**Suspected Fetal Anomalies**

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**Abstract**

As part of the national screening programme, fetal anomaly screening is offered as part of the routine antenatal care in the NHS. The identification of suspected fetal anomalies causes stress and anxiety in the expectant parents. Therefore, a thorough understanding of the issues as described can help alleviate this to a degree. This problem-based review presents two case histories describing issues encountered during first and second trimester screening, and principles behind subsequent management.

Key words: fetal anomalies, screening, karyotyping, pregnancy

**Introduction**

Fetal anomalies are recognised as single or multiple structural or functional changes anomalies that occur in utero. Major abnormalities occur in 2-3% of fetuses but account for 20-30% of perinatal mortality in the developed world. The prenatal diagnosis of such anomalies can be used to make informed decisions of the future and ongoing investigations and management of the pregnancy.

Fetal anomalies not only increases the risk of infant death but can also cause pain, stress and anxiety to the expectant parents and family members. Therefore, timely and accurate diagnosis of anomalies are needed to determine appropriate intervention if available. The diagnosis of such anomalies historically involved ultrasound scanning of the unborn fetus, invasive sampling of either fetal cells or fluid, or maternal biomarkers. However, more recently progress in genetics, immunology, embryology, biochemistry and epidemiology research have led to improvements in the diagnosis of congenital fetal anomalies. This has allowed a wider range of anomalies more accurately identified at an earlier stage in pregnancy.

Ultrasound was first developed in 1957 by Tom Brown and Ian Donald. Initially it was not clinically used but it developed into a valuable non-invasive technology to aid prenatal diagnosis. One of the first clinical uses of ultrasound, in 1966, was to assist in performing amniocentesis in older patients at risk of trisomy 21. Screening by age, followed by diagnostic amniocentesis, allowed a basic risk assessment and diagnosis to be available for trisomy 21 for the first time. This subsequently developed into the now recognised first trimester scan and combined screening. Its development has continued to a point that ultrasound demonstrates a high detection rate of fetal anomaly, but also can be repeatedly used to monitor the pregnancy without adverse effects on the pregnant woman and fetus.

Aside from ultrasound, the first serum biomarker α-fetoprotein (AFP) was developed as a test for open neural tube defects (NTDs) followed the recognition in the mid -1970s that AFP level was elevated in anencephaly and “open” spina bifida cases while, closed cases had normal levels. Further biomarkers were subsequently discovered and improvements in ultrasound technology led to the identification and prediction of an ever-growing number of conditions. Today, human chorionic gonadotropin (hCG) and pregnancy-associated plasma protein A (PAPP-A) are used as first trimester biomarkers for screening of trisomy 13,18 and 21, while the quadruple test uses four biomakers - AFP, hCG, unconjugated estriol (uE3) and Inhibin-A.

Screening for fetal anomalies within the UK was organised at a local level and practices varied. It was not until the establishment of a national screening programme in 2001 that it was coordinated and standards and practices aligned. This developed into the combined test which is now the recommended method of screening in the first trimester, combining maternal age, biochemistry and ultrasound measurement of fetal nuchal translucency (NT) to provide a pregnant woman with her chance of having a baby with Down’s syndrome, Edwards’ syndrome or Patau’s syndrome. If the women did not have a nuchal translucency measurement performed in the first trimester, for example if the Crown-Rump Length (CRL) is greater than 84.0 mm, the second trimester quadruple test should be offered between 14+2 to 20+0 weeks of gestation. In the second trimester, a fetal anomaly scan is offered and where accepted, should be undertaken between 18+0 to 20+6 weeks of pregnancy. The fetal anomaly scan screens for 11 conditions which is outlined in the Fetal Anomaly Screening Programme handbook.

**Case 1**

A 33-year-old booked with the midwife at 7 weeks of gestation from her last menstrual period. She was defined as low risk. She attends her routine dating scan at 12+6 weeks into her first pregnancy and is asked by the sonographer performing her scan whether she is interested in screening for Patau’s syndrome, Edwards syndrome and Down’s syndrome (trisomy 13, 18 and 21). She is aware of the availability of screening as her midwife had discussed the screening process, the consequences of a positive result and the option to decline screening at her booking appointment. Following discussion with her partner she accepts screening and proceeds to have screening. Her combined test results showed that she has an Edward’s or Patau’s syndrome risk of less than 1 in 10,000 but a Down’s syndrome risk of 1 in 96.

She is seen in the fetal medicine clinic and a further non-invasive screening test (NIPT) is discussed. She considers NIPT which she has heard is available privately but decides not to proceed with this on a cost basis. She is then counselled for an amniocentesis by the fetal medicine team. This was carried out which showed a normal fetal karyotype. The patient continues to have an uneventful pregnancy and spontaneously labours at 39 weeks and 2 days of gestation. She has an uneventful normal vaginal delivery complicated by a second-degree tear which was sutured and was she was discharged home with no maternal or neonatal concerns.

**Discussion**

The patient illustrated in the case is a young woman who booked at the routine time into her first pregnancy. She is fit and well and has no risk factors to make her obstetrically high risk. Therefore, she is suitable for routine midwifery care.

**First trimester ultrasound scan**

The patient in the case attends her first trimester ultrasound scan as part of the NHS screening programme. The first trimester ultrasound scan has several purposes and is the first step to the identification of fetal anomalies. The scan can confirm the presence of a viable pregnancy, determine if it is a single or multiple pregnancy and major structural anomalies can be identified at this early stage. Examples of fetal anomalies that can be detected include anencephaly, and neural tube defects. Measurement of the NT is carried out, which refers to the normal subcutaneous space between the skin and the cervical spine in the fetus. Increased NT measurement is known to be associated with increased risk of aneuploidy, particularly with Down’s syndrome. Multiple studies have now identified increased NT as a nonspecific marker of a wide range of fetal structural abnormalities, to include congenital diaphragmatic hernia, cardiac defects, and various genetic syndromes. Therefore, this can be used as a soft marker for anomalies not identified on first trimester ultrasound.

As part of the first trimester screening utilising the NT measurement on ultrasound is screening for Patau’s syndrome, Edward’s syndrome and Down’s Syndrome by the combined test. This screening test does not offer diagnosis but a “chance” of the pregnancy being affected by Trisomy 13, 18 or 21. It is calculated using the NT measurement combined with maternal age and two biochemical markers, free beta hCG and PAPP-A. The optimal time to perform the combined test is between 11+2 weeks to 14+1 weeks of gestation, corresponding to a CRL of 45.0 mm to 84.0 mm. This screening method is associated with high sensitivity and a relatively low false‐positive rate. It is worth noting that women with a twin pregnancy are still eligible for combined screening.

While all women have a chance of having a baby with Down’s syndrome, this chance increased with age, the older the mother the greater chance of having an affected baby. A 20-year-old woman at 16 weeks’ gestation has a 1 in 1500 (0.07%) chance of having a child with Down’s syndrome, while for a 40-year-old woman at a similar gestation this chance is increased to 1 in 100 (1%).

**Further non-invasive screening or straight to invasive testing?**

Following the identification of the pregnancy as at high risk of trisomy 21 on the combined screening, the individual typically has choices of no further investigation or an invasive test to reach a diagnosis. The invasive testing comprises of chorionic villus sampling (CVS) or amniocentesis to obtain fetal genetic material. As invasive tests they are as such not without risks to mother and the pregnancy which may be deemed unacceptable to some individuals.

The discovery of fetal reticulocytes and of cell-free fetal DNA (cffDNA) in peripheral blood samples of pregnant women has led to the development of NIPT. The sequencing of this cell-free DNA in maternal plasma allows a further highly effective non-invasive screening test for Down’s syndrome. The cffDNA, small fragments of fetal DNA circulating within the maternal plasma comprises of 10% of the total cell free DNA in circulation, the remainder being maternal. it is detectable from a gestational age of 10 weeks so allowing an early test. The cffDNA is cleared rapidly following delivery of the pregnancy making it specific to the pregnancy.

This non-invasive test therefore avoids procedural risks associated with CVS and amniocentesis and therefore becomes more acceptable to patients. It however remains as a secondary screening test, only reducing the need for an invasive test

in women with false-positive screening results for Down’s syndrome, or as an alternative to the traditional first‐ or second‐trimester screening test.

NIPT used for the prediction of Down’s syndrome has improved sensitivities around 99% with a false positive rate of less than 0.1%, in both high risk and general populations. NIPT can also be used to screen for trisomies 13 and 18 and sex chromosome aneuploidies. However, there is poorer performance in these areas. With higher sensitivity and specificity than standard combined screening, it offers a second non-invasive screening test but cannot as of yet be offered as a diagnostic test. Therefore, it might still be necessary to proceed to invasive testing for diagnostic purposes.

As yet NIPT is not offered on the NHS but is facilitated and therefore a necessary charge is made. Although not currently part of the NHS screening programme, its future role is being investigated with a plan to roll out in the near future. A potential advantage of NIPT is that it can be carried out at an earlier gestation. This brings the advantage of identification of significant chromosomal abnormalities and enables the option for early termination before women feel fetal movements. Early termination of pregnancy has physical and physiological advantages for women and their families compared with late termination.

The patient illustrated in this case declined NIPT due to the additional cost and therefore was left with the choice of no additional tests to aid diagnosis or amniocentesis. The patient opted to have an amniocentesis for a definitive diagnosis, which also allowed further option of termination of pregnancy if needed.

**Invasive testing**

The patient is seen in the fetal medicine clinic and is counselled about the risks and benefits of invasive testing to definitively determine the pregnancy karyotype. This allows the patient the option to make an informed decision regarding the future of her pregnancy.

Invasive testing comprises of CVS and amniocentesis. Chorionic villus sampling is usually performed between 11 (11+0) and 13 (13+6) weeks of gestation and involves aspiration or biopsy of placental villi. CVS can be performed using either a transabdominal or a transcervical approach. Early CVS prior to 11 weeks of gestation has been associated with facial and limb defects. Amniocentesis is performed from 15+0 weeks onwards and is the most common invasive prenatal diagnostic procedure undertaken in the UK. Under ultrasound guidance a needle is inserted to obtain amniotic fluid for karyotyping. Prior to this gestation amniocentesis is associated with higher rate of pregnancy loss and talipes (RCOG, 2010).

Following counselling by the fetal medicine team the patient undergoes an amniocentesis. Invasive testing remains the only method of diagnostic testing for chromosomal abnormalities. The limitations of the screening tests, combined screening and NIPT need to be discussed with the patient. Patients must understand that combined screening ang NIPT are not diagnostic tests, a negative test does not ensure a normal pregnancy, and that all positive results should be confirmed by invasive testing. Therefore, amniocentesis should still be offered to all women who desire complete genetic testing. As it is an invasive test it has associated risks and these would need to be discussed with the patient prior to the procedure.

Every pregnancy carries a risk of miscarriage. With invasive testing there is an additional risk of miscarriage to the background risk, including the potential of increased risks due to the condition that the invasive testing was required for. The additional overall risk of miscarriage from CVS is 1-2% and from amniocentesis is approximately 1%. Amniotic cells that are obtained by amniocentesis are cultured in sufficient quantity to be karyotyped. This can either be a rapid form to obtain the diagnosis, absence or presence of trisomy 21 or a full karyotyping.

In case 1, the mother sought a conclusive diagnosis which was completed. Despite the combined test demonstrating a high risk of Down’s syndrome, amniocentesis confirmed a normal karyotype and therefore the pregnancy continued. She had an uneventful remainder of pregnancy and delivered a live infant.

**Laboratory techniques**

The cells obtained from invasive prenatal testing are used to perform fetal chromosome evaluation. Historically structural karyotypic abnormalities are defined and reported with increasing resolution throughout the years. Fetal karyotyping by G-band analysis is now the conventional standard and requires a skilled cytogenetic analyst to report results. It requires cultured cells and this process can take between 10 and 21 days. This delay can increase anxiety for expectant parents and delay diagnosis of the anomaly being investigated.

A more recently developed test that has the advantage of providing a quicker result is quantitative fluorescence polymerase chain reaction (QF-PCR). This aims to target specific whole chromosomal anomalies (typically Trisomy 13, 18, 21, and sex chromosome anomalies X and Y). It provides a cheap and rapid test result (within 48–76 hours) in response to a prenatal screening test reported as ‘high risk’. This is often carried out alone after a high-risk screening result with conventional full karyotyping only carried out when there is a high suspicion of more complex chromosome anomalies.

The recent development of chromosomal microarray analysis (CMA) can be used for the detection of clinically-significant microdeletions or duplications. CMA involves hybridisation of the fetal DNA obtained from invasive testing onto predetermined targets representative of the whole genome. It is able to detect changes as small as 5-10Kb in size - a resolution up to 1000 times higher than that of conventional karyotyping. CMA uses DNA extracted from uncultured cells therefore reducing the time needed to report results. It is more cost-effective, amenable to automation with high throughput analysis. A potential disadvantage of CMA is that it is only able to detect unbalanced chromosomal changes. Furthermore, CMA can detect abnormalities where the clinical significance is not yet determined. This can lead to difficulties in clinical management due to uncertainties of the clinical effect.

Within clinical practice in the UK, QF-PCR is likely to continue to be used in preference to CMA as a rapid and cost-effective screen for the common autosomal and sex aneuploidy and triploidy that will need to be investigated as a result of prenatal screening.

**Case 2**

A 28-year-old at 19+2 weeks into her second pregnancy attended for her routine anomaly scan. Her first child was delivered by a caesarean section. Her fetus was found to have an isolated omphalocele which contained only bowel. She underwent a further fetal medicine scan which confirmed the findings. An omphalocele is associated with chromosomal abnormalities. Although her first trimester screening had a low risk result of 1 in 35,000, the need for invasive testing in the form of amniocentesis was discussed.

She was referred to the paediatric surgical unit in a tertiary centre and discussed in their multi-disciplinary meeting. The patient was counselled regarding the outlook of omphalocele and abdominal wall defect, as well as the resulting need for surgical repair.

A plan for Caesarean delivery was made in the obstetric department of the tertiary centre with the paediatric surgical unit. She underwent an uneventful Caesarean section with a delivery of a live male infant in the presence of the neonatal team. Clamping of the umbilical cord was carried out after careful assessment of the umbilical defect due to the presence of bowel at the base of the umbilical cord. The baby was transferred to the neonatal unit where he underwent primary closure of the defect in the days following delivery.

**Discussion**

This patient illustrated in this case was considered at the booking of her pregnancy to be low risk and took part in the routine NHS screening programme. She underwent the first trimester ultrasound examination that revealed no abnormalities and accepted the offer of screening for trisomy 13, 18 and 21. This came back as low risk and consequently invasive testing or cffDNA techniques were not required nor deemed appropriate.

**The second trimester ultrasound**

The second trimester ultrasound screening is routinely carried out between the 18-23 weeks of gestation and is used for anomaly screening although it is widely accepted that most anomalies can be detected earlier. The aim of the second trimester scan is to identify conditions that may: i) benefit from treatment before or after birth, ii) indicate that delivery should be in an appropriate hospital/centre and/or to optimise treatment after the baby is born, and iii) Identify conditions that the baby may die from shortly after birth. The ultrasound scan has specific measuring techniques and defines the anatomical structures to be assessed including detailed cardiac views. This promotes consistency in the examination and allows the anomalies to be identified.

The scan is typically offered at this gestation for three reasons. Firstly, in the second trimester, all fetal organs are formed and most anatomical anomalies can be diagnosed by ultrasound. The second reason for offering the scan at 18 – 23 weeks is that at this gestation, the chance of having a ‘complete’ anatomy survey in a single scan is the greatest. Any earlier and this increases the risk for incomplete scans and, a need for repeat assessment, which is not beneficial from a health economics point of view, while adding stress and anxiety for parents. The final reason for not offering screening ultrasound later in pregnancy is that in many countries, the option of pregnancy termination is only available until 22 – 24 weeks’ gestation. Hence patients should therefore have knowledge on any fetal anomalies by this gestation to make an informed decision regarding the future of the pregnancy.

In this case the anomaly identified is an exomphalos (omphacele). Exomphalos is the commonest abdominal wall defect seen and results from the failure of loops of bowel to return to the abdominal cavity after physiological herniation into the umbilical cord. This occurs from the 6th to 10th week of gestation It is thought that delayed closure of the lateral folds in association with a large umbilical ring is responsible for this failure. Infants with exomphalos usually have an associated non-rotation or malrotation of their intestine. The liver, spleen, and ovaries are frequently present in the sac. Compared to exomphalos, the more common abdominal wall defect gastroschisis is caused by a smaller defect in the abdominal wall, located to the right side of the anatomically normal umbilical cord. The complete intestine is often herniated through the defect; however, the testes, ovary, and liver are less commonly involved. There is no associated membranous covering present in gastroschisis unlike in exomphalos. Therefore, the herniated bowel is directly exposed to the contents of the amniotic cavity. As a result, the bowel wall develops an inflammatory peel and the mesentery becomes thickened.

Prenatal diagnosis may be made as early as the first trimester on ultrasound but is more commonly made on routine second trimester ultrasound. The incidence of omphalocele seen on first trimester ultrasound is as high as 1 in 1100, but due to both spontaneous intrauterine fetal death and pregnancy termination, the incidence in live births is 1 in 4000.

Exomphalos is associated with chromosomal abnormalities, occurring in up to 49% of fetuses affected. The most common abnormalities are trisomies 13, 18 and 21. Of those fetuses with normal karyotypes, nearly 80% have multiple other anomalies. A large proportion have cardiac anomalies and therefore fetal cardiac echocardiography is often performed to investigate this further. Pulmonary hypoplasia is also commonly associated with a giant omphalocele and can result in respiratory distress requiring intubation and ventilatory support soon after of delivery. The association of exomphalos with chromosomal abnormalities and congenital heart defects means that prenatal diagnosis usually leads to an offer of fetal karyotyping.

Surgical repair is carried out on the abdominal wall defect soon following delivery. There are multiple strategies to close the defect but the primary goal of every surgical repair is to return the viscera to the abdominal cavity whilst minimizing risk of damage to the bowels due to direct trauma or increased intra-abdominal pressure. Options include of closure include: i) primary reduction with closure of the fascia, ii) serial reductions and delayed fascial closure, and (iii) primary or delayed reduction without fascial closure. Due to these postnatal surgical interventions, it is sensible for the baby to be delivered in a unit that is capable of closure of the defect as ex-utero transfer leads to poorer outcomes. The ability to diagnose such conditions prenatally allows for appropriate planning of delivery.

**Termination of pregnancy**

Although neither patients in the cases considered a termination of pregnancy, it is worth commenting on this option. Within the UK this is covered by the Abortion Act of 1967 which specifies that pregnancies can be terminated up to 24 weeks of gestation for specific grounds which one or more must be met. Each of the grounds for termination of pregnancy has to be believed by two medical practitioners in good faith. The particular elements pertaining to fetal anomalies are provisions A and D:

(A) the pregnancy has not exceeded its 24th week and that the continuance of the pregnancy would involve risk, greater than if the pregnancy were terminated, of injury to the physical or mental health of the pregnant woman or any existing children or her family;

(D) 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 (Ground E on the abortion notification form).

There is a distinction between pregnancies of up to 24 weeks and those of later gestation. Pregnancies of up to 24 weeks of gestation can be terminated under Section 1(1)(a), and therefore doctors dealing with fetal abnormality have the option of choosing either 1(1)(a) or 1(1)(d). A pregnancy may be terminated at any stage (including after 24 weeks) for fetal abnormality under Section 1(1)(d) (Ground E), which specifies that there is a substantial risk that if the child was born it would suffer from such physical and mental abnormalities as to be severely handicapped. There is however no legal definition of risk to physical or mental health or substantial risk of severe handicap, and therefore this is open to subjective interpretation on a case to case basis. Additionally, it would be difficult if not impossible to demonstrate that a decision to terminate the pregnancy was not taken in good faith.

The most recent statistics from 2017 state that congenital malformations were reported as the principal medical condition in nearly half (49%; n=1,632) of terminations taking place under ground E. Chromosomal abnormalities were reported as the principal medical condition for just over a third (34%; n=1,131) of ground E cases. Down’s syndrome was the most commonly reported chromosomal abnormality (20%; n=655).

There are broadly two methods of termination of pregnancy. Before 15 weeks of gestation it can be performed surgically. Uterine evacuation is achieved by vacuum aspiration with or without cervical preparation with misoprostol or gemeprost. After 15 weeks, the size of the fetus prevents complete aspiration and dilatation and evacuation becomes necessary. This should be undertaken by specialist practitioners with a caseload to maintain their skill. The second more common method is medical termination which is performed by mifepristone (200 mg) followed 36–48 hours later by a course of either misoprostol or gemeprost.

Feticide should be offered if the decision to terminate pregnancy is made after the gestation of 21+6, as the risk of livebirth is increasingly common after 22 weeks of gestation. Feticide should be offered routinely after explaining to the parents there is a risk of livebirth. A child that is born alive with a fetal abnormality is legally deemed a person and must be treated in best interests. If abnormalities are incompatible with long-term survival the child should be managed maintaining comfort and dignity during terminal care.

**Conclusion**

In this article we have looked at two cases of suspected fetal anomalies from their identification to their subsequent investigation and management. The identification of a fetal anomaly affects the expectant parents causing stress and anxiety about their unborn child. Therefore, a thorough understanding of the issues as described can help alleviate this to a degree.

**Conflicts of interests**

None declared.

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**Practice points**

* The combined test is used in first trimester screening, which combines maternal age, biochemistry (hCG and PAPP-A) and nuchal transluscency on ultrasound.
* Though not currently part of the national screening programme, non-invasive prenatal testing is a form of screening that reduces the need for an invasive test in women with false-positive screening results for Down’s syndrome, or as an alternative to the traditional first‐ or second‐trimester screening test.
* Invasive testing comprises of CVS and amniocentesis, and some patients may opt for termination of pregnancy for specific grounds covered by the Abortion Act.
* Chromosomal microarray analysis is more cost-effective, amenable to automation with high throughput analysis, but can detect abnormalities where the clinical significance is not yet determined.
* The fetal anomaly scan screens for 11 conditions which is outlined in the Fetal Anomaly Screening Programme handbook by Public Health England.

**Single best answer questions:**

1. Which biomarkers are included in the quadruple test?

1. AFP, hCG, uE3 and PAPP-A
2. **AFP, hCG, uE3 and Inhibin-A**
3. AFP, hCG, PAPP-A and Inhibin-A
4. AFP, PAPP-A, uE3 and Inhibin-A
5. hCG, PAPP-A, uE3 and Inhibin-A

2. From which gestational weeks is cell-free fetal DNA is detectable in maternal circulation?

1. 8 weeks
2. 9 weeks
3. **10 weeks**
4. 11 weeks
5. 12 weeks

Table 1. The conditions screened for as a minimum in England. Adapted from NHS Fetal Anomaly Screening Programme Handbook, 2018.

|  |  |
| --- | --- |
| Conditions | Detection rate (%) |
| Anencephaly | 98 |
| Open spina bifida | 90 |
| Cleft lip | 75 |
| Diaphragmatic hernia | 60 |
| Gastroschisis | 98 |
| Exomphalos | 80 |
| Serious cardiac anomalies includes the following: • Transposition of the Great Arteries (TGA) • Atrioventricular Septal Defect (AVSD) • Tetralogy of Fallot (TOF) • Hypoplastic Left Heart Syndrome (HLHS) | 50 |
| Bilateral renal agenesis | 84 |
| Lethal skeletal dysplasia | 60 |
| Edwards’ syndrome (Trisomy 18) | 95 |
| Patau’s syndrome (Trisomy 13) | 95 |

**Further reading**

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