Value of routine ultrasound examination at 35–37 weeks' gestation in diagnosis of fetal abnormalities

Alessandra Ficara,[1] Argyro Syngelaki,[1] Aymen Hammami,[1] Ranjit Akolekar,[2,3] Kypros H. Nicolaides[1]

1. Fetal Medicine Research Institute, King's College Hospital, London, UK
2. Fetal Medicine Unit, Medway Maritime Hospital, Gillingham, UK
3. Institute of Medical Sciences, Canterbury Christ Church University, Chatham, UK

Correspondence:
Professor KH Nicolaides,
Harris Birthright research centre for Fetal Medicine,
Fetal Medicine Research Institute,
King's College Hospital,
16-20 Windsor Walk, Denmark Hill, London SE5 8BB
Telephone: +442032998256; email: kypros@fetalmedicine.com

Keywords: Third trimester screening, Fetal abnormalities, Prenatal diagnosis, Ultrasound examination.

Short title: Fetal abnormalities in third trimester

ABSTRACT

Objective: To investigate the potential value of routine ultrasound examination at 35-37 weeks' gestation in the diagnosis of previously unknown fetal abnormalities.

Methods: This was a prospective study in 52,401 singleton pregnancies attending for a routine ultrasound examination at 35^{+0} - 36^{+6} weeks' gestation; all pregnancies had a previous scan at 18-24 weeks and 47,215 also had a scan at 11-13 weeks. We included pregnancies resulting in livebirth or stillbirth but excluded those with known chromosomal abnormalities. The abnormalities were classified according to affected major organ system and the type and incidence of new abnormalities was determined.

Results: In the study population the incidence of fetal abnormalities was 2.2% (1,168 / 52,401), including 847 (72.5%) that had been previously diagnosed during the first and / or second trimester, 247 (21.2%) that were detected for the first time at 35-37 weeks and 74 (6.3%) that were detected for the first time postnatally. The most common abnormalities that were diagnosed during the first and / or second trimester, that were also observed at 35-37 weeks, included aberrant right subclavian artery, ventricular septal defect, talipes, unilateral renal agenesis and / or pelvic kidney, hydronephrosis, duplex kidney or unilateral multicystic kidney, cystic pulmonary airway malformation, ventriculomegaly, cleft lip and palate, polydactyly, abdominal cyst or gastroschisis. The most common abnormalities seen at 35-37 weeks were hydronephrosis, mild ventriculomegaly, ventricular septal defect, duplex kidney, ovarian cyst and arachnoid cyst. The incidence of abnormalities first seen at 35-37 weeks was 0.5% and the most common were ovarian cysts, microcephaly, achondroplasia, dacryocystocele and hematocolpos. The incidence of abnormalities first seen postnatally was 0.1% and the most common were isolated cleft palate, polydactyly or syndactyly and ambiguous genitalia or hypospadias; prenatal examination of the genitalia was not a compulsory part of the protocol.

Conclusions: A high proportion of fetal abnormalities are detected for the first time during a routine ultrasound examination at 35-37 weeks' gestation. Such diagnosis and subsequent management, including selection of time and place for delivery and postnatal investigations, could potentially improve postnatal outcome.

INTRODUCTION

Assessment of pregnancy at 35-37 weeks' gestation is useful in the prediction of subsequent development of pre-eclampsia (PE) and the birth of small and large for gestational age neonates.[1-10] An additional benefit of such ultrasound examination is the detection of previously undiagnosed fetal abnormalities, because, first, they were missed during previous scans, which are commonly performed routinely at 11-13 and 18-24 weeks' gestation, second, the phenotypic expression of abnormalities becomes apparent only after 20 weeks, such as short limbs in the case of achondroplasia, dilated bowel in the case of bowel atresias or abnormal shape of the head in the case of craniosynostosis, or third, the abnormalities develop only during the third trimester, such as ovarian cysts in response to maternal estrogenic stimulation or ventriculomegaly following fetal brain hemorrhage or maternal infection.

The objective of this screening study involving ultrasound examination of the fetal anatomy at 35-37 weeks' gestation was to define the types and incidence of new fetal abnormalities identified by this examination.

METHODS

Study population

This was a prospective study in women attending for a routine hospital visit at 35^{+0} - 36^{+6} weeks' gestation at King's College Hospital, London or Medway Maritime Hospital, Gillingham, UK between between March 2014 and March 2019. This visit included ultrasound examination for fetal anatomy and fetal biometry. Gestational age was determined by the measurement of fetal crown-rump length at 11-13 weeks or the fetal head circumference at 19-24 weeks.[11,12] In all cases a fetal anomaly scan had been undertaken at 18-24 weeks' gestation and in most cases a scan was also carried out at 11-13 weeks. The inclusion criteria for this study were singleton pregnancies examined at 35^{+0} - 36^{+6} weeks' gestation and resulting in a livebirth or stillbirth. We excluded pregnancies with known aneuploidies. Data on pregnancy outcome were collected from the hospital delivery records or the patient general practitioners and all prenatal and postnatal findings were recorded in a Fetal Database. This study constitutes a retrospective analysis of data derived from a routine clinical examination and did not require ethics committee approval.

Ultrasound examinations

All ultrasound examinations were carried out according to standardized protocols by sonographers that had obtained the Fetal Medicine Foundation Certificate of Competence in ultrasound examination for fetal abnormalities or by trainees under the supervision of certified sonographers. The ultrasound examinations were essentially performed transabdominally, using 3-7.5 MHz curvilinear transducers, but in 2-3% of cases when there were technical difficulties to obtain adequate views a transvaginal scan (3-9 MHz) was also carried out. The time allocated for the ultrasound examination of the fetus was 30 minutes.

At 11-13 weeks it was aimed to obtain a transverse section of the head to demonstrate the skull, midline echo and the choroid plexuses, a mid-sagittal view of the face to demonstrate the nasal bone, midbrain and brain stem, transverse views to demonstrate orbits, upper lip and palate, sagittal section of the spine to demonstrate the spine and overlying skin, transverse section of the thorax and use of color Doppler to assess the 4-chamber view of the heart and outflow tracks, record blood flow across the tricuspid valve, transverse and sagittal sections of the trunk and extremities to demonstrate the stomach, kidneys, bladder, abdominal insertion of the umbilical cord, all the long bones, hands and feet.

In the second trimester scan it was aimed to obtain the following views: transverse section of the head at the level of the septum cavum pellucidum and lateral ventricles, sub-occipito-bregmatic view to examine the midbrain, cerebellum and vermis, mid-sagittal view of face to examine the nasal bone and exclude micrognathia, transverse views of the orbits, upper lip and palate, sagittal, coronal and transverse views of the spine, sweep through heart in transverse plane to include 4-chamber view, outflow tracts and 3-vessel view, transverse and sagittal sections of the thorax and abdomen to examine the lungs, diaphragm, liver, stomach and bowel, umbilical cord insertion and kidneys, bladder and ureters, systematic examination of upper and lower limbs for length and shape of each bone, position and movement of each joint and examination of both hands and feet, including the digits. Examination of the genitalia was not a compulsory part of the protocol.

The third trimester scan was primarily aimed at assessing fetal growth, amniotic fluid volume and Doppler measurements in the uterine, umbilical and middle cerebral arteries. The sonongraphers were also instructed to assess the fetal anatomy in the same systematic way as in the second trimester, but it was accepted that depending on the fetal position examination of the fetal face, sacrum and extremities may not be possible.

All cases of suspected fetal abnormalities were examined by a fetal medicine specialist and all cases of suspected fetal cardiac defect were examined by a fetal cardiologist.

Outcome measures

We included all abnormalities diagnosed antenatally and in the neonatal period. All babies in our hospitals are examined in the neonatal period by a pediatrician, but certain asymptomatic internal abnormalities are inevitably missed. We classified abnormalities according to the major organ systems of central nervous system, face, heart and great arteries, thorax, gastrointestinal, abdominal wall, urogenital, skeletal, and multiple for those involving more than one organ system. Ventriculomegaly was classified according to atrial width into mild (10-12.9 mm), moderate (13-14.9 mm) and severe (≥ 15 mm). Hydronephrosis was considered to be present if there was pelvicalyceal dilatation with an anteroposterior diameter ≥ 10 mm. Polydactyly was considered to be present if the extra digit contained bone and talipes was considered to be present if the baby required postnatal treatment. We included all cases of abnormalities of the heart and great vessels but excluded cases of persistent left superior vena cava and aberrant right subclavian artery because these are variants of normal rather than true defects. Cases with coarctation of the aorta, aortic arch hypoplasia and interrupted aortic arch were classified as arch abnormalities. Similarly, cases with Epstein's anomaly or tricuspid dysplasia were classified

as tricuspid valve abnormalities. Cases with at least two different major heart defects were classified as complex.

RESULTS

Study population

A routine ultrasound examination at 35^{+0} - 36^{+6} weeks' gestation was carried out in 52,714 singleton pregnancies but in 313 (0.6%) there was no follow up. In the study population of 52,401 pregnancies ultrasound scans were carried out at both 18-24 and 35-37 weeks and in 47,215 cases a scan was also carried out at 11-13 weeks. At the time of the third trimester scan the median maternal age was 31.7 (interquartile range 27.5-35.4) years, the median weight was 79.0 (interquartile range 70.8-90.0) Kg and the median body mass index was 29.1 (interquartile range 26.2-33.0) kg/m^2, the racial origin of the women was White in 39,465 (74.9%), Black in 8,107 (15.4%), South Asian in 2,549 (4.8%), East Asian in 1,042 (2.0%) and mixed in 1,551 (2.9%).

Fetal abnormalities

In the study population the incidence of fetal abnormalities was 2.2% (1,168 / 52,401), including 847 (72.5%) that had been previously diagnosed during the first and / or second trimester, 247 (21.2%) that were detected for the first time at 35-37 weeks and 74 (6.3%) that were detected for the first time postnatally (Table 1).

The most common abnormalities seen at 35-37 weeks were hydronephrosis, mild ventriculomegaly, ventricular septal defect, duplex kidney, ovarian cyst and arachnoid cyst. The incidence of abnormalities first seen at 35-37 weeks was 0.5% and the most common were ovarian cysts, microcephaly, achondroplasia, dacryocystocele and hematocolpos. The incidence of abnormalities first seen postnatally was 0.1% (74/52,401) and the most common were ambiguous genitalia or hypospadias, isolated cleft palate, and polydactyly or syndactyly.

<u>Central nervous system abnormalities</u>

Most of the fetal abnormalities seen at 35-37 weeks had already been diagnosed in the first and or second trimester. The only exceptions were mild ventriculomegaly, arachnoid cysts and microcephaly where most of the cases were detected in the third trimester.

<u>Face abnormalities</u>

Most of the fetal abnormalities seen at 35-37 weeks had already been diagnosed in the first and or second trimester, except for dacryocystocele that was first detected in the third trimester. The most common abnormality was cleft lip and palate and all cases were diagnosed previously; in contrast, none of the cases of isolated cleft palate were detected prenatally.

Heart abnormalities

Most of the abnormalities of the heart and great arteries seen at 35-37 weeks had already been diagnosed in the first and or second trimester. The most common were aberrant right subclavian artery, ventricular septal defect and right aortic arch. In the case of ventricular septal defects 18.3% (22/120) were first diagnosed in the third trimester and 4,2% (5/120) were diagnosed postnatally. Most cases of rhabdomyomas were first diagnosed in the third trimester. Some of the cases of coarctation of the aorta, pulmonary and aortic stenosis and tricuspid valve defect were detected for the first time in the third trimester and some were diagnosed only postnatally.

Thorax abnormalities

Most of the cases of congenital pulmonary airways malformation, congenital diaphragmatic hernia and pleural effusions seen at 35-37 weeks had already been diagnosed previously, except for one case of diaphragmatic hernia that was first detected in the third trimester.

Gastrointestinal abnormalities

The most common abnormality seen at 35-37 weeks was an abdominal cyst and about half of these were first diagnosed in the third trimester. In the study population there were eight cases of esophageal atresia; four were suspected in the second trimester by the persistently small stomach, two in the third trimester and two postnatally. One case each of duodenal atresia and small bowel atresia were not diagnosed at the routine 20 weeks scan but in the late second trimester after presenting with polyhydramnios. All three cases of imperforate anus or rectovaginal fistula were diagnosed postnatally.

Abdominal wall abnormalities

All cases of gastroschisis, exomphalos and bladder exstrophy seen at 35-37 weeks had already been diagnosed in the first and or second trimester.

Genitourinary abnormalities

The most common abnormalities seen at 35-37 weeks were hydronephrosis, unilateral renal agenesis with or without a pelvic kidney, duplex kidney and unilateral multicystic kidney and most of these, except hydronephrosis, were diagnosed previously. Most cases of megaureter and all cases of ovarian cysts and hematocolpos were first diagnosed in the third trimester. Prenatal examination of the genitalia was not a compulsory part of the protocol and 93% (27/29) of cases with ambiguous genitalia or hypospadias were diagnosed postnatally.

Skeletal abnormalities

Most skeletal abnormalities seen at 35-37 weeks had already been diagnosed in the first and or second trimester and the most common were talipes and polydactyly. Some of the cases of talipes and polydactyly and most cases of syndactyly were diagnosed postnatally. The two cases of achondroplasia were first detected in the third trimester.

Multiple abnormalities

There were six cases of multiple abnormalities and they were all diagnosed in the second trimester.

DISCUSSION

Main findings of the study

The findings of this study of routine assessment of singleton pregnancies at 35-37 weeks' gestation demonstrate the following: first, most of the fetal abnormalities (73%) seen at 35-37 weeks had already been diagnosed in the first and or second trimester; second, the incidence of abnormalities first seen at 35-37 weeks was 0.5% and the most common were hydronephrosis, mild ventriculomegaly, ventricular septal defect, duplex kidney, ovarian cyst and arachnoid cyst; third, the abnormalities that presented for the first time during the third trimester were ovarian cysts, microcephaly, achondroplasia, dacryocystocele and hematocolpos; and fourth, the incidence of abnormalities first seen postnatally was 0.1% and the most common were isolated cleft palate, polydactyly or syndactyly and ambiguous genitalia or hypospadias; prenatal examination of the genitalia was not a compulsory part of the protocol.

Comparison with findings from previous studies

Our results are consistent with those of the only one previous third trimester screening study which examined 5,044 pregnancies at 28-32 weeks' gestation; in these women previous scans at 11-14 and 18-24 weeks' gestation showed no fetal abnormalities.[13] The third trimester scan identified 44 (0.9%) new abnormalities; the most common were hydronephrosis, ventricular septal defect, ventriculomegaly, unilateral renal agenesis and ovarian cysts. The study also reported on 27 abnormalities diagnosed postnatally; the most common were ventricular septal defect, aortic stenosis, anal atresia, mild ventriculomegaly, microcephaly, cleft palate and talipes.

There are two groups of brain abnormalities that can only be identified in the third trimester; the first group consists of acquired lesions, such as stroke, hemorrhage, infection and tumors, and the second group includes developmental anomalies, such as lissencephaly, microcephaly and macrocephaly, which become evident during rapid brain enlargement after the end of the proliferation and migration period (2–5 months of gestation).[14] A previous study reported that >15% of central nervous system abnormalities detected in the third trimester had a previous normal second trimester scan; the most common abnormalities included ventriculomegaly, dysgenesis of the corpus callosum or vermis, arachnoid cysts, cerebral cysts or hemorrhage, migrational disorders, macrocephaly and microcephaly.[14] In another study of 47 fetuses with brain abnormalities detected >24 weeks' gestation following a normal

scan at 21-24 weeks, the most common abnormalities were intracranial cysts, mild ventriculomegaly, absence or dysgenesis of the corpus callosum, and intracerebral hemorrhage.[15]

The most common heart abnormality in our series was ventricular septal defects; in most cases the diagnosis was made in the second trimester and the ones reported in this series are those that persisted until at least 36 weeks' gestation. Previous studies reported contradictory results concerning the incidence of spontaneous intrauterine closure of ventricular septal defects diagnosed in the second trimester, ranging from 5% to 84%.[16,17] Three of our 10 cases of aortic stenosis or tricuspid valve defect were first detected in the third trimester and two were diagnosed postnatally. These abnormalities evolve with advancing gestational age and it is possible that they were not present at the time of the second trimester scan. A previous study of 117 neonates with critical aortic stenosis and biventricular outcome reported that only 10 were diagnosed prenatally and suggested that this failure is likely to be due to a relatively normal 4-chamber view in mid-gestation with development of significant obstruction only in the third trimester.[18] Five of our six cases of rhabdomyomas were diagnosed in the third trimester; this finding is consistent with the results of a meta-analysis of 124 cases of antenatally diagnosed rhabdomyomas where the median gestational age at diagnosis was 31 weeks' gestation and only 14% were detected at <24 weeks.[19]

Hydronephrosis was the most common urogenital abnormality diagnosed at the 35-37 weeks scan and in most cases the diagnosis was first made in the third trimester. Such late diagnosis of hydronephrosis can be attributed to the exponential increase in fetal urine production during the third trimester of pregnancy unmasking underlying urinary tract abnormalities.[20] This is also likely to be the explanation for the finding that 30% of cases of duplex kidneys and most cases of renal cysts and dilated ureters were first detected at the 35-37 weeks scan.

All of our cases of ovarian cysts were first diagnosed in the third trimester and this is consistent with the results of a meta-analysis on fetal ovarian cysts which reported that in 299 cases the median gestational age at diagnosis was 33 weeks, which is the traditional gestational age for the routine third trimester scan.[21]

Implications for clinical practice

An integrated clinical visit at 35-37 weeks' gestation, which includes assessment of fetal anatomy, fetal growth and measurement of biomarkers, identifies a high proportion of pregnancies that subsequently develop PE and those delivering small and large for gestational age neonates.[1-10]

This study has highlighted the additional benefit of the late third trimester scan in the detection of fetal abnormalities that were either missed in previous first and second trimester scans or they became apparent only during the third trimester. In exceptional cases of abnormalities that are associated with severe handicap, such as severe ventriculomegaly and microcephaly, in countries where late abortion is legal, the parents may be offered this option. In some cases of progressive heart abnormalities, such as coarctation of the aorta and pulmonary and aortic stenosis it may be advisable for the babies to be born in centres with available pediatric cardiac expertise; similarly, babies with diaphragmatic hernia are best born in centres with facilities for pediatric surgery. In other cases, such as those with hydronephrosis, megaureters, duplex kidneys, ventriculomegaly, arachnoid and ovarian cysts, craniocynososis, rhabdomyomas and hematocolpos, the pediatricians can be alerted to the need for appropriate postnatal investigations and follow up.

Strengths and limitations of the study

The strengths of our study are first, examination of a large number of pregnancies attending for routine assessment at a prespecified gestational-age range at the end of the third trimester of pregnancy, and second, systematic examination of the fetal anatomy in the first, second and third trimesters of pregnancy by appropriately trained sonographers in units with expertise in fetal medicine and fetal cardiology.

The main limitation of this and most previous studies investigating the effectiveness of routine first and second trimester ultrasound examination in the prenatal diagnosis of fetal abnormalities relates to the postnatal ascertainment of congenital abnormalities. Although in our centres all neonates are examined by pediatricians, certain asymptomatic internal abnormalities are inevitably missed. For example, ventricular septal defects or coarctation of the aorta with patent arterial duct may be missed by early neonatal examination, which does not include echocardiography. However, all children with cardiac abnormalities diagnosed prenatally or postnatally from our area are examined in a regional pediatric cardiac centre which notifies us of any such abnormalities.

Another potential limitation relates to the general applicability of our results because the routine ultrasound examinations were carried out within the framework of fetal medicine units

with readily available expertise. Consequently, in a routine ultrasound department some of the abnormalities we have detected could have been missed; however, this would also be true for the first and second trimester scans which could have potentially resulted in a higher proportion of abnormalities being detected in the third trimester.

Conclusions

A high proportion of fetal abnormalities are detected for the first time during a routine ultrasound examination at 35-37 weeks' gestation. Such diagnosis and subsequent management, including selection of time and place for delivery and postnatal investigations, could potentially improve postnatal outcome.

Sources of Funding: The study was supported by a grant from the Fetal Medicine Foundation (Charity No: 1037116).

REFERENCES

1. Ciobanu A, Wright A, Panaitescu A, Syngelaki A, Wright D, Nicolaides KH. Prediction of imminent preeclampsia at 35-37 weeks' gestation. Am J Obstet Gynecol 2019; **pii**: S0002-9378(19)30289-3. doi: 10.1016/j.ajog.2019.01.235.

2. Ciobanu A, Rouvali, A, Syngelaki A, Akolekar R, Nicolaides KH. Prediction of small for gestational age neonates: Screening by maternal factors, fetal biometry and biomarkers at 35-37 weeks' gestation. *Am J Obstet Gynecol* 2019; doi: 10.1016/j.ajog.2019.01.227.

3. Andrietti S, Silva M, Wright A, Wright D, Nicolaides KH. Competing-risks model in screening for pre-eclampsia by maternal factors and biomarkers at 35-37 weeks' gestation. *Ultrasound Obstet Gynecol* 2016; **48**: 72-79.

4. Panaitescu A, Ciobanu A, Syngelaki A, Wright A, Wright D, Nicolaides KH. Screening for pre-eclampsia at 35-37 weeks' gestation. *Ultrasound Obstet Gynecol* 2018; **52**: 501-506.

5. Fadigas C, Peeva G, Mendez O, Poon LC, Nicolaides KH. Prediction of small-for-gestational-age neonates: screening by placental growth factor and soluble fms-like tyrosine kinase-1 at 35-37 weeks. *Ultrasound Obstet Gynecol* 2015; **46**: 191-197.

6. Fadigas C, Guerra L, Garcia-Tizon Larroca S, Poon LC, Nicolaides KH. Prediction of small-for-gestational-age neonates: screening by uterine artery Doppler and mean arterial pressure at 35-37 weeks. *Ultrasound Obstet Gynecol* 2015; **45**: 715-721.

7. Akolekar R, Panaitescu A, Ciobanu A, Syngelaki A, Nicolaides KH. Two-stage approach for prediction of small for gestational age neonates and adverse perinatal outcome by routine ultrasound examination at 35-37 weeks' gestation. *Ultrasound Obstet Gynecol* 2019; in press.

8. Akolekar R, Ciobanu A, Zingler E, Syngelaki A, Nicolaides KH. Routine assessment of cerebroplacental ratio at 35-37 weeks' gestation in the prediction of adverse perinatal outcome. Am J Obstet Gynecol 2019; **pii**: S0002-9378(19)30477-6.

9. Sovio U, Moraitis AA, Wong HS, Smith GCS. Universal vs selective ultrasonography to screen for large-for-gestational-age infants and associated morbidity. *Ultrasound Obstet Gynecol* 2018; **51**: 783-791.

10. Khan N, Ciobanu A, Karampitsakos T, Akolekar R, Nicolaides KH. Prediction of large for gestational age neonates by routine third trimester ultrasound. Ultrasound Obstet Gynecol 2019; in press

11. Robinson HP, Fleming JE. A critical evaluation of sonar crown rump length measurements. *BJOG* 1975; **82**: 702-710.

12. Snijders RJ, Nicolaides KH. Fetal biometry at 14-40 weeks' gestation. *Ultrasound Obstet Gynecol* 1994; **4**: 34-48.

13. Manegold G, Tercanli S, Struben H, Huang D, Kang A. Is a routine ultrasound in the third trimester justified? Additional fetal anomalies diagnosed after two previous unremarkable ultrasound examinations. *Ultraschall Med* 2011; **32**: 381-386.

14. Malinger G, Lerman-Sagie T, Watemberg N, Rotmensch S, Lev D, Glezerman M. A normal second-trimester ultrasound does not exclude intracranial structural pathology. *Ultrasound*

Obstet Gynecol 2002; **20**: 51-56.

15. Yinon Y, Katorza E, Nassie DI, Ben-Meir E, Gindes L, Hoffmann C, Lipitz S, Achiron R, Weisz B. Late diagnosis of fetal central nervous system anomalies following a normal second trimester anatomy scan. *Prenat Diagn* 2013; **33**: 929-934.

16. Chau AC, Jones A, Sutherland M, Lilje C, Sernich S, Hagan J, Miller J. Characteristics of Isolated Ventricular Septal Defects Less Likely to Close In Utero. J Ultrasound Med 2018; 37: 1891-1898.

17. Gómez O, Martínez JM, Olivella A, Bennasar M, Crispi F, Masoller N, Bartrons J, Puerto B, Gratacós E. Isolated ventricular septal defects in the era of advanced fetal echocardiography: risk of chromosomal anomalies and spontaneous closure rate from diagnosis to age of 1 year. Ultrasound Obstet Gynecol 2014; 43: 65-71.

18. Freud LR, Moon-Grady A, Escobar-Diaz MC, Gotteiner NL, Young LT, McElhinney DB, Tworetzky W. Low rate of prenatal diagnosis among neonates with critical aortic stenosis: insight into the natural history in utero. *Ultrasound Obstet Gynecol* 2015; **45**: 326-332.

19. Chao AS, Chao A, Wang TH, Chang YC, Chang YL, Hsieh CC, Lien R, Su WJ. Outcome of antenatally diagnosed cardiac rhabdomyoma: case series and a meta-analysis. *Ultrasound Obstet Gynecol* 2008; **31**: 289-295.

20. Rabinowitz R, Peters MT, Vyas S, Campbell S, Nicolaides KH. Measurement of fetal urine production in normal pregnancy by real-time ultrasonography. *Am J Obstet Gynecol* 1989; **161**: 1264-1266.

21. Tyraskis A, Bakalis S, David AL, Eaton S, De Coppi P. A systematic review and meta-analysis on fetal ovarian cysts: impact of size, appearance and prenatal aspiration. *Prenat Diagn* 2017; **37**: 951-958.

Table 1.

Defect	Total	Stage at first diagnosis		
		11-13 w / 18-24 w	35-37 w	Postnatal
Central nervous system				
Ventriculomegaly mild	68	22	46	
Ventriculomegaly moderate	8	3	5	
Ventriculomegaly severe	4	3	1	
Arachnoid cyst	12	3	9	
Corpus callosum agenesis or hypoplasia	9	8	1	
Septo-optic dysplasia	1	1		
Spina bifida	5	5		
Hypoplastic cerebellum / vermis	7	7		
Blake's pouch cyst	3	3		
Microcephaly	5		5	
Craniosinostosis	2	1	1	
Dural venous sinus thrombosis	2	2		
Face				
Cleft lip and palate	28	28		
Cleft lip only	14	10		4
Cleft palate only	12			12
Micrognathia	5	5		
Dacryocystocele bilateral	2		2	
Microopthalmia	1	1		
Cataract bilateral	1			1
Cervical lymphangeoma	3	2	1	
Heart				
Aberrant right subclavian artery	173	173		
Ventricular septal defect	120	93	22	5
Right aortic arch	24	24		
Transposition of great arteries	10	8	1	1
Coarctation of the aorta	10	6	3	1
Tetralogy of Fallot	6	5		1
Atrioventricular septal defect	3	3		
Pulmonary atresia	1	1		
Pulmonary stenosis	7	5	1	1
Aortic stenosis	3	1	1	1
Tricuspid valve defect	7	4	2	1
Aortic valve atresia	1	1		
Aortic arch hypoplasia	1	1		
Left atrial isomerism	2	2		
Rhabdomyomas	6	1	5	
Double aortic arch	5	5		
Thorax				
Congenital pulmonary airways malformation	30	30		
Congenital diaphragmatic hernia	6	5	1	
Pleural effusion	2	2		

Gastrointestinal				
Adrenal, hepatic, choledochal, splenic or mesenteric cyst	19	10	9	
Esophageal atresia	8	4	2	2
Duodenal atresia	1	1		
Bowel atresia	1	1		
Imperforated anus	2			2
Rectovaginal fistula	1			1
Abdominal wall				
Gastroschisis	16	16		
Exomphalos	4	4		
Bladder exstrophy	1	1		
Genitourinary				
Hydronephrosis	118	48	70	
Unilateral renal agenesis +/- pelvic kidney	88	81	7	
Duplex kidney	60	42	18	
Unilateral multicystic kidney	32	32		
Lower urinary tract obstruction	3	2	1	
Renal agenesis bilateral	3	3		
Polycystic kidneys (adult type)	5	5		
Polycystic kidneys (infantile type)	1	1		
Horseshoe kidney	3	3		
Renal cyst unilateral	9	5	4	
Dilated ureter unilateral	9	2	7	
Ovarian cyst	17		17	
Ambiguous genitalia / hypospadias	29	2		27
Hematocolpos	2		2	
Skeleton				
Talipes	63	60	1	2
Polydactyly	34	26		8
Absent arm, leg, hand or foot	6	6		
Syndactyly	4			4
Skeletal dysplasia	4	4		
Achondroplasia	2		2	
Hemivertebra/Scoliosis	9	9		
Multiple				
Cleft lip and palate, agenesis of corpus callosum	1	1		
Cleft lip and palate, unilateral renal agenesis	1	1		
Cleft lip and palate, coarctation of the aorta	1	1		
Duplex kidney unilateral, bilateral talipes	1	1		
Tetralogy of Fallot, hemivertebra, bilateral talipes	1	1		