Invasive techniques for prenatal diagnosis and therapy

Peter W. Soothill, Kypros H. Nicolaides, and Charles H. Rodeck

Harris-Birthright Research Centre for Fetal Medicine, Department of Obstetrics and Gynaecology, King's College School of Medicine and Dentistry, London, U.K.

1 Introduction

The need for prenatal diagnosis of fetal disease in order to proceed to abortion or altered delivery management has stimulated the development of a range of techniques of fetal tissue biopsy. More recently, in utero therapy of some abnormalities has been possible such as direct blood transfusion for anemia or drainage of obstructed systems. Rapid improvements in ultrasound technology have not only increased the safety and success of amniocentesis, fetoscopy and placental biopsy but has also allowed the development of direct ultrasound guided techniques for fetal blood and tissue sampling.

Invasive procedures should only be performed when the benefits of the knowledge obtained outweigh the risks to the pregnancy. Such a decision can only be made in consultation with the parents and is affected by the prevailing moral views, as well as the safety, effectiveness and availability of the individual technique. Invasive procedures should only be performed after a thorough ultrasound examination to detect multiple pregnancy, fetal malformation and placental localization and confirm fetal viability and gestational age. Rhesus negative mothers should be given anti-D Ig G.

Accurate assessments of complications are difficult since only high risk pregnancies are offered invasive investigation. Spontaneous pregnancy problems are more common in this group and are likely to be attributed to the invasive test. Finding suitable control pregnancies is difficult while randomizing such patients is almost impossible.

In this article invasive methods of prenatal diagnosis and fetal therapy are discussed.

2 Techniques

2.1 Fetoscopy

Percutaneous, transabdominal, uterine endoscopy allows both the diagnosis of serious structural abnormalities, too small to be detected
ultrasonographically, and the visual guidance of fetal tissue biopsy [20]. Fetoscopy is done after 15 weeks' gestation; before this time the size of the uterus and amniotic fluid volume are too small for safe transabdominal entry. The most appropriate gestation depends on the procedure planned; for fetal examination orientation is easier with the smaller fetuses and clear amniotic fluid of 15—18 weeks, whereas fetal blood sampling is usually performed from 18 weeks onwards. After 20 weeks the amniotic fluid is cloudy but fetoscopy is possible until late in the third trimester.

By detailed ultrasound examination a site of entry can be identified which avoids damage to the placenta, umbilical cord or fetus but allows access to the fetal part being examined or biopsied. It is usually possible to find an area free of placenta even when the latter is anterior. Under sedation (which reduces fetal and maternal movements) and local anesthesia, a trocar and cannula (R. M. Surgical Developments, Croydon) is inserted transabdominally into the amniotic cavity using a full aseptic technique. A rigid fetoscope with fibre-optic illumination, such as the Olympus Selfoscope, then replaces the trocar (figure 1). It has a field of view of 55° and magnification, depending on distance from the object of up to 30 times. If required, a blood sampling needle or biopsy forceps can be passed through the side channel of the cannula.

No major maternal complications have been reported in over 6000 fetoscopies (8th International Fetoscopy Meeting, 1985). The risks to the fetus depend on operator experience; in centers which have performed more than 100 fetoscopies the fetal mortality is less than 5% and in the largest series it is about 2%. Morbidity includes preterm labor (8—10%), amniotic fluid leakage (10%) and amnionitis (0.5%).

### 2.2 Ultrasound-guided procedures

Ultrasound allows the inspection of internal anatomy. By scanning in each of the three dimensions the site of entry, direction and depth required to reach an intended location can be selected. When a needle is inserted its tip can be identified by placing a real time curvi-linear ultrasound-transducer parallel to it, allowing the needle to be followed or guided (figures 2, 3). Some operators prefer sector or linear-array scanners and we use either depending on the uterine size.

There is less experience of ultrasound guided biopsy than fetoscopy and its risks need further evaluation but reports of ultrasound guided cord blood sampling are very encouraging.

**Invasive procedures to aid fetal imaging** are being developed. The instillation of ultrasound contrast media, such as physiological saline solution, into the amniotic cavity in severe oligohydramnios or into the fetal peritoneal cavity for better definition of a renal abnormality may be useful (unpublished observations).

Figure 1. Olympus Selfoscope, trocar and cannula (R. M. Surgical Developments).
3 Prenatal diagnosis by fetal tissue biopsy

These techniques are restricted to patients at high risk as indicated by family history, advanced maternal age, abnormal maternal serum alpha-fetoprotein (MSAFP) or a structural abnormality detected by ultrasound scanning. A new indication may be suspected intrauterine hypoxia when estimation of fetal blood gas and acid-base status [16, 27, 28] may help to time the delivery.

The tissue that can give an accurate diagnosis as quickly as possible is the one selected for biopsy. This depends on the condition being investigated and each tissue is now considered in turn.

3.1 Amniotic fluid

Amniocentesis to diagnose inherited abnormalities is done at about 16 weeks gestation because the volume of amniotic fluid (150 — 200 ml) and concentration of viable cells is sufficient and the uterus is readily accessible transabdominally. The site of entry, direction and depth required to enter a pocket of fluid while avoiding fetal structures is identified. After antiseptic skin cleaning, a needle, usually 21 gauge, with or without a stillette, is inserted using a no-touch technique. Once through the skin it can be followed using real time ultrasound scanning to allow correction of the needle direction, if necessary, and to avoid a mobile fetus. The first 1 ml is discarded to avoid contamination with maternal blood and then 15 — 20 ml is aspirated.
Although amniocentesis is widely available its disadvantage is that it is done after 15 weeks and cytogenetic or enzymatic analysis requires cell culture which in practice takes 3 — 4 weeks resulting in much anxiety and a late termination of pregnancy in the event of an abnormality.

Amniocentesis can also be performed later in pregnancy to assess fetal lung maturity or the severity of rhesus disease and to diagnose amniotic infection. In the past it was used for amniography.

Three major collaborative studies on the risks of amniocentesis have been published. Two with a total of 2060 patients did not detect any increased risk after amniocentesis compared with matched controls or population data [13, 25]. One (2428 patients) found 1.7% more spontaneous abortions or stillbirths in the amniocentesis group [12]. However, the control group in the latter study had fewer pregnancy complications than expected.

### 3.2 Placental (chorionic villus) biopsy

Ultrasound guided placental biopsy can be done as early as 8 weeks gestation. Placenta has fetal genetic material and cytogenetic or DNA analysis potentially allows the diagnosis of any fetal genetic disease at an early stage of pregnancy. The rapid rate of cell division of this tissue means cytogenetic preparations can be made either directly [24] of following a short period of culture which allows a faster and earlier diagnosis than any other method. As the membranes are not punctured this may be the safest and quickest method of karyotyping at any gestation [17]. Although both blind and endoscopically guided placental biopsy have been tried, greater success in obtaining tissue with fewer complications has been found with ultrasound guided biopsy, either transcervically [30] or transabdominally [26].

A variety of instruments have been described for transcervical biopsy including polyethylene (Portex) or silver cannulae, biopsy forceps or endoscopes but the principle of passing the instrument through the cervix and into the placenta with ultrasound guidance is the same. The tissue obtained is examined microscopically and chorionic villi are identified and separated from decidual or blood contamination. For transabdominal placental biopsy a sector or curvilinear scanner is used to direct a guide-needle through the abdominal wall and uterus into the placenta [26]. A finer biopsy needle is then inserted through the guide needle and villi are aspirated with a syringe. Repeated insertions of the fine needle are possible if the sample is inadequate. This technique is particularly suitable for later gestational ages when the cervix is a long way from the placenta and it may also have a lower risk of introducing infection than transcervical biopsy. However experience with this method is limited and it requires further investigation.

The main short-term risk of this procedure is that of miscarriage which occurs in 2 — 5% of pregnancies. The “expected” miscarriage rate for a control population has not yet been accurately established. Whether there is an increase in longer term sequelae e. g. IUGR, abruptio placentae or malformation is not known either. Small fetoplacental haemorrhages have been detected by MSAFP assay in about 50% of patients [31].

### 3.3 Blood

Fetal blood is valuable for the diagnosis of a large number of disorders and can be used to clarify equivocal results from other tissues, for example when detailed banding is required or after failure of, or mosaicism in, amniotic fluid cell culture [21]. Vessels in the chorionic plate (placentesis) or umbilical cord, or the fetal heart can be punctured. The needle can be guided either by fetoscopy [18] or by ultrasound [5].

Placentesis involves multiple punctures of the chorionic plate to produce bleeding into the amniotic fluid which is then aspirated and checked for the presence of fetal cells. This procedure has the risk of producing excessive fetal bleeding and there is a 10% fetal mortality.
Furthermore, contamination with amniotic fluid or maternal blood may make diagnosis difficult.

By fetoscopy the umbilical cord placental insertion can be identified and the vessels seen through the Whartons' jelly. This site has the advantages that blood coming from a cord vessel must be fetal and that hemostasis is excellent. Pure fetal blood can be achieved in 100% of patients but a particle size analyzer (Coulter Channelyzer) should be available to provide confirmation.

For ultrasound-guided needling of the cord, the placental insertion is identified sonographically. An entry site is chosen so that the needle approaches the cord nearly parallel to the intended vessel. If the placenta is anterior, a transplacental route is easiest and does not puncture the membranes. With a posterior placenta, a transamniotic approach may be necessary and is usually more difficult. Initial results are very encouraging, with high success and low complication rates [6]. This technique is a quick, outpatient procedure and has been used for antepartum diagnosis of fetal asphyxia by measuring fetal blood gases in high risk pregnancy [16, 27, 28]. Furthermore by sampling placental lakes of maternal blood it has been possible to study placental transfer [29].

The fetal heart has also been used as a source of blood [1]. A 1.2 mm guide needle is directed into the fetal thorax and a 0.6 mm diameter needle is passed down this into the left ventricle. The technique does not appear to have harmful effects on the fetal heart but it also needs further evaluation.

### 3.4 Skin

Fetal skin is required for the prenatal diagnosis of severe skin diseases that do not effect other systems and cannot yet be identified at the gene level. The fetoscope allows precise identification of the area to be biopsied and selection of the type of skin desired (e.g. a hairy area, such as the scalp or eyebrows, for the diagnosis of oculocutaneous albinism). The specimen is immediately examined microscopically by an experienced histologist to ensure adequacy of the biopsy.

Biopsy forceps can be passed down the fetoscope cannula after removal of the endoscope and the biopsy guided by ultrasound. Special skin biopsy instruments have also been devised which are inserted transabdominally and guided by ultrasound to the fetal skin. The great advantage of ultrasound in being able to "see" through tissues is not useful in this procedure whereas the ability to see surfaces in great detail makes fetoscopy especially successful.

### 3.5 Liver

Some rare enzyme deficiencies of the urea cycle are expressed only in the liver e.g. carbamyl phosphate synthetase and ornithine carbamyl transferase (OCT). They can be diagnosed prenatally using fetal liver [23], although a gene probe is available for some cases of OCT deficiency. By fetoscopy the right nipple and umbilicus are identified and a point half-way between these is chosen. A needle is inserted subcostally into the liver, strong suction is applied and the needle withdrawn, obtaining a core of tissue.

Similarly an ultrasound guided method has been described [9]. Ultrasound scanning allows identification of the needle tip within the liver.

### 3.6 Urine

When an obstruction of the fetal urinary system is detected by ultrasound examination, further investigation should include an assessment of residual renal function. A needle can be guided by ultrasound into the fetal bladder and urine aspirated for biochemical analysis. Furthermore after emptying the bladder the rate of refilling can be observed by serial ultrasound examinations. This information helps decide whether a vesico-amniotic shunt would be beneficial.
3.7 Tumors

Similar techniques to those for liver biopsy can be used for fetal tumors. We have diagnosed type 3 cystic adenomatoid malformation of the lung by ultrasound guided fetal lung biopsy at 20 weeks’ gestation.

4 Fetal therapy

When the diagnosis of a potentially reversible or treatable fetal abnormality is made, the delivery should be in a specialist center. To prevent further damage or fetal death in utero due to a progressive lesion early delivery for surgery or therapy may be indicated. If the fetus is too premature for delivery in utero treatment may be considered. This should only be undertaken after exclusion of associated structural or chromosomal abnormalities and after demonstration that the primary lesion or its secondary effects are indeed progressive and that residual function compatible with postnatal life remains. Parents should be fully involved and warned of range of possible outcomes.

4.1 Blood transfusion

Severe rhesus isoimmunization can cause fetal anemia, hydrops fetalis and intrauterine death before the fetus is capable of extruterine survival. Ultrasound scanning to time, guide and follow-up fetal transfusion and for monitoring during and between transfusions has greatly improved the prognosis of severely affected fetuses and has replaced the original X-ray techniques. Blood can be given into the fetal peritoneal cavity (IPT) [10] or intravascularly (IVT) [19]. A pure fetal blood sample is obtained using the methods described earlier and the fetal hemoglobin concentration and blood group determined and a direct Coomb’s test performed. An empirical but safe estimate of the volume of blood to be given intraperitoneally is [7]:

\[(\text{gestation in weeks} - 20) \times 10 \text{ ml}\]

Recently the volume of blood required for IVT has been calculated from previously obtained data on the feto-placental blood volume [14] and the donor and fetal hematocrits.

4.1.1 Intraperitoneal transfusion

Under sedation and local anesthesia a 16-gauge Tuohy needle is inserted into the uterus so as to allow access to the antero-lateral aspect of the fetal abdomen. A linear-array, real-time ultrasound transducer is aligned so as to identify the needle-tip and fetal abdomen. The needle is inserted into the peritoneal cavity between the umbilicus and bladder and any ascites aspirated. The needle position is confirmed by a 4—5 ml injection of isotonic saline and then packed adult blood, compatible with the mothers’, is injected through the needle at a rate of 3—5 ml/min. IPT can also be performed with combined fetoscopic and sonographic guidance by passing a 21 gauge Tuohy needle (R. M. Surgical Developments) down the side arm of the fetoscope cannula. This may be done, after a fetal blood sample has been taken, when the amniotic fluid is very cloudy, in early pregnancy (eg. < 20 weeks), or when a large volume of blood is required, in combination with IVT.

4.1.2 Intravascular transfusion

After fetal blood sampling with fetoscopic or ultrasonic guidance (for hematocrit estimation with a Coulter Channelizer) the needle tip is kept in the lumen of the vessel and donor blood is injected at a rate of 1—3 ml/min, while observing the fetal heart continuously with ultrasound. The aim is to achieve a final fetal hematocrit of 35—45% and this is checked by aspirating a post-transfusion sample. There is much greater experience of this technique by fetoscopy [22]. Exchange transfusion has been performed fetoscopically before mid-trimester abortion [11] but the risk to continuing pregnancies seems to be greater than “top-up” transfusion.

Alternative methods of IVT include ultrasound-guided puncture of the intrahepatic umbilical vein [2] or fetal heart. Experience with
4.1.3 Albumin infusion

Fetuses with non-immune hydrops have very low blood albumin concentrations [15] and it has been suggested that the low oncotic pressure increases the loss of fluid from the vascular compartment. We have given albumin infusions to several fetuses but the results need further evaluation.

4.2 Drainage procedures

Obstruction of fetal systems can cause dilatation and damage to both the primary organ and the adjacent structures. By-passing the obstruction and reducing the pressure may prevent further damage until delivery when more definitive surgery is possible. These procedures are only helpful if there is no major untreatable abnormality and if useful residual organ function remains.

4.2.1 Obstructive uropathy

Complete obstruction of the urinary system from an early gestation leads to renal dysplasia and absence of renal function. Incomplete or late onset obstruction may allow good renal development but still compromise renal function to a degree that depends on the duration and completeness of obstruction. Renal parenchymal thickness and consistency, assessed ultrasonographically, and urine biochemistry can help to estimate residual renal function [21].

Experimental work suggested that relief of obstruction in utero was beneficial [8] and subsequently suprapubic insertion of a vesico-amniotic shunt was performed in several centers. A cannula (Rocket of London) is guided into the distended fetal bladder by ultrasound. Through this, a double “pig-tail” catheter is introduced so that one end curls up inside the bladder and the other outside the fetal trunk in the amniotic cavity. Urine is thus released, amniotic fluid is formed, and the secondary complications of both renal damage and oligohydramnios can be reduced in some cases.

4.2.2 Obstructive hydrocephalus

High-pressure ventricular dilatation causes brain damage. After delivery, ventricular shunting limits further structural damage and may improve the prognosis. If prematurity prevents delivery and there is sonographic evidence of increasing ventriculomegaly, in utero drainage could be beneficial.

Repeated ultrasound guided cerebro-spinal fluid (CSF) aspiration (encephalocetesis) has been attempted but ventricular dilatation still
occurred because of rapid reaccumulation [3]. Ventriculo-amniotic shunts, with a one-way valve allowing CSF out of the brain, have been inserted under ultrasound guidance [4]. Reduction in ventricular dilatation has been achieved but follow-up developmental studies have been discouraging (Fetal Surgery Registry 1986) and major problems have been experienced in maintaining shunt patency and position.

4.2.3 Pleural effusions

Fetal pleural effusions can occur as part of generalised hydrops fetalis or as an isolated abnormality (chylothorax) and prevent expansion and development of the fetal lung. A pleuro-amniotic shunt can be inserted with ultrasound guidance using similar equipment to that described for bladder catheterization. We have now treated four such fetuses in this manner and in one, associated generalized hydrops was reversed. Post-natal outcome in these babies has been excellent.

4.2.4 Cyst aspiration

Large fetal cysts occur as an isolated abnormality or as part of a syndrome (e.g. cystic hygroma in Turner's syndrome). Pressure effects or obstruction at delivery may be prevented by needle puncture and aspiration.

4.3 Drug therapy

Fetal drug therapy such as digoxin in hydrops fetalis or anti-arrhythmic agents for fetal cardiac arrhythmias is usually administered across the placenta through the mother [32]. Substances that are not adequately transferred may be injected into the amniotic cavity or directly into the fetal blood stream. For resuscitation of previable fetuses with reversible causes of cardiovascular collapse transplacental therapy is too slow. We have successfully administered adrenaline, calcium and atropine directly to fetuses when cardiac arrest occurred during an invasive procedure such as blood transfusion (unpublished).

Keywords: Fetal therapy, fetal tissue biopsy, fetoscopy, prenatal diagnosis, ultrasound guided needle biopsy.

Zusammenfassung

Invasive Techniken zur pränatalen Diagnose und Therapie

Bei der Fetoskopie wird ein Endoskop transabdominal in die Amnionhöhle vorgeschoben und somit die Diagnose kleiner struktureller Defekte sowie die Biopsie von fetalem Gewebe unter Sichtkontrolle ermöglicht. Mit Hilfe des Ultraschalls wird der Zugang so gewählt, daß sich das Endoskop an dem fetalen Abschnitt, der untersucht oder biopsiert werden soll, befindet und eine Verletzung der Plazenta, der Nabelschnur oder des Feten vermieden wird.


sous contrôle échographique est le même. Pour la biopsie placentaire transabdominale on introduit une aiguille à travers la paroi abdominale et l'utérus dans le placenta. Cette méthode est particulièrement adaptée pour les âges gestationnels plus tardifs et elle présente un risque moindre d'introduire une infection que par la voie transcervicale. Nous avons récemment montré que l'on peut réaliser le caryotype sur les tissus placentaires pour toute grossesse.

Le sang fœtal est obtenu par ponction du cordon ombilical au niveau de son insertion placentaire. On peut localiser l'insertion du cordon par fœtoscopie ou par échographie, et on introduit l'aiguille dans un des vaisseaux. Pour le diagnostic prénatal de certaines affections cutanées graves il faut de la peau fœtale. On peut faire passer la pince à biopsie dans le canal latéral du fœtoscope. Certains déficits enzymatiques rares du cycle de l'urée ne s'expriment qu'au niveau hépatique. On introduit une aiguille en sous-costal dans le foie et par aspiration on obtient un fragment tissulaire.

Thérapeutique fœtale: Pour les transfusions intrapéritonéales (IPT) on introduit dans l'utérus puis dans l'abdomen fœtal, entre l'ombilic et la vessie, une aiguille de Tuohy de calibre 16, sous contrôle échographique. On injecte du sang adulte, compatible avec la mère, au rythme d'environ 3 à 5 ml/min. Les transfusions intra-vasculaires sont réalisées après prélèvement de sang fœtal par fœtoscopie ou sous contrôle échographique, l'extrémité de l'aiguille laissée en place dans la lumière vasculaire, on injecte du sang de donneur. Le but est d'obtenir à la fin un hématocrite fœtal de 35—45%. Nous avons réalisé des perfusions d'albumine chez des fœtus avant la viabilité à l'aide d'adrenaline, de calcium et d'atropine en intraveineux ou intra-musculaire, lorsque les concentrations d'albumine plasmatique étaient très basses.

Techniques de drainage: Certains fœtus présentant une uropathie obstructive peuvent bénéficier d'un drainage intra-utéro. On introduit dans la vessie distendue sous contrôle échographique une canule à travers laquelle on fait passer un cathéter doubleConverter (de cocoon) de telle sorte que l'une des extrémités forme une boucle à l'intérieur de la vessie et l'autre dans l'utérus. On peut installer des shunts pleuro-vasculaires en utilisant un matériel similaire au cœlome pédiatrique. On peut aspirer les kystes fœtaux volumes pour éviter une compression ou un obstacle lors de l'accouchement.

Treatments médicamenteux: On a essayé d'administrer des médicaments directement au fœtus quand ils ne traversent pas le placenta de façon adéquate ou quand le transfert est trop lent. Nous avons réanimé avec succès des fœtus ayant la viabilité à l'aide d'adrénaline, de calcium et d'atropine en intraveineux ou intra-musculaire lorsque survient un collapsus cardio-vasculaire au cours des techniques invasives.

Mots-clés: Biopsie à l'aiguille écho-guidée, biopsie de tissus fœtaux, diagnostic prénatal, fœtoscopie, thérapeutique fœtale.

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Peter W. Soothill, BSc, MBBS
Harris-Birthright Research Centre
for Fetal Medicine
Department of Obstetrics & Gynaecology
King's College School of Medicine and Dentistry
Denmark Hill
London SE 5 8 RX, U. K.