Prenatal diagnosis: Types and techniques

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Abstract

Up to 3% of UK pregnancies will be affected by congenital abnormality. Prenatal diagnosis allows the parents to make informed decisions about their pregnancy, healthcare professionals to optimise the antenatal care and families prepare for the birth of the baby. There are many techniques employed which range from the non-invasive ultrasonography to the highly invasive amniocentesis. This review explores the methods currently available in the UK as well as considering the newer minimally-invasive technologies available including cell-free fetal DNA and pre-implantation genetic diagnosis.

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1. Introduction

Approximately 2–3% of UK pregnancies will be affected by one or more congenital abnormalities. This accounts for around 21% of perinatal and infant deaths, as well as causing significant disability and morbidity later in life. Although some pregnancies are known to be at high risk of anomaly, such as those of diabetic mothers or parents with previously affected offspring, most congenital defects occur unexpectedly in otherwise normal pregnancies. Prenatal diagnosis of these conditions may be helpful in several ways:

• Preparing parents for the birth (or potential in utero demise) of an affected child
• Ensuring appropriate fetal surveillance to provide the best possible outcome for the individual situation
• Helping decision making on timing, mode and place of delivery
• Introducing parents to specialist neonatal services
• Potentially allowing in utero treatment
• Providing parents with the option of terminating the pregnancy.

The difference between screening and diagnostic tests is often poorly understood and care must be taken to counsel parents before embarking on either. It is also important for women to understand that a negative test result for a certain condition does not guarantee that her baby does not have another abnormality. Detailed, unbiased, written information should be given before any tests are undertaken; counselling should be non-directive. Any diagnostic test used should fulfil accepted criteria:

• Needs to be able to definitely confirm or reject the suspected diagnosis (e.g. the fetus does, or does not, have Down’s syndrome)
• Must be as safe as possible
• Must have sensitivity and specificity approaching 100%
• The implications of the disorder being tested for must be serious enough to warrant the risks of the test.

2. Non-invasive techniques

2.1. Ultrasound

The NHS now routinely recommends two ultrasound scans during pregnancy. A first trimester dating scan, usually with a Nuchal Translucency measurement as part of the screening for Down’s syndrome, and an anomaly scan at around 20 weeks of gestation. The detection rate for abnormalities may vary and is dependant on:

• The anatomical system affected
• Skill of the operator
• BMI of the patient
• Quality of the ultrasound equipment
• Gestational age and fetal position at the time of the scan

2.1.1. Routine first trimester ultrasound

Visualising the fetus between 11 and 14 weeks has improved estimates of gestational age as well as confirming viability. It has also improved diagnosis of multiple pregnancy and identification of chorionicity. With higher order multiple pregnancies it enables discussion with parents about management options including fetal reduction at an early stage.

The principal use of the first trimester ultrasound scan is for screening for aneuploidy. The nuchal translucency (NT) refers to the sonographic appearance of the fluid filled fold at the back of the fetal neck in the first trimester of pregnancy. It is often enlarged when the fetus has Trisomy 21, other genetic abnormalities or a major cardiac defect. Just using the measurement of the NT alone will identify 62% of all Trisomy 21 cases with a false positive rate of 5%. However, used in combination with maternal age, pregnancy associated plasma protein A (PAPP-A) and β human Chorionicgonadotrophin (βhCG) in the first trimester can rise to a 90% detection rate for a 5% false positive [1]. The National Screening Committee in the UK recommends a cut off of 1:150 as high risk which produces a 75% detection rate for a 3% false positive rate.

The sensitivity and specificity can be further improved by repeating tests in the second trimester to give an ‘integrated test’, which decreases the false positive rate to 1.2% for 85% detection [1]. Whilst this ‘integrated test’ appears to offer the most effective and safest method, many women feel that they need an answer in the 1st trimester whilst surgical termination remains an option. The addition of other ultrasound markers known to be associated with Trisomy 21 such as nasal bone hypoplasia and significant tricuspid regurgitation will increase the accuracy of the first trimester combined test. However, they are not routinely used within the NHS as they require time and considerable experience to measure accurately.

A 3% false positive rate is taken for the routinely used test in the UK, so most of the fetuses screened as high risk will be normal at birth. Women need to be made aware of the limitations of this screening test and consequences of a ‘high risk’ result before they embark on it.

First trimester ultrasound also provides an opportunity for early detection of fetal abnormalities. However, the sonographer must understand embryological development when interpreting their findings to prevent normal processes being interpreted as anomalies e.g. the physiological herniation of the midgut may be incorrectly diagnosed as an exomphalos. Many anomalies may be seen at this gestation with some authors reporting a structural anomaly detection rate as high as 59% [2]. Whilst there is a lack of other studies to confirm this rate, certain anomalies are clearly evident at this gestation given optimal scanning conditions. These include anencephaly [3], exomphalos and gastrochisis [4], cystic hygroma, body stalk anomalies [5] and conjoined twins. However, many significant structural malformations including cardiac anomalies, skeletal dysplasias and neural tube defects can be easily missed at this early stage. Due to a lack of evidence regarding the precise diagnostic value, NICE does not currently recommend changing the routine structural abnormality scans from 20 weeks to the first trimester.

2.1.2. Ultrasound: the “20 week” anomaly scan

The current UK NICE guideline states that ultrasound screening for fetal abnormalities should be routinely offered, normally between 18 weeks 0 days and 20 weeks 6 days [6]. To ensure optimal performance of this national screening test the Royal College of Obstetricians and Gynaecologists (RCOG) has published a Working Party Report which includes a minimum standard for the “20 week” anomaly scan (see Table 1) [7]. The detection rates of major structural abnormalities at this gestation are generally good but highly dependant on the anatomical system affected. The results of a meta-analysis of 17 studies [6,5] looking at the prevalence and detection rates of antenatal ultrasound in the second trimester are given in Table 2. However, as ultrasonography is significantly operator dependant these rates are now better in many centres.

2.1.3. Ultrasound: detailed fetal echocardiography

In the UK women with risk factors known to increase the incidence of congenital heart disease should be offered an extra fetal cardiac scan between 21 and 24 weeks of gestation. This improves the sensitivity for detecting cardiac defects to 85%. These factors may be familial (e.g. a first degree relative with congenital heart disease), maternal (e.g. diabetes mellitus), pregnancy related (including a high nuchal translucency result) and environmental (e.g. fetal exposure to known teratogens such as sodium valproate).

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<th>Table 1</th>
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<tr>
<td><strong>RCOG working party report on ultrasound screening minimum standard for the “20 week” anomaly scan</strong> [7].</td>
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<tr>
<th><strong>Fetal normality</strong></th>
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<tr>
<td>• Head shape and internal structures: <strong>cavum septi pellucidi, cerebellum, ventricular size at atrium (≤ 10 mm)</strong></td>
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<td>• Spine: longitudinal and transverse</td>
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<td>• Abdominal shape and content at level of stomach</td>
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<td>• Abdominal shape and content at level of kidneys and umbilicus</td>
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<td>• Renal pelvis (&lt;5 mm AP measurement)</td>
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<td>• Longitudinal axis — abdominal-thoracic appearance (diaphragm/bladder)</td>
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<td>• Thorax at level of 4 chamber cardiac view</td>
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<td>• Arms — three bones and hand (not counting fingers)</td>
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<td>• Legs — three bones and foot (not counting toes)</td>
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<th><strong>Optimal standard if resources allow:</strong></th>
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<td>• Cardiac outflow tracts</td>
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<td>• Face and lips</td>
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2.1.4. Ultrasound: non-invasive detection of fetal anaemia

The physiological response to anaemia seen in the fetus has enabled development of an ultrasound test now widely regarded as the non-invasive ‘gold-standard’. As anaemia develops the fetus responds by peripheral vaso-constriction and cerebral vaso-dilatation to preferentially shunt the available oxygen to the developing brain. Recognition of this led to the development of several tests for anaemia including spleen perimeter, ductus venosus Doppler and thoracic aorta Doppler. However, the most commonly used test is the middle cerebral artery (MCA) Doppler peak systolic velocity (PSV). A recently published meta-analysis of non-invasive methods for detecting fetal anaemia [8] identified 23 studies of MCA-PSV, nine of which were high enough in quality to pool the data. This revealed a positive likelihood ratio of 4.30 (95% CI: 2.50 to 7.41) and a negative likelihood ratio of 0.30 (95% CI: 0.13 to 0.69) for detecting severe anaemia in 675 cases. This is similar to that of OD450 from amniocentesis but without the risks of invasive testing. Therefore, although not an ideal screening test, MCA-PSV is the best currently available for fetal anaemia and has replaced speculative cordocentesis. It is used as a screening test up to 35 weeks of gestation and with fetal anaemia being suspected if the result is above 1.5 MoMs (multiples of the mean) or greater than 2 standard deviations above the mean.

2.1.5. Ultrasound: diagnosis of intra-uterine growth restriction (IUGR)

Customised growth charts have been developed which aim to identify the optimal growth curve for an individual fetus. Use of these appears to reduce the rate of constitutionally small babies being classed as IUGR (false positive rate) whilst helping to increase detection of pathologically small babies [9]. Using these customised growth charts it is estimated that IUGR is not only the single largest category of conditions associated with stillbirth [10] but may put the child at a five to seven fold increased risk of developing cerebral palsy [11]. Early recognition, leading to appropriate monitoring and timely delivery may potentially avoid some of the many still-births secondary to IUGR. Ultrasound is the ‘gold-standard’ for diagnosing IUGR. Although its accuracy is reduced by increased BMI it is probably less affected by the worldwide obesity epidemic than the simpler methods of screening for growth such as symphysis-fundal height measurement.

Serial monitoring of fetal parameters, notably abdominal circumference is undoubtedly helpful in both the diagnosis and management of IUGR as it allows an assessment of both the rate and consistency of fetal growth. Differentiating between symmetrical and asymmetrical patterns of IUGR may help diagnose growth restriction secondary to utero-placental insufficiency.

Once IUGR has been diagnosed, other ultrasound markers can be used to monitor for evidence of fetal compromise. These include the volume of amniotic fluid and the umbilical artery and ductus venosus Doppler waveforms. Assessment of the level of fetal compromise and the rate at which it is changing is often vital for planning delivery of an IUGR baby especially at very early gestations.

An accurate estimate of fetal weight may also be important especially when deciding the point of viability for very small babies. A recent systematic review of the available methods for estimating fetal weight [12] has highlighted that all the widely used formulas have large random errors which are exacerbated by inter and intraobserver error. The 95% confidence intervals exceeded 14% of birth weight in all studies and no technique was shown to be consistently superior. There is promising data appearing using 3-D volumetric analysis but this is currently of unproven clinical usefulness.

2.2. Magnetic Resonance Imaging (MRI)

When MRI was introduced 30 years ago the long image acquisition time made it highly susceptible to fetal movement artefacts. Development of ultrafast T2-weighted sequences has greatly increased its usefulness for fetal imaging. The advantage of MRI over ultrasound for imaging intracranial abnormalities is well recognised especially for brainstem, posterior fossa and neural tube anomalies [13].

MRI has also been shown to be of benefit in congenital thoracic malformations (such as cystic adenomatoid malformation and congenital diaphragmatic hernia). This is due to enhanced intra-thoracic tissue differentiation which enables measurement of relative volumes of normal and abnormal lung tissue as well as identifying the presence of fetal liver in the thoracic cavity. These are vital for counselling parents regarding the prognosis and potential benefits of any available in-utero treatments. MRI is also good at imaging bowel, with the high signal from meconium seen on T-1 weighted sequences making MRI “colonography” possible.

Other advantages of MRI include the fact that the images can be examined off-line by several readers whereas 2-D ultrasound images usually require real-time interpretation by the operator. The development of 3-D ultrasound is rapidly changing this but is not yet widely routinely used. MRI can also be useful in imaging the fetus of obese women. However, like ultrasound, there are also issues with extreme obesity including difficulty fitting inside the MRI unit and impaired image quality.

MRI is a useful adjuvant to ultrasound in prenatal diagnosis but is not yet poised to replace it. This is due to many issues including its lack of resolution, capability to accurately image the first trimester fetus, relatively short safety track record and greatly increased cost.

3. Minimally invasive techniques

3.1. Cell free fetal DNA (cffDNA)

The identification of cffDNA in the maternal circulation by Lo and colleagues in the late 90s [14] triggered an increase in research with the aim of developing safer, minimally invasive prenatal diagnosis. It arises from the placenta, is detectable from four weeks of gestation and is rapidly cleared after delivery. The majority of cffDNA is maternal with only 3 to 6% originating from the fetus. Difficulties with separating these means that applications have focused on detection of genetic material that should not be present in the mother such as Y chromosome sequences or rhesus D (RhD) in RhD-negative women [15].

Fetal Rh-D typing using cffDNA has now almost completely replaced invasive testing for determination of fetal blood group in

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<td>Anencephaly</td>
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<td>Encephalocoele</td>
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<td>Bilateral renal agenesis</td>
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<td>Anterior abdominal wall defects</td>
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<td>Renal dysplasia (unilateral)</td>
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<td>Holoprosencephaly</td>
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<td>Spina bifida</td>
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<td>Congenital diaphragmatic hernia</td>
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<td>Talipes</td>
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<td>Facial clefts</td>
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<td>Atrioventricular septal defect</td>
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<td>Tracheo-oesophageal atresia</td>
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the UK. Detection of other fetal blood groups has also been reported. Studies to investigate the clinical validity of using it to identify the fetal RhD type in all RhD negative women are underway.

Fetal sex determination using cfDNA may also be useful in pregnancies at risk of congenital adrenal hyperplasia as well as X-linked disorders. A recent national audit of the two UK laboratories offering the test showed a concordance rate of 97.8% between sex reported by cfDNA and sex confirmed by either invasive testing or determined at birth [15]. This was for samples taken after seven weeks of gestation. Samples taken before this time appear to be less accurate. However, there are concerns regarding the technology as the UK has yet to introduce national laboratory protocols and standards. Also, in some countries, fetal sex testing is being offered directly to the consumer which raises difficult ethical issues.

Using cfDNA to diagnose single gene disorders is problematic. There are reports of it being successful for paternally inherited autosomal dominant conditions such as Huntington’s [16] and some de novo point mutations but it is currently impossible to differentiate maternally-inherited fetal genetic material from the mother’s own cfDNA. Considerably more research is required before it will be useful for this. A novel method using cfDNA was recently described by Lo and colleagues for the diagnosis of Down’s syndrome [17]. Although the study only included 67 women, the test produced promising results with a sensitivity of 90% (95% CI 60.6–99.5%) and a specificity of 96.5% (95% CI 89.4–99.5%).

3.2. Pre-implantation genetic diagnosis (PGD)

For couples known to be carrying a genetic disorder, the process of invasive prenatal diagnosis and potential termination of pregnancy can be daunting and distressing. Many prefer the option of PGD which has been available for some conditions since the early 1990s. The process involves generation of embryos by in-vitro fertilisation (IVF) then sampling at the eight cell stage. The genetic analysis is carried out the same day and only unaffected embryos are transferred into the uterus.

The most common indications are chromosomal abnormalities, usually Robertsonian or reciprocal translocations, X-linked diseases and single gene disorders [18]. PGD has been successfully used for autosomal recessive disorders such as cystic fibrosis, autosomal dominant diseases including Huntington’s disease and X-linked disorders including fragile X syndrome and Duchenne muscular dystrophy. The number of disorders that can be tested for is rapidly increasing as worldwide expertise grows. As with any new treatment its safety and standards. Also, in some countries, fetal sex testing is being offered directly to the consumer which raises difficult ethical issues.

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The benefits of CVS mostly arise from the gestation at which it can be performed. This allows early diagnosis potentially reducing the amount of distress caused to the parents from waiting for a diagnosis, and enables them to have the option of surgical termination of pregnancy.

The risk of miscarriage from invasive testing is inherently difficult to assess as the procedure related risk must be separated from the background rate. This background rate is likely to be higher than that of the general population due to the indications for testing such as advanced maternal age and a high risk screening result. There have been no high quality randomised studies comparing CVS with no invasive testing. A Cochrane review concluded that the total pregnancy loss rate of transabdominal CVS was comparable to second trimester amniocentesis (Relative Risk (RR) 0.9 with 95% CI 0.66–1.23) although this was the result of just one study [24]. However, CVS is more technically difficult than amniocentesis so any risk must be considered in the context of operator experience.

4. Invasive techniques

All invasive techniques carry a fetal loss rate greater than the absolute background risk for that pregnancy. Therefore it is important that women are adequately counselled about the procedure including the risks, the reason it is being recommended and what the alternatives are. All invasive procedures must be accompanied by anti-Rh D immunoglobulin prophylaxis in Rh-D negative. Women with HIV should be counselled that the risks of mother-to-child transmission remain uncertain. Where it is contemplated, the advice of the fetal medicine specialist and HIV physician should be sought and prophylaxis is with HAART considered [22].

4.1. Chorionic villus sampling (CVS)

This is an invasive diagnostic procedure carried out after 10 weeks of gestation. CVS before 66 days was implicated in limb reduction defects in a study of 539 pregnancies. Although this finding was not substantiated by a later World Health Organisation review of 200,000 procedures, it is not recommended before this gestation [23]. In the UK it is most often used for karyotyping when first trimester screening suggests a high risk of aneuploidy. It may also be used for fetal DNA analysis if the parents are known to be carriers of an identifiable gene mutation such as cystic fibrosis or thalassaemia.

The procedure involves aspiration of trophoblastic tissue under continuous ultrasound monitoring. The transcervical route was reported to have a higher miscarriage rate in some randomised trials but this may be due to lack of operator experience [23]. In the UK the vast majority of operators use the transabdominal approach. The amount of tissue obtained is small but tissue culture failure requiring a repeat test is rare. The development of fluorescence in situ hybridisation (FISH) and highly sensitive polymerase chain reaction (PCR) has made rapid analysis possible. Parents are usually offered rapid testing for Trisomy 21, 13, and 18 and sex chromosome aneuploidy, then receive a full tissue culture karyotype later. Improved laboratory techniques ensure that errors in the results due to maternal tissue contamination have become extremely rare. However, evidence of placental mosaicism may be found in 1% of CVS samples. This is considerably greater than for samples from amniocentesis which may be offered to confirm the result.

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4.2. Amniocentesis

This requires taking a small sample of amniotic fluid transabdominally under ultrasound guidance usually after 15 weeks of gestation when it is safer and technically less demanding. This is demonstrated by a Cochrane review which indicates that the pregnancy loss after early amniocentesis (<15 weeks) was significantly higher than mid-trimester amniocentesis (RR 1.29; 95% CI 1.03 to 1.61) and the number of babies with talipes equinovarus was significantly higher in early group (1.3% versus 0.09%) [24].

A single randomised controlled trial provides the best available evidence of the actual procedure related risk of amniocentesis in low-risk women. This showed a statistically significant increase in spontaneous miscarriages of 0.8% (RR 1.60; 95% CI 1.02 to 2.52) [24]. This is in agreement with the review of 68,119 amniocenteses...
which reported an increase in the rate of pregnancy loss of only 0.6% (P = 0.0042; 95% CI, 0.19, 1.03) [25].

The laboratory techniques are similar to those used for CVS. The RCOG has produced advice for clinicians regarding consent for amniocentesis [26]. This states that experienced operators are likely to be successful at the first attempt 94% of the time. The technical difficulty is higher in obese women with a subsequent increase in the complication rate.

4.3. Percutaneous umbilical blood sampling (cordocentesis)

This invasive technique involves direct sampling of fetal blood from the umbilical cord, usually close to the insertion into the placenta. It has a much higher procedure related pregnancy loss rate than CVS and amniocentesis, estimated to be 3% in the low risk population and 7.2% in all cases [27]. It is now largely only performed for potentially lifesaving therapeutic in utero transfusion procedures in severe feto anaemia. It has been used to assess the fetal platelet count in severe cases of alloimmune thrombocytopenia, although this use remains somewhat controversial.

5. Conclusions

The development of highly sensitive and specific, minimally-invasive methods for detecting aneuploidy and structural abnormalities has undoubtedly led to a decrease in the number of invasive tests being carried out in the UK. As the safety of any invasive technique appears to be directly related to operator experience it could be argued that these tests should only be undertaken in specific centres by operators who perform enough to maintain their expertise.

All screening and diagnostic methods have their own specific risks and benefits. It is vital that adequate time and importance is given to exploring the parents understanding and expectations before any test is embarked on, no matter how ‘safe’ it is perceived to be.

6. Key guidelines

- All women contemplating any form of prenatal diagnosis should be adequately counselled about the risks, benefits and limitations of any test, and provided with non-directional written information.
- All women in the UK should be offered a first trimester screening test for Down’s syndrome with a 75% sensitivity for a 3% false positive rate and a ‘20 week’ scan for structural anomalies.
- Women at risk of having a baby with congenital heart disease should be offered an extra fetal echocardiogram at 21–24 weeks.
- The middle cerebral artery Doppler peak systolic velocity can be used as a non-invasive method for diagnosing of fetal anaemia.
- Serial ultrasound measurements are of undoubted use in monitoring fetal growth but all formulae currently used to estimate fetal weight are inherently flawed and may give errors up to +/−14%.
- MRI is a useful adjunct to ultrasound in prenatal diagnosis especially in the diagnosis of intra-cranial, intra-thoracic and gastrointestinal anomalies.
- Cell free fetal DNA testing has become widely established for the management of Rhesus disease and certain sex linked genetic disorders. With further research it is poised to offer much greater benefits in the field of minimally invasive prenatal diagnosis.
- Pre-implantation genetic diagnosis provides the opportunity for parents to avoid the distress of invasive testing and possible termination. However, the ethical and legal debate is set to continue for many years.
- CVS should not be performed before 10 weeks of gestation as it has been associated with limb reduction abnormalities. It appears to be safer if it is performed transabdominally rather than transcervically.
- Amniocentesis should not be performed at less than 15 weeks of gestation before this it is associated with greater risk of pregnancy loss and possible talipes in the fetus.
- In experienced hands CVS and amniocentesis both carry a similar procedure related risk of miscarriage of 0.5–1%.
- Percutaneous umbilical blood sampling is now limited to potentially lifesaving in utero transfusion procedures for severe feto anaemia.

7. Research directions

The field of cfDNA and PGD are already rapidly expanding and could both have profound implications on screening and prenatal diagnosis. It is important that healthcare professionals and policy makers alike remain up to date with advances to ensure that patients receive the best available care whilst minimising the risk of improperly implemented new technology.

References


