Ultrasound Obstet Gynecol 2020; **55**: 75–80
Published online 8 October 2019 in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.20857

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

A. FICARA[1], A. SYNGELAKI[1], A. HAMMAMI[1], R. AKOLEKAR[2,3] and K. 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*

KEYWORDS: fetal abnormality; prenatal diagnosis; third-trimester screening; ultrasound examination

CONTRIBUTION

What does this work add to what is already known?
This study summarizes fetal anomalies that are diagnosed for the first time on routine ultrasound examination at 35–37 weeks' gestation.

What are the clinical implications of this work?
Ultrasound examination at 35–37 weeks' gestation may reveal new fetal abnormalities that could not be diagnosed at earlier examinations.

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 of 52 400 singleton pregnancies attending for a routine ultrasound examination at 35 + 0 to 36 + 6 weeks' gestation; all pregnancies had a previous scan at 18–24 weeks and 47 214 also had a scan at 11–13 weeks. We included pregnancies resulting in live birth or stillbirth but excluded those with known chromosomal abnormality. Abnormalities were classified according to the affected major organ system, and the type and incidence of new abnormalities were determined.*

Results *In the study population, the incidence of fetal abnormality was 1.9% (995/52 400), including 674 (67.7%) that had been diagnosed previously during the first and/or second trimester, 247 (24.8%) that were detected for the first time at 35–37 weeks and 74 (7.4%) that were detected for the first time postnatally. The most common abnormalities that were diagnosed during the first and/or second trimester and that were also observed at 35–37 weeks included ventricular septal defect, talipes, unilateral renal agenesis and/or pelvic kidney, hydronephrosis, duplex kidney, unilateral multicystic kidney, congenital pulmonary airway malformation, ventriculomegaly, cleft lip and palate, polydactyly and abdominal cyst or gastroschisis. The most common abnormalities first 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 those that were detected exclusively for the first time at this examination were ovarian cyst, 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 timing 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 and delivery of a small- or large-for-gestational-age neonate[1–10]. An additional benefit of such ultrasound examination is the detection of a previously undiagnosed fetal abnormality, because, first, it was missed during previous scans, which are commonly performed routinely at 11–13 and 18–24 weeks' gestation, second, the phenotypic expression of the

Correspondence to: Prof. K. H. 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, UK (e-mail: kypros@fetalmedicine.com)

Accepted: 16 July 2019

abnormality becomes apparent only after 20 weeks, such as short limbs in the case of achondroplasia, dilated bowel in the case of bowel atresia or abnormal shape of the head in the case of craniosynostosis, or, third, the abnormality develops 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 previously undetected fetal abnormalities identified by this examination.

METHODS

Study population

This was a prospective study of women attending for a routine hospital visit at 35 + 0 to 36 + 6 weeks' gestation at King's College Hospital, London or Medway Maritime Hospital, Gillingham, UK 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 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 had also been carried out at 11–13 weeks. The inclusion criteria for this study were singleton pregnancy examined at 35 + 0 to 36 + 6 weeks' gestation and resulting in a live birth or stillbirth. We excluded pregnancies with known aneuploidy. Data on pregnancy outcome were collected from the hospital delivery records or the patients' general practitioners and all prenatal and postnatal findings were recorded in a fetal database. This study constitutes a retrospective analysis of data derived from routine clinical examination and did not require ethics committee approval.

Ultrasound examination

All ultrasound examinations were carried out according to standardized protocols by sonographers who 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 primarily performed transabdominally, using a 3–7.5-MHz curvilinear transducer, but in 2–3% of cases in which there were technical difficulties in obtaining adequate views, a transvaginal scan (3–9 MHz) was also carried out. The time allocated for the ultrasound examination of the fetus was 30 min.

First trimester

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

Second trimester

During the second-trimester scan, we aimed to obtain the following views: a transverse section of the head at the level of the cavum septi pellucidi and lateral ventricles; a suboccipitobregmatic view to examine the midbrain, cerebellum and vermis; a midsagittal view of the 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; a sweep through the heart in the transverse plane to include four-chamber view, outflow tracts and three-vessel view; transverse and sagittal sections of the thorax and abdomen to examine the lungs, diaphragm, liver, stomach, bowel, umbilical cord insertion, 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.

Third trimester

The third-trimester scan was aimed primarily at assessing fetal growth, amniotic-fluid volume and Doppler measurements in the uterine, umbilical and fetal middle cerebral arteries. The sonographers 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 abnormality 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 neonates at our hospitals are examined by a pediatrician, but certain asymptomatic internal abnormalities are inevitably missed. We classified abnormalities according to the major organ system affected, as central nervous system, face, heart and great arteries, thorax, gastrointestinal, abdominal wall, urogenital, skeletal or multiple for those involving more than one organ system. Ventriculomegaly was classified according to atrial width as mild (10–12.9 mm), moderate

(13–14.9 mm) or 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 fetus 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 Ebstein'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 to 36 + 6 weeks' gestation was carried out in 52 713 singleton pregnancies but in 313 (0.6%) there was no follow-up. In the study population of 52 400 pregnancies, ultrasound scans were carried out at both 18–24 and 35–37 weeks and in 47 214 cases a scan was also carried out at 11–13 weeks. At the time of the third-trimester scan, median maternal age was 31.7 (interquartile range, 27.5–35.4) years, median weight was 79.0 (interquartile range, 70.8–90.0) kg, median body mass index was 29.1 (interquartile range, 26.2–33.0) kg/m^2, and the racial origin was white in 39 255 (74.9%) women, black in 8037 (15.4%), South Asian in 2536 (4.8%), East Asian in 1035 (2.0%) and mixed in 1537 (2.9%).

Fetal abnormalities

In the study population, the incidence of fetal abnormality was 1.9% (995/52 400), including 674 (67.7%) that had been diagnosed previously during the first and/or second trimester, 247 (24.8%) that were detected for the first time at 35–37 weeks and 74 (7.4%) that were detected for the first time postnatally (Table 1).

The most common abnormalities seen for the first time 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 those that were detected exclusively for the first time at this examination were ovarian cyst, microcephaly, achondroplasia, dacryocystocele and hematocolpos. The incidence of abnormalities first seen postnatally was 0.1% (74/52 400) and the most common were ambiguous genitalia or hypospadias, isolated cleft palate and polydactyly or syndactyly.

Central nervous system abnormalities

Many fetal central nervous system abnormalities seen at 35–37 weeks had already been diagnosed in the first and/or second trimester, though most cases of mild and moderate ventriculomegaly and arachnoid cysts, and all cases of microcephaly were detected for the first time in the third trimester.

Facial abnormalities

Most of the fetal facial abnormalities seen at 35–37 weeks had already been diagnosed in the first and/or second trimester, except for dacryocystocele which was first detected in the third trimester. The most common facial abnormality was cleft lip and palate, all cases of which were first diagnosed in the first or second trimester; in contrast, none of the cases of isolated cleft palate was 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 ventricular septal defect and right aortic arch. Of the cases of ventricular septal defect, 18.3% (22/120) were first diagnosed in the third trimester and 4.2% (5/120) were diagnosed postnatally. Most cases of rhabdomyoma were first diagnosed in the third trimester. Some cases of coarctation of the aorta, pulmonary or aortic stenosis and tricuspid valve defect were detected for the first time in the third trimester and some were diagnosed only postnatally.

Thoracic abnormalities

Most of the cases of congenital pulmonary airway malformation, congenital diaphragmatic hernia and pleural effusion seen at 35–37 weeks had been diagnosed previously, except for one case of diaphragmatic hernia which was first detected in the third trimester.

Gastrointestinal abnormalities

The most common gastrointestinal 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, of which four were suspected in the second trimester due to a persistently small stomach, two in the third trimester and two postnatally. The one case each of duodenal atresia and small bowel atresia were not diagnosed at the routine 20-week 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.

Table 1 Diagnosis of fetal abnormalities in 52 400 pregnancies undergoing routine ultrasound examination

Defect	Total	Stage at first diagnosis: 1st or 2nd trimester	3rd trimester	PN
Central nervous system				
Mild VM	68	22	46	0
Moderate VM	8	3	5	0
Severe VM	4	3	1	0
Arachnoid cyst	12	3	9	0
ACC or hypoplasia of CC	9	8	1	0
Septo-optic dysplasia	1	1	0	0
Open spina bifida	5	5	0	0
Hypoplastic cerebellum/vermis	7	7	0	0
Blake's pouch cyst	3	3	0	0
Microcephaly	5	0	5	0
Craniosynostosis	2	1	1	0
Dural venous sinus thrombosis	2	2	0	0
Face				
CLP	28	28	0	0
Cleft lip only	14	10	0	4
Cleft palate only	12	0	0	12
Micrognathia	5	5	0	0
Bilateral dacryocystocele	2	0	2	0
Microphthalmia	1	1	0	0
Bilateral cataract	1	0	0	1
Cervical lymphangioma	3	2	1	0
Heart				
VSD	120	93	22	5
Right aortic arch	24	24	0	0
TGA	10	8	1	1
CoA	10	6	3	1
ToF	6	5	0	1
AVSD	3	3	0	0
Pulmonary atresia	1	1	0	0
Pulmonary stenosis	7	5	1	1
Aortic stenosis	3	1	1	1
Tricuspid valve defect	7	4	2	1
Aortic valve atresia	1	1	0	0
Aortic arch hypoplasia	1	1	0	0
Left atrial isomerism	2	2	0	0
Rhabdomyoma	6	1	5	0
Double aortic arch	5	5	0	0
Thorax				
CPAM	30	30	0	0
CDH	6	5	1	0
Pleural effusion	2	2	0	0
Gastrointestinal				
Adrenal, hepatic, choledochal, splenic or mesenteric cyst	19	10	9	0
Esophageal atresia	8	4	2	2
Duodenal atresia	1	1	0	0
Bowel atresia	1	1	0	0
Imperforate anus	2	0	0	2
Rectovaginal fistula	1	0	0	1
Abdominal wall				
Gastroschisis	16	16	0	0
Exomphalos	4	4	0	0
Bladder exstrophy	1	1	0	0
Genitourinary				
Hydronephrosis	118	48	70	0
Unilateral renal agenesis with or without pelvic kidney	88	81	7	0
Duplex kidney	60	42	18	0
Unilateral MK	32	32	0	0
LUTO	3	2	1	0
Bilateral renal agenesis	3	3	0	0
Polycystic kidneys				
Adult type	5	5	0	0
Infantile type	1	1	0	0
Horseshoe kidney	3	3	0	0
Unilateral renal cyst	9	5	4	0
Unilateral dilated ureter	9	2	7	0
Ovarian cyst	17	0	17	0
Ambiguous genitalia/ hypospadias	29	2	0	27
Hematocolpos	2	0	2	0
Skeleton				
Talipes	63	60	1	2
Polydactyly	34	26	0	8
Absent arm, leg, hand or foot	6	6	0	0
Syndactyly	4	0	0	4
Skeletal dysplasia	4	4	0	0
Achondroplasia	2	0	2	0
Hemivertebra/scoliosis	9	9	0	0
Multiple				
CLP, ACC	1	1	0	0
CLP, unilateral renal agenesis	1	1	0	0
CLP, CoA	1	1	0	0
Unilateral duplex kidney, bilateral talipes	1	1	0	0
ToF, hemivertebra, bilateral talipes	1	1	0	0
Total	995	674	247	74

Data are given as *n*. ACC, agenesis of the corpus callosum; AVSD, atrioventricular septal defect; CC, corpus callosum; CDH, congenital diaphragmatic hernia; CLP, cleft lip and palate; CoA, coarctation of the aorta; CPAM, congenital pulmonary airway malformation; LUTO, lower urinary tract obstruction; MK, multicystic kidney; PN, postnatal; TGA, transposition of the great arteries; ToF, tetralogy of Fallot; VM, ventriculomegaly; VSD, ventricular septal defect.

Genitourinary abnormalities

The most common genitourinary 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 cases of these, except hydronephrosis, had been 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 cases of talipes and polydactyly and all cases of syndactyly were diagnosed postnatally. The two cases of achondroplasia were first detected in the third trimester.

Multiple abnormalities

There were five cases of multiple abnormalities, all of which were diagnosed in the second trimester.

DISCUSSION

Main findings

The findings of this study of routine assessment of singleton pregnancies at 35–37 weeks' gestation demonstrate the following: first, most (68%) of the fetal abnormalities 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 exclusively for the first time during the third trimester were ovarian cyst, 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

The only previous third-trimester screening study examined 5044 pregnancies at 28–32 weeks' gestation; these women also had previous scans at 11–14 and 18–24 weeks' gestation[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 cyst. 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 be identified only 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 pregnancies with a fetal central nervous system abnormality 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, migration disorders, macrocephaly and microcephaly[14]. In another study of 47 fetuses with a brain abnormality 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 defect; 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 four-chamber view in midgestation with development of significant obstruction only in the third trimester[18]. Five of our six cases of rhabdomyoma were diagnosed in the third trimester; this finding is consistent with the results of a meta-analysis of 124 cases of antenatally diagnosed rhabdomyomas in which the median gestational age at diagnosis was 31 weeks' gestation and only 14% were detected at < 24 weeks[19].

Hydronephrosis was the most common genitourinary abnormality diagnosed at the 35–37-week 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 abnormality[20]. This is also likely to be the explanation for the finding that 30% of cases of duplex kidney, 44% of cases of renal cyst and most cases of dilated ureter were first detected at the 35–37-week 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 pre-eclampsia and those delivering a small- or large-for-gestational-age neonate[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 at previous first- and second-trimester scans or became apparent only during the third trimester. In exceptional cases of an abnormality that is associated with severe impairment, such as severe ventriculomegaly and microcephaly, in countries in which late abortion is legal, the parents may be offered this option. In some cases of progressive heart abnormality, such as coarctation of the aorta and pulmonary or aortic stenosis, it may be advisable for delivery to be scheduled in a center with pediatric cardiac expertise; similarly, fetuses with diaphragmatic hernia are best delivered in centers with facilities for pediatric surgery. In other cases, such as those with hydronephrosis, megaureter, duplex kidney, ventriculomegaly, arachnoid or ovarian cyst, craniosynostosis, rhabdomyoma and hematocolpos, the pediatricians can be alerted to the need for appropriate postnatal investigations and follow-up.

Strengths and limitations

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 examinations in the prenatal diagnosis of fetal abnormalities relates to the postnatal ascertainment of congenital abnormalities. Although in our center 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 at a regional pediatric cardiac center 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 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 timing and place for delivery and postnatal investigations, could potentially improve postnatal outcome.

ACKNOWLEDGMENT

This 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; **220**: 584.e1–11.
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; **220**: 486.e1–11.
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; **54**: 484–491.
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; **221**: 65.e1–18.
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-neonate by routine third-trimester ultrasound. *Ultrasound Obstet Gynecol* 2019; **54**: 326–333.
11. Robinson HP, Fleming JE. A critical evaluation of sonar "crown-rump length" measurements. *Br J Obstet Gynaecol* 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.