Current state of antenatal in utero surgical interventions

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Antenatal ultrasound scanning has facilitated the prenatal diagnosis of many fetal anomalies. The improved understanding of fetal pathophysiology, combined with increased accuracy of fetal diagnosis and knowledge of the clinical postnatal outcome, have culminated in the development of fetal treatment. This is usually considered when a potentially life threatening and/or disabling, but correctable, condition is diagnosed antenatally. The decision for fetal surgical intervention carries with it the potential of dual mortality (mother and fetus).[1–5]

Fetal anomalies can adversely affect the mother by causing hypertension, oedema, and pulmonary failure. The condition, known as the maternal mirror syndrome, may prove fatal but appropriate fetal intervention can save the life of the mother. This syndrome has been reported in cases of antenatally diagnosed sacrococcygeal teratoma and cystadenomatoid malformation of the lung.

The decision to undertake fetal intervention must be the prerogative of the mother. A clear explanation of the risk of survival and quality of life of the fetus with and without surgical intervention is essential.[5] Maternal informed consent includes the risk of fetal intervention to the mother, although there have been no reported maternal deaths from open fetal surgery.[7–9]

Fetal interventions

NEEDLE ASPIRATION

Ultrasound guided percutaneous sampling of blood, urine, pleural effusion and hydrocephalus have been established since 1983.[10–13] Exchange transfusion via the umbilical cord is the standard treatment for haemolytic disease caused by Rhesus incompatibility. Diagnostic bladder aspiration and fetal urinalysis are undertaken to determine the severity of renal damage in obstructive uropathy. Fluid collections can be identified and aspirated under fetal ultrasound guidance. Ovarian cysts have been needled, perhaps unnecessarily, and large exophytic sacrococcygeal teratomas have been aspirated to facilitate delivery.[13–15] The rate of fetal loss after these aspirations has not been determined, but is probably similar to that following amniocentesis—around 0.5%.[15]

FETO-AMNIOTIC SHUNTING

Insertion of double J stents under ultrasound guidance has been used to relieve compression of normal developing tissues by fluid collections and cystic structures. The procedure is performed under local anaesthetic for a number of specific conditions. The most common indications are lower urinary tract obstruction, pleural effusions, and cystadenomatoid malformation of the lung.[16–19] Although

these shunts may drain the fluid effectively, improved survival following these interventions has been difficult to prove.[11] There is a direct fetal loss related to the procedure of 8-10%. Over one third of the shunts fail to function, with a blockage rate of 10-15% and dislodgement rate of 20-30%.[20] Other reported complications of feto-amniotic shunting include iatrogenic abdominal wall defects and maternal amnio-peritoneal leaks.[19–23] The benefit of feto-amniotic shunting remains unproved.

OPEN FETAL SURGERY

Open fetal surgery has been performed in several centres during the past decade. The aim of the surgery is to replicate the neonatal operations on the fetus. The surgical procedures that have been performed most commonly in the fetus include correction of congenital diaphragmatic hernia, resection of cystadenomatoid malformation of the lung, vesicostomy and excision of large sacrococcygeal teratomas.[9]

These highly specialised operations require a team approach. Surgery is performed at 24-30 weeks gestation under general endotracheal anaesthesia and through a classic mid-line hysterotomy which avoids the placenta.[23] A major disadvantage of this approach is that the surgery is performed on a stressed fetus as the amniotic fluid is removed and the fetus exposed to the operating theatre environment. Consequently, the attendant fetal mortality following open fetal surgery is high and can reach 50%.[24] Small centres attempting one to two cases have reported high fetal operative death rates.[8] The Fetal Surgical Centre in San Francisco has the widest experience and after 15 years of open surgery, the unit is now abandoning most open fetal operations.[9 25 26]

The maternal morbidity related to a large classic caesarean section is high.[26] Premature labour, which occurs in virtually all cases (or is almost inevitable), is often difficult to control. Amniotic fluid leaks occurred in 15% of the 47 cases reported from San Francisco.[26] Uterine disruptions and blood transfusions in subsequent pregnancies have been reported, but subsequent fertility does not seem to be affected.[26]

Although it is difficult to assess the benefits of open fetal surgery, the success has been limited at best. It is likely that at least some of these fetuses would have died in utero had an open fetal repair not been performed. The natural history of some conditions operated on in utero is still unknown. Long term follow up of survivors of fetal surgery has revealed a 21% incidence of severe central nervous system injury, which may be attributable to hypoten-

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sion during the surgical intervention, fetal exposure during the operation, or to drug treatment given to the mother.[27]

FETAL ENDOSCOPIC SURGERY

Direct endoscopic visualisation of the fetus was first described by Westin in 1954.[28] Since then fetoscopy has developed into a safe and reliable procedure with a similar fetal risk as amniocentesis.[16] The main problem is the limited vision allowed by the viscous and debris filled amniotic fluid. The development of fetal endoscopic surgery is a natural progression in fetal intervention and carries two distinct advantages: it avoids the maternal morbidity associated with a large hysterotomy and substantially reduces the stress to the fetus during the procedure.[29]

Simple endoscopic (visually guided) interventions have been performed on the fetus for several years.[30] Procedures such as diagnostic endoscopy and interventions which require application of high frequency electrocoagulation are carried out through one or two ports. Even these simple interventions are difficult in a mother with oligohydramnios.[31]

The execution of more complex fetal endoscopic operations relies on technological developments related to ancillary devices, dedicated instrumentation, and miniature optical systems. There is considerable scope for technological research and developments to establish safe and effective endoscopic operating systems. There are a number of considerations.

Safe uterine access
The insertion of trocar/cannulae (access ports) into the uterus has, to date, been performed by laparotomy and delivery of the uterus.[2] The use of the optically guided cutting ports developed for adult human laparoscopic surgery, such as the optical scalpel[32] and the disposable Visiport (USSC, Norwalk, CT, USA), may well avoid the need for laparotomy because these systems should permit safe entry into the maternal peritoneal cavity and through the uterine wall until the amniotic sac is reached.

Following open exposure of the uterus, sharp tipped trocar/cannulae can be inserted under ultrasound control.[25][33] The potential complication of this closed technique is stripping of the amnion and chorion from the uterine wall, creating a placental abruption. For this reason, Luks and Deprest recommend port insertion using the open technique.[33][34] The use of radially expanding ports which initially surround a thin Veress type needle should permit safe closed insertion of instrument ports.

Creation of intrauterine work space
Even a small oligohydramniotic uterus can be expanded to twice its volume to permit the creation of an adequate work space. The techniques are twofold: insufflation of gas and amnio-infusion of crystalloid solution.

Gas insufflation—the initial animal models for fetal endoscopic surgery used carbon dioxide insufflation at pressures of 5-10 mm Hg and this facilitated clear vision and the use of

monopolar high frequency electrosurgery.[35] There are, however, several disadvantages. Placental-uterine separation in sheep can occur at a pressure of > 5 mm Hg.[36] Carbon dioxide insufflation causes fetal acidosis and may induce fetal hypothermia and dehydration.[29][37] Maternal gas embolism is also possible. Some of the adverse effects on the fetus can be prevented by warm CO_2 insufflation and good anaesthesia, with monitoring of the end tidal pCO_2. Currently, however, gas insufflation of the uterine cavity with CO_2, nitrous oxide, and other inert gases is generally considered unsafe for fetal endoscopic surgery.[33]

Amnio-infusion—intrauterine infusion of warm Hartmann's crystalloid solution at low pressures (2-3 mm Hg) is safe in both sheep and humans.[29] Hartmann's amnio-infusion provides adequate vision, prevents fetal acidosis, hypothermia and dehydration during the procedure and permits the use of bipolar high frequency electrosurgery. It is currently the recommended technique for providing a safe working space.[33] Solutions such as glycine and sorbitol which are electrolyte depleted are potentially toxic to the fetus.[20] It should be possible to develop a pressure controlled isothermically heated closed amnio-infusion system which permits precise thermal control as well as allowing frequent exchanges to maintain a clear view throughout the intrauterine operation.

Optical and instrument ports
There is considerable scope for development of the existing trocar/cannulae systems for fetal endoscopic surgery as the current laparoscopic versions can cause chorio-uterine separation and leak amniotic fluid, especially when amnio-infusion is started. Luks has designed fetal ports with an intrauterine balloon to prevent dislodgement and minimise leakage.[29] These are similar to existing balloon tipped disposable cannula for adult laparoscopic surgery. The ideal configuration of ports should be based on the radial expansion system already developed for adult laparoscopic surgery. These are inserted in the collapsed mode around a fine Veress type needle and then expanded to the desired diameter commensurate with the size of the instrument (3-10 mm). These radially expanding ports would have to include a distal balloon proximal to the tip to prevent dislodgement.

Telescopes, endocameras, and light sources
In most instances 5 millimetre, zero to 30 degree rigid Hopkins rod lens telescopes have been used for fetal endoscopic work. There is considerable scope for improvement—for example, use of the new rigid quartz rod mini-telescopes (2-3 mm), flexible miniscopes (1-2 mm) and operating telescopes which include an instrument channel. In most instances the telescope can be coupled to a high resolution charged couple device (CCD) camera. Endoscopes are currently available which incorporate the CCD (chip on stick technology), although these are about 10 mm

in outer diameter which is too large for intra-uterine fetal procedures.

The choice of light source is between the xenon and the halide. All available light sources heat up the end of the telescope due to fibre mismatch and the infrared component of the white light (despite the filtering within the light source). In experiments carried out in Dundee this averages 70° at the end of the telescope in room air.[38] This temperature risk is likely to be less in the amnio-infusion system where the tip of the telescope is submerged in Hartmann's solution, although specific experiments to measure the temperature rise with time are needed. There is also the theoretical concern that a high intensity light within the uterine cavity may damage the fetal eyes.

Instrumentation and ancillary equipment
The development of specific instrumentation for fetal endoscopic surgery is an obvious requirement. The instruments have to be fine in calibre and preferably multifunctional to reduce instrument traffic and the number of ports required. Use of nickel/titanium alloy shape memory components will overcome some of the problems related to the miniaturisation of instruments. Coaxial microinstruments with a blunt nose seem to be the logical choice.[39] Haemostasis is achieved by high frequency electrosurgery. Monopolar high frequency electrosurgery is unsuited to fetal intrauterine procedures because of the risks of current leakage and capacitance coupling.[29] The latter only arises if a metal port is isolated from the uterine wall and the abdominal parities by a non-conducting fixation device. The Leuven team have designed a specific microbipolar generator for fetal surgery.[33] The high frequency generators for endoscopic fetal surgery should ideally be microprocessor controlled with sensor feedback from the electrode-tissue interface to the generator, to ensure the lowest energy needed for both cutting and coagulation.[40 41] Gas vapour lasers, such as the YAG system (Wv = 1066nm) and excimer laser, have been used in humans for endoscopic fetal vesicostomy.[42 43] There is justifiable concern about the potential damage to fetal eyes from the collimated laser light. The gas vapours are also bulky, require three phase electricity, and a pressurised water supply. The new generation of solid state diode array lasers, such as the Diomed laser, which outputs light at 750 nm, overcome most of these problems and are virtually maintenance free. These solid lasers may be useful for some fetal work in the future, although their advantages over microprocessor controlled high frequency electrosurgical systems remains to be established.[39]

FETAL MONITORING
Prolonged and complex operations performed on fetuses require accurate fetal monitoring. This can be achieved by placing a pulse oximeter and temperature probes on the fetus once they have been introduced into the amniotic cavity.[29 44] The development of ultrasound scans with Doppler imaging for the monitoring of the fetal cardiovascular system during interventions would be an advance. The use of flexible high resolution (7.5 mHz) linear array endoscopic probes similar to those used in adult laparoscopic surgery will permit better definition of the abnormal anatomy of the fetus and may allow precise ultrasound guided interventions to be carried out on specific organs and lesions.

Specific morbid conditions requiring fetal surgery

CONGENITAL DIAPHRAGMATIC HERNIA (CDH)
This carries a mortality of up to 70% due to the severe pulmonary hypoplasia.[44] It is difficult to predict mortality in the fetus: polyhydramnios is a poor prognostic indicator while gestational age at diagnosis, lung:thorax ratio, and stomach in the chest are not predictive. In utero repair should prevent the pulmonary hypoplasia encountered at birth by allowing lung development and growth. Several centres have attempted open fetal surgery with mixed success. The San Francisco group reported four live babies out of 14 in utero open repairs.[45] One third of the fetuses died during the repair. The main technical problems reported by Harrison *et al* are the presence of a friable liver within the chest, fetal distress, and postoperative premature labour. Alternative surgical strategies using the open fetal approach involve the creation of an artificial gastroschisis or using a thoracic silo.[46–49] A more logical, effective, and safer means of treating CDH in the fetus consists of tracheal occlusion. This important experimental advance arose from the observation that congenital laryngeal atresia is accompanied by enlarged fluid filled hyperplastic lungs.[50 51] Fetal lungs normally produce fluid that flows through the upper airway into the amniotic fluid. Thus occlusion of the tracheal lumen in fetuses with CDH, as a result of obstructing the flow of lung fluid, may expand the lung and displace the viscera back into the abdomen. Experiments in lambs and rabbits have confirmed this phenomenon.[51–54] The studies showed that plugging the upper airway (by tracheal ligation) reduces the abdominal viscera from the chest, accelerates fetal lung growth, and improves oxygenation and ventilation after birth.[55] It should be possible to block the lumen of the affected lung by an endobronchially placed pressure controlled valve, and this approach is eminently feasible in the human fetus with a flexible mini-bronchoscope.

CONGENITAL CYSTADENOMATOID
MALFORMATION (CCAM)
CCAM covers a spectrum of solid and cystic congenital lung abnormalities. Large lesions in the chest can prevent lung growth and cause polyhydramnios, hydrops, and the maternal mirror syndrome.[56] Despite this, up to 25% of large lesions detected antenatally disappear during the third trimester.[57 58] The San Francisco group reported four survivors from six attempted fetal CCAM resections.[59] Most centres would consider fetal hydrops as the indication for in utero lung resection.

SACROCOCCYGEAL TERATOMA

This large benign cystic lesion is a rare tumour that may cause in utero death by its mass effect and is associated with polyhydramnios and the development of the maternal mirror syndrome. Large tumours can obstruct labour or rupture during delivery. Sacrococcygeal teratomas are usually cystic and simple needle aspiration is complicated by recurrence.[15] All three reported attempts at open in utero resection have resulted in fetal death.[26] With the development of appropriate technology, endoscopic in utero resection of these tumours should be possible, although extraction of the tumour will require special technical considerations.

ABDOMINAL WALL DEFECTS

Exomphalos diagnosed antenatally is often associated with major congenital anomalies including trisomy, cardiac disease, Beckwith-Wiedemann syndrome and hypothyroidism. Termination is often performed with early diagnosis, and no antenatal surgical intervention has been attempted.[60]

Gastroschisis is an isolated second trimester defect consisting of herniation of intestines into the amniotic fluid through a small right sided abdominal wall defect. The condition is diagnosed prenatally by a raised α feto-protein and visualisation of the lesion on ultrasound scanning. The exteriorised bowel may become atretic (10%) and its exposure to the amniotic fluids cause thickening/hyperplasia of the intestinal smooth musculature. These fetuses are likely to be growth retarded and develop in utero stress.[61] Up to 10% die in utero and over half of the fetuses with dilated small bowel (>11mm) require emergency caesarean section for fetal distress.[62] Some of these babies also die after birth. They also have an increased risk of developing necrotising enterocolitis. Multiple operations may be required and prolonged parenteral nutrition is common. Percutaneous amnio-exchange in chick embryos can reduce the small bowel thickening by diluting the amniotic fluid.[53] Gastroschisis has been created in fetal lambs of 80 days gestation using hysterotomy and endoscopic techniques. Small bowel dilatation took 20 to 25 days to develop in an experimental model created in the fetal lamb at 80 days gestation.

Experimental open fetal surgery carries a mortality approaching 50% and is not recommended. Endoscopic in utero correction of gastroschis has not yet been developed and is unlikely to alter survival.

FETAL OBSTRUCTION UROPATHY

Congenital urinary anomalies are commonly detected during antenatal ultrasound scanning. The indication for intervention is severe urethral obstruction with bilateral renal dysplasia and oligohydramnios. Fetal bladder aspiration is performed to assess urinary sodium, chloride, and osmolality. If this demonstrates adequate renal function in the presence of obstruction, bladder decompression is indicated.[20] It has been difficult to prove, however, that bladder drainage alters postnatal renal function. This was originally performed by vesico-amniotic shunting using a double J stent, but is attended by a high failure rate. More recently techniques have been developed for in utero vesicostomy. This type of open fetal intervention has been performed in seven fetuses with six subsequent live born deliveries and four long term survivors.[11 20] Endoscopic vesicostomy is a safer alternative. Harrison's group have successfully placed wire mesh stents using CO_2 insufflation in lambs and monkeys.[35] MacMahon used a YAG laser under vision with a 5 mm telescope to create a vesicostomy in three human fetuses.[42] The laser vesicostomy lasted about six weeks before spontaneous closure, but this was sufficient to restore renal function to normal. Creation of a fetal vesicostomy permits subsequent fetal cystoscopy and this technique has been performed in 11 cases.[64] Definitive treatment of posterior urethral valves should eventually be feasible with this approach.

SPINA BIFIDA

Most neural tube defects diagnosed antenatally by ultrasound scanning are terminated. Recent experiments in fetal lambs have indicated that the neurological defect associated with spina bifida is related to the exposure of the neural tissue to the amniotic fluid.[65] In utero correction of the defect at an intermediate stage in lambs has shown near normal neurological function.[66] These experiments have been performed using the open fetal surgical technique. The timing of the repair seems to be critical for avoiding neurological deterioration. Spinal closure during mid-pregnancy seems to be the best time for intervention and should become technically possible with fetal endoscopic surgery.[67]

FETAL WOUND HEALING

Wounds heal without scar formation in the fetus. The mechanisms of wound healing and repair process are completely different from those observed in postnatal life.[68] The change from fetal to "adult" healing occurs late in gestation. The fetal healing/repair process is characterised by the absence of the inflammatory (lag phase) of healing encountered in postnatal life.[69] Inflammatory mediators, including transforming growth factor β and platelet derived growth factor, are virtually absent.[69] The extracellular matrix has a very high content of hyaluronic acid which accelerates cell migration and regeneration.[70] Collagen deposition occurs in an organised way with well configured and orientated bundles quite dissimilar to the disorganised pattern with subsequent remodelling seen in the adult. Wound contraction does not occur. As a consequence of all these changes, fetal wounds in mid-gestation heal without scarring. All these changes can be demonstrated in a serum and amniotic fluid free environment, indicating that this distinctive healing/repair process is intrinsic to fetal tissues.

CLEFT LIP AND PALATE

Scar formation following the postnatal correction of cleft lip and palate leads to abnormal soft

tissue, bone, and dental growth.[71] Correction of these deformities in utero would result in scarless surgery and avoids the complications of postnatal repair.[72] Lamb models of cleft lip and palate have been developed and these defects have been repaired successfully by both open hysterectomy and with the closed endoscopic approach.[73] The timing of the repair influences the degree of scarring. When the repair is carried out in lambs after 112 days of gestation (145 = full term), adult scarring is demonstrated both clinically and histologically.[74] By contrast, midgestation correction results in scarless healing. Once the endoscopic techniques have been developed, closure of the cleft lip should prove relatively simple and safe.[75]

Conclusions

Fetoscopy is a safe and well established procedure. Needle aspiration of the fetus may aid diagnosis, but is rarely therapeutic. Fetoamniotic shunting is unreliable and hazardous. Open fetal surgery through a generous hysterotomy, though possible, is accompanied by an unacceptable fetal mortality and maternal morbidity. Close fetal endoscopic surgery is the only viable option. The development of safe access amnio-infusion based systems and the related instrumentation and technology to permit closed fetal intervention will ensure the in utero correction of at least some of the congenital defects which are compatible with otherwise normal growth and development. Experimental fetal surgery is necessary for this objective but, it should also provide models for basic research into the pathophysiology of fetal maldevelopment.

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