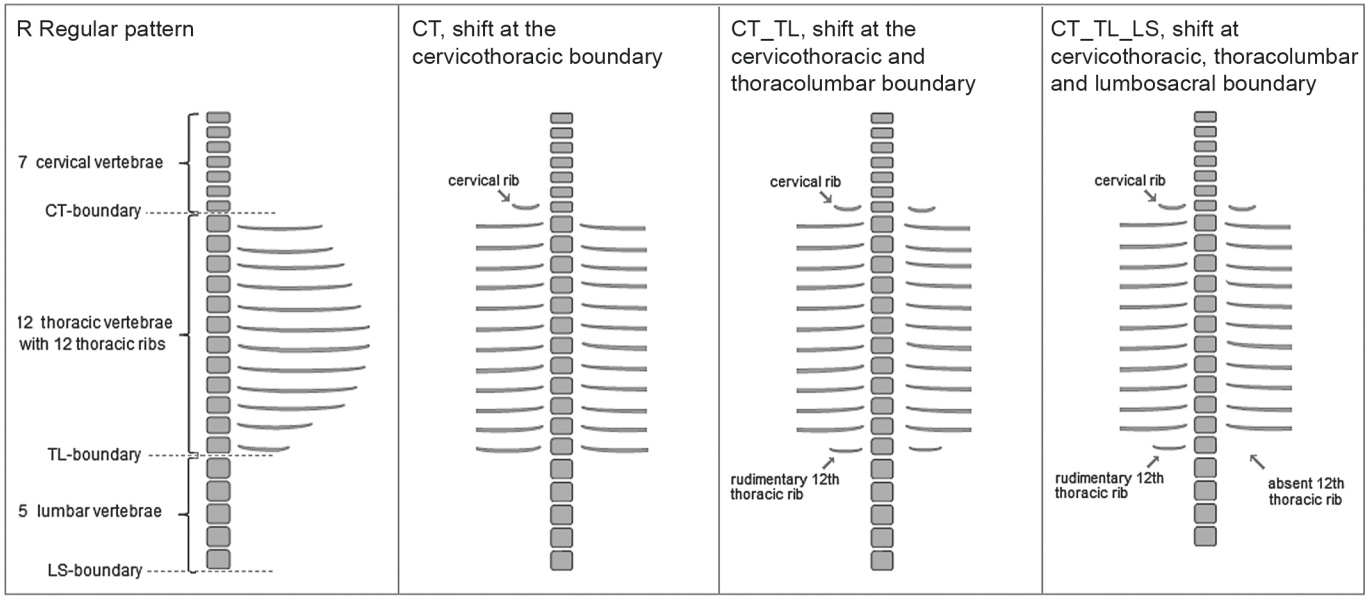

Fig. 1. Overview of different vertebral patterns. From left to right: R, regular pattern; CT, shift at the cervicothoracic boundary; CT_TL, shift at the cervicothoracic and thoracolumbar boundary; CT_TL_LS, shift at cervicothoracic, thoracolumbar, and lumbosacral boundary.

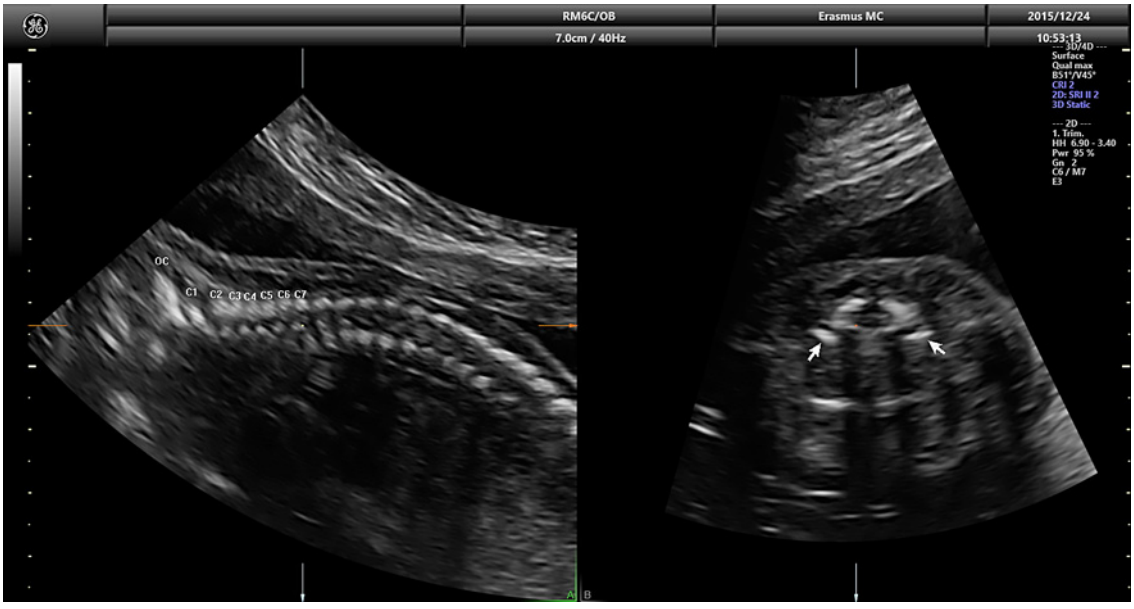

Fig. 2. Sagittal and transverse ultrasound view of the vertebral column. In 4DView, the transverse view at the level of the seventh cervical vertebral column can be visualized simultaneously, corresponding with the yellow dot in the sagittal view. The arrows point to the bone-white structures that were classified as bilateral rudimentary cervical ribs. OC, occiput; C1, first cervical vertebra; C2, second cervical vertebra.

postnatal assessments was calculated as percentage agreement, using Gwet's AC1 agreement coefficient [15]. This statistic is a chance-corrected agreement coefficient which aims to circumvent undesired behavior of Cohen's kappa. The benchmarking method used takes the estimation error of the statistic into account to determine

whether agreement should be categorized as poor (AC1 <0.2), fair (0.4> AC1 ≥0.2), moderate (0.6> AC1 ≥0.4), good (0.8> AC1 ≥0.6), or very good (AC1 ≥0.8) [16]. A single (imprecise) estimate does not necessarily predict agreement well across repeated trials. Therefore, using the estimated value and the standard deviation of each AC1 statistic, we determined for each of these ordinal categories what the probability was that an estimate would fall within it. It was then rejected that agreement would be lower than a given category if the summed probabilities of all categories below it would be smaller than 0.05. Equivalently, one can then conclude that agreement was at least as good as according to that category. Thus, the category is reported for which the cumulative probability of obtaining an AC1 estimate at the categories' lowest boundary or larger is at least 0.95 and the probability of observing a lower agreement category is at most 5% [15]. We interpreted these agreements as degrees of accuracy to which vertebral traits can be determined using three-dimensional ultrasound.

Data regarding pregnancy, delivery, fetal and neonatal outcome were collected from electronic patient files or requested from other hospitals and/or midwifes. The presence of structural abnormalities was based on the following (in hierarchically descending order): autopsy reports, postnatal imaging reports, postnatal surgery, postnatal external inspection. If postnatal examinations were not performed, it was based on the findings of advanced ultrasound examinations. Structural abnormalities were categorized using the Eurocat classification [17].

Genomic single-nucleotide polymorphism (SNP) array (Illumina Infinium BeadChip 0.15 Mb) and/or karyotyping were performed on material collected in patients opting for invasive prenatal or postnatal diagnostic testing. This included amniocentesis, chorion villus biopsy, and skin biopsy. Additional DNA testing or whole exome sequencing was performed when requested by a clinical geneticist or for specific indications (e.g., cystic fibrosis in case of echogenic bowel on advanced ultrasound scan). DNA copy number alterations were determined using genotyping arrays (Illumina, San Diego, CA, USA) as described previously [18] and classified according to diagnostic guidelines released by the American College of Medical Genetics and Genomics [19].

Statistical analysis was performed using SPSS Statistics (IBM Corp., Released 2016, IBM SPSS Statistics for Windows, Version 24.0., Armonk, NY: IBM Corp.) and R [20]. Descriptive analyses were used to describe and compare the incidence of maternal, fetal, and neonatal characteristics. Chi-square or Fisher's exact tests were used to determine incidence differences between groups. Throughout, p values <0.05 were considered statistically significant. One-way ANOVA F tests were used to compare continuous response variables between two or more groups when residuals were normally distributed. We studied associations between the occurrence of abnormalities of the vertebral pattern and other variables by means of log-linear modeling [21], using Poisson generalized linear models for counts in R. Per vertebral trait, a maximal model was fitted with all three-way associations (interactions) of the presence of that trait and two categorical explanatory variables. This model was then simplified by means of model comparisons using likelihood ratio tests, until a minimum adequate model remained which only contained significant effects. This last model per trait included at least all main effects of the trait and the explanatory variables. During model simplification, nonsignificant three-way interactions were removed first; two-way interactions were removed subsequently. We removed nonsignificant interactions involving the vertebral trait last within each group of interactions (hence those only containing explanatory variables first). We also removed interactions when the estimated effects did not allow us to interpret them, i.e., with very wide errors of the estimates, due to zero occurrences in small samples with specific combinations of variables. Explanatory variables for which there were many missing observations were not included in the maximal model, but tested with respect to the minimum adequate model retained. We tested for associations with the number of organ systems affected by structural abnormalities using logistic regression models containing that number and the variables above as explanatory variables, and including two-way interactions between the number of organ systems affected and the other explanatory variables. Model selection was again carried out as above.

We only report the results of model selection procedures on vertebral traits for which the agreement between prenatal and postnatal assessments was at least good. When agreement was lower than that, we assumed that the prenatal vertebral trait had not been determined reliably and we would therefore be modeling assessment errors confounded with the trait. Anticipating on some of the results on agreement below, we performed model selection procedures to determine associations of explanatory variables with the presence of a lumbar rib. To reduce the number of parameters to be estimated, explanatory variables were fitted with a low number of categories each. We fitted variables for maternal smoking (at intake), use of folic acid (pre- or postconceptional), assisted conception (ovulation induction, insemination, IVF, and IVF/ICSI), the occurrence of previous miscarriages, fetal gender, the presence of structural

abnormalities, birth outcome (stillbirth, termination of pregnancy, immature delivery, or live birth), and the occurrence of neonatal death. The possible association with an abnormal array or with a different karyotype (both many missing values) was studied by adding these variables to the selected models. When they had a significant effect in such a model, their association was also tested with a marginal Fisher's exact test.

Results

Informed consent was obtained in 1,138 pregnancies. After exclusion of pregnancies without volumes of sufficient quality or follow-up, 802 pregnancies were available for analysis. Women for whom it was technically not feasible to acquire the correct volumes and those with volumes of insufficient quality had a significantly higher BMI than those with available volumes of sufficient quality of at least one vertebral region (25.69 [s.e. 0.56] and 26.20 [s.e. 0.62] versus 23.71 [s.e. 0.14], overall test $F_{2,\ 960} = 17.34$, $p < 0.01$). No statistically significant differences were seen in the presence of structural abnormalities between pregnancies with and without volumes of sufficient quality (263/801, 32.8% vs. 100/322, 31.1%; $p = 0.57$, Fisher's exact), nor in gestational age at the time of volume acquisition (median 20.57 weeks [IQR 1.14] vs. 20.43 weeks [IQR 1.29], respectively). In one fetus with trisomy 21, intrauterine fetal death occurred at 19.4 weeks' gestation. Besides acquisition of data volume sets of the spine, the advanced ultrasound examination was not completed, nor was autopsy performed. Summary statistics on the included pregnancies are provided in Table 1.

Most pregnancies ($n = 730/802$, 91.0%) resulted in live births. Indications for termination of pregnancy before 24 weeks' gestation were structural and/or chromosomal abnormalities in most cases ($n = 58/60$, 96.7%). One pregnancy was terminated because of a severe fetal growth restriction and one because of premature rupture of membranes and oligohydramnios before 24 weeks' gestation. Intrauterine fetal death occurred in nine pregnancies (1.1%). In seven of these, chromosomal or structural abnormalities were present. One intrauterine fetal death was caused by placental abruption, and one fetal death at term occurred in a growth-restricted fetus with anhydramnios. Neonatal death occurred in 11 live births, including 10 patients with severe congenital abnormalities. The gestational age at birth, cause of death, and assessment of the vertebral pattern on prenatal ultrasound examination and postnatal radiographic images (if available) in these deceased patients are shown in Table 2.

About one-third of the total number of included fetuses and neonates had a structural abnormality. The numbers of structural abnormalities according to affected organ system are shown in Figure 3. In more than a quarter of fetuses with a structural abnormality, more than one organ system was affected (77/264, 29.2%). Cardiovascular, craniofacial, and urogenital organ systems were most frequently affected.

A SNP array was available in 206/802 (25.7%) patients and a karyotype in two patients (0.2%). Aneuploidies were diagnosed in 19 fetuses, and other chromosomal abnormalities were identified in 31 fetuses. Additional DNA analysis was requested in 42 patients (5.2%) and showed an abnormality in 13 cases (31.0%, online suppl. Table S1).

An overview of the prenatal assessment of the number of vertebrae and ribs in the total population and in fetuses with and without structural abnormalities is provided in online supplementary Table S2. Postnatal radiographs, MRI, or CT scans were available in 132 fetuses and neonates.

Cervical Ribs

In the majority of fetuses (399/611, 65.3%), echogenic structures at the level of the 7th cervical vertebrae, which were interpreted as (rudimentary) cervical ribs, were found. An example is shown in Figure 2. Most of these were rudimentary and bilateral (361, 90.5%), followed by rudimentary left (24, 6.0%), rudimentary right (13, 3.3%), and bilateral cervical ribs (1, 0.3%). The cervical region could be assessed both prenatally and postnatally in 85 patients. Prenatal and postnatal assessments were in fair or poor agreement (cervical rib categories estimate AC1 = 0.41 [s.e. 0.07], presence of cervical ribs estimate AC1 = 0.24 [s.e. 0.11]). Only in 35 of 60 patients (58.3%) in whom cervical ribs were identified on prenatal ultrasound, the presence of cervical ribs was confirmed on postnatal radiographic images. The absence of cervical ribs was confirmed in 16 of 25 patients (64.0%) in whom cervical ribs were prenatally not identified. An example of both absence and presence of cervical ribs on prenatal and postnatal images is shown in Figure 4.

Thoracic Ribs

The number of thoracic vertebrae and ribs could be assessed in the majority of fetuses (93.3% and 92.9%, respectively). In 131/745 (17.6%) fetuses, fewer than 24 thoracic ribs were present. However, these were rarely

Table 1. The baseline characteristics of the included pregnancies

	N (%)
Pregnancies	802
Singleton	792 (98.8)
Multiple	10 (1.2)
Maternal age, years	30 (18–46)
Preconception maternal BMI	23 (15.9–43.2)
Maternal smoking	
Yes	64 (8.0)
Quit during pregnancy	64 (8.0)
Unknown	1 (0.1)
Nullipara	378 (47.1)
Method of conception	
Spontaneous	646 (80.5)
ICSI	94 (11.7)
IVF	14 (1.7)
Other	34 (4.2)
Unknown	14 (1.7)
Indication for advanced ultrasound scan	
Suspected structural abnormality	394 (49.1)
Family history	189 (23.6)
ICSI	85 (10.6)
Maternal diabetes mellitus	30 (3.7)
Fetal growth restriction	20 (2.5)
Enlarged nuchal translucency first trimester	18 (2.2)
Teratogenic medication	16 (2.0)
Other	50 (6.2)
GA at time of advanced ultrasound scan, week)	20.6 (15.7–29.3)
Fetal and neonatal outcome	
Termination of pregnancy	60 (7.5)
Immature delivery	3 (0.4)
Intrauterine fetal death	9 (1.1)
Live birth	730 (91.0)
Neonatal death (<28 days after birth)	11 (1.5)
GA at time of birth, weeks[a]	39.3 (26.1–42.4)
Birth weight, g[a]	3,310 (410–5,320)
Structural abnormality	264/801 (33.0)
Unknown[b]	1

Data presented as median and range or as number and percentage. BMI, body mass index, ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilization; GA, gestational age. [a]Stillbirths, terminations of pregnancy, and immature deliveries were excluded. [b]In one fetus with trisomy 21, intrauterine fetal death had occurred. Data volume sets of the spine were obtained, but the advanced ultrasound scan was not completed, nor was autopsy performed.

fewer than 22 (4/745, 0.5%). In only 4/745 fetuses (0.5%), more than 24 thoracic ribs were present.

The total number of thoracic ribs was determined both prenatally and postnatally in 110 patients. The assessments of an abnormal number of thoracic ribs had a percentage agreement of 70.9%, and the AC1 statistic indicated that the agreement was fair (AC1 = 0.50, s.e. 0.09). For the number of thoracic ribs, the agreement was moderate (AC1 = 0.64 [s.e. 0.05]). In most patients (26/37, 70.3%) in whom prenatal and postnatal assessment differed, 24 thoracic ribs were identified on prenatal ultrasound volumes, while on postnatal radiographic images, the 12th

Table 2. Gestational age at birth, age at death, and cause of death of the included neonatal deaths

GA at birth, weeks	Age at death, days	Cause of death	Cervical ribs (ultrasound)	Vertebral pattern (ultrasound)	Cervical ribs (radiograph)	Vertebral pattern (radiograph)
26.1	2	Respiratory insufficiency due to pulmonary bleeding with thrombocytopenia Unsuccessful resuscitation	Unknown	Unknown	No	R
27.7	5	Cardiorespiratory insufficiency, bowel perforation, dysmature	No	Unknown	No	R
29.6	21	Cardiorespiratory insufficiency. Hypotonia and intraventricular hemorrhage	No	TL	–	–
31.6	2	Noonan syndrome. Hydrops, hypertrophic cardiomyopathy, persisting pulmonary hypertension. Discontinuation of treatment	Unknown	Unknown	Yes, bilateral rudimentary	CT
32.9	2	Multiple abnormalities, including left diaphragmatic hernia and hypoplastic left heart syndrome. Palliative care	Yes, bilateral rudimentary	CT_LS	No	LS
33.6	0	Cardiorespiratory insufficiency, cord prolapse, asphyxia and severe pulmonary hypoplasia, left diaphragmatic hernia	Yes, bilateral rudimentary	Unknown	Yes, bilateral rudimentary	CT_TL
34.1	0	Multiple abnormalities, including right diaphragmatic hernia and complex cardiac abnormality. Palliative care	Yes, bilateral rudimentary	CT	–	–
34.9	0	Encephalocele	Yes, bilateral rudimentary	CT	–	–
35.1	0	Pulmonary hypoplasia, bilateral multicystic dysplastic kidney. Palliative care	Unknown	Unknown	–	–
35.4	1	Trisomy 13. Multiple abnormalities, including hypoplastic left heart syndrome. Palliative care	No	Unknown (but 11 thoracic rib pairs)	–	–
39.3	10	Multiple organ failure caused by circulatory shock due to minimal systemic flow with complex cardiac abnormality	Unknown	Unknown	Yes, bilateral rudimentary	CT

Assessment of the presence of cervical ribs and vertebral pattern on prenatal ultrasound and radiographs after birth (if available) is also provided. R, regular pattern; CT, shift at the cervicothoracic boundary; TL, shift at the thoracolumbar boundary; LS, shift at the lumbosacral boundary; CT_TL, shift at the cervicothoracic boundary and at the thoracolumbar boundary; CT_LS, shift at the cervicothoracic boundary and at the lumbosacral boundary.

thoracic rib was classified as unilateral or bilateral rudimentary, leading to a thoracic rib count of 23 or 22, respectively. When fewer than 24 thoracic ribs were identified prenatally, this was confirmed after birth in 15/18 patients (83.3%). Postnatal images were available in two of the four patients who were prenatally suspected to have 26 thoracic ribs, and this was confirmed in 1 patient; in the other, the 26th thoracic rib was considered rudimentary.

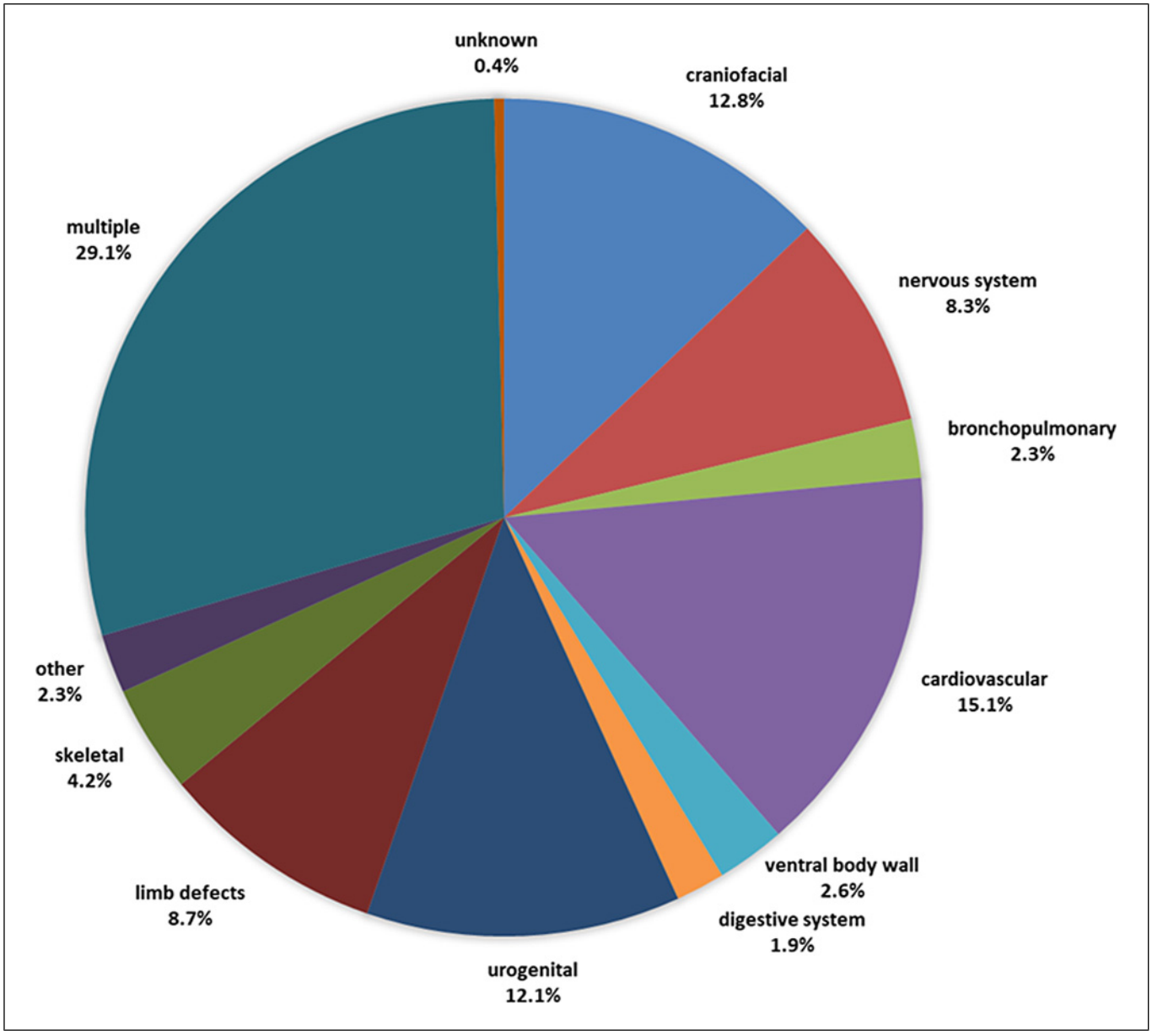

Fig. 3. Distribution of the different types of structural abnormalities (n = 264).

Lumbar Ribs

The presence or absence of lumbar ribs could be assessed in 95.8% of fetuses. Lumbar ribs (10/768, 1.3%) were infrequent, and all were rudimentary. The percentage agreement between prenatal and postnatal assessments of the presence of lumbar ribs was 98.8% (79/80), and the agreement was very good according to the AC1 statistic (0.99, s.e. 0.01). In one of the two patients with a lumbar rib that was seen on prenatal images of whom a postnatal radiograph was available, a discrepancy was noted, namely, a unilateral lumbar rib that was only identified on prenatal images. Lumbar ribs were associated with female gender (9/397 = 2.3% versus 1/371 = 0.2%, $\chi^2(1) = 11.45$, $p = 0.0007$) and not with any other explanatory variables. Lumbar ribs were thus not significantly more frequent in fetuses with structural abnormalities (3/246, 1.2%) compared with those without structural abnormalities (7/526, 1.3%, Fisher's exact $p = 1.0$), nor in fetuses with an abnormal array (1/47, 2.1%) compared to those with a normal array (0/144, Fisher's exact $p = 0.25$).

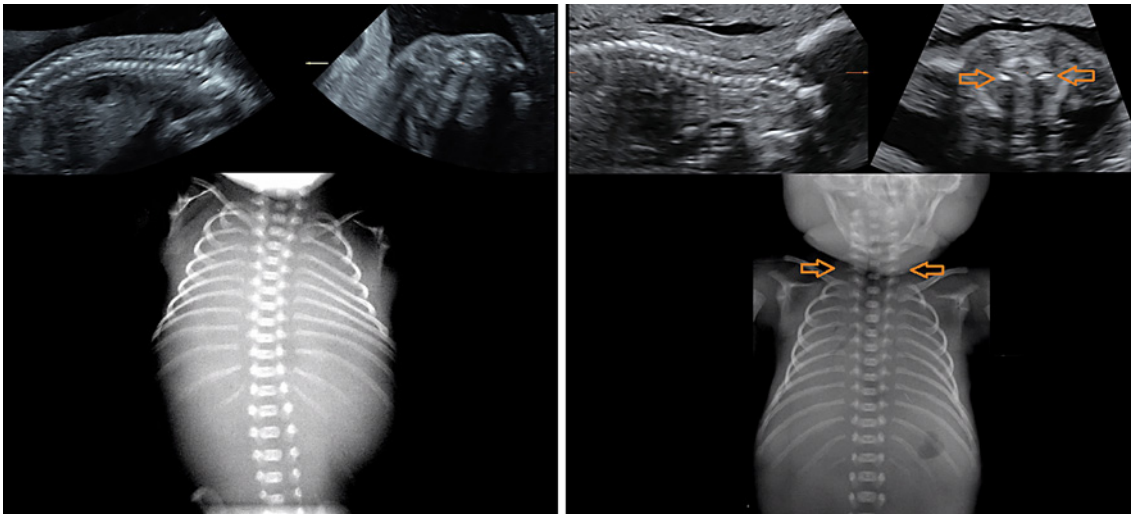

Fig. 4. Example of sagittal and axial prenatal ultrasound images analyzed using 4DView and postnatal radiographic images of a fetus without (left) and with (right) bilateral rudimentary cervical ribs (orange arrows).

Presacral Number of Vertebrae

A normal number of 24 presacral vertebrae was counted in most fetuses (562/605, 92.9%). The presacral number of vertebrae could be assessed on postnatal images in 21 fetuses, and the percentage agreement was 76.2% (16/21), which was moderate, based on AC1 (AC1 = 0.73 [s.e. 0.12]).

Vertebral Pattern

The complete vertebral pattern could be assessed in 535 fetuses (66.7%). Inability to assess the vertebral pattern was caused by insufficient quality of the volumes, which could be due to fetal position, movement artifacts, high maternal BMI, or because the volumes did not include all regions of the vertebral column. Only 154 fetuses (28.8%) had a regular vertebral pattern. The most common deviation from a regular vertebral pattern was caused by shifts at the CT boundary (CT; 262, 49.0%), which was caused by the presence of echogenic foci that were interpreted as cervical ribs. An abnormal vertebral pattern including shifts at all three boundaries (CT-TL-LS) was seen in 12 (2.2%) of fetuses. The vertebral pattern was classified on both prenatal and postnatal images in 35 patients. The percentage agreement between these assessments was poor (estimate AC1 = 0.27 [s.e. 0.10]).

Number of Affected Organ Systems and Vertebral Patterning Anomalies

We found that the presence of a lumbar rib depends in a gender-specific manner on the number of organ systems affected ($\chi^2(1) = 4.20$, $p = 0.040$). The parameter estimates of the gender-specific effects were overall positive in males (95% confidence interval [−0.06, 2.8]) and not in females (c.i. [−2.2, 0.4]), entailing a correlation between the presence of a lumber rib and the number of affected organ systems in males. This can be explained by the presence of only one male fetus with a lumbar rib that had abnormalities in three different organ systems.

Discussion

Main Findings

Prenatal assessment of the presence of lumbar ribs by three-dimensional ultrasound is feasible in most pregnancies. Determination of the presence of cervical ribs and determination of the complete vertebral pattern using three-dimensional ultrasound are more complex. This could not be assessed in approximately one-quarter and one-third of the included fetuses, respectively. In addition, compared to available postnatal images, prenatal assessment of the presence of cervical ribs, (rudimentary) thoracic ribs, presacral vertebrae, and the vertebral pattern could not be performed with sufficient accuracy, which makes this technique at this moment unsuitable for clinical use. The hypothesized indirect selection against variations occurring at the cervical vertebral region could therefore not be confirmed or rejected by the data from this study.

The high prevalence of echogenic structures that were interpreted as (rudimentary) cervical ribs in both fetuses

with and without structural abnormalities according to prenatal assessment on ultrasound volumes was unexpected and not in line with previous studies [1, 4, 10, 12]. An overestimated prevalence of cervical ribs could be due to the lower resolution of ultrasound, complicating accurate assessment of the cervical region, a region with a relatively high concentration of different anatomic structures. The discrepancy could also be explained by the possibility that these echogenic structures may not represent actual (rudimentary) cervical ribs. Most of these structures may have been too small to protrude beyond the transverse process of the first thoracic vertebra, a criterion that has been used to define cervical ribs in studies in which the presence of cervical ribs was assessed on radiographs [1, 10, 18]. Because the transition between vertebra and transverse process could not be precisely identified on prenatal ultrasound volumes, it was not possible to use this criterion. Instead of forming rudimentary cervical ribs, these structures may represent the pleurapophysis and fuse with the vertebral body at a later stage [22]. Alternatively, these echogenic foci could be artifacts or resolve later in fetal or neonatal development, which also applies to intra-abdominal microcalcifications or echogenic cardiac foci [23, 24]. In order to evaluate the evolution of these echogenic structures, a longitudinal follow-up study should be performed. A much better agreement of prenatal assessment lumbar ribs is probably caused by the larger size of these ribs, compared to rudimentary cervical ribs.

Overall, the incidence of fewer than 24 thoracic ribs was 11.4%, which is high in comparison with previous studies assessing fetal rib number on three-dimensional ultrasound [12, 25, 26]. This could be due to the fact that these studies only included absent ribs and did not describe the presence of rudimentary thoracic ribs. In the total study population, no association was found between an abnormal number of lumbar ribs and structural or chromosomal abnormalities, or adverse fetal or neonatal outcome. This corresponds with a previous ultrasound study [12] and also with the hypothesis that selection against abnormalities of the thoracic vertebral pattern is less strong, because this part of the vertebral column is formed later in fetal development compared to the cervical vertebral pattern [6].

In female fetuses, the presence of lumbar ribs occurred more frequently. Cervical ribs have been reported to occur more often in women [27, 28], but this has not been reported for lumbar ribs or an abnormal number of thoracic ribs [29, 30]. In many studies, the distribution of an abnormal rib number according to gender was not reported [31–33]. A potential explanation for the female predisposition of the abnormalities in rib number in this study could be the hypothesized higher vulnerability of male embryos and fetuses to intrauterine fetal demise compared with female embryos and fetuses [34]. Abnormalities in embryonic development, such as abnormal development of the vertebral pattern, could make male embryos and fetuses more susceptible to intrauterine fetal death, compared with female embryos and fetuses, leading to a lower number of live males with abnormalities of the vertebral pattern. It remains questionable whether this so-called male disadvantage really exists, as this has been questioned by various studies [35, 36].

Because the isolated presence of lumbar ribs does not seem to have clinical implications, routine prenatal assessment of the presence of lumbar ribs using three-dimensional ultrasound does not seem indicated. For better visualization of abnormalities of the vertebral column, such as hemivertebrae, three-dimensional ultrasound can be of added value [37]. When encountered with isolated lumbar ribs, based on the data of this study and on the current literature, reassurance seems appropriate. When isolated rudimentary or absent 12th thoracic rib is visualized on prenatal ultrasound, this finding should be interpreted with caution, due to the moderate agreement with postnatal imaging. Considering these results, patients should be referred to a prenatal diagnostic center if an abnormal number of fetal ribs is suspected, for appropriate counseling by a fetal medicine specialist.

Strengths of this study were the inclusion of a large study population with and without structural abnormalities. Only a small number of cases were lost to follow-up. All volumes were assessed by two observers, who were blinded to the fetal and neonatal outcome. In addition, postnatal images were available in a relatively large number of neonates, enabling determination of agreement between prenatal and postnatal assessments of the vertebral pattern.

A limitation of this study was the inability to acquire accurate volumes in part of the included pregnancies, in particular in women with a higher BMI, while abnormalities of the vertebral column may be more prevalent in this population. Additional limitations were the lower number of postnatal radiographs in healthy neonates to confirm the prenatal findings and the lack of longitudinal follow-up in the prenatal period. Due to the period of inclusion of patients, SNP array was most frequently used, while whole exome or genome sequencing is currently more often performed, which could lead to detection of previously missed genetic abnormalities.

Future research should include longitudinal assessment of the fetal vertebrae and ribs by 3D ultrasound, especially in fetuses with echogenic foci at the seventh cervical vertebrae, and determination of the feasibility of postnatal ultrasound to confirm presence or absence of cervical ribs, which would make it possible to assess the cervical region in healthy neonates without the use of radiographs. Prenatal MRI could also be of added value in the detection of fetal cervical ribs and an abnormal rib number, as the diagnostic accuracy of MRI has been shown to be significantly higher compared to ultrasound for the detection of fetal vertebral abnormalities, such as hemivertebrae. [38] By gaining more experience with prenatal evaluation of fetal rib number using 3-dimensional ultrasound and particularly by reviewing prenatal ultrasound images with the knowledge of the final definitive diagnosis, the diagnostic accuracy of prenatal ultrasound is expected to improve. Subsequently, if ultrasound studies confirm the association between vertebral pattern abnormalities and specific chromosomal and structural abnormalities, as identified in studies involving postnatal radiographic assessments, this technique could be incorporated into the array of noninvasive prenatal diagnostic options.

Clinical Implications

If lumbar ribs are detected on three-dimensional ultrasound as an isolated finding in the prenatal period, reassurance seems appropriate. In this study, adequate volumes of the fetal spine could not be obtained in the entire population, which hinders the use in clinical settings. As detection of lumbar ribs improves with growing expertise and advancements in ultrasound technology, this could become possible in the future.

Conclusions

The presence of lumbar ribs could be reliably assessed on prenatal three-dimensional ultrasound volumes. Lumbar ribs are not associated with structural or chromosomal abnormalities, nor with fetal or neonatal death. The reliability of assessment of the vertebral pattern, the presence of (rudimentary) cervical, and an abnormal number of thoracic ribs was insufficient. The prevalence of prenatal cervical ribs seemed overestimated, and correct identification on prenatal ultrasound images did not seem feasible.

Statement of Ethics

This study protocol was reviewed and approved by the Ethics Committee of the Erasmus University Medical Center, Approval No. MEC-2014-098. Written informed consent was obtained from participants to participate in the study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

P.C.S.: conceptualization, methodology, formal analysis, investigation, writing – original draft, and visualization. T.E.C.-O. and A.J. E.: conceptualization, methodology, writing – review and editing, and supervision. T.J.M.D.: formal analysis, visualization, and writing – review and editing. A.H., M.H.G.D., and E.B.: investigation and writing – review and editing. F.G.: conceptualization, methodology, and writing – review and editing.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its supplementary material files. Further inquiries can be directed to the corresponding author.

References

1 Ten Broek CM, Bakker AJ, Varela-Lasheras I, Bugiani M, Van Dongen S, Galis F. Evo-Devo of the human vertebral column: on homeotic transformations, pathologies and prenatal selection. Evol Biol. 2012;39(4):456–71. https://doi.org/10.1007/s11692-012-9196-1

2 Furtado LV, Thaker HM, Erickson LK, Shirts BH, Opitz JM. Cervical ribs are more prevalent in stillborn fetuses than in live-born infants and are strongly associated with fetal aneuploidy. Pediatr Dev Pathol. 2011;14(6):431–7. https://doi.org/10.2350/11-01-0974-OA.1

3 Castori M, Servadei F, Laino L, Pascolini G, Fabbri R, Cifani AE, et al. Axial skeletogenesis in human autosomal aneuploidies: a radiographic study of 145 second trimester fetuses. Am J Med Genet. 2016;170(3):676–87. https://doi.org/10.1002/ajmg.a.37510

4 Schut PC, Cohen-Overbeek TE, Galis F, Ten Broek CM, Steegers EA, Eggink AJ. Adverse fetal and neonatal outcome and an abnormal vertebral pattern: a systematic review. Obstet Gynecol Surv. 2016;71(12):741–50. https://doi.org/10.1097/OGX.0000000000000388
5 Schut PC, Ten Broek CMA, Cohen-Overbeek TE, Bugiani M, Steegers EAP, Eggink AJ, et al. Increased prevalence of abnormal vertebral patterning in fetuses and neonates with trisomy 21. J Matern Fetal Neonatal Med. 2019;32(14):2280–6. https://doi.org/10.1080/14767058.2018.1431622
6 Galis F, Dooren TJMV, Feuth JD, Metz JA, Witkam A, Ruinard S, et al. Extreme selection in humans against homeotic transformations of cervical vertebrae. Evolution. 2006;60(12):2643–54. https://doi.org/10.1111/j.0014-3820.2006.tb01896.x
7 Galis F. Why do almost all mammals have seven cervical vertebrae? Developmental constraints, Hox genes, and cancer. J Exp Zool. 1999;285(1):19–26. https://doi.org/10.1002/(sici)1097-010x(19990415)285:1<19::aid-jez3>3.0.co;2-z
8 Varela-Lasheras I, Bakker AJ, van der Mije SD, Metz JAJ, van Alphen J, Galis F. Breaking evolutionary and pleiotropic constraints in mammals: on sloths, manatees and homeotic mutations. EvoDevo. 2021;12(1):13.
9 Galis F, Van Dooren TJM, van der Geer AAE. Breaking the constraint on the number of cervical vertebrae in mammals: on homeotic transformations in lorises and pottos. Evol Dev. 2022;24(6):196–210. https://doi.org/10.1111/ede.12424
10 Schut PC, Eggink AJ, Boersma M, Tibboel D, Wijnen RMH, Brosens E, et al. Cervical ribs and other abnormalities of the vertebral pattern in children with esophageal atresia and anorectal malformations. Pediatr Res. 2020;87(4):773–8. https://doi.org/10.1038/s41390-019-0631-1
11 Dall'Asta A, Paramasivam G, Lees CC. Crystal Vue technique for imaging fetal spine and ribs. Ultrasound Obstet Gynecol. 2016;47(3):383–4. https://doi.org/10.1002/uog.15800
12 Hershkovitz R. Prenatal diagnosis of isolated abnormal number of ribs. Ultrasound Obstet Gynecol. 2008;32(4):506–9. https://doi.org/10.1002/uog.5296
13 Gindes L, Benoit B, Pretorius DH, Achiron R. Abnormal number of fetal ribs on 3-dimensional ultrasonography: associated anomalies and outcomes in 75 fetuses. J Ultrasound Med. 2008;27(9):1263–71. https://doi.org/10.7863/jum.2008.27.9.1263
14 Esser T, Rogalla P, Sarioglu N, Kalache KD. Three-dimensional ultrasonographic demonstration of agenesis of the 12th rib in a fetus with trisomy 21. Ultrasound Obstet Gynecol. 2006;27(6):714–5. https://doi.org/10.1002/uog.2785
15 Gwet KL. Handbook of inter-rater reliability: the definitive guide to measuring the extent of agreement among raters. Advanced Analytics LCC. 2014.
16 Altman DG. Practical statistics for medical research. London: Chapman and Hall; 1991.
17 EUROCAT 2012 coding of EUROCAT subgroups of congenital anomalies. Chapter 3.3, Guide 1.4.
18 Schut PC, Brosens E, Van Dooren TJM, Galis F, Ten Broek CMA, Baijens IMM, et al. Exploring copy number variants in deceased fetuses and neonates with abnormal vertebral patterns and cervical ribs. Birth Defects Res. 2020;112(18):1513–25. https://doi.org/10.1002/bdr2.1786
19 Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405–24. https://doi.org/10.1038/gim.2015.30
20 R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2020.
21 Agresti A. Categorical data analysis. New Jersey: John Wiley & Sons, Inc; 2013.
22 Cave AJE. The morphology of the mammalian cervical pleurapophysis. J Zool Lond. 1975;177(3):377–93. https://doi.org/10.1111/j.1469-7998.1975.tb02240.x
23 Ji EK, Lee EK, Kwon TH. Isolated echogenic foci in the left upper quadrant of the fetal abdomen: are they significant? J Ultrasound Med. 2004;23(4):483–8. https://doi.org/10.7863/jum.2004.23.4.483
24 Hamdan MA, El Zoabi BA, Al Shamsi A, Bekdache GN, Chedid F. Fetal echogenic cardiac foci: prospective postnatal electrocardiographic follow-up. J Perinatol. 2013;33(4):268–70. https://doi.org/10.1038/jp.2011.113
25 Kalelioglu IH, Gursoy Erzincan S, Erturk E, Has R. Prenatal incidence and clinical value of the absence of 12th ribs in a population in a setting of detailed second-trimester sonography. Fetal Diagn Ther. 2019;46(6):368–75. https://doi.org/10.1159/000497159
26 Khodair SA, Hassanen OA. Abnormalities of fetal rib number and associated fetal anomalies using three dimensional ultrasonography. Egypt J Radiol Nucl Med. 2014;45(3):689–94. https://doi.org/10.1016/j.ejrnm.2014.03.009
27 Spadliński Ł, Cecot T, Majos A, Stefańczyk L, Pietruszewska W, Wysiadecki G, et al. The epidemiological, morphological, and clinical aspects of the cervical ribs in humans. BioMed Res Int. 2016;2016:8034613. https://doi.org/10.1155/2016/8034613
28 Rani A, Chopra J, Singh R. Prevalence of various anomalies of costal element at cervico-thoracic junction in and around lucknow region of uttar pradesh: a radiological study. Biomed Res India. 2021;32(1):7–14.
29 Nakajima A, Usui A, Hosokai Y, Kawasumi Y, Abiko K, Funayama M, et al. The prevalence of morphological changes in the thoracolumbar spine on whole-spine computed tomographic images. Insights Imaging. 2014;5(1):77–83. https://doi.org/10.1007/s13244-013-0286-0
30 Spencer HT, Gold ME, Hresko MT. Abnormal rib count in scoliosis surgery: impact on the reporting of spinal fusion levels. J Child Orthop. 2014;8(6):497–503. https://doi.org/10.1007/s11832-014-0623-y
31 Schumacher R, Mai A, Gutjahr P. Association of rib anomalies and malignancy in childhood. Eur J Pediatr. 1992;151(6):432–4. https://doi.org/10.1007/BF01959357
32 Bates AW, Nale K. Segmentation defects of the human axial skeleton without dysostoses or skeletal dysplasias. Fetal Pediatr Pathol. 2005;24(2):121–7. https://doi.org/10.1080/15227950500257333
33 Loder RT, Huffman G, Toney E, Wurtz LD, Fallon R. Abnormal rib number in childhood malignancy: implications for the scoliosis surgeon. Spine (Phila Pa 1976). 2007;32(8):904–10. https://doi.org/10.1097/01.brs.0000259834.28893.97
34 Kraemer S. The fragile male. BMJ. 2000;321(7276):1609–12. https://doi.org/10.1136/bmj.321.7276.1609
35 Inkster AM, Fernández-Boyano I, Robinson WP. Sex differences are here to stay: relevance to prenatal care. J Clin Med. 2021;10(13):3000. https://doi.org/10.3390/jcm10133000
36 Orzack SH, Stubblefield JW, Akmaev VR, Colls P, Munné S, Scholl T, et al. The human sex ratio from conception to birth. Proc Natl Acad Sci U S A. 2015;112(16):E2102–11. https://doi.org/10.1073/pnas.1416546112
37 Benoit B. The value of three-dimensional ultrasonography in the screening of the fetal skeleton. Childs Nerv Syst. 2003;19(7–8):403–9. https://doi.org/10.1007/s00381-003-0776-3
38 Cai X, Chen X, Wei X, Liu W, Hou X, Gong T, et al. Use of magnetic resonance imaging in the diagnosis of fetal vertebral abnormalities in utero: a single-center retrospective cohort study. Quant Imaging Med Surg. 2022;12(6):3391–405. https://doi.org/10.21037/qims-21-1070