How often do we incidentally find a fetal abnormality at the routine third-trimester growth scan? A population-based study

Lior DRUKKER[1,2] MD, Angelo CAVALLARO[1,2] MD, Ibtisam SALIM[1,2] MD, Christos IOANNOU[2] MD, Lawrence IMPEY[2*] MD, Aris T. PAPAGEORGHIOU[1*] MD
* Joint senior authors

Affiliation
1. Nuffield Department of Women's and Reproductive Health, University of Oxford, John Radcliffe Hospital, Oxford, UK
2. Fetal Medicine Unit, Department of Maternal and Fetal Medicine, Women's Centre, John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

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Corresponding author
Prof. Aris Papageorghiou
Nuffield Department of Women's & Reproductive Health, John Radcliffe Hospital, University of Oxford, Oxford OX3 9DU
E: aris.papageorghiou@wrh.ox.ac.uk
T: +44 (0)1865 221019

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Condensation

After first- and second-trimester screening, during routine third-trimester growth scans, a previously undiagnosed fetal malformation is incidentally identified in approximately 1 in 300 women.

Short title

Third-trimester malformations

AJOG at a Glance

A. Why was the study conducted?

- Third-trimester growth scans are increasingly offered. Incidental fetal malformations detected during routine third-trimester growth scan are rarely discussed

B. What are the key findings?

- After first- and second-trimester screening, during routine third-trimester growth scans performed by sonographers, a previously undiagnosed fetal malformation is incidentally identified in approximately 1 in 300 women
- The majority of malformations detected at routine third-trimester growth scans are renal, and these are most likely to present spontaneous postnatal resolution

C. What does this study add to what is already known?

- Unexpected diagnosed of a fetal malformation at the third-trimester is infrequent
- Management changing malformations are rarely identified at a routine third-trimester growth scan

Keywords: pregnancy care, congenital malformation, fetal anomaly, fetal abnormality, anomaly scan, third-trimester, incidental finding

ABSTRACT

Background: Third-trimester scans are increasingly used to try to prevent adverse outcomes associated with abnormalities of fetal growth. Unexpected fetal malformations detected at third-trimester growth scans are rarely reported.

Objective: To determine the incidence and type of fetal malformations detected in women attending a routine third-trimester growth scan.

Study design: This was a population-based study of all women with singleton pregnancy attending antenatal care over a 2-year period in Oxfordshire, UK. Women who had a viable singleton pregnancy at dating scan were included. Women had standard obstetric care including the offer of a routine dating scan and combined screening for trisomies; a routine anomaly scan at 18-22 weeks; and a routine third-trimester growth scan at 36 weeks. The third-trimester scan comprises assessment of fetal presentation, amniotic fluid, biometry, umbilical and middle cerebral artery Dopplers, but no formal anatomical assessment is undertaken. Scans are performed by certified sonographers or clinical fellows (n = 54), and any suspected abnormalities are evaluated by a team of fetal medicine specialists. We assessed the frequency and type of incidental congenital malformations identified for the first time at this third trimester scan. All babies were followed-up after birth for a minimum of six months.

Results: There were 15,244 women attending routine antenatal care. Anomalies were detected in 474 (3.1%) fetuses: 103 (21.7%) were detected before the anomaly scan, 174 (36.7%) at the anomaly scan, 11 (2.3%) after the anomaly scan and before the third-trimester scan, 43 (9.1%) at the third-trimester scan and 143 (30.2%) after birth. The 43 abnormalities were found in a total of 13,203 women who had a 36 weeks scan, suggesting that in 1 out of 303 (95% CI 233-

79 432) women attending such a scan, a new malformation was detected. Anomalies detected at
80 the routine third-trimester scan were of the urinary tract (n=30), central nervous system (5),
81 simple ovarian cysts (4), chromosomal (1), splenic cyst (1), skeletal dysplasia (1), and
82 cutaneous lymphangioma (1). The majority of the urinary tract anomalies were renal pelvic
83 dilatation, which showed spontaneous resolution in 57% of the cases.
84
85 **Conclusion:** When undertaking a program of routine third-trimester growth scans in women
86 who have had prior screening scans, an unexpected congenital malformation is detected in
87 approximately 1 in 300 women.

INTRODUCTION

Although not usually actively sought[1], fetal anomalies can be incidentally found at a third-trimester ultrasound for fetal growth. This scenario can occur either because a fetal anomaly was previously undetected, or because it manifests only in late pregnancy. The first group comprises abnormalities that remain undiagnosed despite first and second-trimester scans, such as a small ventricular septal defect (VSD) [2-6]. The latter includes malformations and insults that develop or present for the first time during late second- and third- trimester, for example developmental central nervous system anomalies (such as malformations of cortical development), cystic lesions, bowel obstruction, urinary tract obstruction and reflux, signs of fetal infection and tumors, and some non-lethal skeletal dysplasias [6-11].

In many settings, ultrasound is not offered in the third trimester, and these abnormalities remain undetected until birth or later when symptoms appear. However, third-trimester scans are increasingly used to try to prevent adverse outcomes associated with abnormalities of fetal growth. Routine third-trimester ultrasound increases the detection of small for gestational age (SGA) fetuses, large-for-gestational-age fetuses, and breech presentation, all conditions associated with a higher risk of adverse perinatal outcome [12-18]. Because of this, efforts are underway to assess clinical and cost-effectiveness of routine third-trimester ultrasound [19].

Detection of anomalies at a growth scan in late pregnancy may cause considerable anxiety and alter the management of pregnancy. In order to investigate these considerations further, we wanted to establish how commonly anomalies are detected at a third-trimester growth scan. Therefore, the objective of this study was to report of unexpected congenital malformations (including insults, genetic and structural) diagnosed incidentally in an unselected population of women undergoing routine third-trimester growth scan, and who have had routine antenatal care including a second-trimester anomaly scan.

MATERIALS AND METHODS

This was a two-year retrospective population-based study of prospectively collected data of all pregnant women with a singleton pregnancy booked for antenatal care at Oxford University Hospitals National Health Service (NHS) Foundation Trust, Oxfordshire, United Kingdom. Included women were those who had a viable singleton pregnancy at dating scan, and an estimated due date (EDD) ranging between 1st October 2016 and 30th September 2018. We also included women who were late bookers; and those who had their dating scan in another hospital and then moved to Oxfordshire for their routine pregnancy care, provided that they had a routine second-trimester anomaly scan in our setting. Importantly, we did not include women referred to our unit from other institutions for tertiary fetal medicine assessment in order to avoid referral bias.

Settings

All pregnant women in the United Kingdom, as part of a national screening program, are offered two routine obstetric ultrasound scans which are carried out according to the fetal anomaly screening program (FASP)[20] guidelines which include detailed scan protocols. The first, at around 12 weeks, is performed for gestational age assessment by measurement of the fetal crown-rump length (CRL) in combination with nuchal translucency (NT) and biochemical screening for fetal trisomies. Women are required to provide written consent for the first trimester combined screening test. All women are then offered a routine scan around 20 weeks with the principal aim of fetal congenital anomalies detection. Any additional ultrasound examinations are then carried out based on risk factors, or if deemed necessary by the obstetric care provider.

Since September 2016, all pregnant women in Oxfordshire are also offered a routine growth scan at 35+0 to 36+6 weeks' gestation with the principal aim of detecting fetal growth

aberrations. At this growth scan, operators record the presentation, amniotic fluid level, placental location, measurement of three standard biometric planes (head circumference, abdominal circumference, and femur length) as well as umbilical and middle cerebral artery Doppler. Repeat fetal anatomy is not a part of this scan, however, sonographers are instructed to report any unexpected findings. The time slot assigned is 20 minutes. All obstetric ultrasound examinations in Oxfordshire are carried out in one of only two maternity ultrasound services at the John Radcliffe Hospital, Oxford and the Horton General Hospital, Banbury. The two centers belong to the same medical center, with unified management protocols, similar ultrasound systems and centralized databases. Scans are performed and reported by accredited sonographers or clinical fellows. For quality control, stored images and the reliability of measurements are assessed according to INTERGROWTH-21st quality criteria[21]. All routine scans are performed using commercially available ultrasound machines (General Electric E6/E8, Zipf, Austria or Philips EPIQ-7, Philips Ultrasound, Bothell, WA, USA). Scan results are recorded and coded prospectively using commercially available archiving software (Viewpoint version 5.6.25.281, GE Healthcare).

Women are referred from this routine screening service for further evaluation to the tertiary referral fetal medicine unit at the John Radcliffe Hospital if referral criteria are met, such as a high risk combined screening result, suspected fetal abnormality or fetal growth abnormality.

Databases

Maternal, fetal and neonatal follow up data were systematically extracted from the ultrasound archiving database (Viewpoint version 5.6.25.281, GE Healthcare); the electronic patient record (EPR, Cerner Millennium, London, UK); the electronic neonatal care record (Badgernet, Clevermed, Edinburgh, UK); the National Congenital Anomaly and Rare Disease

Registration Service (NCARDRS, Public Health England) with a minimum six months follow up post-birth; the Hospital clinical intranet (Radiology and laboratory reporting system that includes the cytologic laboratory, Oxford University Hospitals). Prenatal and postnatal data were merged using the unique maternal and unique offspring NHS number. All records of suspected and detected abnormality were manually reviewed, including image review, to validate the correctness of the diagnosis. This manual review was conducted using the aforementioned databases as well as the NHS Summary Care Record (SCR) that includes general practitioners (GP) care.

Maternal population demographics, including age, height, weight, parity, employment status, socio-economic status, smoking status, substance misuse, preexisting diabetes and assisted reproduction, are collected. Maternal residential postcode was used in order to calculate the Income Deprivation Affecting Children Index (IDACI) decile, according to the online database of the UK Department for Communities and Local Government.

Definitions

For the purpose of the current study, gestational age window for the routine dating scan was defined as 11+0 to 15+6 weeks; all pregnancy routine dating was carried out using either the CRL measurement from 45 to 84mm or the head circumference (HC) when the CRL was 85mm or more. The routine anatomy scan was at 18+0 to 22+6 weeks of gestation. Finally, the gestational age window for the routine 36-week growth scan was defined as being from 35+0 to 36+6 weeks' gestation. Anomaly detection time was classified into five categories: 1. pre-anomaly scan (usually based on a first-trimester scan, combined trisomy screening or second trimester serum screening); 2. at the anomaly scan; 3. Post anomaly scan and prior to the 36 weeks scan; 4. at the 36 weeks growth scan; and 5. after birth. Infant follow up was available for 6-30 months post-birth.

184 *Classification of malformations*

185 We report all major anomalies as classified by National Congenital Anomaly and Rare
186 Disease Registration Service (NCARDRS)[22] and European Surveillance of Congenital
187 Anomalies and Twins (EUROCAT)[23]. In addition, we report minor single-gene disorders,
188 ventriculomegaly even in absence of an underlying condition[24] and abdominal cysts. Infections
189 not resulting in malformations were excluded. Hypospadias was excluded because the high
190 prevalence would impact the proportion of undiagnosed anomalies before birth, which could
191 be misinterpreted by non-cautious readers. We included structural cardiac malformations but
192 excluded fetal arrhythmias since these are not included in the EUROCAT / NCARDRS
193 databases. For the purpose of the current analysis, isolated biometric outliers such as short
194 femur or third-trimester intrauterine growth restriction IUGR were not included unless an
195 underlying genetic or syndromic condition was diagnosed. Soft markers and isolated findings
196 such as single umbilical artery (SUA), persistent right umbilical vein (RPUV), and aberrant
197 right subclavian artery (ARSA) in the absence of aneuploidy were not included in the analysis.
198 Isolated abnormalities of the placenta, membranes, umbilical cord, and amniotic fluid were
199 beyond the scope of the current analysis and were also excluded.

200 *Ethical approval*

201 This study was granted ethical approval reference 17/SC/0374 by the National Health Services
202 (NHS) Health Research Authority (HRA).

203 *Statistics*

204 The study outcome was the incidence and type of congenital malformations detected at the
205 third-trimester growth scan. We report on the entire population taking an “intention to treat”
206 approach, for the purposes of the patient flow diagram, but women who did not attend scans

were not included in the prevalence analysis. Statistical analyses were performed using the statistical software package SPSS 25.0 (SPSS Inc, Chicago, IL). We report descriptive statistics and 95% Confidence Intervals (CI).

RESULTS

During the study period, 15,244 women attended routine antenatal care with a viable singleton pregnancy (Figure). Of these, 14,387 (94.4%) women attended a routine dating scan at Oxford University Hospitals, while 857 (5.6%) had a late dating scan (16+0 to 23+6; before or at the anomaly scan) or had a dating scan elsewhere. During the dating scan, the NT was measured in 11,323 (78.7%) singletons. In the remainder of pregnancies, NT was not measured because it was declined, technically difficult, too late in gestation, done elsewhere, or the woman opted for cell-free DNA testing. After exclusions, 14,568 women had a routine second-trimester scan, and 13,023 had a third-trimester growth scan, all performed in our premises. The routine scans were carried out by one of 54 operators. The maternal demographics are displayed in Table 1.

In total, 474 (3.1%) malformations were found in the 15,244 pregnancies; 331 (69.8%) of these were detected prior to birth: 103 (31.1%) were detected before the anomaly scan; 174 (52.6%) at the time of anomaly scan; 11 (3.3 %) after the anomaly scan and before the 36 weeks scan; and 43 (13.0%) at the 36 weeks scan. A further, 143 (30.2%) abnormalities were detected after birth (Figure). A detailed description of the abnormalities identified after birth is presented in supplementary table 1. Overall, the five most common malformations were chromosomal abnormalities, urinary system anomalies, cardiac disorders, skeletal anomalies, and central nervous system abnormalities (Table 2). There were 96 chromosomal abnormalities, and 70% were detected in the first trimester, while 15 (16%) remained undiagnosed until birth. Most

cardiac conditions (63%) were diagnosed after birth, however the majority of conditions diagnosed after birth were atrial or ventricular septal defects.

Overall, 13,023 women with no known fetal malformation attended the 36 weeks scan. In 1 of 303 (95% CI 233-432) third-trimester scans, an unexpected abnormality was detected. Detailed pre- and post-natal diagnoses for anomalies detected at the 36 weeks scan are listed in Table 3. The average BMI of these 43 women was 23.9 ± 3.8 kg/m^2. Obesity was noted in 2/43 (4.7%) cases. Of the 43 anomalies detected, there were 30 (70%) urinary anomalies. These were either isolated renal pelvic dilatation (21 cases); or other urological abnormalities (9 cases) such as duplex kidneys, unilateral renal agenesis, multicystic dysplastic kidney, posterior urethral valve and pelvic kidney. In more than half of the fetuses with isolated renal pelvic dilatation (12 out of 21 cases), spontaneous resolution of the dilatation was evident on an ultrasound scan performed at six weeks postnatally.

Five fetuses (5/43, 12%) were diagnosed with ventriculomegaly at the 36 weeks scan. In all cases, further investigation was carried out, and invasive testing discussed. Postnatally, one baby (where invasive testing had been declined) was diagnosed with trisomy 21. The remaining four did not show any abnormality with a follow-up period of 18-30 months.

A further fetus with severe intra-growth restriction (estimated fetal weight <1st centile; femur length<1st centile) diagnosed at the 36-week scan was diagnosed prenatally with a de-novo 2q36.3 deletion and Xp22.33 duplication.

Finally, there were four (9%) simple ovarian cysts, one splenic cyst, one skeletal dysplasia, and one neck lymphangioma. There was spontaneous postnatal resolution in three out of four cases of ovarian cysts (Table 2).

COMMENT

Principal Findings

We show that an unexpected malformation is incidentally found in approximately 1 in 300 women who attended a universal routine third-trimester ultrasound scan intended to identify abnormal fetal growth. The overall detection rate of major abnormalities is, however, affected little. The most common newly diagnosed malformations were dilatation of the renal pelvis, duplex kidney(s), ventriculomegaly, and simple ovarian cysts. As routine third-trimester growth scans are not aimed at detecting anomalies, it is important to highlight that this figure is, essentially, the chance of an incidental finding. The information is important for women who are undergoing a growth scan; for practitioners of ultrasound; and for those planning resource allocation in the context of implementing a protocol of routine growth scanning.

Results

In our cohort, the overall incidence of abnormalities was 3.1%. This figure is similar to the 2-4% reported rate of congenital malformations[11, 25, 26]. Our overall prenatal detection rate was near 70%, which is in accordance with the detection rate in previous cohorts[11, 25, 27]. However, the sensitivity and specificity of ultrasound screening in the detection of malformation depend on a number of factors relating to the type of abnormalities included, investigation carried out, and post-natal follow-up period which varies greatly in different studies[28]. Recently Ficara et al. [29] reported the value of routine repeat anomaly scan at 35-37 weeks' gestation in the diagnosis of fetal abnormalities. In this study, a new fetal malformation was identified in approximately 1 in 200 women. However, in their settings, sonographers are requested to repeat the anomaly scan at the third-trimester and are allocated 30 minutes for this purpose, whereas, in our settings, sonographers are allocated 20 minutes and the policy is to only perform a growth scan, comprising basic biometric measurements, amniotic fluid assessment and Dopplers. The effect of performing a growth scan vs. repeating an anomaly scan is easily

noticeable in cardiac malformations. In our cohort, there were 76 cardiac conditions: 28 (37%) detected before, none at the routine third-trimester growth scan, and 48 (63%) after birth. In the study by Ficara et al. [29] 17% of the cardiac anomalies were detected during the repeat third-trimester anomaly scan, most of which were VSDs. Similar findings apply for congenital diaphragmatic hernia, and other malformations. Therefore, in our study, we present incidental findings, while repeat anomaly scan reveals abnormalities that were actively sought for.

About half of the malformations we detected in the third-trimester had documented postnatal spontaneous resolution. For the fetuses with renal pelvis dilatation, spontaneous resolution occurred in 12/21 (57%) cases, which is comparable with other publications[30, 31]. Simple ovarian cysts also usually resolved spontaneously (in 3/4 babies)[32]. Likewise, ventriculomegaly did not have documented short-term consequences in 4/5 babies, while one was diagnosed with trisomy 21 postnatally[24].

In our cohort, some conditions were mainly (or only diagnosed) after birth, including cystic fibrosis and biliary atresia. In the UK, screening for cystic fibrosis is offered to all newborn babies as part of the newborn blood spot test; however, routine prenatal screening is not offered, unless at risk. Screening for Biliary Atresia is not routine. Nevertheless, we chose to include these conditions in our results to allow readers to generalize our experience to their settings[33].

Clinical Implications

The performance of first- and second-trimester ultrasound will alter the number of remaining undiagnosed malformations in the third trimester. Accurate ultrasound diagnosis of congenital fetal malformations depends on many aspects, including maternal habitus, fetal lie, operator skills, type of equipment, and allocated scan duration[34, 35]. Therefore, we felt that it is crucial to report the anomalies detected before and after the third-trimester scan. Of the abnormalities detected in the third trimester, there were a few that could have been diagnosed earlier, such as

duplex kidney, or unilateral renal agenesis. However, the majority could probably not have been identified before and represent progressive conditions, including renal pelvic dilatation or skeletal dysplasia with shortening of the limbs in late pregnancy.

In our settings, the third-trimester scan aims to primarily assess the fetal growth to provide better detection of growth restricted fetuses, and therefore, operators are not requested to repeat an anatomy scan. Nonetheless, incidental abnormal findings are reported and further evaluated. Owing to the nature of the growth scan, there are two types of abnormal findings that operators commonly notice: abnormal biometric measurement, such as microcephaly; and dilated fluid-filled spaces, like a distended renal pelvis, abdominal cyst, or a dilated occipital horn of the lateral ventricle. In our cohort 41 of the 43 malformations detected in the third trimester (95%) related to dilated / fluid-filled spaces, while the other two were identified as a result of abnormal biometry. Postnatally, the most common malformation detected was a cardiac anomaly; no serious cardiac conditions were picked up during the third-trimester scan, and this is probably because these are not likely to be incidentally spotted.

The detection of a structural malformation at any gestational age, provokes emotional, moral, ethical, and legal concerns[36]. The benefits of a late diagnosis may be limited and the emotional effects should not be discounted. Nevertheless, the diagnosis of abnormalities affecting the renal tract, for instance, is important as it allows postnatal follow up of babies at risk of chronic and progressive renal disease[37]. Additionally, in the UK, late termination of pregnancy is possible if there is a substantial risk that if the child were born it would suffer from such physical or mental abnormalities as to be seriously handicapped. However, this may not be acceptable and, in many countries, termination of pregnancy is illegal at advanced gestation.

In our cohort, 143 malformations were diagnosed after birth. These included abnormalities that may be difficult or not possible to detect on ultrasound, such as rare

chromosomal abnormalities, single-gene mutations, small VSDs, isolated cleft palate, and abnormal digits. Other malformations, such as trisomy 21 - especially those not complicated by a major structural anomaly - may also be diagnosed only after birth, in particular in women who opt against prenatal screening. Nevertheless, we chose to report all malformations, including those diagnosed in infancy, to allow comparison to other centers, studies and to describe our population.

Research Implications

In our study, several severe conditions such as cardiac malformations and diaphragmatic hernia remained undiagnosed until birth. Obviously, identification of such conditions before birth would have important implications for babies, mothers and care providers. Future studies focusing on third-trimester scans should report the incidence and type of newly diagnosed abnormalities, as these are rarely described[38]. Such information would be valuable when comparing clinical and cost effectiveness of differing third-trimester screening protocols. For example, institutions may elect to routinely offer cardiac reassessment rather than purely growth or Doppler assessment[39].

Strengths and Limitations

There are a number of important strengths of the study. The prospective collection of data from more than 15,000 consecutive pregnancies over a two-year period offered universal third-trimester scans in addition to first- and second-trimester ones mean that we were able to assess the finding of anomalies in a population that had prior screening at a high standard of care. We used data from high-quality population-based registers that are notified of cases from multiple sources, ensuring high case ascertainment. We also undertook a careful analysis of malformations detected after birth. We undertook the analysis on the basis of an “intention to treat” approach: in any programme of universal third trimester ultrasound screening, some women will not have a third-trimester scan because of preterm birth, or because they failed to

attend their appointment. Finally, the population-based sampling approach means that our data are unlikely to be influenced by referral bias and represent true screening performance at the population level. This means that the findings can be generalized to national and international centers that offer (or are considering offering) routine third-trimester growth scans. The main limitation of our study is that it is only partially applicable to centers offering a routine repeat third-trimester anomaly scan. Another important limitation, not unique to this study, is that postnatal data may be incomplete as NCARDRS registration takes up to a year's time. This risks the problem of lack of ascertainment: for example, prenatally undiagnosed absence of the corpus callosum (ACC) may be asymptomatic or not show any manifestations before several years of age, which is beyond the follow up period for most studies. Taking this example further, in our cohort, one case of agenesis of the corpus callosum (ACC) was diagnosed at 20 weeks. This represents a lower than expected prevalence (assuming a prevalence of 2.6 per 10,000) [40]. Nevertheless, it should be noted that fetuses with ACC often have other associated congenital anomalies – in the study suggesting this prevalence, 75% had associated abnormalities [40]. In our study, when ACC was diagnosed and invasive testing revealed a chromosomal problem, this case was then classified under chromosomal conditions. Further, we do not report false-positive findings; previous studies have suggested that the rate of false-positive is low[27, 41]. Accurate figures are difficult to calculate because terminations of pregnancy without postmortem confirmation, for example, in the first trimester, could hypothetically constitute false-positive diagnoses. In our study, of the 43 anomalies detected at the growth scan, all were reviewed postnatally. In our view, hydronephrosis that resolves should not be considered as a “false positive”; rather, it is a “true positive” with a natural history that includes a high chance of resolution. Our study was designed to report on malformations diagnosed in the third trimester; abnormalities of growth and Doppler, without an underlying fetal structural anomaly, were beyond the scope of this study. Lastly, throughout the study,

about 10% of women were “lost to follow up” by not attending a scheduled scan or delivery elsewhere which may affect the overall number of abnormalities detected through the study.

Conclusion

In conclusion, in about 1 in 300 women attending a routine third-trimester growth scan, who have had a previous first and second-trimester screening, a previously undetected congenital malformation is incidentally found. Where the third-trimester scan is limited to growth assessment, this scan has little effect on overall detection rates. Nevertheless, such abnormalities may result in important information for the parents and physicians which can result in a change in management of the pregnancy or neonate after birth. This information should be available to women attending a third-trimester growth scan; to sonologists undertaking such screening; and should be taken into consideration of cost analysis when planning universal third-trimester ultrasound scanning.

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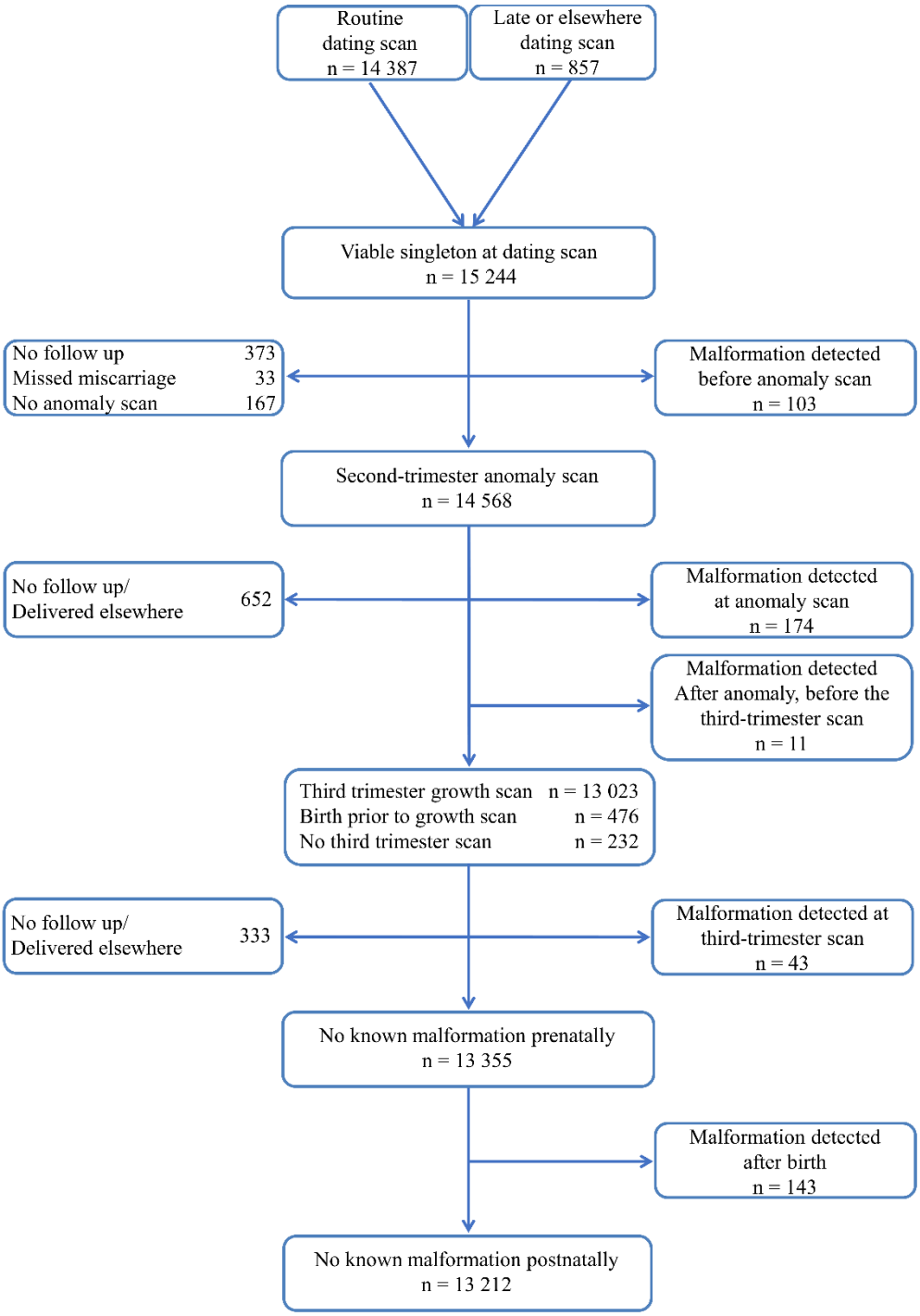
518 **Figure:** Description of the study population



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521 **Table 1** Baseline demographics of the study population

Characteristic	Study population[1]
Age (years)	31.1 ± 5.4
> 35 years	2892 (21.2%)
Height (cm)	165.4 ± 6.6
Weight at booking (kg)	70.2 ± 16.3
BMI at booking (kg/m^2)	25.6 ± 5.5
Obesity class I (BMI 30.0-34.9)	2015 (13.7%)
Obesity class II (BMI 35.0-39.9)	660 (4.5%)
Obesity class III (BMI ≥ 40.0)	360 (2.5%)
Parity	
Nulliparous	7437 (49.0%)
Multiparous	7753 (51.0%)
Employment status	
Full time paid	7196 (56.7%)
Part time paid	2665 (21.0%)
Looking after family	1625 (12.8%)
Permanently disabled	31 (0.2%)
Self-employed	348 (2.7%)
Student	208 (1.6%)
Unemployed	601 (4.7%)
Voluntary work	21 (0.2%)
IDACI	
1st decile (most deprived)	360 (2.8%)
2nd decile	636 (4.9%)
3rd decile	883 (6.8%)
4th decile	1282 (9.9%)
5th decile	1119 (8.6%)
6th decile	1557 (12.0%)
7th decile	1342 (10.3%)
8th decile	1077 (8.3%)
9th decile	2504 (19.3%)
10th decile (least deprived)	2222 (17.1%)
Smoking	
Current smoker	1287 (9.4%)
Ex-smoker	4225 (31.0%)
Never smoked	8117 (59.6%)
Substance use disorder	
Currently using	45 (0.3%)
Previously used	879 (6.7%)
Never used	12187 (93%)
Preexisting diabetes mellitus	240 (1.6%)
In Vitro Fertilization	373 (2.9%)

522 [1]Data available for 12,609 to 15,066 women

523 BMI, Body Mass Index; IDACI, Income Deprivation Affecting Children Index

524 Data are mean ± SD (standard deviation) or number (%)

Table 2 Diagnosis of malformations according to affected system and time of detection

Affected System	Total	Pre-anomaly scan	Anomaly scan	Post anomaly and pre third-trimester scan	Third trimester (35-37 weeks) scan	Postnatal
Chromosomal	**96**					
Down syndrome (Trisomy 21)	35	27 (77.1)	4 (11.4)			4 (11.4)
Patau syndrome (Trisomy 13)	5	4 (80.0)	1 (20.0)			
Edwards syndrome (Trisomy 18)	18	16 (88.9)	2 (11.1)			
Turner syndrome (45, X0)	8	7 (87.5)	1 (12.5)			
Klinefelter syndrome (47,XXY)	2	2 (100.0)				
DiGeorge syndrome (22q11 del)	6	3 (50.0)	2 (33.3)			1 (16.7)
Triploidy	3	3 (100.0)				
Other chromosomal anomaly	19	5 (26.3)	3 (15.8)		1 (5.3)	10 (52.6)
Central nervous system	**48**					
Neural Tube Defect: Anencephaly	9	7 (77.8)	2 (22.2)			
Neural Tube Defect: Spina bifida	7		7 (100.0)			
Holoprosencephaly	2	2 (100.0)				
Ventriculomegaly- mild	22		15 (68.2)	2 (9.1)	5 (22.7)	
Ventriculomegaly- severe/hydrocephalus	4		3 (75.0)			1 (25.0)
Posterior fossa abnormality	2		2 (100.0)			
Agenesis of the corpus callosum	1		1 (100.0)			
Microcephaly	1		1 (100.0)			
Face and Neck	**19**					
Cleft lip	3		3 (100.0)			
Cleft lip and palate	6		6 (100.0)			
Cleft palate	4					4 (100.0)
Microphthalmos	1					1 (100.0)
Cataract	2					2 (100.0)
Ear anomaly	2					2 (100.0)
Other face anomaly	1					1 (100.0)

Third-trimester malformations

Thorax	**12**				
Congenital pulmonary airway malformation	2		2 (100.0)		
Bronchopulmonary sequestration	2		1 (50.0)		1 (50.0)
Diaphragmatic hernia	6		3 (50.0)	1 (16.7)	2 (33.3)
Bronchogenic cyst	1		1 (100.0)		
Pleural effusion	1		1 (100.0)		
Cardiac	**76**				
Valve atresia/stenosis	10		1 (10.0)	1 (10.0)	8 (80.0)
Hypoplastic left heart	4		3 (75.0)		1 (25.0)
Tetralogy of Fallot	5		2 (40.0)		3 (60.0)
Arch abnormality	9	1 (11.1)	2 (22.2)	1 (11.1)	5 (55.6)
Transposition of the great arteries	5		3 (60.0)		2 (40.0)
Great vessel variant	9		9 (100.0)		
Cardiomyopathy	1				1 (100.0)
Ventricular septal defect	24		3 (12.5)		21 (87.5)
Atrial septal defect	6				6 (100.0)
Other cardiac anomaly	3		2 (66.7)		1 (33.3)
Gastrointestinal tract	**9**				
Anal atresia	2				2 (100.0)
Biliary atresia	1				1 (100.0)
Bowel obstruction	1		1 (100.0)		
Cyst	4	1 (25.0)	2 (50.0)	1 (25.0)	
Tracheoesophageal fistula	1		1 (100.0)		
Abdominal wall	**8**				
Body stalk anomaly	1	1 (100.0)			
Gastroschisis	2	1 (50.0)	1 (50.0)		
Omphalocele	5	5 (100.0)			
Genitourinary	**97**				
Lower urinary tract obstruction	7	3 (42.9)	3 (42.9)	1 (14.3)	
Agenesis bilateral	3		3 (100.0)		
Agenesis unilateral	6		3 (50.0)	2 (33.3)	1 (16.7)

Duplex kidney/s	14		6 (42.9)	1 (7.1)	4 (28.6)	3 (21.4)
Multicystic Dysplastic Kidney/s	9	1 (11.1)	7 (77.8)		1 (11.1)	
Horseshoe kidney	1					1 (100.0)
Renal Pelvic Dilatation	46		21 (45.7)	1 (2.2)	21 (45.7)	3 (6.5)
Ovarian cyst	5			1 (20.0)	4 (80.0)	
Ambiguous genitalia	1					1 (100.0)
Other renal anomaly	5		1 (20.0)		1 (20.0)	3 (60.0)
Skeletal	**50**					
Arthrogryposis	2		1 (50.0)			1 (50.0)
Skeletal dysplasia	6	1 (16.7)	3 (50.0)	1 (16.7)	1 (16.7)	
Hemivertebra	1		1 (100.0)			
Limb reduction	1					1 (100.0)
Abnormal digit/s	19		1 (5.3)			18 (94.7)
Talipes bilateral	13		11 (84.6)			2 (15.4)
Talipes unilateral	8		3 (37.5)			5 (62.5)
Tumor	**3**					
Lymphangioma	1				1 (100.0)	
Sacrococcygeal teratoma	2	1 (50.0)	1 (50.0)			
Multiple malformations	**21**					
All	21	3 (14.3)	10 (47.6)			8 (38.1)
Other	**35**					
Cystic Fibrosis	4					4 (100.0)
Other single gene mutation disorder	14	3 (21.4)	3 (21.4)			8 (57.1)
Syndrome	7	1 (14.3)	3 (42.9)			3 (42.9)
Non-immune Hydrops	5	3 (60.0)	1 (20.0)	1 (20.0)		
Infection resulting in malformation/s	2			1 (50.0)		1 (50.0)
Any other	3	2 (66.7)	1 (33.3)			
Grand Total	**474**	**103 (21.7)**	**174 (36.7)**	**11 (2.3)**	**43 (9.1)**	**143 (30.2)**

Data are number (percent)

Table 3 Anomalies detected at the third-trimester ultrasound scan

Affected system	Prenatal findings	Number detected	Postnatal diagnosis
Urinary tract (n = 30)	Renal pelvic dilatation (n = 21)		
	Unilateral		
	Mild (7.0-9.9mm)	3	2 transient renal pelvic dilatation; 1 confirmed postnatally
	Moderate (10.0-14.9mm)	11	6 transient renal pelvic dilatation; 5 confirmed postnatally
	Bilateral		
	Mild (7.0-9.9mm)	3	2 transient renal pelvic dilatation; 1 confirmed postnatally
	Moderate (10.0-14.9mm)	3	1 transient renal pelvic dilatation; 2 confirmed postnatally
	Severe (≥15mm)	1	1 confirmed postnatally
	Duplex kidney (n = 4)		
	Unilateral	3	All confirmed postnatally
	Bilateral	1	
	Agenesis – unilateral (contralateral hydronephrosis)	2	Confirmed postnatally
	Multicystic dysplastic kidney (MCDK) unilateral	1	Confirmed postnatally
	Posterior urethral valve	1	Confirmed postnatally
	Pelvic kidney unilateral	1	Confirmed postnatally
Central Nervous System (n = 5)	Ventriculomegaly 10.1-12.0mm	3	1 Trisomy 21; 2 Normal
	Ventriculomegaly 12.1-13.0mm	2	2 Normal
Reproductive	Simple ovarian cyst (largest diameter 30-45mm)	4	3 spontaneous resolution; 1 persistent cyst
Chromosomal	Severe growth restriction <1st centile, femur length < 1st centile; Microarray: de-novo 2q36.3 del; Xp22.33 dup	1	Termination of pregnancy
Splenic cyst	Splenic cyst (largest diameter 30mm)	1	Confirmed postnatally
Skeletal	Skeletal dysplasia	1	Achondroplasia
Cutaneous	Neck cavernous lymphangioma	1	Confirmed postnatally