Implementation of Open Fetal Surgery for Spina Bifida in the UK

Thesis presented for the degree of MD(Res) in the Faculty of Maternal and Fetal Medicine, University College London

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Signed Declaration

‘I, Adalina Sacco confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.'

Acknowledgements

I would like to thank my supervisors Professor Donald Peebles and Professor Anna David for giving me the opportunity to pursue this MD. I am enormously grateful for their support and guidance, and also for their willingness to step back and allow me to try to tackle things myself, whilst waiting in the wings in case I needed help.

I would also like to thank Professor Jan Deprest for his unwavering belief in me and for the warm welcome I have received in his department and home. If I am only half of the brilliant researcher, dedicated doctor and genuinely good person that he is by the end of my career then I will be happy.

By far the best part of this project has been the patients I have met and travelled some of their journey alongside. I have learnt something from every single one of them and am grateful for their trust and confidence in me. I am also grateful to the extensive fetal surgery team at UCLH, GOSH and UZ Leuven for all their help and obliging, and to all the extra people who have assisted me without recognition.

My family are my constant support and truly deserve my thanks (and to see me a bit more frequently!), as do Dr Hannah Tharmalingam and Dr Rosie Townsend, both of whom started parallel journeys with me two years ago and have kept me sane throughout.

Finally I would like to dedicate this thesis to my dear friend Dr Kirsty Paterson, who loved fetal medicine long before I did. I am constantly aware that I am living the life that you wanted. I will try to make it a good one for you.

Abstract

Spina bifida is a congenital neurological condition with lifelong physical and mental effects. Open fetal repair of the spinal lesion has been shown to improve hindbrain herniation, ventriculoperitoneal shunting rates, independent mobility and bladder outcomes for the child and, despite an increased risk of prematurity, does not seem to increase the risk of neurodevelopmental impairment.

We proposed to set up a fetal surgery centre in London, as a joint venture between UCLH and GOSH in collaboration with UZ Leuven, Belgium. Implementation of this treatment option for patients from the UK and Republic of Ireland has been the subject of my two year project.

I performed an initial review of existing global centres to establish what was already available, which techniques were being used and to confirm that a centre was required in the UK. I also conducted a systematic review into maternal outcomes of this and other fetal surgery, as this appeared to be a neglected area. This demonstrated the maternal morbidity associated with fetal surgery; the risk of severe complications was found to be approximately 4.5% for open fetal and 1.7% for fetoscopic surgery.

I have, with the help of many other people, set up this new clinical service and have developed local pathways and protocols to facilitate this. I have performed a cost-analysis study to evaluate the cost implications of this surgery; this showed

that surgery itself is roughly equal to, if not slightly cheaper than, than the standard postnatal surgery at the point of operation. Prematurity (if it occurs) will bring the cost up, but the expected reduced healthcare utilisation of these children over their lifetime should bring the cost down.

Acceptability is an important consideration when introducing a new and potentially controversial technique. I surveyed healthcare workers throughout the UK and found there was general support for the concept of fetal surgery, but concern about long-term outcomes, which we have been mindful of in our planning.

We began seeing patients in January 2018 and to date we have evaluated 27 patients at UCLH and operated on 13 of them, either in London or Leuven. Eight of these patients have delivered and initial outcomes have been good, with no major maternal or fetal/neonatal morbidity. We will be following outcomes very closely to monitor for long-term data and complications. I have assessed patient experience and acceptability with all women we have seen, and this has been extremely positive.

Now this service is established, future work should include monitoring long-term patient outcomes, developing techniques for earlier detection of spina bifida (which we have attempted to do in our department, and is described in chapter 5.1) and evaluating emerging evidence regarding less-invasive methods of surgery.

Impact Statement

The work presented in this thesis has already had a direct effect on patient care at a national level and will continue to do so in the near future. I have coordinated the implementation of a new service which is the first of its kind in the UK. This has enabled patients to access a potentially beneficial surgery with much greater ease than before. In doing so I have increased the awareness of this treatment option amongst the fetal medicine community in this country. My work on service set-up and cost evaluation has contributed to the NHS England Specialist Commissioners plans for the establishment of an NHS-funded service. Finally, the media publicity that has surrounded our launch has increased knowledge about spina bifida nationally, and perhaps contributed to a national discussion regarding disability.

Additionally, my work has contributed to the argument for large-scale registries of fetal surgery cases. By assessing the global availability of fetal surgery for spina bifida I have demonstrated that there is an increasing number of centres offering this treatment and that several are operating using different criteria or techniques. By conducting a systematic review into maternal outcomes following fetal surgery I have shown that these are often not reported or are reported variably, and the rates of maternal complications may be higher than previously estimated. Fetal surgery is still a relatively small field with limited patient numbers. The creation of an international registry of fetal surgery for all techniques and indications would allow more accurate estimations of benefit and risk to be established and would increase the chances of detecting rare complications.

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Abbreviations

ACOG	American College of Obstetricians and Gynecologists
APH	Antepartum haemorrhage
BCC	Bipolar cord coagulation
BMI	Body mass index
CCAM	Congenital cystic adenomatoid malformation
CDH	Congenital diaphragmatic hernia
CHAOS	Congenital high airway obstruction syndrome
CHOP	Children's hospital of Philadelphia
CI	Confidence interval
CMS	Chorionic membrane separation
CO	Cord occlusion
COXi	Cyclooxygenase inhibitor
CRL	Crown rump length
CSF	Cerebrospinal fluid
CVS	Chorionic villus sampling
DA	Ductus arteriosus
DIC	Disseminated intravascular coagulation
EXIT	Ex-utero intrapartum treatment
FETO	Fetoscopic endoluminal tracheal occlusion
FMU	Fetal medicine unit
GI	Gastrointestinal
GOSH	Great Ormond Street Hospital
HLHS	Hypoplastic left heart syndrome
ICU	Intensive care unit
IFMSS	International fetal medicine and surgery society
ISPD	International society for prenatal diagnosis
LUTO	Lower urinary tract obstruction

MCMA	Monochorionic monoamniotic
MFM	Maternal fetal medicine
MMC	Myelomeningocele
MOMS	Management of myelomeningocele study
MRI	Magnetic resonance imaging
NAFTNet	North American fetal therapy network
NICE	National institute for health and care excellence
NICU	Neonatal intensive care unit
OEIS	Omphalocele-exstrophy-imperforate anus-spinal
PACI	Partial amniotic carbon dioxide insufflation
PE	Pulmonary embolism
PPH	Postpartum haemorrhage
PPROM	Preterm prelabour rupture of membranes
PROM	Preterm rupture of membranes
PTL	Preterm labour
RFA	Radiofrequency ablation
SCT	Sacrococcygeal teratoma
sFGR	Selective fetal growth restriction
TAPS	Twin anaemia-polycythaemia sequence
TO	Tracheal occlusion
TRAP	Twin reversed arterial perfusion sequence
TTTS	Twin to twin transfusion syndrome
UCLH	University College London Hospital
USS	Ultrasound scan
VTE	Venous thromboembolism

Chapter 1 **Introduction**

1.1 The History of Fetal Surgery

1.1.1 General

Fetal surgery, meaning to operate on the fetus, cord, placenta or membranes, is not a new concept. Observations of the fetus have been noted from the sixteenth century; the development of anaesthesia in the 19th century allowed the fetus to be manipulated for the first time, and in the early 20th century the first operations on animal fetuses were described. In 1920 a limb amputation of a fetal guinea pig was reported[1] and in the 1930s and 1940s surgery on lamb fetuses through a small uterine incision under spinal anaesthesia was developed[2]. In 1946, the removal of fetal rabbit testes was shown to have a profound effect on sexual development[3] and in the 1950s the first animal fetal model of human disease was made in fetal puppies by interruption of the mesenteric blood supply to produce intestinal atresia[4].

The first documented fetal intervention in humans was in 1961, when an in-utero blood transfusion was given to a human fetus suffering from severe hydrops fetalis secondary to maternal rhesus isoimmunisation[5]. The blood was injected blindly into the fetal abdomen and this resulted in an improvement in the hydrops. This case led to the consideration of whether a full exchange transfusion would be possible, and cases of exchange transfusion by uterine incision and

cannulation of jugular and femoral vessels were described[6]. However, the outcomes from these procedures were considered disappointing and were not revisited until many years later.

Throughout the 1960s and 1970s, further work to expand fetal therapies continued both in animals and humans. However, it was the advances in imaging technology that also occurred during this period which allowed the progression of fetal surgery and the development of fetal medicine as a new specialty. From the discovery of the piezo-electric effect by Pierre and Jacques Curie in 1880, ultrasound was developed rapidly and was first used medically in 1920[7]. Ultrasound was initially used therapeutically due to the heat intensity generated, but in the 1940s it's use as a diagnostic tool was developed. In 1950 the first commercially available "Ultrasonic Locator" was marketed and throughout the 1950s the work of Professor Ian Donald, Regius Chair of Midwifery at the University of Glasgow, established the use of ultrasound in obstetrics and gynaecology[8]. From the 1960s to the current day, improvements in technology and image quality have continued apace, often fuelled by developments in telecommunications, radar and consumer electronics.

By 1982, the diagnostic and therapeutic possibilities in fetal medicine had progressed extensively[9], and an international symposium of experts was held in California. This group would later become the International Fetal Medicine and Surgery Society (IFMSS) and the meeting became an annual event. Following this symposium a consensus framework for fetal interventions was published[10]

and a registry for fetal interventions was established[11]. The framework consisted of five criteria for fetal surgery, which remain applicable today:

1. Accurate diagnosis and staging is possible, with exclusion of associated anomalies.

2. The natural history of the disease is documented, and prognosis is established.

3. There is currently no effective postnatal therapy.

4. In utero surgery has proven feasible in animal models, reversing deleterious effects of the condition.

5. Interventions are performed in specialised multidisciplinary fetal treatment centres within strict protocols and approval of the local Ethics Committee with informed consent of the mother or parents.

The final major advancement in the 20th century accelerating the progression of fetal surgery is that of minimal access surgical equipment. Although fetoscopy had been developed in the 1970s for diagnostic purposes, the improvement in ultrasound technology rendered this unnecessary. In the 1990s the development of small fibre-optic endoscopes along with miniature instruments and cameras allowed a resurgence in fetoscopy for therapeutic indications[12]. The Eurofoetus project[13], funded by the European Commission, was established in 1998. This propelled the development of purpose-designed fetoscopic instruments and established a fetoscopy registry and clinical studies. The main theoretical

advantages of fetoscopic surgery compared to open fetal surgery are that of reduced invasiveness and the potential for vaginal delivery, and therefore interest in fetoscopy remains high for many conditions.

There are many conditions which may potentially benefit from fetal intervention, in order to either save the life of the fetus or reduce long-term morbidity, and for several conditions fetal surgery is feasible. Some examples are discussed below.

1.1.2 Lower Urinary Tract Obstruction

Lower urinary tract obstruction (LUTO) in the fetus can be caused by posterior urethral valves, stenosis of the urethral meatus, urethral atresia, ectopic insertion of a ureter and vesical tumours. In severe cases, obstruction leads to oligohydramnios, pulmonary hypoplasia and renal failure. The first case of open fetal surgery[14] was performed in such a case at the University of California, San Francisco in 1981 at 18 weeks' gestation by performing a hysterotomy and vesicostomy. The fetus never produced urine, but the procedure demonstrated feasibility and safety for the mother. Following this, vesicoamniotic shunting and, more recently, cystoscopic treatment were developed. In utero therapy (mainly vesicoamniotic shunting), has been shown to improve perinatal outcomes compared with no treatment in a systematic review[15] of cohort studies, although the Percutaneous Vesicoamniotic Shunting Versus Conservative Management for Lower Urinary Tract Obstruction (PLUTO) randomised trial[16] was stopped early due to poor recruitment, leading to uncertainty regarding the beneficial effect of treatment. The trial reported 15 cases of intervention amongst 31

participants and analysis based upon treatment received (rather than intention-to-treat) demonstrated increased perinatal survival with vesicoamniotic shunting. A systematic review of fetal cystoscopy[17] demonstrated that fetal cystoscopy altered the prenatal diagnosis in 25–36% of cases, which is important as the underlying cause of LUTO affects the prognosis. It showed improved perinatal survival compared with no intervention but no significant improvement when compared with vesicoamniotic shunting.

1.1.3 Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia (CDH) is a defect of the muscular diaphragm which allows abdominal contents to enter the chest cavity, impeding pulmonary development. Open fetal repair of the defect was first attempted in the 1980s[18]; however, trial results were mixed and concern about the risks of neurological morbidity and mortality meant that the surgery was not widely accepted. In the 1990s, there was renewed interested in treating this condition prenatally, this time via an endoscopic route. Based on the concept of tracheal occlusion preventing drainage of pulmonary fluid and encouraging lung growth[19], a variety of methods of occlusion were developed. The Fetoscopic Endoluminal Tracheal Occlusion (FETO) Task Force developed a technique of percutaneous access and balloon inflation[20]. A randomised trial of fetal tracheal occlusion in 2003[21] did not show any benefit over standard postnatal care, but a cohort study of 210 cases from the FETO Task Force in 2008[22] showed a survival benefit in severe cases. A randomised trial[23] comparing FETO to expectant management in moderate and severe cases is currently underway.

1.1.4 Sacrococcygeal Teratoma

Sacrococcygeal teratomas (SCT) are germ cell tumours arising at the base of the spine. Predominantly benign, they can grow exceptionally large and in severe cases lead to fetal anaemia and high-output cardiac failure. Prenatal open surgical resection has been described in a small number of severe cases[24] and seems to improve survival, although complication rates are high.

1.1.5 Congenital Cystic Adenomatoid Malformation of the Lung

Congenital cystic adenomatoid malformations (CCAM) are cystic lesions affecting the lung; severe cases can compress the fetal heart or airway and lead to hydrops fetalis. Open fetal resection or cyst puncturing has been reported to increase survival in cohort studies of both microcystic[25] and macrocystic[26] disease.

1.1.6 Hypoplastic Left Heart Syndrome

Fetal surgery for cardiac indications has been limited by a lack of good animal models of the human fetal circulation, and improvements in postnatal cardiac surgery have made these conditions less appealing for fetal correction. However, despite advances in cardiac care, hypoplastic left heart syndrome (HLHS) still

has a mortality rate of 25-35%[27] and there is morbidity and long-term effects associated with a Fontan circulation. Balloon valvuloplasty in fetuses with aortic stenosis was first described in 1989[28] and by 2010 it was estimated that just under 200 cases had been performed globally, leading to the International Society for Prenatal Diagnosis (ISPD) Special Interest Group Report on Fetal Cardiac Interventions[29]. In 2014, a scientific statement from the American Heart Association[30] suggested that fetal cardiac intervention can be considered in the following cases:

- Aortic stenosis with evolving HLHS
- HLHS with restrictive or intact atrial septum
- Dilated left ventricle with severe mitral regurgitation, aortic stenosis, restrictive or intact atrial septum
- Pulmonary atresia with an intact ventricular septum.

A recent report of 123 cases of fetal aortic valvuloplasty from Boston Children's Hospital[31] showed an improvement in outcomes over time.

1.1.7 Twin to Twin Transfusion Syndrome

Twin to twin transfusion syndrome (TTTS) is a complication of monochorionic twins involving an unequal blood supply through a shared placenta. Severe forms can lead to fetal hydrops and death. Laser coagulation of placental anastomoses

was suggested in 1983[32] and first performed via a hysterotomy in 1990[33]. A percutaneous method under local anaesthetic was developed in 1995[34] and in 2004 a randomised trial[35] of fetoscopic laser coagulation of the placenta versus amniodrainage, funded by the Eurofoetus project, showed increased survival and decreased prematurity. Since then, fetoscopic laser coagulation has become a relatively common invasive prenatal treatment and is widely performed around the world.

As well as the above-mentioned conditions, fetal surgery has been attempted in a number of other situations such as bronchopulmonary sequestration of the lung, congenital high airway obstruction syndrome, cervical and mediastinal teratomas and complete heart block; however, case numbers are small. The condition with the largest case numbers and strongest evidence of benefit in all fetal surgery is spina bifida, which is now the most commonly performed surgery on the fetus (as opposed to the placenta, as in TTTS) worldwide.

1.2 The Background of Open Fetal Surgery for Spina Bifida

1.2.1 Spina Bifida

Spina bifida - clinical

Spina bifida is a congenital neurological condition caused by incomplete closure of the neural tube by 28 days gestation, leading to a defect in the bony spine. The worldwide incidence of spina bifida is approximately 4.63 per 10 000 births[36] and in the UK it is estimated that 700 to 900 pregnancies a year are affected[37].

Spina bifida occulta (closed spina bifida) involves an intact layer of skin covering the spinal cord; this is generally a milder form of the disease and will not be considered further in this chapter. Spina bifida aperta (open spina bifida, Figure 1.1) involves either a bulging of the meninges through the skin (meningocele), or a bulge of the meninges with the spinal cord and nerve tissue included (myelomeningocele, MMC) or a direct opening of the skin exposing the underlying neural tissue (myeloschisis); these will be collectively referred to as “spina bifida” throughout.

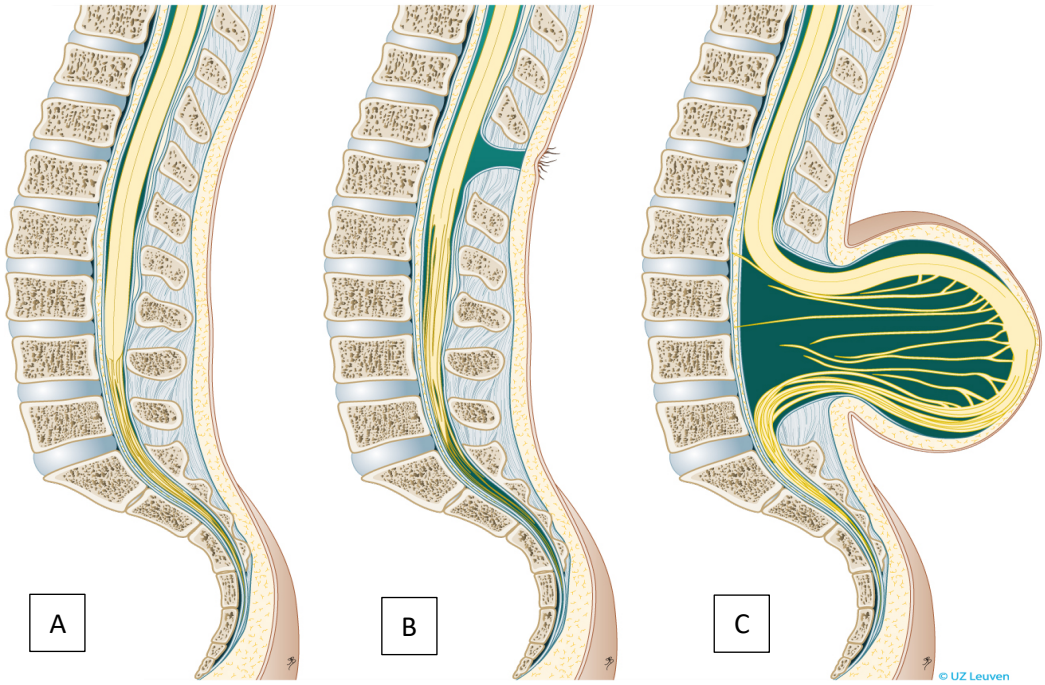

Figure 1.1: Types of spina bifida: (A) normal situation, (B) spina bifida occulta, (C) spina bifida aperta (myelomeningocele)

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Clinically, spina bifida leads to difficulties with mobility and ambulation which is largely dependent on lesion level; wheelchair use has been reported as 90%, 45% and 17% for patients with a thoracic level, lumbar and sacral level lesion respectively[38]. Sensory deficits and orthopaedic abnormalities such as talipes (clubfoot), kyphosis and scoliosis can also occur. Most patients with spina bifida experience difficulties with bladder and bowel emptying and control, which are commonly managed with a combination of toileting regimens, clean intermittent self-catheterisation and medication such as laxatives, enemas and anticholinergics[39 40].

Sexual dysfunction may occur for a variety of reasons, including erectile dysfunction for men, reduced genital sensation and psychological issues[41],

although parenthood is possible. Brain changes usually develop in spina bifida as a result of leakage of cerebrospinal fluid through the spinal lesion, causing hindbrain herniation (the Arnold-Chiari or Chiari II malformation) to develop. Enlargement of the cerebral ventricles often occurs and, if severe, hydrocephalus can be managed with a ventriculoperitoneal shunt or, in selected older children, endoscopic third ventriculostomy[42]. Shunt complications, including failure and infection, may occur[43]. Intelligence quotient (IQ) falls into the normal range for many adults with MMC, although the need for shunts and shunt complications is associated with a reduced IQ[44]. Although not technically a lethal condition, spina bifida is associated with a reduced life expectancy and early mortality can occur, particularly in those with higher lesions[45]. Having a child with spina bifida is associated with higher levels of parental[46] and sibling[47] stress. When questioned, children and adolescents with spina bifida have lower self-worth scores than their peers[48] but express positivity towards their condition and hopefulness regarding their future[49].

Spina bifida - prevention

Spina bifida is a multi-factorial disease for which multiple underlying environmental[50], metabolic[51] and genetic[52] aetiologies have been proposed. An increased rate of spina bifida has been observed in women taking anticonvulsants[53] and women who have diabetes[54] and/or are obese[55]. The role of folic acid has been the most widely investigated, and in 1991 the Medical Research Council Vitamin Study[56] demonstrated that pre- and post-conception folic acid reduced the rate of spina bifida by approximately 70% in high-risk women. The World Health Organisation recommends supplementation with 400ug of folic acid daily from two months prior to conception[57]. However, it has

been shown in the UK that only 31% of women take pre-conceptual folic acid, and this figure is lower amongst younger and non-Caucasian women[58]. A study in 2017[59] reported that 59 countries had implemented mandatory folic acid fortification of wheat and/or maize flour, which had prevented approximately 50,270 cases of spina bifida and anencephaly. The UK currently does not have mandatory folic acid fortification of any food sources; it has been suggested that doing so in the ten years following publication of the MRC evidence would have prevented over 2000 cases of neural tube defects[60]. The UK Department of Health and Social Care launched a public consultation to consider the evidence, practicality and safety of mandatory folic acid food supplementation in 2019[37].

Spina bifida - diagnosis

Antenatal diagnosis of spina bifida initially developed in the 1970s due to the finding of raised alpha-fetoprotein (AFP) levels in the amniotic fluid of affected pregnancies[61 62]. Shortly after, these levels were found to also be raised in the maternal serum of affected pregnancies, although the overlap with non-affected pregnancies was higher[63 64]. Screening by maternal serum AFP then required an amniocentesis to confirm raised levels. A collaborative study of 301 pregnancies with neural tube defects in 1977 showed that maternal AFP screening detected 79% of spina bifida cases[65].

Over a similar time period, ultrasound technology and knowledge was improving. In 1973 the first ultrasound detection of spina bifida was published, with a description of the spinal lesion as a double-ring structure[66]. Ultrasound findings of an open neural arch[67] and small biparietal diameter[68] were also described. A review of over 2500 pregnancies scanned from 1977-1982[69] reported an ultrasound detection rate for open spina bifida of 33% in a general population and

80% in a high-risk population. In 1986 a landmark paper was published[70] describing the “lemon sign” of frontal bone scalloping and “banana sign” of anterior cerebellar curvature with obliterated cisterna magna (Figure 1.2), along with other common findings of absent cerebellum and ventriculomegaly. These signs were shown prospectively to detect over 95% of open spina bifida cases[71] and these findings were replicated in subsequent publications. In 1990 it was suggested that ultrasound screening was more sensitive than screening by AFP, and did not infer any risks to the pregnancy[72]. In the UK and many countries, screening for spina bifida is now entirely performed by ultrasound with no programme of AFP screening.

The detection rate for spina bifida in populations routinely offering second trimester ultrasound has been estimated at 68-100%[73] [74] [72]. In the UK, the Fetal Anomaly Screening Programme advises a minimum standard of 90% for detection of spina bifida[75].

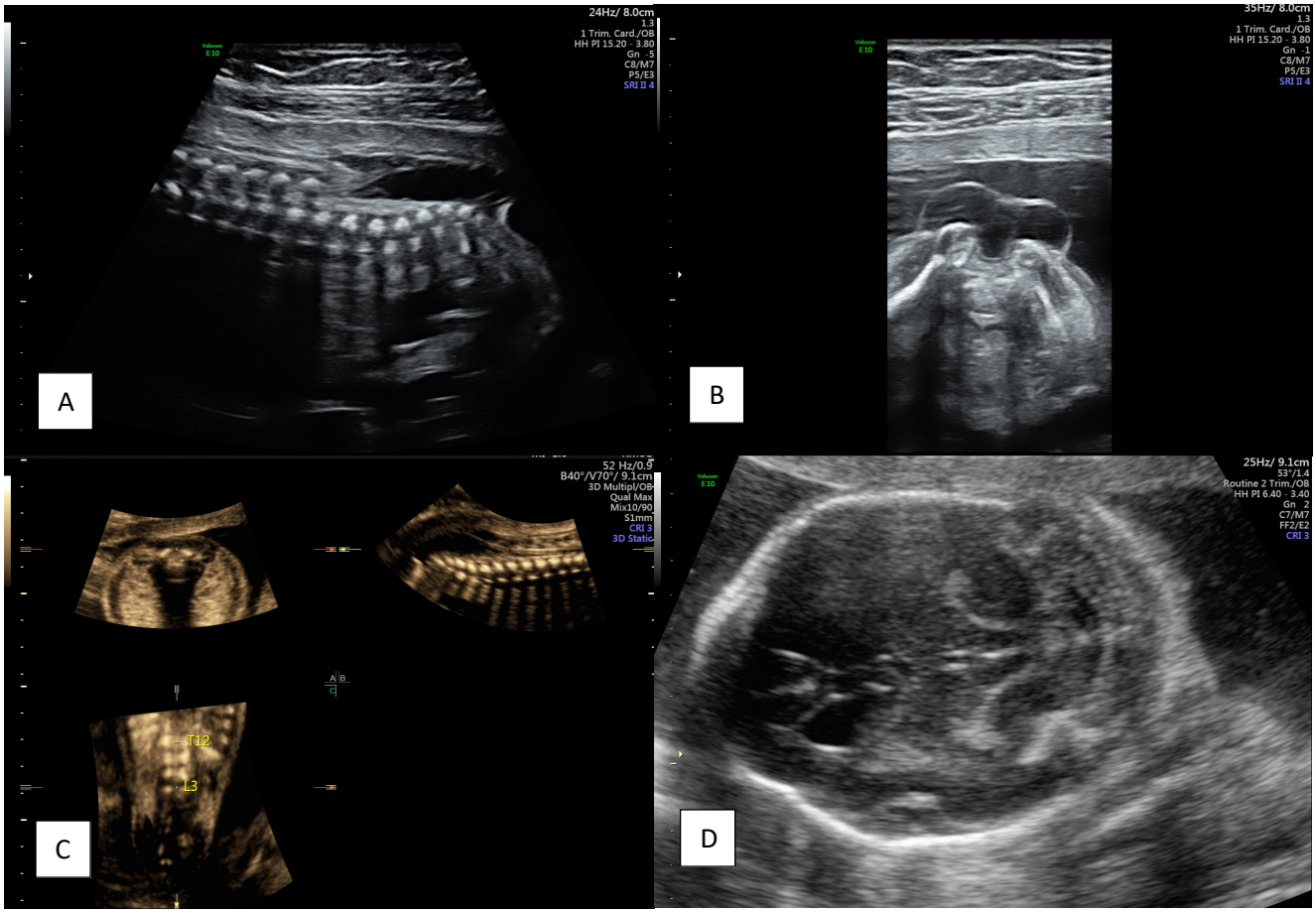

Figure 1.2: Antenatal diagnosis of spina bifida: spinal lesion seen in (A) sagittal plane, (B) transverse plane and (C) 3D reconstruction; (D) transverse section of fetal brain demonstrating “lemon” shaped skull, “banana” shaped cerebellum and hindbrain herniation

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Spina bifida - treatment

Termination of pregnancy following an antenatal diagnosis of spina bifida is legal in many countries including England, Wales and Scotland without gestational age limit. A study in Belgium and Holland showed that 76% of patients chose this option[76]; from 1991 to 2012 in the UK this figure was 81%[60].

For ongoing pregnancies, the standard treatment option is postnatal surgery to close the defect, protect the spinal cord and prevent ascending infection, and is typically performed in the first 48 hours of life[77]. The standard multi-layer repair comprises a circumferential skin incision and dissection of the residual zona epithelioserosa in order to untether the neural placode, followed by multi-layer closure of the dural sac, lumbodorsal fascial flaps and skin. This is shown in Figure 1.3. Delivery of women planning postnatal spina bifida repair is usually by caesarean section, although it is unclear whether this confers a benefit over vaginal delivery[78].

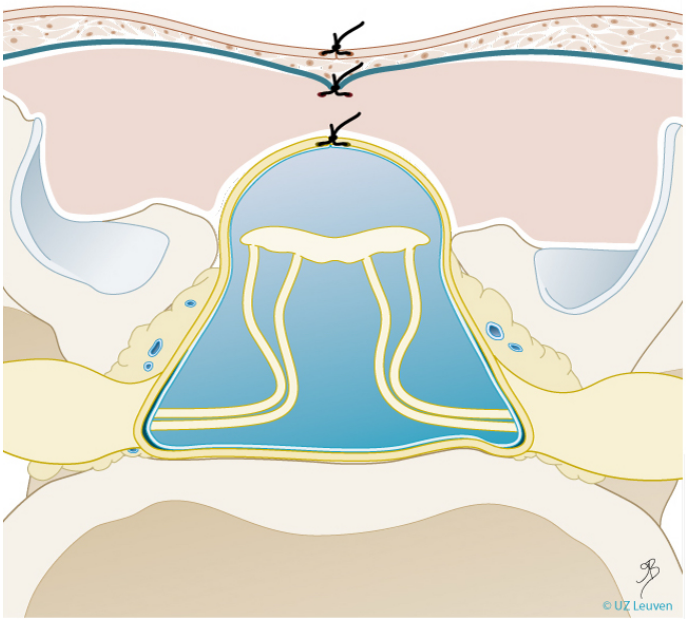

Figure 1.3: Technique of multi-layer repair of spina bifida

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1.2.2 Rationale for Fetal Repair

The vast majority of open spina bifida are diagnosed using antenatal ultrasonography; repeating ultrasound scans during pregnancy often suggests a deterioration of neurological function. Hindbrain herniation and ventriculomegaly are often seen to progress throughout gestation. Lower extremity movement can be seen early in gestation and then reduce or stop[79]. Talipes also appears to develop and worsen throughout pregnancy. Early animal models of spina bifida also showed worsening of the condition throughout gestation in sheep[80] and rats[81] and experimental work in other areas of nervous system development suggest that plasticity is greatest in the young brain and nervous system[82].

These observations led to the development of a "two-hit" hypothesis, in which the final neurological deficit results from a combination of the primary failure of neural tube formation and further injury from trauma and amniotic fluid toxicity throughout pregnancy. The corollary of this theory is therefore that earlier repair, whilst still in-utero, should result in an improved outcome for the patient.

1.2.3 Animal Experiments

Models of open spina bifida have been created by mechanical disruption in a number of animal groups. Some of the earliest of these were primates; in 1985 a study[83] performed fetal laminectomy from L3 to L5 in monkeys; this was then either repaired immediately or left unrepaired. At birth, the unrepaired group had MMC-type lesions whereas the repaired group were neurologically intact. In 1993, similar findings were reported in rat and pig models[84] and in 1995 a fetal lamb model was created that was suggested[85] to be the most similar to human

disease. In this study[86], lambs undergoing fetal repair using a latissimus dorsi flap had near-normal neurological function whereas control animals had MMC-like lesions and deficits. This lamb model was later shown to lead to hindbrain herniation when unrepaired and that hindbrain herniation was reversible with mid-gestation repair of the defect[8788].

1.2.4 Early Clinical Experience

The first attempt at fetal repair of MMC in humans was in 1994 using a fetoscopic approach[89]; the first four cases had a fetal mortality rate of 50% and the procedure was temporarily abandoned. The first open repair of MMC repair was in 1998[90]. At 23 weeks' gestation, a fetus with a thoracic MMC, hindbrain herniation and normal lower extremity movements underwent in-utero repair. Delivery occurred at 30 weeks' gestation by caesarean section due to preterm labour. The infant was assessed to have a functional level of L4-5, which is much lower than would be expected by the level of the spinal defect, and did not have hindbrain herniation or hydrocephalus. These results were extremely encouraging, and in 1999 a series of ten patients undergoing fetal surgery at the Children's Hospital of Philadelphia (CHOP) was published[91]. This showed improvement in hindbrain herniation and it was estimated that fetal surgery reduced the need for a ventriculoperitoneal shunt by over 30% compared with historical controls. Also in 1999, a series of 26 patients undergoing fetal surgery at Vanderbilt University Medical Centre (VUMC) was published[92]. This reported a reduction in the incidence of moderate to severe hindbrain herniation from 50% in historical controls to 4% in those undergoing fetal repair, and a reduction in

shunt-dependent hydrocephalus from 92% in controls to 58% in the fetal surgery group. In 2003, as series of 11 patients undergoing fetal surgery at University of California, San Francisco was also published with similar results[93]. By this time, over 200 fetuses had undergone in-utero repair of open spina bifida with generally encouraging results; however, all reports were observational studies with comparison to non-randomised controls, leading to significant concern regarding selection, treatment and reporting bias.

Operating on the fetus whilst still in-utero is, understandably, not without risks. For the mother there are the risks of a laparotomy (bleeding, wound infection or breakdown, uterine infection, damage to adjacent organs such as the bowel or bladder, damage to the uterus requiring hysterectomy, pulmonary oedema, allergic reactions to medications and death) without any direct benefit to her own health. In the observational studies until 2003 there were no reported maternal deaths or serious maternal morbidity. As fetal repair of MMC requires a hysterotomy prior to development of the lower uterine segment, a caesarean delivery is required in the index and subsequent pregnancies to avoid uterine scar dehiscence or rupture which, in turn, may affect the health of the mother at a later stage.

For the fetus the most serious risk is that of death. In the reported cases until 2003, at CHOP one neonatal death occurred and at University of California, San Francisco (UCSF) there were two fetal deaths and one death from complications of prematurity.

Other fetal risks include asphyxia from cord compression during surgery, damage to the fetal spinal cord or adjacent structures and infection. Intrauterine infection requiring preterm delivery was reported twice in the Vanderbilt series[92]. Oligohydramnios occurred at least transiently in about one third of the patients in the Vanderbilt series, although only one significant neonatal problem occurred as a result. Prematurity, and its subsequent health risks (intraventricular haemorrhage, respiratory distress syndrome, necrotising enterocolitis and death) are increased by fetal surgery. In August 2001, the average gestational age at delivery was 33.2 weeks at CHOP, 33.2 at Vanderbilt and 31 at UCSF.

1.2.5 The Management of Myelomeningocele (MOMs) Trial

Following the clinical experience of MMC repair as described above, the US National Institutes of Health (NIH) sponsored a multi-centre, prospective, randomised clinical trial comparing outcomes after in-utero and postnatal surgery in 2003[94].

Three US centres already performing fetal MMC repair - the Children's Hospital of Philadelphia (CHOP), Vanderbilt University Medical Centre (VUMC), and the University of California, San Francisco (UCSF) - participated in the trial. Importantly, all other fetal medicine centres in the US agreed not to perform the surgery whilst the trial was ongoing. A standardised method of repair was agreed across the three centres; this included a maternal laparotomy, a stapled hysterotomy, dissection of the neural placode from surrounding tissues, primary closure of the dura and primary closure of the fetal skin (see Figure 1.3).

Inclusion criteria were a singleton pregnancy, myelomeningocele (including myeloschisis) between T1 and S1, evidence of hindbrain herniation, a gestational age of 19 weeks 0 days to 25 weeks 6 days gestation, a normal karyotype, US residency, and maternal age of at least 18 years. Major exclusion criteria were a fetal anomaly unrelated to spina bifida, severe kyphosis, increased risk of preterm birth (including short cervix and previous preterm birth), a body mass index (the weight in kilograms divided by the square of the height in meters) of 35 or more, and increased risk of uterine rupture (including previous hysterotomy in the active uterine segment). Children were reviewed at 12 and 30 months of age. A sample size of 100 women in each arm (control and fetal surgery) was planned; however, the trial was terminated prematurely following an interim analysis on the basis of efficacy of prenatal surgery, and initially reported the first 158 women only.

The main outcomes are shown in Table 1.1, alongside previous case series.. The primary outcome, a composite measure of fetal or neonatal death or the need for a cerebrospinal fluid shunt by the age of 12 months, occurred in 68% of infants in the prenatal surgery group and in 98% in the postnatal surgery group. Rates of actual shunt placement were 40% in the prenatal surgery group and 82% in the postnatal surgery group. Hindbrain herniation at 12 months of age was 25% in the prenatal group and 67% in the postnatal group. The ability to walk independently was 42% in the prenatal group and 21% in the postnatal group. On average, infants in the prenatal surgery group were more likely to have a level of function that was two or more levels better than expected according to the anatomical level (32% vs. 12%) and less likely to have a level of function that was two or more levels worse than the expected level (13% vs. 28%).

Table 1.1: Summary of main risks and benefits of prenatal surgery from the MOMS trial and prior cohort studies.

Centre	**CHOP** **1999**	**Vanderbilt** **1999**	**UCSF** **2003**	**MOMS trial 2011**		
Patients	**Prenatal surgery 10 n (%)**	**Prenatal surgery 26 n (%)**	**Prenatal surgery 11 n (%)**	**Prenatal surgery 80 n (%)**	**Postnatal surgery 78 n (%)**	**P value**
Fetal benefits						
Shunt criteria met	1 (10)	15 (58)	3 (27)	51 (65)	74 (92)	<0.001
Hindbrain herniation at 12 months	NS	NS	NS	45 (64)	66 (96)	<0.001
Independent walking at 30 months	NS	NS	NS	26 (42)	14 (21)	0.01
Maternal risks						
Pulmonary oedema	0 (0)	NS	0 (0)	5 (6)	0 (0)	0.03
Placental abruption	0 (0)	NS	0 (0)	5 (6)	0 (0)	0.03
Blood transfusion at delivery	NS	NS	NS	7 (9)	1 (1)	0.03
Status of hysterotomy at delivery:			NS			
- Intact, well healed	NS	NS		49 (64)		
- Very thin	NS	NS		19 (25)		
- Area of dehiscence	NS	1 (3.8)		7 (9)		
- Complete dehiscence	0 (0)	NS		1 (1)		
Spontaneous membrane rupture	NS	NS	8 (73)	36 (46)	6 (8)	<0.001
Chorionic membrane separation	NS	NS	NS	20 (26)	0 (0)	<0.001

Fetal/neonatal risks						
Bradycardia during repair	NS	NS	NS	8 (10)	0	0.003
Perinatal death	1 (10)	0 (0)	3 (27)	2 (3)	2 (2)	1.00
Average gestational age at birth	33.2	33.2	31	34.1+/-3.1	37.3+/-1.1	<0.001
Gestational age at birth: - ≤30 weeks - 30-34 weeks - 35-36 weeks - ≥37 weeks	 4 (40) 0 (0) 5 (50) 1 (10)	 4 (15)	 7 (64) 4 (36) 0 (0) 0 (0)	 10 (13) 26 (33) 26 (33) 16 (21)	 0 (0) 4 (5) 8 (10) 68 (85)	
Average birth weight (g)	2138	NS	NS	2383+/-688	3039+/-469	<0.001
Respiratory distress syndrome	NS	NS	NS	16 (21)	5 (6)	0.008

CHOP: Children's Hospital of Philadelphia; UCSF: University of California, San Francisco; NS: not stated

There were no maternal deaths in the study. Maternal complications included pulmonary oedema (6% prenatal surgery vs 0% postnatal surgery) and the need for blood transfusion at delivery (9% vs 1%). The hysterotomy scar was examined at delivery and found to be well-healed in 64% of women, very thin in 25%, partially dehisced in 9% and completely dehisced in 1%.

Pregnancy complications included chorioamniotic membrane separation (26% prenatal surgery vs 0% postnatal surgery), spontaneous rupture of membranes

(46% prenatal surgery vs 8% postnatal surgery) and placental abruption (6% prenatal surgery vs 0% postnatal surgery).

In the prenatal surgery group, two patients died - one stillbirth at 26 weeks' gestation, and one neonatal death due to prematurity at 23 weeks' gestation. In the postnatal surgery group, there were also two deaths; both babies had severe symptoms of hindbrain herniation and had both had received shunts.

Prematurity was confirmed as a complication of fetal surgery; the average gestational age at birth was 34.1 weeks' gestation in the prenatal surgery group and 37.3 weeks' gestation in the postnatal surgery group, and 13% of the prenatal surgery group delivered at less than 30 weeks' gestation. Correspondingly, the mean birthweight was lower in the prenatal group (2383g vs 3039g in the postnatal group) and the incidence of respiratory distress syndrome was higher in the prenatal group compared to the postnatal group (21% vs 6%).

The authors concluded: "In our study, prenatal surgery for myelomeningocele reduced the need for shunting and improved motor outcomes at 30 months, but the early intervention was associated with both maternal and fetal morbidity."

Reports of the MOMS full patient cohort (183 women)[95 96] confirmed the findings of the initial study and showed that ventriculoperitoneal shunt placement was associated with pre-surgery ventricular size. In patients with a ventricle size <10mm at assessment, 20% required shunting after prenatal surgery (vs 79% undergoing postnatal surgery) whereas when the ventricle size was >15mm at

assessment, 79% of patients required shunting after prenatal surgery (vs 87% after postnatal surgery). The benefit of fetal surgery regarding ventriculoperitoneal shunt rate is therefore best seen in patients who do not already have severe ventriculomegaly at assessment.

1.2.6 Clinical Experience Following the MOMs Trial

Following publication of the MOMs trial in 2011, further non-randomised studies of open fetal closure of spina bifida have been published, generally showing similar short-term outcomes. These are discussed further below.

A non-randomised study in Poland published in 2014[97] reported on 46 cases of spina bifida operated prenatally and 47 cases operated postnatally. As in the MOMS trial, they reported a decrease in ventriculoperitoneal shunt placement in prenatally operated infants (27.8% vs. 80%) and a higher incidence of preterm prelabour rupture of membranes (52.2% vs 20%) in this group.

The CHOP team reported on 100 cases of open prenatal closure of spina bifida that were performed after the MOMS study[98], following the same inclusion and exclusion criteria as the trial. In these 100 cases, no evidence of hindbrain herniation was seen in 71.1% of infants and two infants required ventriculoperitoneal shunts. The functional spinal level was improved compared to prenatal sonographic lesion level in 55% of neonates. The average gestational age at delivery of 34.3 weeks, with 54.2% of infants delivering at or after 35

weeks' gestation. Other complications included membrane separation (22.9%), preterm premature rupture of membranes (32.3%) and preterm labour (37.5%). These results were comparable to the MOMs trial and showed the same outcomes and risks could be expected in a non-trial setting.

A conference abstract from Professor Meuli's group in Switzerland in 2016[99] described neurological outcomes in their first 29 patients. They showed a 93% rate of hindbrain reversal, a shunt placement of 38% and at 24 months the average cognitive developmental age was 21 months.

The largest case series of fetal MMC repair was published by the team in Sao Paolo, Brazil in 2018[100]. It presented the immediate outcomes for 237 women undergoing surgery (until delivery only) and found an average gestational age at delivery of 33.6 weeks' gestation and a preterm prelabour rupture of membranes (PPROM) rate of 26%. For the mother, the risk of pulmonary oedema was 2.5% and the risk of placental abruption was 0.8%.

With particular regard to the risks of chorioamniotic membrane separation, preterm premature rupture of membranes and preterm birth, a review of cases from the CHOP group in 2016[101] showed that all of these risks were increased with earlier gestational age at the time of fetal surgery. Therefore, although the MOMs trial allowed entry from 19 weeks' gestation, they recommended that fetal surgery should not be performed at less than 23 weeks' gestation. This recommendation has been widely accepted into clinical practice, with the original MOMs upper limit of 26 weeks' gestation remaining.

A study published in 2016[102] looking at the impact of prenatal closure of spina bifida on family and parental stress was favourable for prenatal closure. In this study, 171 families completed the Impact on Family scale and Parent's Stress Index at 12 and 30 months. They found that the overall negative family impact of caring for a child with spina bifida up to 30 months of age was lower in the prenatal surgery group compared to the prenatal surgery group. Factors independently associated with both scores were family resources at 12 months and the ability of the child to walk independently at 30 months.

1.2.7 Longer Follow Up of Fetal Surgery Cases

The MOMs trial[94] followed up infants until 30 months of age, but clearly longer-term data is needed to ensure the benefit of surgery is maintained in later childhood and adulthood, and to monitor for late complications.

Five-year follow up studies of 30 fetal surgery cases performed prior to the MOMS trial have reported a shunt rate of 47-55%. Average or high-average IQ scores were found in 90% of patients; this was significantly lower in those who had required a ventriculoperitoneal shunt compared to those who hadn't[103]. Functional and self-care scores were lower than for age-matched population norms[104] but behavioural problems were no higher in fetal surgery patients compared to healthy controls[105].

A ten-year follow up of 42 fetal surgery cases[106] performed prior to the MOMs trial reported that 79% of patients were “community ambulators”, 9% were “household ambulators” and 14% were wheelchair dependent, with preschool ambulation being predictive of long-term ambulation. “Normal bladder function” (continence at all times) was reported in 26% of patients and normal bowel function in 31%; 74% of patients performed clean intermittent catheterisation. The overall rate of ventriculoperitoneal shunt placement was 43%, of which 61% had required at least one revision. No shunts had been inserted after 12 months of age. The majority of children scored within the average range for executive functioning, but when scoring below average fetal surgery patients were more likely than population norms to be impaired rather than borderline. Symptomatic spinal cord tethering with or without intradural inclusion cyst was associated with functional loss.

The complication of inclusion cysts has previously been described in a study from 2008[107]. In this review of 54 fetal surgery cases operated before the MOMs trial, 30% of patients presented with symptomatic tethered cord syndrome at a median age of 27 months (range 4-93 months). Sixty-three percent of these (10 patients) developed tethered cord syndrome in association with an intradural inclusion cyst. After cyst removal, 6 children were asymptomatic at a median follow-up of 36 months (range 12-63 months); however, 4 children lost normal bladder function, and one lost normal leg function. The potential complication of intradural inclusion cysts is an important one as it can lead to the later loss of previously established function.

For obvious developmental and social reasons, urological outcomes take longer to assess than motor ones. In a five-year follow up of 58 fetal surgery cases performed prior to the MOMs study[108], 18.5% successfully toilet trained.

For the mother, follow up at 3-14 years[109] after open fetal surgery for spina bifida and other conditions showed that 57% of women had experienced a further pregnancy, with a uterine dehiscence rate of 14% and a uterine rupture rate of 14% in future pregnancies.

The MOMS 2 long-term follow up study of the original MOMS cohort is expected to report shortly.

1.4 Work Planned and Work Contributions

I joined UCLH as a clinical research fellow in April 2017 in order to implement open fetal surgery for spina bifida at our institution. From my reading in order to gain an overview of the topic as described in chapters 1.1 and 1.2, I was struck that fetal outcomes appeared much more widely reported in the literature than maternal ones. I therefore planned a systematic review to evaluate this further. In planning development of this service I became aware that a small number of women from the UK had already had this surgery performed by travelling to European centres. I therefore also planned to evaluate the availability of fetal surgery for spina bifida internationally before proceeding. The aims of my thesis were therefore:

- To evaluate the global availability of fetal surgery
- To perform a systematic review of maternal complications of fetal surgery
- To set up fetal surgery as a clinical service in a logical and evidence-based manner, in line with best principles of service implementation
- To assess the cost of this surgery and compare this to the current standard
- To assess healthcare worker and patient acceptability
- To follow the patient cohort, once the service was established, and monitor for outcomes and complications

Throughout this thesis I use the term “we” to describe work done as the clinical set up of this service has resulted from the work of a large team. However, this thesis was composed by myself, and the work contained herein is my own except where explicitly stated otherwise in the text. This work has not been submitted for any other degree or professional qualification.

Chapter 2 **Reviews**

2.1 Global Availability of Fetal Surgery

2.1.1 Introduction

Following the publication of the Management of Myelomeningocele (MOMs) trial in 2011[94], there was an increase in the number of centres offering fetal surgery for open spina bifida (myelomeningocele, MMC). In the United States, a survey of fetal care centres conducted in 2014[110] showed that approximately 9 centres were offering this service. However, the response rate was under 50% and it seems likely that this was an underestimation. The North American Fetal Therapy Network (NAFTNet) was founded in 2010[111] and currently lists 29 fetal therapy centres in the US and Canada, although it does not specify which of these centres are offering fetal surgery for MMC.

The availability of fetal surgery for MMC was more slowly established in western Europe than in the United States. It has been suggested that physician's attitudes to open fetal surgery is a limiting factor in Europe[9]; it is also clear that the availability of termination of pregnancy is likely to play a role in patient request for fetal surgery. A study in Belgium and Holland in 2014[76] showed that in these countries over three quarters of patients diagnosed with fetal MMC opted to end the pregnancy. This may partly explain why, in eastern Europe and South America, fetal surgery for MMC was more rapidly established. Prior to the MOMs

trial, the fetal therapy centre in Bytom, Poland had already performed 46 cases of open fetal surgery for MMC[97].

An American College of Obstetricians and Gynecologists (ACOG) Committee Opinion[112] observed that the MOMs trial was undertaken in a rigorous fashion with strict patient selection and surgery limited to only three centres which already had extensive experience; therefore, the outcomes were likely to be the "best-case scenario". They recommended that fetal surgery for MMC "should only be offered at facilities with the expertise, multidisciplinary teams, services, and facilities to provide the intensive care required for these patients".

It has also been recommended that all centres performing invasive fetal procedures should report their maternal, fetal, and newborn outcomes and that more formalised fetal intervention training should be developed[113].

It is apparent from conference abstracts and discussions that many other centres both in Europe and worldwide are now offering fetal surgery for spina bifida. It is also clear that there is a variety of inclusion criteria and surgical techniques in use. This is particularly the case in fetoscopic surgery, for which multiple surgical techniques exist[114115]. We therefore performed a study to assess the availability and types of fetal surgery for MMC worldwide.

2.1.2 Methods

Through the ISPD[116] and NAFTNet, fetal therapy centres believed to be offering fetal MMC repair and other centres where the availability of this surgery was unknown were identified. A questionnaire survey was then distributed to all centres and specialists identified.

Participants were asked to provide the following information:

- Is fetal surgery for MMC available in your centre/ country?
- Who are the lead clinicians for this service?
- What sort of repair is offered (open or fetoscopic)?
- What repair techniques are used?
- What is the estimated number of cases performed to date?
- What criteria do you use when offering surgery?
- Has your outcome data been published or presented?
- Where do your patients come from?
- Other comments.

The responses were collated and analysed by the team in London and published in an interactive map on the ISPD website[117].

2.1.3 Results

Units Offering Fetal Surgery

Fifty-nine fetal therapy centres were identified as potentially offering fetal MMC surgery (Figure 2.1), of which contact details were available for 56 centres. Responses were received from 44 of the 56 centres (74.6%). Three centres did not have a fetal surgery service and were excluded from further analysis. Thirty-four centres were performing fetal surgery for MMC and seven centres had set up a fetal surgery service but were still awaiting a first case. Most centres providing or setting up a fetal surgery service were in North America (19/41, 46.3%) and Europe (9/41, 30.0%). Details of fetal therapy centres performing fetal surgery for MMC are listed in Table 2.1.

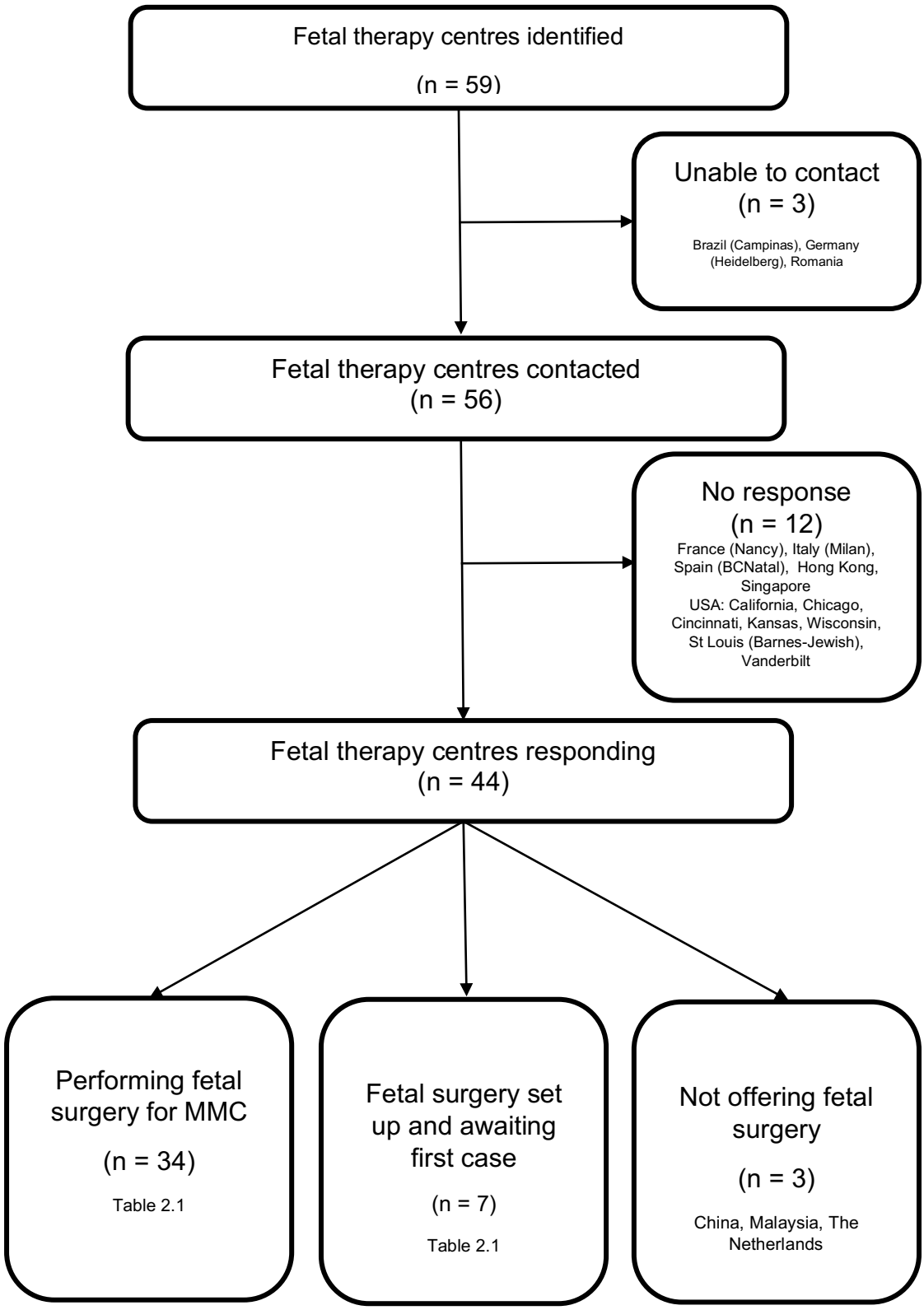

Figure 2.1: Questionnaire responses and availability of fetal surgery

Table 2.1: Fetal therapy centres offering fetal surgery for MMC

North America	Europe	South and Central America
California	**Belgium**	**Argentina**
UCSF Fetal Treatment Center, San Francisco	Universitaire Ziekenhuizen (UZ) Leuven	Hospital Universitario Austral, Pilar, Buenos Aires
California*	**France**	**Brazil**
Lucile Packard Children's Hospital, Stanford	Armand Trousseau Hospital, Paris	Hospital Albert Einstein, Sao Paulo
Canada	**France**	**Brazil**
Mount Sinai Hospital and Hospital for Sick Children, Toronto	Necker-Enfants-Malades Hospital, Paris	Centro Paulista de Medicina Fetal / Hospital e Maternidade Santa Joana, São Paulo
Colorado	**Germany**	**Colombia**
Colorado Fetal Care Center, Aurora	German Center for Fetal Surgery and Minimally Invasive Therapy, Mannheim	Clinica Universitaria, Universidad Pontificia Bolivariana, Medellin
Connecticut*	**Poland**	**Mexico**
Yale Fetal Care Center, New Haven, Connecticut	Fetal Surgery Center, Bytom	Department of Fetal Surgery, Children's and Women's Specialty Hospital of Queretaro
Florida	**Spain**	**Mexico**
Arnold Palmer Hospital for Children, Orlando, Florida	Vall d'Hebron Hospital, Barcelona	Medicina Perinatal Alta Especialidad, Unidad Cirugía Fetal Hospital Christus Muguerza Alta Especialidad, Monterrey N.L. México
Maryland	**Spain**	**Peru**
John Hopkins Center for Fetal Therapy, Baltimore	Department of Maternofetal Medicine, Genetics and Reproduction, University Hospital Virgen del Rocío, Sevilla	Fetal Medicine Unit, Instituto Nacional Materno Perinatal, Lima
Michigan	**Switzerland**	**Peru**
Fetal Diagnostic and Treatment Center, University of Michigan, Ann Arbor	Zurich Center for Fetal Diagnosis and Therapy	Fetal Medicine Unit, Clinica Angloamericana / Instituto Peruano de Medicina y Cirugia Fetal
Minnesota	**United Kingdom**	
Mayo Clinic, Rochester	University College London Hospital, London	

Minnesota		
Midwest Fetal Care Center, Minneapolis		**Others**
Missouri		**Australia**
St Louis Fetal Care Institute, St Louis		Mater Centre for Maternal Fetal Medicine, Brisbane
New York*		**India***
Columbia University Medical Center, New York City		Amrita Institute of Medical Science, Kochi
North Carolina		**Iran**
University of North Carolina School of Medicine Fetal Care Program, Chapel Hill		Mother and Child Hospital, Shiraz
Ohio*		**Taiwan***
Cleveland Clinic Fetal Center, Cleveland, Ohio		Chang Gung Memorial Hospital, Taipei, Taiwan
Pennsylvania		**Turkey**
Center for Fetal Diagnosis and Treatment, Children's Hospital of Philadelphia		Istanbul Bilim University, Istanbul
Pennsylvania*		
Magee-Womens Hospital of University of Pittsburgh Medical Center (UPMC)		
Rhode Island		
Fetal Treatment Program of New England, Providence, Rhode Island		
Texas		
Texas Children's Fetal Center at Texas Children's Hospital, Houston		
Texas		
University of Texas Health Center at Houston		

*Centres starting programs who have not performed their first case as of June 2018

Patient Criteria

All centres reported following the MOMs trial patient criteria[94], modified more recently to allow BMI up to 40. Modifications or alterations to these criteria were reported by eight centres, as follows:

- An upper gestational age limit of 28 weeks' gestation (26 weeks in MOMs) was reported by four centres.
- A relaxation of the minimum age restriction (18 years in MOMs) and the requirement for US citizenship or residency was reported by two US centres.
- One centre reported offering fetal surgery up to a BMI of 45 if the placenta was posterior.
- One centre reported that fetal kyphosis greater then 30° and a short cervix were not used as exclusion criteria (this unit also reported an upper gestational age limit of 28 weeks).

Type of Fetal Surgery Offered

Figure 2.2 summarises the types of fetal MMC surgery currently being offered. The majority of centres performing fetal surgery for MMC were using an open technique (23/34, 67.6%). Five centres (Vall d'Hebron Hospital, Spain; Necker-Enfants-Malades, France; German Center for Fetal Surgery and Minimally Invasive Therapy, Germany; Hospital Albert Einstein, Brazil and Medicina Perinatal Alta Especialidad/Unidad de Cirugia Fetal, Monterrey City, Mexico) were performing only fetoscopic surgery (5/34, 14.7%) and six centres (Texas Children's Hospital, Texas; Mayo Clinic, Minnesota; John Hopkins Center for Fetal Therapy, Baltimore, Instituto Peruano de Medicina y Cirugia Fetal, Peru;

Mother and Child Hospital, Iran and Istanbul Bilim University, Istanbul) were performing both open and fetoscopic surgery (6/34, 17.6%).

Three centres offering fetoscopic surgery were doing so as an experimental therapy under US Food and Drug Administration (FDA) Institutional Review Board (IRB) oversight. Four centres currently providing only open surgery commented that they would be interested in offering a fetoscopic service when further evidence on efficacy and technique was available.

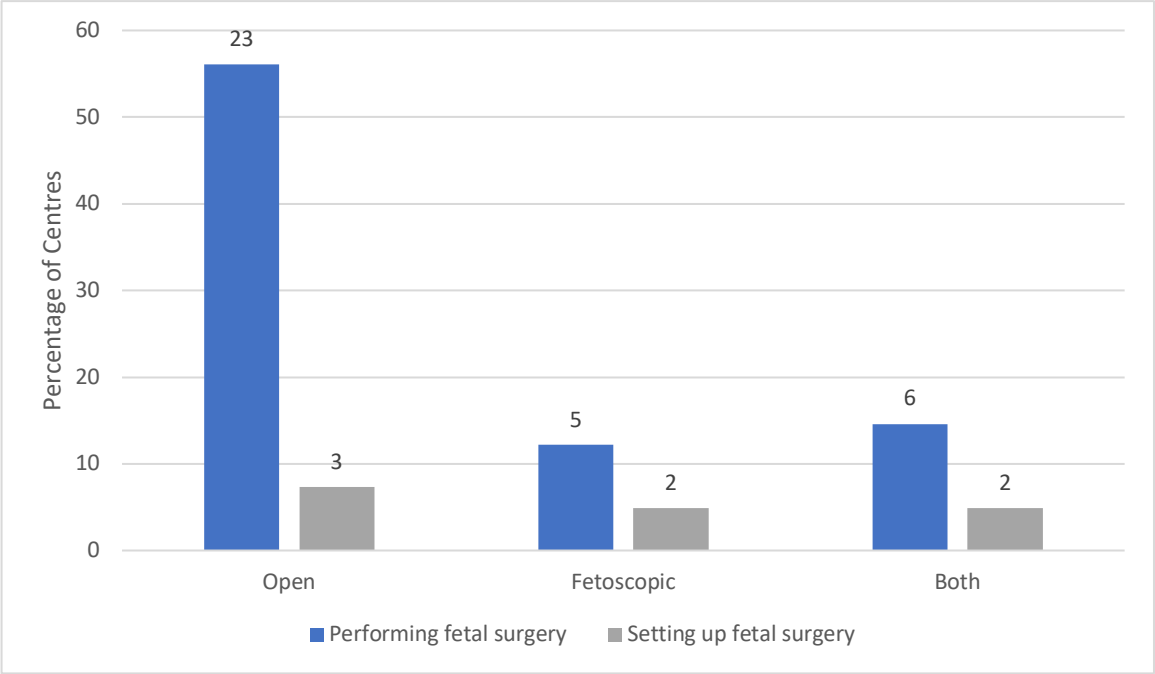

Figure 2.2: Type of fetal surgery for MMC offered by fetal therapy centres.

Technique of Fetal Surgery - Open

Thirty-four centres offering or about to start open fetal MMC repair were identified; of these 29 were already performing open fetal surgery (23 open only, six alongside fetoscopic) and five centres were setting up open fetal surgery (three open only, two alongside fetoscopic).

Of the 34 units offering open surgery, 28 were performing a multi-layer repair as described in the MOMs trial[94] (Figure 1.3); two centres reported using a collagen patch routinely between the placode and skin and four units did not state their repair technique.

Although entry techniques were not specifically enquired about, four centres reported using alternative uterine entry techniques to the auto-stapling device (US Surgical CS-57, Covidien, US) described in MOMS.

Technique of Fetal Surgery - Fetoscopic

Fifteen units performing or planning to perform fetoscopic MMC repair were identified; of these 11 were already performing fetoscopic surgery (five fetoscopic only, six alongside open surgery) and four units were setting up fetoscopic surgery (two fetoscopic only, two alongside open surgery).

All centres reported using or planning to use partial amniotic carbon dioxide insufflation. The main repair techniques described are shown in Table 2.2 and Figure 2.3.

Table 2.2: Techniques of Fetoscopic Surgery for MMC

Used by/ planned to be used by: Technique:	**Texas**[118], **Baltimore, Stanford, Iran, Peru**	**Brazil**[119], **Taiwan, New York**	**Germany**[120 121 122], **Turkey**	**Barcelona, Mexico**	**Paris**
Access to the uterus	Exteriorised	Percutaneous	Percutaneous	Exteriorised	Exteriorised
Ports	2-3	3	3	3	2
Patch	Collagen	Biocellulose	Collagen	None	Biocellulose
Neurosurgical technique (as shown in Figure 2.3)	Dura and skin (B)	Skin if possible; if not 2nd patch (Integra®) (B or D)	None or second patch (Teflon™). Some cases: primary skin closure, no patch (C or D)	Skin (A)	Skin (B)

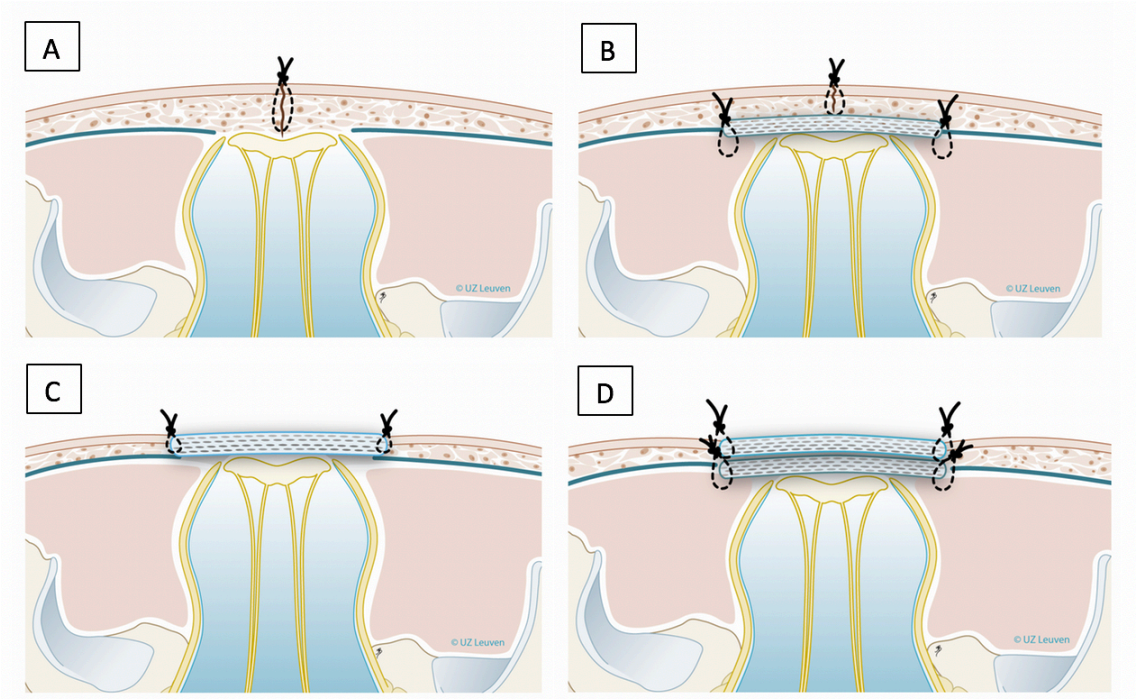

Figure 2.3: Techniques of fetoscopic repair of spina bifida

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Number of Cases

The estimated number of cases of fetal surgery for MMC performed in total (as of June 2018) varied greatly between centres, with a range of 1 to 253. The average number of cases per centre are shown in Table 2.3. Relatively few centres were performing large numbers of cases, whereas many centres were performing relatively few cases, resulting in a skewing of the data and a higher mean than median.

Table 2.3: Numbers of Cases per Centre

	Total number of cases	**Range**	**Median**	**Mean**
All centres	1654	1 - 253	21.5	51.7
Open	1281	1 - 253	21.5	47.4
Fetoscopic	372	1 - 200	8.0	21.5
North America	692	1 - 230	51.0	53.2
Europe	505	1 - 200	36.0	56.1
Centres outside North America and Europe	457	2 - 253	8.0	41.5

Outcome data

All North American centres had submitted their outcome data to the NAFTNet registry; three US centres had also published in peer-reviewed journals[98 118 123], as had three centres outside North America[97 119 120]. Six centres had presented their outcomes at conferences and a further six were planning to publish or present once their case numbers were sufficiently high. Most centres were therefore either contributing to a database of outcomes, publishing and presenting outcomes or planning to do so. Most centres reported their outcomes to be in line with those in MOMS. One centre which had performed 62 open cases reported a "higher premature rupture of membranes rate but lower uterine dehiscence rate" than expected and one centre which had performed 22 open cases reported a fetal mortality rate of 10%.

2.1.4 Discussion

This study provides an update of the current global availability of fetal surgery for MMC. It shows that since the publication of the MOMS trial and ACOG recommendations fetal surgery for MMC has spread rapidly, with some centres now adopting potentially less invasive surgical techniques.

There were a larger number of centres performing fetal surgery for MMC worldwide than has previously been reported[110], with several new centres in the process of setting up, highlighting a continued interest in fetal surgery for MMC.

In some areas there is more than one fetal surgery centre within a narrow geographical location. The concentration of MMC fetal surgery cases to a small number of centres to allow for maintenance of surgical skills and development of expertise has previously been suggested[124]. It has been shown that for fetoscopic placental laser coagulation in twin-to-twin transfusion syndrome, centralisation and concentration of cases is associated with better outcomes[125], and this would also seem logical for other types of fetal surgery. Therefore, it may be the case that in the future collaboration between local centre is established to overcome these issues.

Although most fetal therapy centres perform open fetal surgery, a number offer fetoscopic surgery either alone or as an alternative to open repair; more still expressed interest in moving to this technique in the future. As expected, repair techniques for fetoscopic surgery vary more than for open surgery as the optimal surgical technique remains to be defined[114 115]. Most fetoscopy centres use a technique described by one of five centres (Table 2.2) which have performed the largest numbers of fetoscopic repairs. Given that such heterogeneity makes it difficult to compare “fetoscopic” outcomes to open, it would seem appropriate to compare these four techniques to each other and individually to the standard open technique in future work.

Patient inclusion criteria was very consistent between centres, with an increased gestational age up to 28 weeks the most common cause for deviation from the MOMs standard. This is very likely due to variations in antenatal care and difficulties in establishing a diagnosis prior to 24 weeks’ gestation in some areas;

three of the four countries offering surgery at a later gestational age were in Central or South America. To our knowledge, there has been no publication of outcome data specifically looking at “late” surgeries and it would be useful for centres offering this to do so in order to establish whether results are still positive or indeed equivocal to surgery before 26 weeks’ gestation and therefore should be considered by others.

This study aimed to identify and question fetal therapy centres via their involvement or registration with ISPD and NAFTNet; although an effort was made to identify other groups, it is known that there are fetal therapy centres which were not contacted. As both ISPD and NAFTNet have headquarters in the United States, it seems likely that our knowledge is skewed towards western centres with little known about centres in Russia, the Middle East and Africa. Another limitation was the use of self-reporting which was unverified; reports from each centre were published online[117], which may have influenced responses. Finally, whilst “outcome data” was enquired about, particular parameters were not, which may have been useful.

2.1.5 Conclusion

We have produced the most comprehensive resource of global fetal surgery centres to date; as well as being published in print, our findings have been published as an interactive online map[117] (Figure 2.4) and will continue to update this accordingly. In the future this could be used for improving patient information and to facilitate closer collaboration between centres.

Figure 2.4: Online map of fetal surgery centres

https://ispdhome.org/ISPD/SIGs/Fetal_Therapy_Map.aspx?utm_source=Informz&utm_medium=Email&utm_campaign=eBlasts

2.1.6 Contributions

The work in Chapter 2.1 was produced in collaboration with: Professor Lynn Simpson (Columbia University Medical Center, New York, USA), Professor Jan Deprest (KU Leuven, Belgium) and Professor Anna David (University College London).

2.2 Maternal Complications following Open and Fetoscopic Fetal Surgery: a Systematic Review and Meta-Analysis

2.2.1 Introduction

One of the important findings of the MOMS trial[94] was the maternal morbidity associated with open fetal surgery. The mother has been described as an "innocent bystander" in fetal surgery[126], which is almost exclusively offered to women who are themselves in good health. It is naturally the case that fetal surgery offers no medical benefit to the mother and usually poses only risk. Throughout the evolution of fetal surgery it has been implied that maternal risks should be minor and acceptable to the mother and family[113]. For some fetal surgery procedures there is an evidence base of animal work establishing maternal safety prior to human implementation; for others this does not exist. Fetal surgery poses risk to the mother not only during the procedure itself but also throughout the remainder of the index pregnancy, during any future pregnancies and potentially throughout the woman's reproductive life.

Information regarding safety and potential complications is important when counselling for fetal surgery and for patients informed decision making; however, robust data appears to be lacking. One study concentrating on maternal outcomes following both open and fetoscopic fetal surgery from a single institution[127] showed a number of short-term morbidities, whilst a systematic review of maternal complications following fetoscopic laser coagulation for twin-

to-twin transfusion syndrome[128] suggested an overall adverse event rate of 17.4% with a severe complication rate of 1.8%.

We therefore aimed to establish the immediate and long-term complication rate for women undergoing either fetoscopic or open fetal surgery as reported across the current literature.

2.2.2 Methods

Protocol and Registration

This systematic review was conducted in accordance with Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidance[129]. The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO-CRD42017082411).

Eligibility criteria

All randomised, cohort and case-controlled studies and case series (n≥3) reporting the results of open or fetoscopic fetal surgery in humans from January 1990 to June 2018 were considered eligible. Case reports, systematic reviews and narrative review articles were excluded. No language restrictions were applied.

Search strategy

A systematic review was conducted in MEDLINE, EMBASE and Cochrane databases using free text and Medical Subject Headings (MESH). The electronic search strategy is shown below. Subsequently, a grey literature (first 100 results in Pubmed and Google Scholar) search was performed, and reference lists of relevant review articles were manually checked. Covidence (Veritas Health Innovation Ltd, Melbourne, Australia) was used to eliminate duplicate articles and manage study screening.

Search terms were: “F(o)etal surgery”, “Fetoscopy”; “Fetoscopic surgery”; “Endoscopic f(o)etal surgery”; “Ex-utero intrapartum treatment”; “EXIT procedure”; “Operation on placental support”; “OOPS”; “Airway management on placental support”; “Bipolar cord coagulation”; “Cord ablation”; “Cord coagulation”; “Cord occlusion”; “Cord radiofrequency ablation”; “Selective f(o)etal reduction”; “Selective termination”; “Microwave ablation”; “Multifetal pregnancy reduction”; “F(o)etal endoluminal tracheal occlusion”; “FETO”; “Discordant anomaly”; “Selective fetal growth restriction”; “sFGR”; “Selective intrauterine growth restriction”; “sIUGR”; “Twin anaemia polycythaemia sequence”; “TAPS”; “Twin reversed arterial perfusion”; “TRAP sequence”; “Twin to twin transfusion syndrome”; “TTTS”.

“Maternal” AND [“F(o)etal surgery” OR “Fetoscopy” OR “Fetoscopic surgery” OR “Endoscopic f(o)etal surgery”].

“F(o)etal” AND: [“Amniotic band syndrome” OR “BCC” OR “BPS” OR “Bronchopulmonary sequestration” OR “CCAM” OR “CDH” OR “Cervical lymphangioma” OR “Cervical teratoma” OR “CHAOS” OR “Chest mass” OR “Chorangioma” OR “Congenital cystic adenomatoid malformation” OR “Congenital diaphragmatic hernia” OR “Congenital high airway obstruction syndrome”; OR “Congenital pulmonary airways malformation”; OR “CPAM” OR “Cystoscopy” OR “Endotracheal occlusion” OR “Hydrothorax” OR “Laser” OR “Lower urinary tract obstruction”; OR “LUTO” OR “Mediastinal teratoma”; OR “Meningomyelocele” OR “Micrognathia” OR “MMC” OR “Myelomeningocele” OR “Neck mass” OR “RFA” OR “Sacrococcygeal teratoma” OR “Spina bifida” OR “Teratoma” OR “Uterocele”].

“Delivery” OR “C(a)esarean AND: [“BPS” OR “Bronchopulmonary sequestration” OR “Cervical lymphangioma” OR “Cervical teratoma” OR “CHAOS” OR “Chest mass” OR “Congenital high airway obstruction syndrome” OR “Mediastinal teratoma” OR “Micrognathia” OR “Neck mass”].

Study selection

Two authors (A.S. and L.D.V.) reviewed titles and abstracts independently and excluded irrelevant studies. The same two authors then independently performed full-text screening; disagreements were resolved by discussion. Studies were excluded if the full text was unavailable and the abstract contained insufficient information, if duplication had occurred or if the study was a case report, systematic review or narrative review. Studies with interventions which were not fully described or were performed on the neonate instead of the fetus were excluded. Interventions involving access to the uterus using a device with a total outer diameter of less than 1.5mm were excluded; this cut-off was chosen to avoid procedures performed with needles only (e.g. amniocentesis, in-utero blood transfusion) whilst including the majority of fetoscopic procedures. Studies which did not report maternal outcomes were excluded; for the purpose of this study, preterm rupture of membranes (PROM), chorionic membrane separation (CMS), preterm labour, preterm delivery and gestational age at delivery were not considered to be maternal outcomes. The development of subsequent maternal medical conditions, such as pre-eclampsia or mirror syndrome, were considered to be a consequence of the pregnancy and/or underlying fetal condition and not of fetal surgery and so were also not considered a maternal outcome. Studies from which data could not be extracted (e.g. composite or combined outcomes given) and studies containing patient cohorts which appeared to have been published in another study were excluded.

Data extraction

Two authors independently extracted data (A.S. and E.B. for open fetal surgery studies, A.S. and C.F. for fetoscopic studies) and entered this into a standardised Excel form. Disagreements were resolved by discussion. Study characteristics noted included study design, underlying fetal condition, intervention, control (if present), gestational age at surgery and number of patients. For open surgery, the technique, size and closure of uterine incision was noted; for fetoscopic surgery, the number of ports, size of instruments and/or ports and closure of port sites was noted, along with type of anaesthesia and use of partial amniotic carbon dioxide insufflation (PACI). Outcomes noted for the duration of the index pregnancy included immediate complications during surgery (maternal death, placental abruption, uterine bleeding/ haemorrhage, intra-operative blood transfusion, organ damage or anaesthetic complications), post-operative complications (ICU admission, sepsis, chorioamnionitis, wound, chest or urinary tract infections, pulmonary oedema, amniotic fluid embolism and other respiratory, GI or wound problems), complications at delivery of the index pregnancy (uterine dehiscence or rupture or blood transfusion at delivery) and the need for additional treatment at any point during the pregnancy. Outcomes noted following the index pregnancy included fertility (number of further pregnancies, difficulty conceiving, mean time to conception), future pregnancy complications (miscarriage or pre-term delivery), complications during future deliveries (uterine dehiscence or rupture or haemorrhage at delivery) and gynaecological symptoms outside of pregnancy.

All complications were independently graded according to the Clavien-Dindo classification of surgical complications[130] by two authors (A.S. and L.D.V) (Table

2.4). Clavien-Dindo grade I or II complications were defined as mild; grade III to V complications were defined as severe.

Table 2.4: Classification of surgical complications

Grade	Definition
I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic or radiological interventions. Allowed treatments: antiemetics, antipyretics, analgesics, diuretics, physiotherapy, wound infections opened at the bedside.
II	Requiring pharmacological treatment with drugs other than those allowed for grade I complications, including blood transfusion
III - IIIa - IIIb	Requiring surgical, endoscopic or radiological intervention Intervention not under general anaesthesia Intervention under general anaesthesia
IV - IVa - IVb	Life-threatening complications requiring Intensive Care Unit management Single organ dysfunction (including dialysis) Multiorgan dysfunction
V	Death of a patient

Adapted from Dindo et al 2004[130]. ICU: Intensive Care Unit

Study design

Studies were reviewed to determine study design (cohort, case-control or randomised) and whether data had been collected prospectively or retrospectively. If this was ambiguous studies, were assumed to be retrospective unless specifically stated.

Quality assessment of studies

Two authors independently assessed study quality and risk of bias (A.S. and L.VdV.) and entered this into a standardised Excel form. Disagreements were resolved by discussion. Randomised trials were assessed using the Cochrane Collaboration's tool for assessing risk of bias[131]; case-control studies were assessed using the Newcastle-Ottawa scale for assessing the quality of non-randomised studies[132] and case series were assessed using the National Institutes of Health study quality assessment tool for case series[133].

Assessment of heterogeneity

Methodological and clinical heterogeneity of data per study were evaluated. Variables were tested for statistical heterogeneity by applying the I^2 test to determine whether data could be pooled. An I^2 value less than 40% was taken to indicate minor heterogeneity; 40-75% moderate heterogeneity and >75% substantial heterogeneity[131].

Meta-analysis

Meta-analysis for all outcomes was carried out using MedCalc statistical software version 15.4 (MedCalc Software, Ostend, Belgium). Results were expressed as proportions with 95% confidence intervals (CI) as all outcomes were categorical variables. Pooled proportions were calculated using both the fixed and random effects model in case of homogeneity or heterogeneity respectively.

2.2.3 Results

Study selection

The electronic literature search identified 70,367 studies published between 1990 and 2018 (Figure 2.5); search of the grey literature and reference lists identified a further 16 studies. Following this, 48,248 studies were immediately removed as duplicates. The remaining studies (22,135) were screened by title and abstract, and a further 21,384 were excluded as irrelevant. Full texts of the remaining 751 articles were reviewed, and 585 were excluded for the following reasons: no reporting of maternal outcomes (175/585, 29.9% of studies excluded and 23.3% [175/751] of all studies assessed), insufficient information available (conference abstract/poster only or full text unavailable) (119/585, 20.3%), study design other than randomised trial, case-control trial or case series (110/585, 18.8%) and uterine access using a device <1.5mm (59/585, 10.1%). Thirty studies were translated from French (10), Spanish (7), Polish (5), German (3), Dutch (2), Portuguese (2) and Turkish (1), of which 16 were included following review. Two Chinese-language papers were identified but the full text could not be accessed online. Eventually 166 studies were included; 41 on open fetal surgery, 122 on fetoscopic surgery and three studies including both surgery types.

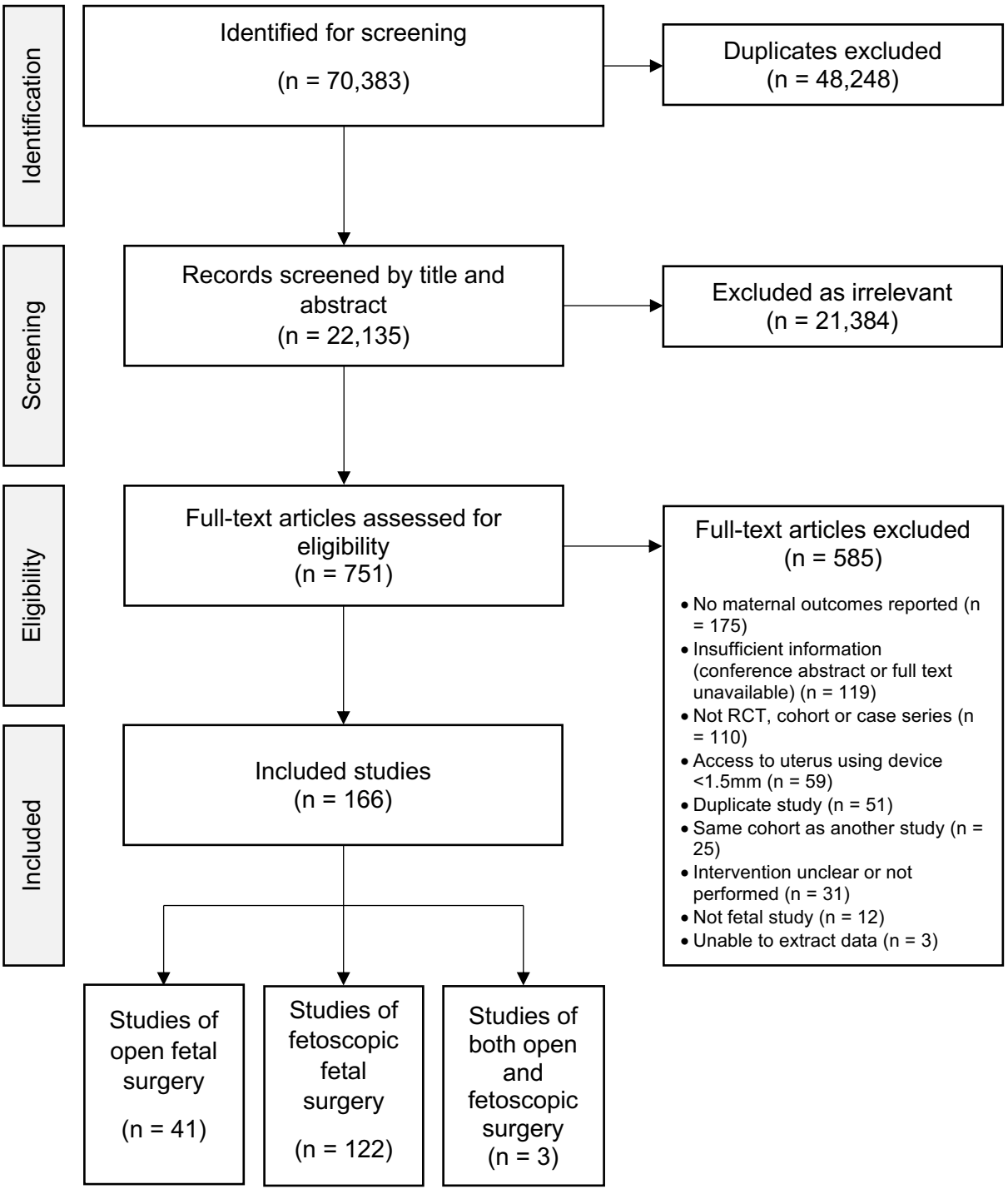

Figure 2.5: Flow diagram of study selection adapted from PRISMA 2009[129]

Study characteristics

Characteristics of included studies are shown below. Studies of open fetal (Table 2.5) and fetoscopic (Table 2.6) surgery are presented and analysed separately as the difference in surgical technique was considered too great for combined analysis. Seven studies specifically focused on late complications, i.e. after the index pregnancy, and are presented separately (Table 2.7).

Study design

The majority of studies included were retrospective cohort studies. A total of 33 prospective studies were included, two of open fetal surgery (121 patients) and 31 of fetoscopic surgery (2662 patients). Eight included studies were randomised, one of open surgery (91 patients) and eight of fetoscopic surgery (515 patients).

Table 2.5: Included studies of open fetal surgery

Category	First author and year of publication	Condition	Procedure	Study design	Prospective or retrospective	No. of patients
EXIT	Barthod 2013[134]	Neck mass, CHAOS	EXIT	Case series	Retrospective	5
	Cass 2013[135]	Lung mass, mediastinal mass	EXIT	Case series	Retrospective	9
	Chen 2018[136]	Omphalocele	EXIT	Case control	Retrospective	7
	Dahlgren 2004[137]	Head or neck tumour	EXIT	Case series	Retrospective	4
	Flake 2000†[138]	CDH	EXIT	Case series	Retrospective	15
	George 2007[139]	Skeletal dysplasia, micrognathia	EXIT	Case series	Retrospective	3
	Hedrick 2003[140]	Multiple	EXIT	Case series	Retrospective	43
	Hedrick 2005[141]	Lung lesions	EXIT	Case series	Retrospective	9
	Kern 2007[142]	CCAM, hydrothorax	EXIT	Case series	Retrospective	5
	Kornacki 2017[143]	Neck mass, CHAOS	EXIT	Case series	Retrospective	4
	Kunisaki 2007[144]	CDH	EXIT	Case control	Retrospective	14
	Laje 2012[145]	Cervical teratoma	EXIT	Case series	Retrospective	17
	Laje 2013[146]	Neck mass	EXIT	Case series	Retrospective	4
	Laje 2015[147]	Cervical lymphatic mass	EXIT	Case series	Retrospective	13
	Lazar 2011[148]	Neck mass	EXIT	Case series	Retrospective	12
	Noah 2002[149]	Not stated	EXIT	Case control	Retrospective	34
	Pellicer 2007[150]	Neck mass	EXIT	Case series	Retrospective	3
	Stoffan 2012[151]	CDH	EXIT	Case control	Retrospective	7
	Tuncay Ozgunen 2010[152]	Neck mass	EXIT	Case series	Retrospective	3
	Zamora 2013†‡[153]	MMC, lung mass, SCT	EXIT	Case series	Retrospective	26
MMC	Bennett 2014[154]	MMC	Neurosurgical repair	Case control	Retrospective	43
	Botelho 2017[155]	MMC	Neurosurgical repair	Case series	Retrospective	45

	Bruner 1999[156]	MMC	Neurosurgical repair	Case control	Retrospective	29
	Bruner 2000*[157]	MMC	Neurosurgical repair	Case control	Retrospective	4
	Farmer 2003[93]	MMC	Neurosurgical repair	Case series	Retrospective	12
	Friszer 2016[158]	MMC	Neurosurgical repair	Case series	Retrospective	3
	Johnson 2016[95]	MMC	Neurosurgical repair	Randomised	Prospective	91
	Marenco 2013[159]	MMC	Neurosurgical repair	Case series	Retrospective	4
	Moldenhauer 2015[98]	MMC	Neurosurgical repair	Case series	Retrospective	100
	Moron 2018[100]	MMC	Neurosurgical repair	Case series	Retrospective	237
	Ochsenbein-Kolble 2017[160]	MMC	Neurosurgical repair	Case control	Prospective	30
	Sinskey 2017[161]	MMC	Neurosurgical repair	Case series	Retrospective	47
	Soni 2016[101]	MMC	Neurosurgical repair	Case series	Retrospective	88
	Zamlynski 2014[97]	MMC	Neurosurgical repair	Case control	Retrospective	46
CDH	Flake 2000†[138]	CDH	Tracheal occlusion	Case series	Retrospective	15
	Harrison 1990[162]	CDH	Diaphragm repair	Case series	Retrospective	6
	Harrison 1993[163]	CDH	Diaphragm repair	Case series	Retrospective	14
	Harrison 1998*[164]	CDH	Tracheal occlusion	Case control	Retrospective	13
CCAM	Adzick 2003[165]	CCAM	Lung resection	Case series	Retrospective	22
SCT	Hedrick 2004[166]	SCT	Debulking	Case series	Retrospective	4
Mixed	Golombeck 2006†*[127]	MMC, CCAM, SCT	Mixed	Case control	Retrospective	79
	Longaker 1991[167]	LUTO, CDH, SCT, CCAM	Mixed	Case series	Retrospective	17
	Zamora 2013†‡[153]	MMC, lung mass, SCT	Mixed	Case series	Retrospective	7

TOTAL				**43 studies**		**1193 patients**

† Studies including patients undergoing a primary fetal and later an EXIT procedure.
* Studies including both open and fetoscopic procedures, also included in Table 2.6
‡ Studies including immediate and late complications, also included in Table 2.7

CCAM - congenital cystic adenomatoid malformation, CDH - congenital diaphragmatic hernia, CHAOS - congenital high airway obstruction syndrome, EXIT - ex-utero intrapartum treatment, LUTO - lower urinary tract obstruction, MMC - myelomeningocele, SCT - sacrococcygeal teratoma

Table 2.6: Included studies of fetoscopic surgery

Category	First author and year of publication	Condition	Procedure	Study design	Prosepective or retrospective	No. of patients
Multiple pregnancy complications treated with laser	Aboudiab 2017[168]	TTTS	Laser photocoagulation	Case series	Retrospective	18
	Baschat 2013[169]	TTTS	Laser photocoagulation	Case control	Retrospective	147
	Chalouhi 2016[170]	TTTS (triplets)	Laser photocoagulation	Case series	Retrospective	22
	Chang 2006[171]	TTTS	Laser photocoagulation	Case series	Retrospective	27
	Chang 2016[172]	TTTS	Laser photocoagulation	Case control	Retrospective	100
	Chmait 2013[173]	TTTS	Laser photocoagulation	Case control	Prospective	318
	Chmait 2017[174]	TTTS	Laser photocoagulation	Case series	Retrospective	19
	Crombleholme 2007[175]	TTTS	Laser photocoagulation	Randomised	Prosepective	20
	De Lia 1995[176]	TTTS	Laser photocoagulation	Case series	Retrospective	26
	De Lia 1999[177]	TTTS	Laser photocoagulation	Case series	Retrospective	67
	De Lia 2009[178]	TTTS (triplets)	Laser photocoagulation	Case series	Retrospective	10
	Deprest 1998[179]	TTTS	Laser photocoagulation	Case series	Retrospective	6
	Draga 2016[180]	TTTS	Laser photocoagulation	Case series	Retrospective	37
	Duron 2014[181]	TTTS	Laser photocoagulation	Case control	Retrospective	85
	Ek 2012[182]	TTTS	Laser photocoagulation	Case series	Retrospective	67
	Habli 2009[183]	TTTS	Laser photocoagulation	Case series	Retrospective	152
	Has 2014[184]	TTTS	Laser photocoagulation	Case series	Retrospective	85
	Hecher 2000[185]	TTTS	Laser photocoagulation	Case control	Prospective	200
	Hernandez-Andrade 2011[186]	TTTS	Laser photocoagulation	Case series	Retrospective	35

	Huber 2008[187]	TTTS	Laser photocoagulation	Case control	Prospective	176
	Ishii 2014[188]	TTTS (triplets)	Laser photocoagulation	Case series	Retrospective	16
	Ishii 2015[189]	sFGR	Laser photocoagulation	Case series	Prospective	10
	Lanna 2017[190]	TTTS	Laser photocoagulation	Case control	Retrospective	373
	Lecointre 2017[191]	TTTS	Laser photocoagulation	Case control	Retrospective	200
	Malshe 2017[192]	TTTS	Laser photocoagulation	Case series	Prospective	203
	Martinez 2012[193]	TTTS	Laser photocoagulation	Case series	Prospective	500
	Middeldorp 2007[194]	TTTS	Laser photocoagulation	Case series	Retrospective	100
	Miyadahira 2018[195]	sFGR	Laser photocoagulation	Case control	Retrospective	67
	Molina-Garcia 2009[196]	TTTS, sFGR	Laser photocoagulation	Case series	Retrospective	22
	Morris 2010[125]	TTTS	Laser photocoagulation	Case series	Prospective	164
	Mullers 2015[197]	TTTS	Laser photocoagulation	Case series	Retrospective	105
	Nakata 2016[198]	TTTS	Laser photocoagulation	Case series	Prospective	6
	Nguyen 2012[199]	TTTS	Laser photocoagulation	Case series	Retrospective	98
	Ozawa 2017[200]	Amniotic fluid discordance	Laser photocoagulation	Case series	Prospective	11
	Papanna 2010[201]	TTTS	Laser photocoagulation	Case control	Retrospective	48
	Papanna 2012[202]	TTTS	Laser photocoagulation	Case control	Retrospective	163
	Peeters 2014[203]	TTTS	Laser photocoagulation	Case control	Retrospective	338
	Persico 2016[204]	TTTS	Laser photocoagulation	Case series	Retrospective	106
	Quintero 2000[205]	TTTS	Laser photocoagulation	Case control	Retrospective	92
	Quintero 2001[206]	sFGR	Laser photocoagulation	Case series	Retrospective	11

	Rossi 2008[207]	TTTS	Laser photocoagulation	Case control	Retrospective	266
	Ruano 2009[208]	TTTS	Laser photocoagulation	Case series	Prospective	19
	Ruegg 2018[209]	TTTS	Laser photocoagulation	Case control	Retrospective	37
	Rustico 2012[210]	TTTS	Laser photocoagulation	Case series	Retrospective	150
	Said 2008[211]	TTTS	Laser photocoagulation	Case series	Retrospective	10
	Senat 2004[212]	TTTS	Laser photocoagulation	Randomised	Prospective	72
	Sepulveda 2007[213]	TTTS	Laser photocoagulation	Case series	Retrospective	33
	Shamshirsaz 2015[214]	TTTS	Laser photocoagulation	Case control	Retrospective	55
	Slaghekke 2014[215]	TTTS	Laser photocoagulation	Randomised	Prospective	274
	Taniguchi 2015[216]	TTTS	Laser photocoagulation	Case series	Retrospective	3
	Tchirikov 2011[217]	TTTS	Laser photocoagulation	Case control	Retrospective	80
	Teoh 2013[218]	TTTS	Laser photocoagulation	Case series	Prospective	49
	Thia 2017[219]	TTTS	Laser photocoagulation	Case series	Retrospective	5
	Ville 1997[220]	TTTS	Laser photocoagulation	Case series	Retrospective	132
	Ville 1998[221]	TTTS	Laser photocoagulation	Case control	Prospective	44
	Weingertner 2011[222]	TTTS	Laser photocoagulation	Case series	Retrospective	100
	Wilson 2016[223]	TTTS	Laser photocoagulation	Case series	Retrospective	151
	Yamamoto 2005[224]	TTTS	Laser photocoagulation	Case series	Retrospective	175
	Yang 2010[225]	TTTS	Laser photocoagulation	Case series	Retrospective	30
	Zaretsky 2018[226]	TTTS	Laser photocoagulation	Case series	Retrospective	749
	Zhao 2016[227]	TTTS	Laser photocoagulation	Case control	Retrospective	62

Multiple pregnancy complications treated with selective reduction	Bebbington 2012[228]	TTTS, TRAP, sFGR, discordant anomaly	RFA	Case control	Retrospective	146
	Berg 2014[229]	TRAP	RFA	Case control	Retrospective	7
	Delabaere 2013[230]	TTTS, TRAP, sFGR, discordant anomaly	BCC, cord compression, cord ligation	Case series	Retrospective	30
	Deprest 2000[231]	TTTS, TRAP	BCC	Case series	Retrospective	10
	Gallot 2003[232]	TTTS, TRAP	CO	Case series	Retrospective	11
	Gouverneur 2009[233]	TTTS, TRAP, sFGR, discordant anomaly	BCC, laser cord photocoagulation	Case series	Retrospective	54
	Gul 2008[234]	TTTS, TRAP, discordant anomaly	BCC	Case series	Prospective	9
	Has 2014[235]	TTTS, TRAP, sFGR, discordant anomaly	BCC	Case series	Retrospective	71
	He 2010[236]	TTTS, TRAP, sFGR, discordant anomaly	BCC	Case series	Retrospective	14
	Ilagan 2008[237]	TTTS, TRAP, discordant anomaly	BCC	Case series	Retrospective	27
	Jelin 2010[238]	TRAP	RFA	Case control	Retrospective	7
	King 2017[239]	TRAP, discordant anomaly	Laser cord photocoagulation	Case series	Retrospective	43
	Lanna 2012[240]	TTTS, TRAP, sFGR, discordant anomaly	BCC	Case series	Retrospective	118
	Lee 2013[241]	TRAP	RFA	Case series	Retrospective	98
	Lewi 2006[242]	TTTS, TRAP, sFGR, discordant anomaly	Laser cord photocoagulation	Case series	Prospective	80
	Moise 2008[243]	TTTS, discordant anomaly	RFA	Case series	Retrospective	9
	Nobili 2013[244]	Discordant anomaly	BCC	Case series	Retrospective	48
	Paramasivam 2010[245]	TTTS, TRAP, sFGR, discordant anomaly	RFA	Case series	Retrospective	35
	Peng 2016[246]	TTTS, TRAP, sFGR, discordant anomaly, TAPS	BCC	Case control	Retrospective	93

	Quintero 1996[247]	TTTS, TRAP, discordant anomaly	CO	Case series	Retrospective	13
	Quintero 2006[248]	TRAP	CO or laser photocoagulation	Case control	Retrospective	51
	Roman 2010[249]	TTTS, TRAP, sFGR, discordant anomaly	RFA	Case control	Retrospective	60
	Schou 2018[250]	TTTS, TRAP, sFGR, discordant anomaly	BCC	Case control	Retrospective	102
	Sugibayashi 2016[251]	TRAP	RFA	Case series	Retrospective	40
	Takano 2015[252]	TRAP	Laser photocoagulation +/- transection of cord (MCMA)	Case series	Retrospective	10
	Taylor 2002[253]	TTTS	BCC	Case series	Prospective	15
	Tsao 2002[254]	TRAP	RFA	Case series	Retrospective	13
	Zhang 2018[255]	TRAP	RFA	Case series	Retrospective	25
CDH	Deprest 2005[256]	CDH	FETO	Case series	Retrospective	20
	Harrison 1998*[164]	CDH	Tracheal clip	Case control	Retrospective	8
	Harrison 2003[21]	CDH	FETO	Randomised	Prospective	11
	Jani 2005[257]	CDH	FETO	Case series	Retrospective	24
	Jani 2006[258]	CDH	FETO	Case series	Prospective	28
	Jani 2009[22]	CDH	FETO	Case series	Prospective	210
	Jimenez 2017[259]	CDH	Fetoscopic balloon removal	Case control	Retrospective	201
	Kosinski 2017[260]	CDH	FETO	Case series	Prospective	28
	Manrique 2008[261]	CDH	FETO	Case control	Prospective	11
	Peralta 2011[262]	CDH	FETO	Case series	Prospective	8
	Persico 2017[263]	CDH	FETO	Case series	Retrospective	21
	Ruano 2012[264]	CDH	FETO	Case control	Prospective	35
	Ruano 2012[265]	CDH	FETO	Randomised	Prospective	20

	Ruano 2013[266]	CDH	FETO	Case control	Prospective	17
MMC	Arens 2017[267]	MMC	Patch	Case series	Retrospective	59
	Belfort 2017[118]	MMC	Single layer suture (skin + dura)	Case series	Retrospective	22
	Bruner 2000*[157]	MMC	Maternal skin graft	Case control	Retrospective	4
	Degenhardt 2014[121]	MMC	Patch	Case series	Retrospective	51
	Kohn 2018[268]	MMC	Patch	Case series	Retrospective	34
	Pedreira 2014[269]	MMC	Patch + skin suture	Case series	Retrospective	4
	Pedreira 2016[119]	MMC	Patch + skin suture	Case series	Prospective	10
	Verbeek 2012[270]	MMC	Patch	Case control	Retrospective	19
	Ziemann 2018[271]	MMC	Patch	Case series	Retrospective	65
LUTO	Morris 2013[272]	LUTO	Vesicoamniotic shunting	Randomised	Prospective	16
	Ruano 2010[273]	LUTO	Cystoscopy	Case control	Prospective	11
	Welsh 2003[274]	LUTO	Cystoscopy	Case series	Retrospective	13
Shunts	Cavalheiro 2011[275]	Ventriculomegaly	Shunting	Case series	Retrospective	30
	Mallman 2017[276]	Hydrothorax	Shunting	Case series	Retrospective	78
Mixed	Golombeck 2006*[127]	TTTS, TRAP, CDH, LUTO	Mixed	Case control	Retrospective	99
	Kohl 2006[277]	MMC, CDH, CHAOS	Mixed	Case series	Retrospective	16
	Kohl 2010[278]	MMC, TTTS, CDH, CHAOS, ABS	Mixed	Case series	Retrospective	37
	Nivatpumin 2016[279]	TTTS, LUTO, CDH, TRAPS	Mixed	Case series	Retrospective	152
	Peralta 2010[280]	TTTS, CDH, TRAP	Mixed	Case series	Retrospective	56
TOTAL				**122 studies**		**9403 patients**

* Studies including both open and fetoscopic procedures, also included in Table 2.5

BCC - bipolar cord coagulation, CDH - congenital diaphragmatic hernia, CHAOS - congenital high airway obstruction syndrome, CO - cord occlusion, FETO - fetoscopic endoluminal tracheal occlusion, LUTO - lower urinary tract obstruction, MCMA - monochorionic monoamniotic, MMC - myelomeningocele, RFA - cord radiofrequency ablation, sFGR - selective fetal growth restriction, TAPS - twin anaemia-polycythaemia sequence, TO - tracheal occlusion, TRAP - twin reversed arterial perfusion sequence, TTTS - twin-to-twin transfusion syndrome.

Table 2.7: Included studies of open and fetoscopic surgery focusing on late complications

First author and year of publication	Type of surgery	Condition	Study design	Prosepective or retrospective	Number of patients
Farrell 1999[126]	Open	CDH, CCAM, LUTO, SCT,	Case series	Retrospective	45
Thom 2016[281]	Open	MMC	Randomised	Prospective	87
Wilson 2010[109]	Open	MMC, CCAM, CDH, SCT, teratoma	Case series	Retrospective	47
Zamora 2013‡[153]	Open	MMC, lung mass, SCT, EXIT	Case series	Retrospective	33
Gregoir 2016[282]	Fetoscopic	CDH	Case control	Retrospective	89
Le Lous 2018[283]	Fetoscopic	TTTS	Case control	Retrospective	122
Vergote 2018[284]	Fetoscopic	TTTS	Case control	Retrospective	92
TOTAL			**7 studies**		**515 patients**

‡ Studies including immediate and late complications, also included in Table 2.5

CCAM - congenital cystic adenomatoid malformation, CDH - congenital diaphragmatic hernia, EXIT - ex-utero intrapartum treatment, LUTO - lower urinary tract obstruction, MMC - myelomeningocele, SCT - sacrococcygeal teratoma, TTTS - twin-to-twin transfusion syndrome

Risk of bias

Quality assessment of the studies is given in Figure 2.6. Most studies (139/166, 83.7%) had a low risk of bias or were high quality. All remaining studies (27/166, 16.3%) had an unclear risk of bias or were fair quality. No studies were found to have a high risk of bias or be low quality overall. For randomised trials, included

studies had a high risk of bias with regards to blinding. For case control studies, included studies did not describe statistical methods well overall.

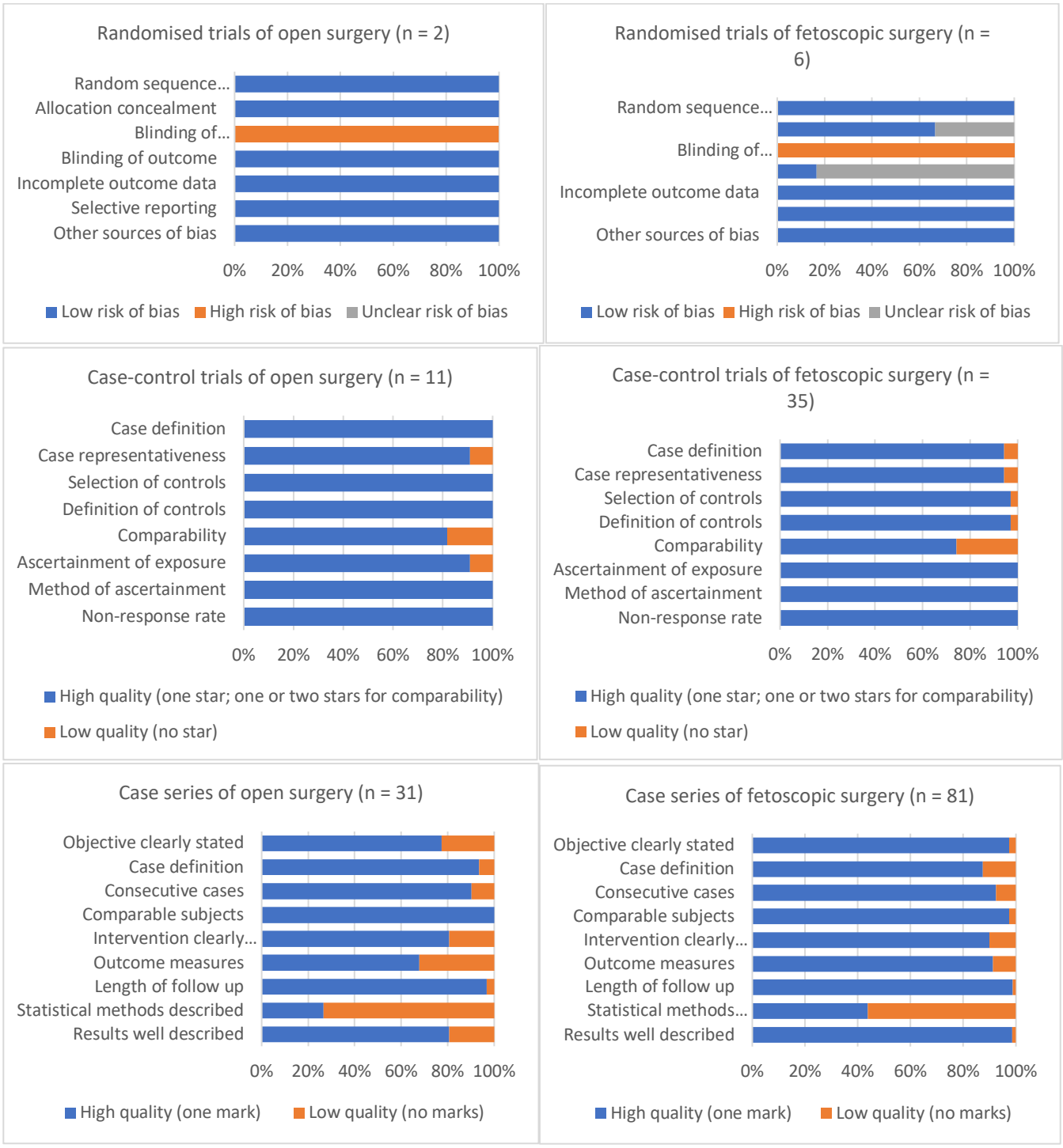

Figure 2.6: Summary of risk of bias according to study type

Statistical heterogeneity

Maternal outcome data was pooled in 64 separate meta-analyses, of which 37.5% (24/64) had no or minor heterogeneity. In 39.1% (25/64) there was moderate heterogeneity and in 23.4% (15/64) there was considerable heterogeneity. As both clinical and statistical heterogeneity were found, pooled proportions were given using the random effects model for meta-analysis.

Maternal complications in the index pregnancy - intra-operative

Table 2.8 summarises maternal complications according to type of surgery performed. No maternal deaths (Clavien-Dindo grade V) due to fetal surgery were reported in any study (10,596 procedures). One study[197] reported a patient at 20 weeks' gestation experiencing a cardio-respiratory arrest *prior* to fetoscopy for laser photocoagulation. The cause was considered to be a combination of morbid obesity, spinal anaesthesia and aorto-caval compression, and not related to the procedure which had not commenced. An immediate delivery was conducted by hysterotomy as part of maternal resuscitation and the patient made a full recovery. Another study[161] reported brief maternal seizure-like activity during open fetal surgery, which was thought to be anaesthesia-related.

Haemorrhage severe enough to prompt delivery or termination of pregnancy at the time of surgery as a life-saving procedure for the mother (Clavien-Dindo grade III) occurred in 0.92% of open fetal (95% CI 0.46-1.62) and 0.26% of fetoscopic surgeries (95% CI 0.17-0.38). Three cases[156 100 160] occurred due to placental abruption during open fetal surgery for myelomeningocele (MMC) repair, following which delivery occurred, with all three fetuses surviving. Two cases[171]

[187] occurred following laser photocoagulation for TTTS said to be due to "excessive bleeding from placental anastomoses" and the uterine wall respectively. Two cases[230] [232] occurred during selective reduction, with haemorrhage from the uterine wall prompting delivery. Finally, one pregnancy was terminated due to bleeding from a trocar placental injury during fetoscopic MMC repair.[278]

In total, placental abruption (Clavien-Dindo grade III) occurred intraoperatively in 1.28% of open fetal (95% CI 0.73-1.98) and in 0.28% of fetoscopic surgeries (95% CI 0.18-0.39). Bleeding during the procedure was noted in 1.97% of open fetal (95% CI 0.97-3.31) and in 1.74% of fetoscopic surgery cases (95% CI 1.25-2.32). Intra-operative blood transfusion was required in 1.00% of patients undergoing open fetal surgery (95% CI 0.53-1.64) and in 0.27% undergoing fetoscopic surgery (95% CI 0.18-0.38). Intra-operative skin burns at the site of diathermy pads occurred in 0.26% of patients (95% CI 0.17-0.37) during fetoscopic surgery; this outcome was not reported in any open fetal surgery.

Maternal complications in the index pregnancy - postoperative

One study on laser photocoagulation for TTTS (n=132)[221] reported a maternal death from disseminated intravascular coagulation (DIC) four weeks following an uneventful procedure. A post-mortem examination did not find any evidence of chorioamnionitis or amniotic fluid embolism and the authors therefore concluded that this death was unrelated to the procedure.

Haemorrhage severe enough to prompt return to theatre for termination or delivery of the pregnancy within 24 hours was not reported following any open fetal surgeries but occurred following 0.25% of fetoscopic procedures (95% CI 0.16-0.37). This included one[277] four hours post-fetoscopic tracheal balloon removal with no cause of the bleeding found. There were two late placental abruptions, one[224] 12 hours post-laser photocoagulation and one[253] within 24 hours of bipolar cord coagulation.

Placental abruption occurred in 1.80% of patients following open fetal (95% CI 1.14-2.63) and in 1.29% following fetoscopic surgery (95% CI 0.90-1.75). Post-operative blood transfusion was given to 3.36% after open fetal surgery (95% CI 1.85-5.29) and in 0.32% following fetoscopic surgery (95% CI 0.22-0.44).

Chorioamnionitis following open fetal surgery or endometritis following an EXIT procedure occurred in 4.13% of women (95% CI 3.03-5.40), and in 1.45% undergoing fetoscopic surgery (95% CI 1.06-1.90). Of those, PROM was reported to have occurred in 47.78% following open fetal surgery (95% CI 23.01-73.16) and in 36.31% following fetoscopic surgery (95% CI 22.00-51.99). One study reported severe chorioamnionitis five days after bipolar cord coagulation[242] with septic shock and acute kidney injury which resolved leaving 70% residual renal function. Sepsis was also reported in one patient[173] with chorioamnionitis following fetoscopic laser photocoagulation and in one patient[97] following open MMC repair who developed post-operative peritonitis requiring an emergency laparotomy and delivery. Post-operative pneumonia occurred in two patients - one[243] following fetoscopic radiofrequency ablation (RFA), necessitating three

days of intubation and intensive care unit (ICU) care; and one requiring ICU admission [154] following open MMC repair.

Pulmonary oedema occurred in 4.32% of open fetal surgery cases (95% CI 2.32-6.90), and in 0.63% of fetoscopic cases (95% CI 0.43-0.87). Three studies in which post-operative pulmonary oedema occurred reported on peri-operative fluid management (3/102, 2.9%) and 33 reported on the use of magnesium sulphate (33/102, 32.4%) without specifically suggesting causality. Six women required ICU admission, with four requiring intubation and ventilation; three following open fetal surgery[127 138] and three following fetoscopic surgery[181 198 210].

Maternal complications in the index pregnancy - at delivery

Only a few fetoscopic surgery studies (4/121 studies, 0.33%) reported findings or complications at delivery. Complications at delivery following open fetal surgery are shown in Table 2.8. Hysterectomy at or around the time of delivery was reported in two patients (Clavien-Dindo grade III). In one case[98], caesarean delivery following open MMC repair in a woman with two previous caesareans, intra-abdominal scarring and friable tissue eventually resulted in hysterectomy. In the second case[210] following laser photocoagulation for TTTS and PROM, a caesarean section was performed at 33 weeks' gestation. A hysterectomy was eventually required due to haemorrhage with DIC and the patient spent five days in ICU, where she also experienced an iatrogenic pneumothorax.

Uterine rupture occurred in 0.90% of patients at delivery following open fetal surgery (excluding EXIT procedures) in the index pregnancy (95% CI 0.41-1.59), and uterine dehiscence occurred in 3.67% (95% CI 2.01-5.81). Blood transfusion was given to 1.83% of women (95% CI 1.16-2.65) at delivery following open fetal surgery.

Overall maternal complication rates

Table 2.8 displays maternal complications. In open fetal surgery there was a 4.51% severe (95% CI 3.24-5.98), a 16.26% minor complication rate (95% CI 11.17-22.09), and a total complication rate of 20.86% (95% CI 15.22-27.13). For fetoscopic surgery, the corresponding rates were: 1.66% severe (95% CI 1.19-2.20), 4.33% minor (95% CI 3.33-5.45) and 6.15% total complications (95% CI 4.93-7.49). Complication rates in the six commonest fetal surgical procedures performed are displayed in Table 2.9.

Table 2.8: Maternal complications occurring with open or fetoscopic fetal surgery

	Severe complications				**Minor complications**		**All complications**
Clavien-Dindo classification	IV (requiring ICU care)		III (requiring surgical intervention)		I-II (requiring treatment)		I - IV
Open surgery n = 1193	*Complication*	*n*	*Complication*	*n*	*Complication*	*n*	**ALL COMPLICATIONS: 20.86% (95% CI 15.22-27.13)**
	Severe infection	2	Haemorrhage requiring delivery	3	Bleeding during procedure	13	
	Pulmonary oedema	4	Placental abruption	28	Transfusion during/after procedure	41	
	Complete heart block†a	1	Bowel obstruction	1	Chorioamnionitis/ endometritis	45	
			Wound drainage	2	Other infections†b	8	
			Uterine rupture	5	Pulmonary oedema	50	
			Laparotomy/ dehiscence repair	1	Transfusion at delivery	17	
			Caesarean hysterectomy	1			
	TOTAL SEVERE: 4.51% (95% CI 3.24-5.98)				**TOTAL MINOR: 16.26% (95% CI 11.17-22.09)**		
Fetoscopic surgery n = 9403	Maternal cardiac arrest and delivery by hysterotomy	1	Sepsis requiring delivery	1	Bleeding during procedure	165	
	Severe infection	2	Haemorrhage requiring delivery	8	Transfusion during/after procedure	16	
	Pulmonary oedema	3	Placental abruption	159	Venous thromboembolism†c	2	
	Lung collapse	1			Chorioamnionitis	114	
	DIC + caesarean hysterectomy	1			Other infections†d	2	
	Amniotic fluid embolism	2			Pulmonary oedema	45	
					Upper GI bleed†e	1	
					Diathermy skin burns	4	

					“Epidural headache” + blood patch	1	**ALL COMPLICATIONS: 6.15% (95% CI 4.93-7.49)**
					Wound hernia	1	
					Pleural effusions	1	
	TOTAL SEVERE: 1.66% (95% CI 1.19-2.20)				**TOTAL MINOR: 4.33% (95% CI 3.33-5.45)**		

Pooled proportions calculated using random effect model for meta-analysis
n: number of women, [†a] Complete heart block considered to be tocolysis-related (magnesium sulphate), [†b] Other infections in open surgery: wound (6), chest (1), urinary tract (1), [†c] Venous thromboembolism: confirmed pulmonary embolism (1); suspected PE with confirmed deep vein thrombosis (1), [†d] Other infections in fetoscopic surgery: wound (1), chest (1), [†e] Upper GI bleed considered to be tocolysis-related (indomethacin)

Table 2.9: Maternal complications according to type of fetal surgery in the six most common procedures

	Severe complications				**Minor complications**		**All complications**
Clavien-Dindo classification	IV (requiring ICU care)		III (requiring surgical intervention)		I-II (requiring treatment)		I - IV
EXIT **n = 237**	*Complication*	*n*	*Complication*	*n*	*Complication*	*n*	**ALL COMPLICATIONS: 20.19%** **(95% CI 4.93-7.49)**
			Placental abruption	5	Bleeding during procedure	11	
					Transfusion during/after procedure	19	
					Endometritis	10	
					Wound infection	5	
	TOTAL SEVERE: 3.62% **(95% CI 1.69-6.24)**				**TOTAL MINOR: 17.53%** **(95% CI 9.86-26.86)**		
Open MMC repair **n = 779**	Severe infection	2	Haemorrhage requiring delivery	3	Bleeding during procedure	1	**ALL COMPLICATIONS: 11.54%** **(95% CI 7.73-15.99)**
	Complete heart block	1	Placental abruption	16	Transfusion during/after procedure	5	
	Pulmonary oedema	1	Bowel obstruction	1	Chorioamnionitis	21	
			Uterine rupture	4	Other infections[†a]	2	
			Caesarean hysterectomy	1	Pulmonary oedema	15	
					Transfusion at delivery	16	
	TOTAL SEVERE: 3.35% **(95% CI 1.70-5.53)**				**TOTAL MINOR: 6.63%** **(95% CI 3.63-10.45)**		

Fetoscopic MMC repair n = 268			Placental abruption	6	Bleeding during procedure	3	**ALL COMPLICATIONS: 12.49%** **(95% CI 4.83-23.06)**
					Chorioamnionitis	10	
					Pulmonary oedema	5	
	TOTAL SEVERE: 2.75% **(95% CI 0.56-6.52)**				**TOTAL MINOR: 9.04%** **(95% CI 3.27-17.40)**		
FETO (insertion or fetoscopic removal of balloon) **n = 634**			Placental abruption	4	Bleeding during procedure	1	**ALL COMPLICATIONS: 3.44%** **(95% CI 0.98-7.32)**
					Transfusion during/after procedure	1	
					Chorioamnionitis	7	
					Wound infection	1	
					Pulmonary oedema	3	
	TOTAL SEVERE: 1.08% **(95% CI 0.23-2.54)**				**TOTAL MINOR: 2.39%** **(95% CI 0.71-5.02)**		
Fetoscopic laser photo-coagulation **n = 6746**	Maternal arrest and delivery	1	Haemorrhage requiring delivery	2	Bleeding during procedure	148	**ALL COMPLICATIONS: 5.86%** **(95% CI 4.33-7.61)**
	Pulmonary oedema	3	Sepsis requiring delivery	1	Transfusion during/after procedure	9	
	Lung collapse	1	Placental abruption	13 0	VTE[†b]	2	
	Amniotic fluid embolism	2			“Epidural headache” + blood patch	1	
	DIC + caesarean hysterectomy	1			Chorioamnionitis	68	
					Pulmonary oedema	11	
					Upper GI bleed[†c]	1	
					Wound hernia	1	
	TOTAL SEVERE: 1.51% **(95% CI 0.91-2.25)**				**TOTAL MINOR: 4.03%** **(95% CI 2.73-5.56)**		

Fetoscopic selective reduction **n = 1239**	Severe infection	2	Haemorrhage requiring delivery	3	Bleeding during procedure	10	**ALL COMPLICATIONS: 5.20%** **(95% CI 3.00-7.96)**
			Placental abruption	1 4	Diathermy skin burns	4	
					Chorioamnionitis	19	
					Chest infection	1	
					Pleural effusion	1	
	TOTAL SEVERE: 1.98% **(95% CI 0.97-3.35)**				**TOTAL MINOR: 3.00%** **(95% CI 1.68-4.68)**		

Pooled proportions calculated using random effect model for meta-analysis
n: number of women, †a Other infections in MMC surgery: chest (1), urinary tract (1), †b Venous thromboembolism: confirmed pulmonary embolism (PE) (1); suspected PE with confirmed deep vein thrombosis (1), †c Upper GI bleed considered to be tocolysis-related (indomethacin)
EXIT - ex-utero intrapartum treatment, FETO - fetoscopic endoluminal tracheal occlusion, MMC - myelomeningocele, DIC - disseminated intravascular coagulation

Maternal outcomes following the index pregnancy (long-term)

Table 2.10 shows subsequent pregnancy outcomes and long-term maternal outcomes following a pregnancy in which fetal surgery was performed. New difficulties in conceiving were described in 3.81% of women after open fetal surgery (95% CI 1.22-7.76, reported in four studies); this outcome was not reported to occur after fetoscopic surgery (three studies). Pregnancy loss prior to 24 weeks' gestation occurred in 19.95% of pregnancies conceived following open fetal surgery (95% CI 13.37-27.48, three studies) and 13.67% of pregnancies conceived after fetoscopic surgery (95% CI 9.34-18.68, three studies). Preterm birth occurred in 20.49% of pregnancies following open fetal surgery (95% CI 10.48-32.81, four studies) and in 2.12% of pregnancies following fetoscopic surgery (95% CI 0.02-9.01; three studies). Uterine rupture or dehiscence occurred respectively in 6.89% (95% CI 1.34-16.27, reported in three studies) and 11.09% (95% CI 5.34-18.59) of pregnancies following open fetal surgery. None were mentioned in fetoscopy studies. The risk of morbidly adherent placenta in subsequent pregnancies was not discussed in any of the studies.

Table 2.10: Long-term maternal complications following open and fetoscopic fetal surgery

		Open surgery†a % (95% CI)	**Fetoscopic surgery†a** % (95% CI)
Conception	Women attempting further pregnancy	50.11 (21.55-78.63)	51.76 (18.63-84.03)
	Women conceiving further pregnancy	48.33 (26.74-70.26)	48.20 (31.46-65.16)
	New sub-fertility	3.81 (1.22-7.76)	NR
Pregnancy outcomes	Miscarriage	19.95 (13.37-27.48)	13.67 (9.34-18.68)
	Pre-term delivery	20.49 (10.48-32.81)	2.12 (0.02-9.01)
	Uterine rupture	6.89 (1.34-16.27)	0
	Uterine dehiscence	11.09 (5.34-18.59)	NR
	Excessive bleeding at delivery	6.84 (2.16-13.88)	5.52 (2.83-9.03)
Non-pregnancy	Abdominal pain	6.38†b	9.01 (3.84-16.06)
	Abnormal menstrual bleeding	NR	6.54 (3.43-10.57)
	Gynaecological surgery†c	8.68 (1.81-19.96)	NR
	Psychological symptoms	9.09†b	32.56 (7.70-64.58)

Pooled proportions calculated using random effect model for meta-analysis
NR - not reported
†a Variable denominator as not all outcomes were reported by all studies
†b No meta-analysis possible as reported by single study
†c Gynaecological surgery following open fetal surgery: endometrial ablation (1), hysterectomy (6): caesarean hysterectomy (1), ovarian cysts+/-menstrual disorder (2), fibroids (1), unknown reason (2)

2.2.4 Discussion

In this systematic review of the literature we found an overall complication rate of approximately 21% for open fetal surgery and 6% for fetoscopic fetal surgery, of which minor complications occurred in 16% and 4% of surgeries respectively. This maternal complication rate excludes obstetric complications which may also have occurred (e.g. PROM, CMS, preterm labour and preterm delivery). Additionally, many studies of fetal surgery fail to document maternal complications. Out of 751 full-text articles reviewed, 175 (23.3%) were excluded as no maternal outcomes were stated. Although 68 of these studies focused on a specific aspect of the surgery or its neonatal outcome, 107 studies (92 fetoscopic and 15 open) involving over 9000 patients did *not* comment on the presence or absence of any complications specifically affecting the mother's health. Often the "maternal outcomes" stated meant in reality obstetric outcomes (e.g. PROM, preterm labour). We also found that maternal complications were often presented from the fetal perspective (e.g. fetal demise caused by placental abruption). Thirty included studies (18.1%) contained a statement that no adverse maternal outcomes were observed without specifying what was meant by maternal outcomes. Among these studies were some large series, including a study of 201 patients undergoing fetoscopic tracheal balloon removal[259] and studies of 200[185] and 500[193] patients undergoing fetoscopic laser coagulation. It is unlikely that such large numbers of procedures had no maternal complications, and more likely that complications were either not perceived as serious, not reported and/or the patient follow-up was incomplete. This lack of reporting has most likely led to an underestimation of the actual risk of maternal complications in our meta-analysis. Conversely, when maternal complications were reported,

there was a wide variability in which outcomes were discussed and how they were presented.

There was a severe complication rate (Clavien-Dindo grade III or IV) of 4.5% in women undergoing open fetal surgery and 1.7% undergoing fetoscopic surgery. This is in keeping with a previous multi-centre review of maternal complications following laser photocoagulation for TTTS[128] which found a 1.0% rate of severe complications and a 5.4% total rate of complications across all studies; however, when the authors only included studies which systematically assessed maternal complications as a primary or secondary outcome, this rose to 1.8% for severe and 17.4% for all complications.

In almost all studies of fetal surgery reviewed, long-term maternal follow up was not described. The seven studies that did so had a wide variation in the parameters described. Fertility does not appear to be negatively affected by fetal surgery, with the rates of de novo difficulties for conceiving in this review (3.81% following open fetal surgery and none following fetoscopic surgery) being comparable, if not less, than published rates of secondary infertility in the general population[285]. Similarly, the rates of miscarriage described (19.85% following open fetal and 13.67% following fetoscopic surgery) are similar to rates of spontaneous miscarriage in women who have not undergone fetal surgery [286] [287] [288]. Epidemiological studies[289] have suggested a worldwide preterm birth rate of 11.1% with a rate of 8.6% in “developed regions”[289]. In the US and UK it is estimated at 9.8%[290] and 7.3%[291] respectively. The preterm birth rate in this review following open fetal surgery (20.49%) is higher than the usual prevalence, but not higher following fetoscopic surgery (2.12%). Open fetal surgery was followed by uterine rupture or dehiscence in 6.89% and 11.09% of subsequent

pregnancies respectively, which is in line with published rates of rupture (6.2%) and dehiscence (12.5%) following a classical caesarean section[292]. Conversely, no uterine ruptures were reported following fetoscopic surgery.

This study included the commonest fetal procedures and, from a maternal perspective, involved similar surgical manipulations yet variable operating times. We included studies from multiple centres worldwide and attempted to identify the non-English literature. It is therefore likely that these results are generalisable to fetal surgery performed outside the included studies. An obvious weakness of this systematic review is that most studies did not include a control group. Furthermore, we decided to pool data for meta-analysis despite having high heterogeneity in some results. Another weakness is the extraction of patient data from papers, which is prone to error given the variable reporting; it is possible that some patients had more than one complication and this was not noted or cumulative rates were as a consequence miscalculated.

This systematic review has identified a significant rate of maternal complications, which should be discussed with patients before embarking on fetal surgery. Large studies allow an estimation of the likelihood of these events, insomuch as the cases in these series are unselected and consecutive. Our systematic review search strategy may have missed relevant yet rare complications. For example, a letter to a journal editor describing maternal convulsions during general anaesthesia[293] was excluded as a case report according to our criteria. In this circumstance, it appears the patient was also part of the cohort of a study that was included[161], but it is possible that other rare events reported as case series have been missed. An international, prospective registry of fetal and fetoscopic surgery, such as the Eurofoetus[294] and NAFTNet[111] registries, would be the best

way to accurately determine complication types and rates and avoid missing rare complications.

2.2.5 Conclusion

The maternal risks of fetal surgery are accepted by many patients and healthcare professionals for the possible benefit to the fetus[295 296]. This systematic review finds that studies of fetal surgery focus on the fetal outcomes of the procedure, and many fail to describe maternal complications. Fetal surgery comes at a risk to the mother, which may be underestimated by fetal therapists due to under-reporting and variable reporting quality. In order to properly quantify maternal risks, outcomes should be reported consistently across all studies of fetal surgery, preferentially in prospective registries.

2.2.6 Contributions

The work in Chapter 2.2 was produced in collaboration with: Dr Lennart Van der Veeken (L.D.V., KU Leuven, Belgium), Miss Emma Bagshaw (E.B., University College London), Miss Catherine Ferguson (C.F., University College London), Dr Tim Van Mieghem (Mount Sinai Hospital and University of Toronto, Canada), Professor Anna David (University College London) and Professor Jan Deprest (KU Leuven, Belgium).

2.3 Background Review of Setting up a Clinical Service

2.3.1 Introduction

Based on the background of open fetal surgery for spina bifida (myelomeningocele, MMC) and international developments, as described in previous chapters, the possibility of setting up a fetal surgery unit in our institution (University College London Hospitals, UCLH) was considered. This resolve was strengthened by increasing recognition of the procedure, and other types of fetal surgery, in media coverage and by patient request. By 2017, five British women with fetal MMC had travelled to centres in western Europe to undergo the procedure.

UCLH has a well-established Fetal Medicine Unit (FMU) which is a regional, national and international referral centre, seeing over 7000 patients a year. It has strong links with UCLH neonatal services and Great Ormond Street Hospital (GOSH) surgical and paediatric services, as well as strong research links with the UCL Institute for Women's Health. The FMU offers invasive fetoscopic procedures on the placenta, cord and membranes - such as laser coagulation, cord occlusion and fetal blood transfusion. Ex-Utero Intrapartum Treatment (EXIT) procedures[297] have previously been performed at UCLH; this a surgical procedure that is used at delivery for babies with potential airway compression. A caesarean section is performed by obstetricians but the baby remains on placental circulation until an airway has been established by a neonatal or paediatric surgical team. This is a multi-disciplinary procedure and success

performing it was considered encouraging for the set-up of open fetal surgery. Following discussions with all clinical groups in November 2013, the option of setting up a fetal surgery service as a collaboration between UCLH and GOSH was agreed.

2.3.2 General Principles on Setting Up a Clinical Service in the UK

There are many models for introducing clinical or organisational change in the UK.

The *"Seven S" framework"*[298] is a management model used for organisational analysis to evaluate possible changes; each of the seven aspects need to be aligned for the change to be successful. Each is considered below using the example of fetal surgery at UCLH:

- Strategy: Is the change in line with the purpose of the organisation?

  The purpose of UCLH is to provide world-class care and, from the evidence discussed in chapter 1.2, offering fetal surgery for MMC would fit with that.

- Structure: Does the existing organisational structure lend itself to supporting this venture in a coordinated approach?

  Previous experience at UCLH with invasive fetal procedures and EXIT procedures suggest this to be the case.

- Systems: Are systems in place to support this change - e.g. administrative systems, information technology and patient support?

Much of this would fit into the existing practice of the FMU, although a "co-ordinator" was considered desirable to ease the process.

- Shared values: All parties involved in the change have to believe in the venture in order for it to be successful.

  Discussions between fetal medicine specialists, obstetricians, neonatal neurosurgeons and neonatologists at an early stage showed this to be the case.

- Skills: Do the staff have the necessary expertise?

  It was established that a good skills base was present but that further training would be required in order for the procedure to be performed safely and smoothly.

- Staff: Are the right staff in place to facilitate the introduction of the new service?

  As discussed above, this was considered true for UCLH/GOSH as a cross-site collaboration.

- Style: Is the current management style appropriate to oversee this?

  There was considerable managerial support for this proposal. Close working with the management team was assisted by the situation of the fetal medicine consultant lead for neurology also being the clinical director of women's services.

A *"step-by-step guide"*[299] to setting up a new clinical service was published in the BMJ online in 2009. The process for proposal, set-up and execution of a new service was as follows, using the example of fetal surgery at UCLH:

- Conception: Assess the current service, analyse the problems and suggest an alternative.

  This is described in the previous chapters.

- Preparation: The authors suggest using the “Seven S” model as discussed above.
- Business case: This should be made to the trust using local protocols.

  This was done at UCLH and will be discussed later in this chapter.

- Project title: This must be succinct and informative.

  “Fetal Surgery for Spina Bifida” was chosen as this appeared most self-explanatory. Alternatives to “fetal” include “in-utero” and “prenatal” but it is possible that “fetal” conveys the time point of surgery more clearly. Similarly, although “myelomeningocele”, or MMC, is technically more correct as this is the open type of spina bifida that will be treated, it was felt that this description would be less easily understandable to patients and non-experts.

- Summary statement: The project must be able to be condensed into two sentences.

  “UCLH/GOSH will introduce fetal surgery for spina bifida in 2018. This has been shown to improve outcomes when compared to neonatal repair in a randomised trial.”

- Background: A summary of why the service is necessary and what is already provided must be known.

  The alternative options of termination of pregnancy and postnatal repair[77] have been discussed in previous chapters.

- Description of the service: A brief overview of the proposed service must be provided.

  "Patients fulfilling criteria and who wish to have fetal surgery will be operated on at 23 to 26 weeks' gestation of pregnancy. It is expected that they will be an inpatient for approximately one week following surgery, and will require close follow-up until delivery."

- Benefits analysis: Clinical benefits will usually have been dealt with already; the economic analysis must be estimated.

  This will be analysed in chapter 2.5.

- Project planning: A timetable and plan for smooth introduction of the service should be created.

  A timeline for service implementation was created, with plans to be offering a clinical service in the next 3-5 years.

- Pilot study (execution): A small number of cases should be performed first and then evaluated.

  Funding secured was estimated to cover service set-up and performing the first 10 cases, after which there would be a review of outcomes and of funding structure.

- Audit: Clinical review of cases performed and learning points prior to progressing further.

  Data collection and evaluation on all referrals and cases was planned.

The *NHS England document* "Planning, assuring and delivering service change for patients"[300], whilst primarily being a good practice guide for commissioners

regarding service reconfiguration, has key themes which are applicable to setting up a fetal surgery service as follows:

- Preparation and planning
- Evidence base
- Leadership and clinical involvement
- Involvement of patients and the public

This final point, describing the need for "ongoing and continuous patient and public engagement" is emphasised and is clearly important in setting up a service which could be viewed as contentious by the public. We therefore have sought to involve the public from the outset and have closely collaborated with SHINE (Spina Bifida, Hydrocephalus, Information, Networking, Equality) Charity[301] throughout our set-up.

2.3.3 Examples of Clinical Services Set Up Within O&G in the UK

A "practical guide" to setting up a preterm birth clinic was published in 2006[302]. This paper explored the problem of preterm birth and the aims of a specialist clinic to reduce and manage the condition. Patient selection, with inclusion and exclusion criteria, was discussed and provides a good example of being specific prior to the service being offered. We have attempted to do this in setting up our fetal surgery service, as discussed further in chapter 3.2.2. Practical needs in setting up a clinic discussed in this paper included the input of an experienced midwife, referral pathways, ultrasound and biochemical services, patient information leaflets, the ability to perform rescue cerclage, departmental protocols and opportunities for research, audit and teaching. With the exception

of cervical cerclage, it would seem that all these practical needs also exist for setting up a fetal surgery service.

A paper published in 2007 discussed setting up an outpatient service for early medical termination of pregnancy[303]. Training and equipment requirements were explored, and the authors concluded that the service was cost effective and "the training and equipment needed benefit other patients". This "knock-on" effect of service development is interesting, and it is possible that developing a programme of fetal surgery for MMC will improve patient care in other ways, for example making clinicians more familiar with spina bifida and therefore improving counselling, or developing surgical skills which are transferable to other procedures.

2.3.4 International Guidance on Setting Up a Fetal Surgery Centre

The Meningomyelocele Maternal-Fetal Management Task Force was convened by the Eunice Kennedy Shriver National Institute of Child Health and Human Development; in 2014 this task force published a Position Statement on fetal myelomeningocele repair[304]. In anticipation of an increasing number of centres setting up a fetal surgery service, it sought to establish minimum criteria for such centres.

The position statement recommendations fell into six categories, which are quoted and discussed in further detail with reference to UCLH/GOSH:

1. Defining a fetal therapy centre

   An experienced fetal care team should exist which includes the following:

   - A functional team experienced in collaborative patient care with a designated leader.
   - Care coordinator.
   - Fetal echocardiographer.
   - Surgeon with experience performing hysterotomy and closure (this could be an obstetrician or paediatric surgeon).
   - Genetic counsellor.
   - Magnetic resonance imaging equipment and expertise to perform and interpret fetal cases.
   - Maternal fetal medicine specialist.
   - Neonatology.
   - Obstetric anaesthesia.
   - Paediatric anaesthesia.
   - Neonatal or paediatric neurosurgeon (with experience performing open repair of spina bifida).
   - Social work.
   - Ultrasound equipment and expertise to perform and interpret fetal cases.

   The existing team, with collaborators from Great Ormond Street Children's Hospital (GOSH) was felt to fulfil all the above criteria.

   Alongside the fetal care team as defined above, it was recommended that the proposed fetal surgery centre have a multidisciplinary spina bifida

clinic (as exists at GOSH), as well as a Level III Neonatal Intensive Care Unit (NICU) and a labour and delivery unit capable of caring for perioperative complications and obstetric emergencies, both of which exist at UCLH.

2. Perioperative management for fetal MMC repair

   The preoperative evaluation (and inclusion/ exclusion criteria), intraoperative procedure and immediate postoperative care should be performed in strict adherence to the MOMs protocol[94].

   This was agreed by the UCLH/GOSH team and written into the local protocol.

3. Long-term care

   Neonates and children should be cared for in multidisciplinary spina bifida clinics which include the following:

   - Developmental paediatrician
   - Neuropsychologist
   - Orthopaedic surgeon
   - Paediatric neurosurgeon
   - Physical therapy/ occupational therapy
   - Psychosocial support
   - Rehabilitation
   - Urology

The recommendations stated that “this can be performed outside the fetal therapy centre as long as the resources are similar to that provided at the fetal centre in order to maintain uniform care for ongoing outcomes evaluation.” The existing spina bifida clinic at GOSH, a tertiary referral centre for spina bifida, fulfils these criteria.

4. Counselling

   A standardised non-directive counselling model must be in place. All management options, including termination of pregnancy and postnatal MMC repair must be discussed. Parents must be given a period for reflection of at least 24 hours.

   This was agreed by the UCLH/GOSH team and written into the local protocol.

5. Reporting and monitoring

   Fetal surgery centres should report short and long-term paediatric and maternal results, including reproductive outcomes in subsequent pregnancies. Centres should join a central registry to track outcome data.

   This was agreed by the UCLH/GOSH team and written into the local protocol.

6. Access and regionalisation

   Fetal surgery centres should be geographically distributed throughout the country to improve access.

No other fetal surgery centres currently exist in the UK, and London is easily accessible from all parts of the UK.

In summary, a UCLH/GOSH collaboration was thought to fulfil all the criteria set out for a fetal surgery centre. From 2014 to 2015, it was negotiated that Professor Jan Deprest, lead clinician for the fetal surgery programme in Leuven, Belgium would be employed at UCLH for two days a week to oversee the introduction of a fetal surgery programme in London. He took up this post in January 2016.

2.3.5 UCLH Service Set-Up Regulations

The UCLH Policy Guideline "New Interventional Procedures: Introduction to UCLH"[305] sets out the process and requirements for introducing a new service in the UCLH NHS Foundation Trust. This is based on the Department of Health Circular "The Interventional Procedures Programme - working with the National Institute of Clinical Excellence to promote safe clinical innovation"[306] which all trusts were expected to implement following publication in 2003. A replacement for this document was proposed by the National Institute for Health and Care Excellence (NICE) in 2017[307] but has yet to be published.

The process of new service approval is as follows:

1. A Lead Clinician is named, who assumes responsibility for all parts of the application including auditing and presenting results.

2. The Divisional Clinical Director is required to approve the application and forward it.
3. The Medical Director is required to approve the application and forward it.
4. The Clinical Effectiveness Steering Group (CESG) is responsible for giving ultimate approval of new interventional procedures on behalf of the Quality and Safety Committee and the Chief Executive.

The application made must include:

- An assessment of the impact on clinical services, staff training and cost implications.
- Plans for auditing and presenting results.
- A patient information leaflet.
- NICE Interventional Procedure Guidance if it exists.

  For fetal MMC repair, there is no NICE IP Guidance. The potential surgery set-up was discussed by the Interventional Procedures Committee (NICE reference number: 949: Prenatal versus postnatal repair of myelomeningocele) in 2016; it was decided that it would be placed on a period of monitoring, until greater clinical experience in the UK existed.

An application for the new interventional procedure of fetal surgery for spina bifida at UCLH, with Professor Anna David named as the Lead Clinician, was made according to the above process and final CESG approval for this service was granted in May 2016.

2.3.6 Funding

Currently, the NHS in England, Wales, Scotland and Northern Ireland does not commission a fetal MMC repair service directly. Thus far, the patients who have wished to have this procedure in European centres have successfully applied for funding via the NHS S2 route.

In October 2015, GOSH Children's Charity awarded £296 000 towards the set-up of fetal MMC surgery as a UCLH/GOSH collaboration; in June 2016 UCLH Charities also awarded £155 000 to the project. Therefore, with an approximate budget of £450 000, the fetal surgery service at UCLH is being set up on a charitable-funding basis. It is estimated that this will cover staffing costs, team training and equipment as well as the first ten cases.

Recognising that applications to travel to Europe for fetal MMC surgery were occurring more frequently than in "exceptional circumstances", in September 2017 the NHS Highly Specialised Services Commissioning Group began a scoping exercise for a clinical service. In October 2017, a Provisional Policy Proposal for a fetal MMC repair service was submitted, with Professor Anna David as Clinical Lead. In December 2018 it was announced that a fetal MMC repair service would be commissioned by NHS England.

Chapter 3 Methodology of Setting up a Clinical Service

3.1 Team and Training

In setting up open fetal surgery for spina bifida at University College London Hospital (UCLH), the first thing we considered was the team who would be providing this service and the training they would need.

3.1.1 Background and Aims

As discussed previously, the Meningomyelocele Maternal-Fetal Management Task Force published a Position Statement on fetal myelomeningocele repair in 2014[304]. This specified the team members who would be required to establish a fetal therapy centre, all of whom were considered to be available across UCLH and Great Ormond Street Hospital (GOSH). From the outset we aimed to have a consistent theatre team performing fetal surgery. Clinically, there is often high rate of "sharing" team members across specialties and procedures, particularly theatre nurses, which has been reported[308] and is often experienced "on the shop floor". This leads to a new team working together each time. In general surgery a lack of team consistency has been associated with prolonged operative times, longer hospital stays and increased readmissions[309].

The position statement emphasised the need for a "functional cohesive multidisciplinary team with the individual members of the team exhibiting and maintaining a level of expertise in their respective fields". Our proposed team

consisted of fetal medicine specialists experienced at diagnosing and counselling regarding fetal anomalies, obstetricians experienced at performing hysterotomies and neonatal neurosurgeons experienced at performing postnatal multi-layer spinal repairs. It was therefore judged that the team had sufficient expertise in their respective fields.

The IfMSS/NAFTNet Joint Opinion in 2017[113] classified fetal procedures into four main groups:

1. Ultrasound-guided needle procedures (e.g. intrauterine transfusion, shunts, balloon valvuloplasty).
2. Fetoscopic procedures (e.g. placental laser ablation, umbilical cord occlusion, tracheal balloon occlusion).
3. Open fetal surgery (e.g. myelomeningocele repair, resection of sacrococcygeal teratomas or lung masses).
4. Ex-utero intrapartum treatment (EXIT) procedures (described in chapter 1.4).

The fact that, at UCLH, fetal procedures in all groups except open fetal surgery were already being performed successfully was considered encouraging in our plans to begin open surgery.

Team cohesiveness, as emphasised by the position statement, was considered central to the success of the proposed service, and it was apparent that a multi-disciplinary operation of this size had not occurred before at our unit. We therefore planned steps to increase team familiarity and collaboration, which will be described in methods below.

The position statement also recommended that new fetal surgery centres should receive guidance and training from established centres and experienced individuals; we therefore made this central to our service set-up and will also describe this further in the methods section.

In addition to the specific guidance for team and training in new fetal surgery centres, we also considered the Royal College of Surgeons "Guide to Best Practice: The High Performing Surgical Team[310]". This encourages clear leadership whilst "minimising status and power differences" and emphasises the importance of clear, respectful communication amongst team members. The WHO Guidelines for Safe Surgery[311] also discusses team culture and communication; it notes that members of surgical teams can often function in "silos", sharing the same physical space but holding distinct expectations and values and sometimes barely interacting. Reflecting on these documents, we aimed to develop a modern multi-disciplinary team with shared aims, a flattened hierarchy and open communication between all members.

3.1.2 Methods in Establishing and Training the Fetal Surgery Team

Guidance and training from those experienced in performing open fetal surgery was considered a pre-requisite in our decision to set up this service. To this end a strong working relationship was established with three major fetal surgery centres; the team at Children's Hospital of Philadelphia (CHOP) who had been at

the forefront of developing this technique and had led on the MOMs trial[94] supported our endeavour by overseeing our protocols and criteria and providing training opportunities at their hospital. The teams in Zurich, Switzerland and Leuven, Belgium both did the same. Most importantly, the lead clinician for fetal surgery in Leuven, Professor Jan Deprest, was employed by UCLH for two days a week to oversee the fetal surgery programme in London.

Team members who had been involved in the initial decision to set up fetal surgery at UCLH approached other specialists as required for the service; individuals with expertise and/or an interest in the project were encouraged to join the team. We then established core groups according to team members' expertise, as follows: research, fetal medicine, surgical (including theatre nurses), anaesthetics (including operating department practitioners), neonatal and midwifery. The development of these core groups or "sub teams" enabled each to take responsibility for the training, protocols and set-up particular to them. Monthly meetings for the whole team were also established to encourage familiarity and collaboration across the large group.

Training was achieved in a number of ways and varied according to the level of expertise required by the team member. Written information, such as leaflets and protocols, were disseminated across the whole group. Team members who would not be involved in the surgery itself but rather the care of the patients afterwards (midwifery and neonatal) were given access to videos of the procedure and standard post-operative or post-delivery regimes used in other centres. All other team members with an active role in theatre were encouraged

to visit one of the three centres above to observe fetal repair of spina bifida and spend time with their counterparts in that unit. The paediatric and neonatal neurosurgeons who would be performing the fetal spinal repair attended multiple cases in existing centres, where they were supported to perform the procedure under the guidance of the host unit. This occurred a minimum of five times before operating in London was considered.

Communication within the team was established by email, phone and regular interactions in person. The author took up the “Fetal Surgery Research Fellow” role in April 2017 and functioned as a central co-ordinator for all team members.

3.1.3 Results and Difficulties Encountered

We established a team of thirty members, split approximately evenly between the six “sub groups” described above. We attempted to have more than one person in each role involved in the project, in order to reduce pressure on any one individual and to avoid surgery being impossible on occasions when that member was unavailable. Although the service is a UCLH/GOSH joint project, as surgery was occurring at UCLH and the two hospitals are not part of the same trust, a number of team members required honorary contracts of employment and occupational health clearance.

All team members who required training travelled to an established centre to observe surgery, although due to the unpredictable nature of fetal surgery cases

and full-time occupation of all team members, this took longer to achieve than anticipated. Communication, both by email and in person, was successfully established across the majority of the team with the exception of theatre nurses. Difficulties were encountered in sharing information regarding fetal surgery and establishing dedicated fetal surgery theatre nurses due to a lack of response from middle-grade theatre managers and a possible unwillingness to engage with the project. This culminated in an angry remonstration by a theatre nurse at a monthly team meeting regarding the perceived lack of communication and overlooking of the theatre staff. Whilst unpleasant to listen to at the time, this incident did have the effect of galvanising efforts to engage with middle-grade theatre managers via the involvement of their seniors. The fact that a junior theatre nurse had felt able to criticise the team gathered, including several professors and consultants, also coincidentally satisfied us that we had been able to establish a flattened hierarchy as was our aim.

3.1.4 Simulated Surgery

The team set-up and training, as described above, took approximately nine months. Although technical skill is clearly necessary in performing a new procedure[312], it is not sufficient[313] and in an era of increased appreciation for "human factors[314]", it is clear that surgical success is equally due to the functioning of the theatre team. As simulation is embedded in UK medical training and has been reported to improve technical and non-technical surgical skills[315], we undertook a full "dummy run" of a fetal surgery operation prior to offering it to a real patient.

Simulation surgery process

A volunteer not involved in the fetal surgery project was engaged to act as the "patient" and be communicated with as such. The obstetric operating theatre planned for fetal surgery was booked for a session (half day) and the entire team was assembled as for a real case, including a full neonatal resuscitation team in the worst-case scenario of intraoperative delivery. The patient was given a set of notes and admitted on the hospital computer system; consent was obtained and electronic prescribing was performed as per hospital protocol. Patient monitoring, intravenous access, arterial cannula placement and epidural and general anaesthesia were all simulated but not performed. The patient lay on the theatre table whilst surgical drapes were applied; the surgical team then held the relevant instruments whilst talking through the procedure in a step-wise fashion. Following the simulated procedure, the patient was returned to the recovery area and postoperative plans were made.

Simulation surgery learning points

Several areas for improvement were highlighted from the simulated surgery, as follows:

- Securing an alternative second theatre for emergencies: although the theatre used was for elective caesarean sections (which had been cancelled) and not the acute labour ward theatre, the obstetric consultant explained that if two emergencies were occurring simultaneously they would usually take over the theatre we were in-between cases. However, in fetal surgery there is one long case rather than three elective

caesareans and so there is no opportunity for the on-call team to use it in an emergency. Following this we proposed a plan of communication and second emergency theatre in another part of the hospital to be designated on fetal surgery days.

- Medication, equipment and instruments: there were several improvements, additions and adjustments required, which will be discussed in chapter 3.3.1.
- Theatre noise and personnel: the patient had a simulated epidural in the anaesthetic room, then entered theatre for the simulated general anaesthetic; on doing so she reported that entering theatre was rather intimidating due to the number of people present. We later debated also performing the general anaesthetic prior to entering theatre but decided that this would likely lead to a longer anaesthesia time for mother and fetus due to the time taken to transfer the patient then set up equipment around her. We resolved that the patient would still enter theatre awake post-epidural, but that personnel present would be kept to a minimum number of people and activity would be as quiet as possible.
- Surgical checklist: the WHO surgical safety checklist[311] ("Time Out"), adapted for obstetrics[316], was used as this was available in theatre but it was clear that it did not correspond well to fetal surgery. Following this a specific surgical safety checklist was developed for fetal surgery cases.
- Decisions regarding resuscitation and steroids: the neonatal team highlighted that prior discussion and documentation of the threshold of fetal/neonatal resuscitation would be extremely important. As fetal surgery is performed at 24 to 26 weeks' gestation, a surgical emergency resulting in delivery of the fetus (e.g. placental abruption) would result in a

potentially viable neonate being born. Whether this neonate would receive full, partial or no resuscitative efforts would depend upon the exact gestation, weight, condition and other prognoses. This also varies between units - for example, at CHOP full resuscitation would be attempted for almost all neonates but in Belgium this would rarely be the case prior to 26 weeks. Although we had discussed this before in our group and decided that this decision would be on a case-by-case basis, undergoing the simulation surgery prompted further discussion of this. It became apparent that the threshold of potential resuscitation must be discussed extensively both with the parents and as a team prior to the mother entering the operating theatre and not left to be decided in an emergency situation. The use of maternal steroids to promote fetal lung maturity prior to fetal surgery would logically follow the decision regarding resuscitative efforts.

Immediately following the simulation surgery, the first patient referral for consideration of fetal surgery was received; however, it was decided that surgery would not proceed whilst there were still any outstanding issues and the patient was transferred to Leuven for surgery whilst the above points were addressed.

3.2 Protocols

Following the Clinical Effectiveness Steering Group approval for fetal repair of spina bifida at UCLH in May 2016, a raft of protocols, procedures, pathways and various other paperwork were required to support and underpin the service set up. These will be described in more detail below.

3.2.1 Protocol

The team at Children's Hospital of Philadelphia (CHOP) shared their trial protocol[94] and departmental protocols with our team and reviewed our protocol once finalised. Our protocol specified inclusion and exclusion criteria, management of complications and standards for follow up and was distributed to all our team.

3.2.2 Inclusion and Exclusion Criteria

The criteria from the MOMs trial[94] are discussed below, along with their adaptation for UCLH:

Inclusion Criteria

1. Myelomeningocele (including myeloschisis) at level T1 through S1 with hindbrain herniation.
2. Maternal age ≥18 years.
3. Gestational age of 19+0 to 25+6 weeks' gestation as determined by clinical information and evaluation of first ultrasound, preferably first trimester when dating will be according to Crown Rump Length (CRL) or if assisted conception, by date of embryo transfer.

   Following the MOMs trial, evidence emerged[101] that the risks of chorionic membrane separation, preterm rupture of membranes and preterm labour were all increased with earlier gestational age at the time of fetal surgery. It then became standard practice at CHOP that fetal surgery should not be performed at less than 23 weeks' gestation. Therefore our inclusion criteria were correspondingly modified to 23+0 to 25+6 weeks' gestation.
4. Normal karyotype with written confirmation of culture results.

Exclusion Criteria

1. Multifetal pregnancy
2. Poorly controlled insulin-dependent pre-existing diabetes
3. Fetal anomaly not related to spina bifida.
4. Kyphosis of the fetal spine of 30 degrees or more
5. Current or planned cerclage or documented history of incompetent cervix.

   We clarified this by specifying that the following would be exclusion criteria: previous mid-trimester loss (12 to 24 weeks' gestation) or previous shortening cervix requiring increased surveillance or treatment.

6. Placenta praevia or history of placental abruption.
7. Short cervix < 20 mm measured by cervical ultrasound.
8. Obesity as defined by body mass index of 35 or greater.

   As per 2016 the BMI limit has been raised to 40 by CHOP and at most other institutions providing this service; we therefore agreed to consider cases up to BMI 40.

9. Previous spontaneous singleton delivery prior to 37 weeks
10. Maternal-fetal Rh isoimmunization, Kell sensitization or a history of neonatal alloimmune thrombocytopenia.
11. Maternal HIV or Hepatitis-B status positive because of the increased risk of transmission to the fetus during maternal-fetal surgery. Results must be known prior to surgery.
12. Known Hepatitis-C positivity. If the patient's Hepatitis C status is unknown, screening is not required.
13. Uterine anomaly such as large or multiple fibroids or Mullerian duct abnormality.
14. Previous uterine surgery: any patient with a previous hysterotomy in the active segment of the uterus (whether from a previous classical caesarean section, uterine anomaly such as an arcuate or bicornuate uterus, major myomectomy resection, or previous fetal surgery). A previous uncomplicated caesarean section scar was an exclusion in the MOMs trial but more recently has been accepted by units globally and so this was considered acceptable at UCLH.
15. Other maternal medical conditions which would be a contraindication to surgery or general anaesthesia.

16. Maternal hypertension which would increase the risk of preeclampsia or preterm delivery (including, but not limited to: uncontrolled hypertension, chronic hypertension with end organ damage and new onset hypertension in current pregnancy).
17. Patient does not have a support person (e.g., husband, partner, mother) or psychosocial concerns regarding the patient's emotional state.
18. Inability to comply with the travel and follow-up requirements needed by UCLH Fetal Medicine Unit.

3.2.3 Theatre Manual

Whilst the main fetal surgery protocol was comprehensive with regards to the areas above, we found it was not specific enough about surgical aspects and, in particular, how to run the theatre. The team from Leuven kindly shared their "theatre manual" with us, which we adapted for use in our setting and distributed to all our team.

The theatre manual we developed has columns for each theatre specialist to read down to establish what they should be doing exactly at each time point in the surgery. We also developed diagrams showing where each member of the surgical team should stand at various points in the surgery. Examples of the theatre manual and diagrams are shown in Figure 3.1.

Step 2: Regional and General Anaesthesia

Obstetrics/ Surgical	Anaesthetics	Nursing/ Midwifery
FET CARD 1 / FET MED 2: • Create and check connection from US machine to second screen, check US function and settings **NEONAT 1:** • Check and set up fetal blood if needed • Prepare intra-amniotic clindamycin 600mg • Check all fetal medication from pharmacy **Fetal Medication for Resuscitation if needed:** • Atropine 20mcg/kg • Adrenaline 10mcg/kg **Fetal Medication for routine administration:** • Fentanyl 10mcg/kg • Vecuronium 0.1mg/kg • Atropine 20mcg/kg	**ANAES 1/2, assisted by ODP 1:** 1. Second IV access 2. Fluids: Hartmanns 60 ml/hr 3. Atosiban loading scheme as above 4. Antibiotics (clindamycin 600mg IV) should have been given 5. Midazolam and fentanyl may be given for anxiolysis 6. Epidural placement in theatre - test dose only Test dose 3 mL of 0.5% Bupivicaine, do not bolus until end of case 7. Positioning for induction - supine with LUD and 'sniffing' position 8. Pre-oxygenation-propofol TCI- remifentanil-rocuronium-suggamadex available! 9. Rapid sequence induction with cricoid pressure 10. Placement of cuffed endotracheal tube (7.0) Start ventilation FiO2 of 30% Mild hyperventilation cfr pregnancy! (continue next page and instruct obstetrician whether she/he can start doing ultrasound) 11. Phenylephrine infusion (0.05 mg/ml) started at 10ml/hr and go up as needed on 1 of the IV lines exclusively used for vasopression! 12. Arterial line; no CVP line required unless hard indication 13. Oro-gastric tube and temperature monitor placement	**CIRC 1:** Preparation of patient: 1. TED stockings and Flowtrons 2. Diathermy pad to legs 3. Position: Supine, both arms along the body (only once second IV line and arterial line are placed) Theatre bed on left lateral tilt Preparation around patient: 1. Diathermy machine left leg end 2. Ultrasound machine right lateral side 3. Two suction machines (maternal and fetal) leg end 4. Level 1 infusion pump head end left side

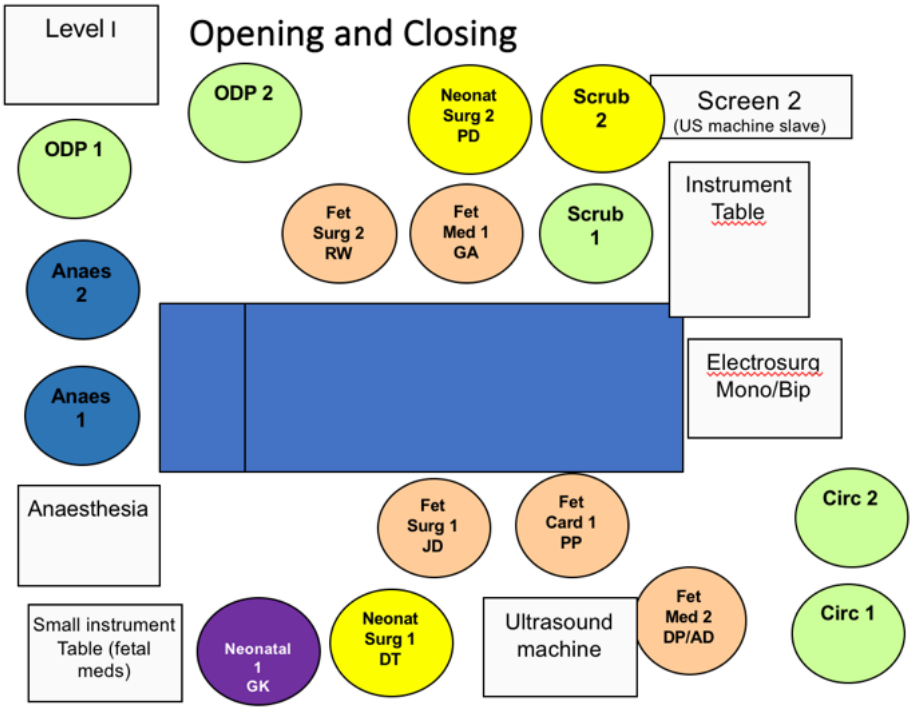

Figure 3.1: Example pages from theatre manual

Reproduced with permission of UZ Leuven, Belgium

3.2.4 Referral Process

When setting up our service we were aware that this would be the first in the UK and Ireland and that patients may have to travel a significant distance to visit

UCLH. We therefore wanted to avoid patients travelling unnecessarily if possible. To aid this we created a short information sheet for referring clinicians, setting out the inclusion/exclusion criteria as well as some practical points and giving contact details for queries. We developed a referral system based on the Belgian one, whereby referring clinicians were asked to send patient details and ultrasound images so this could be reviewed prior to inviting the patient to attend UCLH. We developed a PowerPoint template setting out which information and images we would like to have sent. Once this presentation is received it is reviewed at UCLH by the fetal surgery team and confirmed that the patient appears to be eligible for fetal surgery prior to offering her an appointment.

3.2.5 Pathways

We established that many staff would be involved in only one part of the patient's journey e.g. fetal medicine assessment or post-operative care. As the protocol is a large document with writing in paragraphs, we felt this was not the easiest thing for clinical staff to refer to on the wards. We therefore developed pathways or flow charts to be used in specific areas to enable staff to provide consistent care. Examples of these are given below in Figures 3.2-3.5.

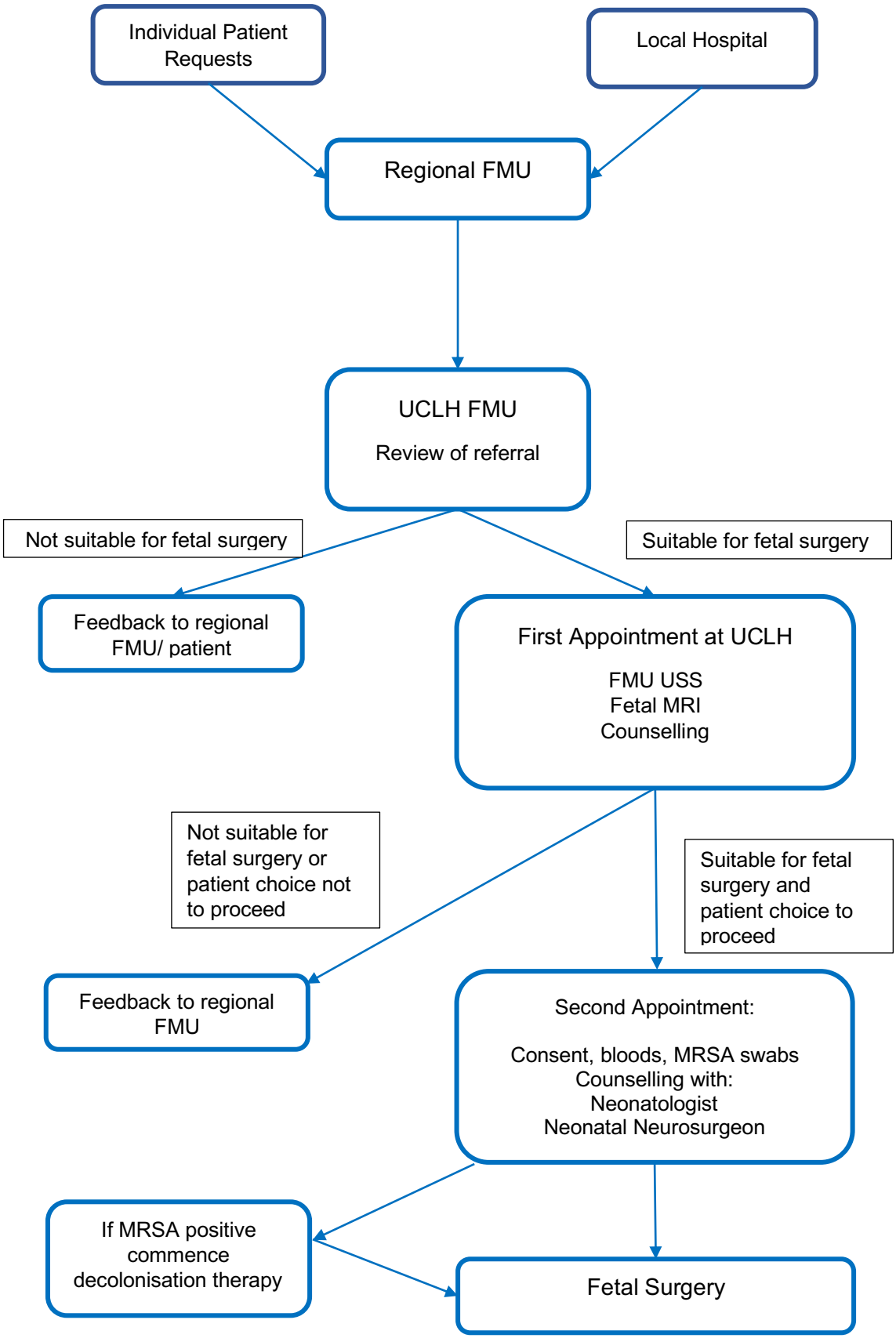

Figure 3.2: Preoperative pathway

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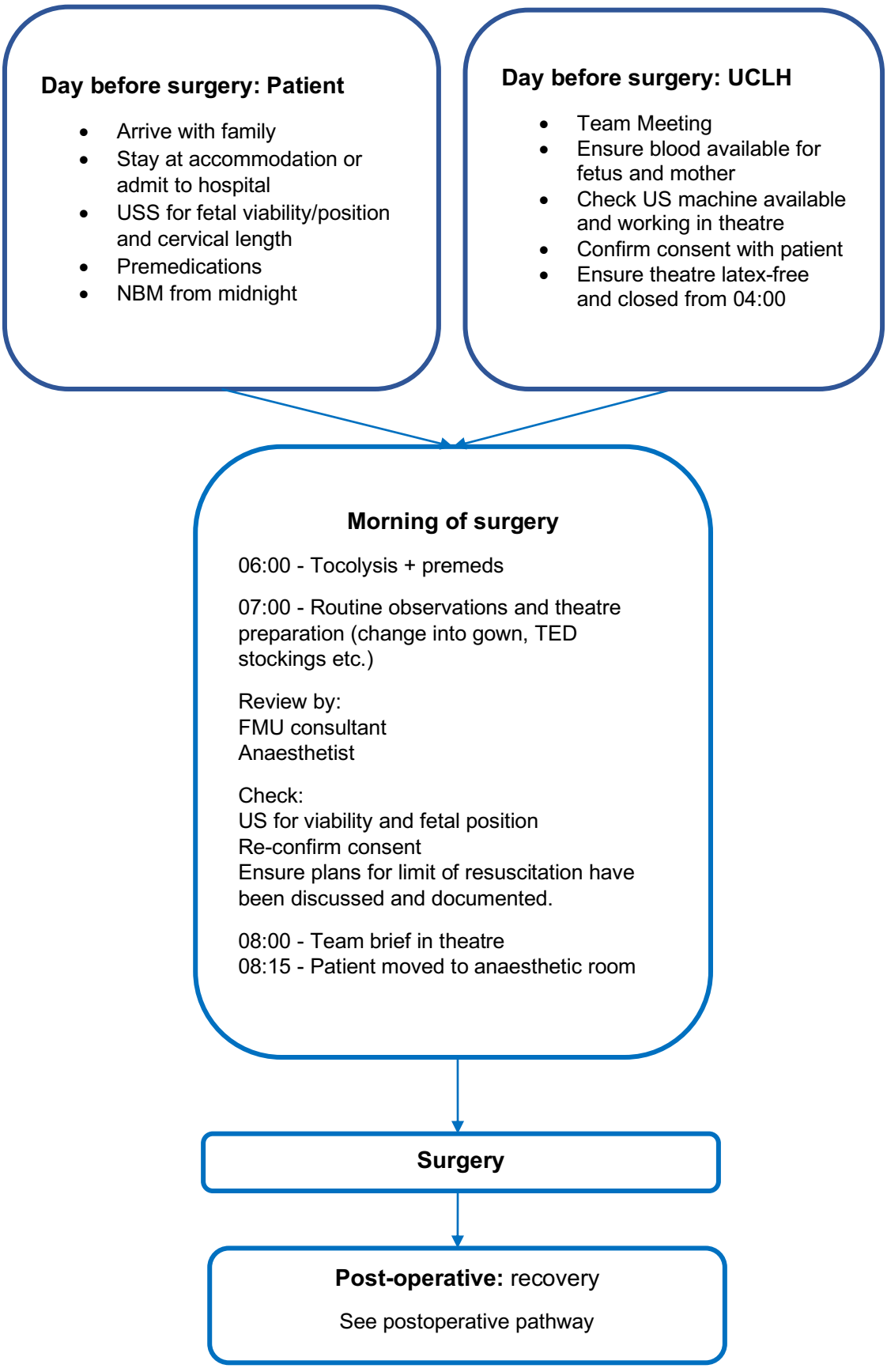

Figure 3.3: Peri-operative pathway

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At any point, if concerns about contractions:
1. Perform tocography part of CTG monitoring to confirm if contractions are occurring
2. Perform cervical length scan if possible
3. Discuss with fetal surgical team
4. If confirmed preterm labour will require emCS due to recent hysterotomy

Day 0: Recovery

- Hourly urine output for first day/night
- Bedside USS for viability
- Epidural catheter to remain in with patient-controlled boluses
- Medication:
  - atosiban maintenance 18mg/hr for 3 hours then 6mg/hr for 24hrs total
  - indomethacin 50mg PO 6hrly for 24hrs
  - clindamycin 600mg IV 8hrly for 24hrs
  - LMWH from evening of day 0
  - IV fluids 4-6hrly (high losses during operation)

Day 1: Recovery

- Bloods: FBC, U&Es, LFTs, CRP
- USS for viability, membrane separation, cervical length, DA
- Consider removal of epidural if not using; do not remove within 12hrs of LMWH
- Commence nifedipine in the evening once atosiban and indomethacin stopped - to continue until discharge

Day 2: Recovery

- Bloods: FBC, U&Es, LFTs, CRP
- USS for viability, membrane separation, cervical length, DA
- Consider removal of epidural if not using; do not remove within 12hrs of LMWH
- Catheter out once epidural out
- Transfer to ACU once epidural out and patient well

Days 3-7: Antenatal ward

- Modified bed rest (can mobilise to toilet)
- Daily US or Sonicaid for fetal viability whilst inpatient
- Repeat bloods day 4 – if normal no further needed unless clinically indicated

Prior to Discharge

- Fetal MRI
- Full FMU USS including cervical length

Figure 3.4: Post-operative pathway (inpatient)

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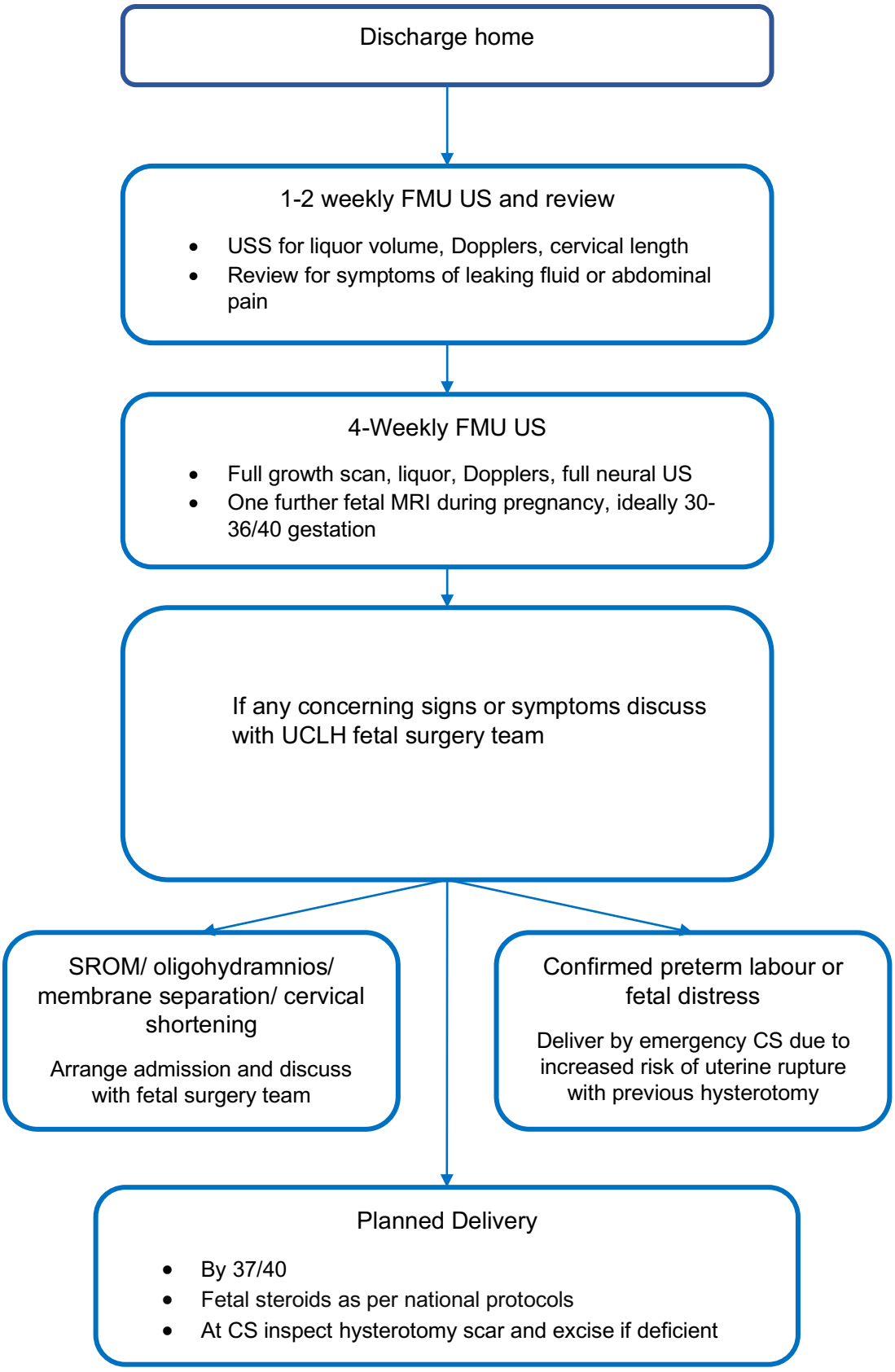

Figure 3.5: Post-operative pathway (outpatient)

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3.2.6 Information Leaflet

We developed an information leaflet for patients regarding spina bifida and fetal repair as there was no specific information for this in the UK. We developed the leaflet in collaboration with all our team and specialists in accordance with hospital guidance. The leaflet was reviewed by lay people for readability and patient representatives prior to publication. Informal feedback we received from patients and referrers was positive and we believe this information leaflet is often used as a first step when a local clinician explores whether the patient would like referral for consideration of fetal surgery.

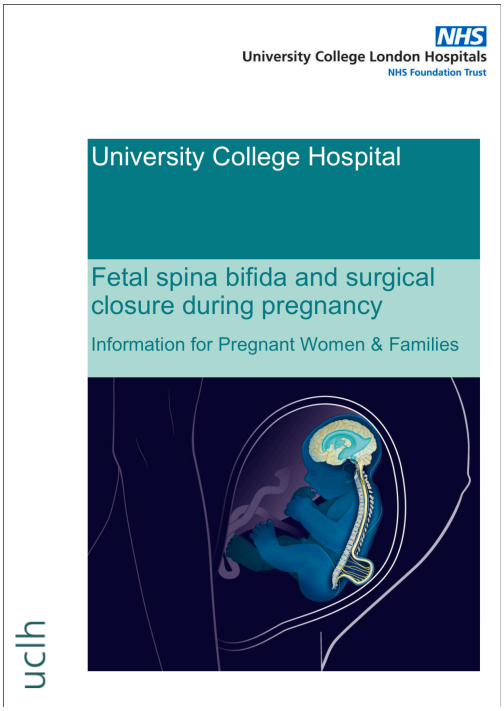

Figure 3.6: Patient information leaflet cover

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3.3 Equipment and Medication

In setting up our clinical service, we were required to develop specific equipment sets and medication protocols, which are discussed further below.

3.3.1 Equipment

In order to perform fetal spina bifida surgery, a maternal laparotomy and hysterotomy are required prior to neurosurgical repair. Like most theatres, ours uses pre-assembled “sets” containing instruments commonly required for certain operations. During our simulation surgery, as described in chapter 3.1.4, we were required to open four sets (Caesarean section, Hysterectomy, Oncology, Majors) in order to obtain all the instruments that were required. However, the majority of the instruments in all of these sets were not required and therefore we created a new “Fetal Surgery” set in order to be more organised and compact. The neurosurgical instruments required were kept in a separate set and two surgical theatre nurses (obstetrics and neonatal neurology) assumed responsibility of their corresponding instruments.

During the simulation surgery, there were some instruments (bulb irrigation, nerve hooks, specific uterine clamps) which were not available on any of the surgical sets and had to be ordered especially. The simulation surgery also helped us identify an issue with the uterine infusion; whilst the uterus is open,

warm crystalloid fluid is infused into the cavity to keep the fetus buoyant and to limit any problems that may occur due to temperature change or cord compression. This fluid is infused via a “Level 1” device (Smiths Medical, USA) which is commonly available in UK theatres. We found that we were unable to infuse fluid directly from the Level 1 to the uterus as the tubing was too large and the lead surgeon required the ability to alter the flow and inject antibiotics at the theatre table; we therefore amended the infusion device to contain an nasogastric (NG) tube with a three-way spigot to allow for this.

There were three pieces of consumable equipment which required individual ordering for this surgery. The first was a uterine “stapler”. This device (Covidien, USA) has been developed to improve blood loss and ease of access during uterine procedures such as caesarean section, although it’s use has not been widely established in the UK. It was used for uterine access in the MOMs trial[94] and subsequently by many fetal surgery centres, who feel that it makes the procedure easier and keeps the membranes “sealed” in the surgical incision and therefore easier to repair.

Secondly, in the small number of cases where the myelomeningocele is too large to allow skin approximation, a skin substitute patch is used.

Finally, in closing the uterus, a specific technique has been developed to try to re-approximate the amniotic membranes as closely as possible and avoid leakage of amniotic fluid. First double-ended sutures are inserted from the inner to outer side of the uterus around 2cm away from the suture line on both sides; around ten of these are used. Next, the uterus is closed with a running suture which is then tightened by nerve hooks. The interrupted sutures which were

previously inserted are then tied over the top, inverting the first layer. This technique requires specific sutures and needles which were not available in our theatres.

All three of these pieces of equipment were ordered especially for the fetal surgery service, although it took some time and effort to obtain them.

3.3.2 Maternal Medication

The use of tocolysis and antibiotics during fetal surgery, for the prevention of preterm birth and infection respectively, required some research and consideration when setting up our service. In looking into these issues further we realised that there is a lack of evidence for optimal medication types, doses and routes in fetal surgery and that most protocols are written based on what has been done by other units in the past and seems to work.

Tocolysis

Women who undergo surgery for fetal spina bifida repair are at an increased risk of preterm birth. Protocols from the MOMs trial and other fetal surgery centres include the use of two preventative tocolytic agents at the time of surgery, and one treatment tocolytic agent if threatened preterm labour occurs post-surgery.

The first tocolytic usually used at the time of surgery (outside the US) is atosiban. This is an oxytocin-receptor antagonist and is licensed in the UK for threatened preterm birth. We did not foresee any concerns with using this around the time of surgery. In the US, atosiban is not licenced and the most commonly used primary tocolytic is magnesium sulphate. However, this has significant maternal side-effects, including pulmonary oedema, and so it was decided that we would use atosiban as per other European centres.

The second tocolytic usually used at the time of surgery in other centres is indomethacin, a cyclooxygenase (COX) inhibitor. Nifedipine, a calcium channel blocker which would more commonly be used in the UK, is usually reserved as "third-line". Indomethacin is not commonly used as a tocolytic in the UK any longer, and so we researched this during our set-up.

A Cochrane review[317] assessed the efficacy of COX inhibitors in preterm labour. In comparative trials, indomethacin reduced the risk of birth within the first 48 hours of treatment compared with betamimetics and appeared to be as effective as calcium channel blockers and magnesium sulphate. There were no significant

differences in neonatal mortality, very preterm birth or maternal death between COX inhibitors and other tocolytics. COX inhibitors resulted in fewer maternal adverse effects compared to betamimetics and magnesium sulphate. No data were available to assess COX inhibitors compared with oxytocin receptor antagonists.

Maternal side effects, including nausea, oesophageal reflux, gastritis, and emesis, are seen in approximately 4% of women treated with indomethacin for preterm labour. Clinically it seems fairly well tolerated compared to calcium channel blockers and oxytocin receptor antagonists. The primary fetal concern with use of indomethacin is constriction of the ductus arteriosus (DA).

Premature narrowing or closure of the DA can lead to pulmonary hypertension and tricuspid regurgitation in the fetus. Several cases of premature ductal constriction have been reported in pregnancies in which the duration of indomethacin exposure exceeded 48 hours; however, this complication has not been reported with shorter durations of indomethacin treatment. Indomethacin is not usually recommended after 32 weeks' gestation, as the risk of ductal constriction is higher. The use of indomethacin therapy for short course tocolysis during fetal surgery in 50 cases was reported in a conference abstract[318]. Post-operative constriction of the ductus arteriosus was detected in 7 fetuses (14%). All affected fetuses showed improvement on stopping indomethacin. The authors concluded that maternal indomethacin therapy after fetal surgery requires careful daily monitoring due to the risk of fetal DA. In the MOMs trial, a fetal echocardiogram was performed on the first two days to evaluate cardiac function

and assess constriction of the ductus arteriosus. We therefore asked our hospital Use of Medicines Committee for permission to use indomethacin as a second preventative tocolytic agent for 24 hours, in line with the Belgian protocol, and to perform fetal echocardiography on days 1 and 2, which was agreed.

Antibiotics

In the MOMs trial, chorioamnionitis occurred in 3% of pregnancies following fetal surgery. In this trial, cefazolin (a second-generation cephalosporin) was given to the mother intravenously (IV) and nafcillin (a penicillin) was instilled intra-amniotically (IA) at the end of the procedure; vancomycin was used in cases of maternal penicillin allergy. The Belgian protocol uses cefazolin both IV and IA. As both cefazolin and nafcillin are not available in the UK, we looked into alternatives. We received advice from the Swiss fetal surgery team that they had experienced trouble nafcillin, and so tried ceftriaxone (a third-generation cephalosporin) but then noticed renal abnormalities in the fetuses, which was later replicated in animal models. The Swiss protocol therefore now uses cefazolin IV and clindamycin IA.

The intra-amniotic route is unusual; when instilling antibiotics into the uterine cavity one bathes the fetus in the substance which will also be ingested and excreted by the fetus. We could find no publications regarding this route of antibiotic administration. In the absence of data, we applied to our Antibiotics Usage Committee for permission to use clindamycin both IV (as is already done for women who are penicillin-allergic undergoing a caesarean section) and IA (as per the Swiss team). This was approved, although the lack of safety data was discussed.

3.3.3 Fetal Medication

During fetal surgery, it is important to ensure that the fetus does not move and that it does not feel pain. The general anaesthetic agents given to the mother will have some effect on the fetus; additionally, it is routine in fetal surgery centres to inject the fetus with anaesthetic, analgesic and antimuscarinic medication prior to surgery. Using the protocols of Philadelphia and Leuven, after discussion with our local pharmacy team we agreed that vecuronium, fentanyl and atropine would be prepared and administered to the fetus intra-operatively. These medications are all given according to weight, and so we planned to obtain an estimated fetal weight by ultrasound scan the day before surgery.

In cases of fetal bradycardia or distress during surgery, the first step is to stop operating and try to correct any precipitating causes (e.g. inadvertent cord compression). If this does not result in resolution, the next step is to commence fetal resuscitation with medication or blood if anaemia is suspected; following this cardiac massage is tried and then delivery. In a follow up study of 100 cases[98] of fetal surgery following publication of the MOMs trial, five fetuses required resuscitation with medication, blood or cardiac compressions and none were delivered. We therefore planned to prepare blood and medication - adrenaline, atropine and sodium bicarbonate - for each surgical case.

All of the medications planned for fetal surgery cases were listed as an “order set” in our electronic prescribing system to reduce error and save time when cases occur.

3.4 Cost Effectiveness

Spina bifida is a life-long condition requiring regular medical follow up to review mobility, neurological issues, bladder and bowel control, surgical issues and psychosocial needs. Surgery or other treatments may be required throughout development.

Data from Germany[319] confirms that, as one would expect, the average annual healthcare expenditure for a person with a neural tube defect is higher than the average standardised healthcare expenditure for non-affected individuals. For those under 1 year of age, expenditure was estimated at €10,971 for affected patients vs €2360 average; for those aged 2 to 5 years, expenditure was €8599 vs €833 and for those aged 6 to 10 years expenditure was €10,601 vs €863. The largest contributors to these costs were outpatient care, pharmacotherapy, medical aids, inpatient care, long-term care and rehabilitation services.

Logically, one might expect that if fetal surgery for open spina bifida improves outcomes then it should reduce expenditure by reducing the number of surgical procedures, necessity for mobility aids and long-term care. Randomised trial data from the MOMS study[94] showed an improvement at 30 months in the rates of ventriculoperitoneal shunting and ambulation. However, in this trial the average gestational age at delivery was 34 weeks', and prematurity can have a significant effect on healthcare expenditure. The procedure requires all future deliveries to

be performed by caesarean section, which also increases healthcare expenditure for those having surgery.

A cost-effectiveness evaluation published in 2012[320] attempted to determine whether fetal surgery for open spina bifida is ultimately cost-effective compared to postnatal surgery. This study used decision-analysis modelling and made assumptions on improvement in clinical outcomes and risks of neonatal prematurity outcomes based on the MOMS trial data. Maternal costs such as readmission with complications were included, and estimations of future pregnancy rates based on survey data[109] were used. Quality-adjusted life years (QALYs) were used in the modelling.

The results from this study suggested that fetal surgery was associated with both a cost saving and a quality of life improvement when compared to postnatal surgery, even when the above risks were taken into account. Based on USA healthcare system costs, they estimated that fetal surgery would save $2 066 778 per 100 repairs. For the affected child, fetal surgery was estimated to gain 98 QALYs per 100 affected neonates. However, fetal surgery lead to 23 fewer maternal QALYs per 100 operations.

Open spina bifida is a rare condition, affecting between 1 in 1000 to 1 in 10 000 births worldwide[321]. Data from fetal surgery centres in western Europe[76] suggests that the majority of patients with a diagnosis of fetal spina bifida will choose to end the pregnancy, and of those remaining the majority will either be ineligible for

or not wish to have fetal surgery. Therefore, it seems unlikely that fetal surgery will have a large impact on national healthcare finances in western Europe.

The modelling and cost effectiveness data discussed above has come from the US, Belgium and Holland, all countries which have different healthcare systems to the UK. In setting up our fetal surgery service we aimed to estimate the costs of fetal surgery in a UK setting and compare that to postnatal surgery. Ultimately, we plan to follow our patients in order to obtain long-term data regarding healthcare usage but in the short-term we conducted a study to assess the immediate cost of fetal surgery for spina bifida in the UK.

3.4.1 Introduction

In the UK, all babies born with open spina bifida will require postnatal repair; this cost is already incurred as part of standard care. As fetal surgery for spina bifida is being offered as an alternative to postnatal repair we therefore aimed to compare the costs of the two treatments in the UK. As the MOMS trial showed fetal surgery for open spina bifida to be clinically superior to postnatal repair in selected cases, we did not seek to establish clinical effectiveness or perform a quality-based analysis. Assuming the outcomes to be at least as good with fetal surgery as postnatal surgery, we performed a cost-minimisation analysis to establish the costs of both options.

3.4.2 Methods

The regional unit currently performing postnatal MMC repair (Great Ormond Street Hospital, GOSH) were contacted and asked to provide costings for their service. Our unit, in setting up fetal MMC repair, calculated the cost of each step of the process. Costs which were considered normal care for all women, regardless of surgery type, were not included. Finance managers, business managers, theatre staff and pharmacists provided costs for relevant parts of the surgery. A health economist assisted with reviewing the data. All costings were obtained from June 2017 to March 2018.

3.4.3 Results

For postnatal repair, the GOSH neurosurgery service manager provided a costings quote based on the national tariff as follows:

HC54B - Major Spinal Reconstructive Procedures with CC Score 2-3.

A498 - Other specified: Repair of spina bifida.

Q068 - Other specified congenital malformations of spinal cord

Cost (£) - 19206.55

In order to calculate the cost of fetal surgery, we broke the procedure down into five phases:

1. Preoperative
2. Intraoperative
3. Post-operative (inpatient)
4. Post-operative (outpatient)
5. Delivery

These results will be displayed in Table 3.1 to 3.5 below, with the combined final costs shown on Table 3.6.

Table 3.1: Preoperative Costs (Assessment)

Item	Cost (£)	Comments
Consultation with fetal surgery consultant	Not costed	Usual care
FMU ultrasound scan	Not costed	Usual care
Amniocentesis/karyotype	Not costed	Usual care
Fetal MRI	249.00	
Blood tests	25.10	Full Blood Count, Group & Screen
TOTAL	274.10	

Table 3.2: Intraoperative Costs

Item	Cost (£)	Comments
Theatre use	2500.00	All costings for single (half day) session
Two consultant anaesthetists	762.00	
Two fetal surgeons	792.00	
One fetal medicine consultant	396.00	Intraoperative echo
Paediatric neurosurgeon	792.00	
Neurosurgical theatre nurses	200.00	
Two obstetric theatre nurses	150.96	
Two Operating Department Practitioners	110.16	
General and regional anaesthesia equipment	Not costed	Included in theatre use charge
Arterial line	Not costed	Included in theatre use charge
Surgical instruments	Not costed	Included in theatre use charge
Uterine staplers	96.00	
Surgical patch	170.07	£850.37/patch, used on average 1:5 cases
Maternal medications	233.79	Ranitidine, metoclopramide, indomethacin, Atosiban, GA meds, epidural meds
Fetal medications	664.50	Atropine, adrenaline, fentanyl, vecuronium, sodium bicarbonate
TOTAL	6867.48	

Table 3.3: Post-operative costs (inpatient)

Item	Cost (£)	Comments
48hrs maternal High Dependency Unit bed	1814.00	
120hrs antenatal ward bed	2100.00	
Medication	489.05	Atosiban, epidural meds 24-48hrs, analgesia 7 days: paracetamol + dihydrocodeine, low molecular-weight heparin
Blood tests	13.35	Full blood count, urea & electrolytes, C-reactive protein
FMU ultrasound scan	24.41	
MRI prior to discharge	249.00	
TOTAL	4689.81	

Table 3.4: Post-operative costs (outpatient)

Item	Cost (£)	Comments
Ultrasound protocol	244.10	£24.10/each, performed weekly for average 10 weeks
Fetal MRI prior to delivery	249.00	
Maternal readmission if complications	1050.00	Assumed in 50% (CHOP data), assumed average stay 5 days
Maternal tocolysis if readmission	2.70	Nifedipine, paracetamol, dihydrocodeine, LMWH for average 5 days = 5.40 x 0.5
TOTAL	1545.80	

Table 3.5: Delivery Costs

Item	Cost (£)	Comments
Delivery by caesarean section	Not costed	Usual care
TOTAL	0	

Table 3.6: Combined Costs

Prenatal Repair		Postnatal Repair	
Phase	Cost (£)	Phase	Cost
1	274.10	Combined cost (tariff)	19206.55
2	6867.48		
3	4689.81		
4	1545.80		
5	0		
TOTAL	13377.19	**TOTAL**	19206.55

3.4.4 Discussion

Our economic evaluation showed that the cost of performing fetal spina bifida repair (£13,377.19) is less than the standard tariff for postnatal repair (£19206.55) when neonatal care is excluded. If prematurity occurs and neonatal care is required then this adds to the total cost. The amount added will depend on the level of neonatal care required and time it is needed for. For the NHS overall this should mean that there is not a large financial implication in providing fetal surgery for spina bifida, especially as it is likely to be suitable for a small number of women each year. However, for individual institutions it may have a financial implication, whereby the central payment for spina bifida closure is paid to centres providing prenatal surgery and not those providing postnatal (neonatal) surgery.

We note that the prenatal repair costs were the costs estimated at face value and not a tariff cost which has been applied to postnatal care. Our estimates of the cost of fetal surgery did not include any set-up costs, such as team travel and training. This is important information when considering setting up this service. We have shared our costings information with the NHS Specialised Commissioning Service and have assisting them in creating a national tariff for this procedure which will adequately reflect the costs.

3.5 Acceptability Amongst Healthcare Professionals

3.5.1 Introduction

Acceptability is a key consideration in the implementation of healthcare interventions. For a new intervention to be successful, it must be acceptable to both the providers and receivers. “Buy in” from healthcare professionals referring, treating or caring for patients is necessary to ensure that the intervention is offered and delivered as intended[322]. Patient acceptability is also necessary for an intervention to be accepted and adhered to; this will be discussed further in chapter 4.7.

Some new interventions may be considered more controversial than others. Within sexual health medicine, the introduction of pre-exposure prophylaxis (PrEP) for prevention of HIV transmission amongst high-risk groups has been debated and discussed at length. A Dutch study[323] showed that acceptability of this amongst healthcare professionals, including HIV specialists, was moderate at best with significant concerns about the effects of implementation such as a possible decrease in condom use and increase in risk-prone behaviour. This level of acceptability amongst healthcare professionals clearly may have an impact on their willingness to prescribe or endorse this strategy. Within stem cell and tissue engineering research, differences between clinicians and researchers have been shown to exist regarding knowledge and acceptability of the risks of this technology[324], which again may have an impact on the success of any therapy introduction.

Fetal surgery can be considered a potentially controversial intervention, with many ethical and social aspects to be considered[325]. A questionnaire study[326] of 670 maternal-fetal medicine (MFM) physicians, neonatologists and paediatric surgeons in the US showed that the majority believed prenatal surgery to be favourable to postnatal. A minority of respondents indicated that they were now less likely to recommend termination of pregnancy, with the majority reporting no change. Attitudes varied according to specialty, with neonatologists and paediatric surgeons more likely to recommend prenatal surgery.

It is clear that acceptability to healthcare professionals, especially when introducing fetal surgery in a country for the first time, is vital to successful implementation.

To successfully set up the first open fetal surgery unit in the UK, acceptability of the service to both staff in our hospital and other healthcare professionals around the country was considered to be highly important. We therefore undertook a survey study to assess current attitudes towards both this intervention and our plans for implementation.

3.5.2 Methods

We designed an electronic questionnaire aimed at healthcare professionals in the UK to assess the respondents' background knowledge of spina bifida and fetal surgery, opinions about fetal surgery and concerns. We also collected

demographic data and the respondents' level of training. In the questionnaire we described the scientific rationale for closure of MMC during fetal life, including earlier reversal of hindbrain herniation and the "two-hit" hypothesis - namely that the neurologic defects seen in spina bifida arise from both the primary neural tube defect and secondary in-utero damage following mechanical and chemical trauma to the exposed neural elements.

The questionnaire was distributed to healthcare professionals (obstetricians, maternal-fetal medicine clinicians and midwives, paediatric surgeons, neonatologists and theatre nurses) nationally via personal contacts, the websites of the British Maternal Fetal Medicine Society (BMFMS) and the British Association of Perinatal Medicine (BAPM) and by email via the British Paediatric Neurosurgery Group (BPNG). Responses were collected and analysed using questionnaire survey software (Google Forms, Alphabet, California, US).

3.5.3 Results

Demographics

Ninety-eight (98) responses were received. Demographics are shown in Table 3.7. The majority of responders were aged 41-60 years and from England. Maternal-fetal medicine specialists, midwives, paediatric neurosurgeons, general obstetricians and neonatologists were the largest groups of responders, and the majority had over ten years' experience in their clinical role.

Table 3.7: Demographics of Responders

		Number (n = 98)	Percentage (%)
Gender	Female	56	57.1
	Male	40	40.8
	Unanswered	2	2.0
Age (years)	26-30	7	7.1
	31-40	21	21.4
	41-50	32	32.7
	51-60	37	37.8
	61-70	0	0
	Unanswered	1	1.0
Professional Role	Maternal Fetal Medicine Clinician	21	21.4
	Midwife (Fetal Medicine)	20	20.4
	Paediatric Neurosurgeon	17	17.3
	Obstetrician (general)	15	15.3
	Neonatologist	13	13.3
	Theatre/ Operating Department Nurse	11	11.2
	NHS Commissioner	1	1.0
Years of Experience in Role	0-2	8	8.2
	2-5	17	17.3
	5-10	21	21.4
	>10	51	52.0
	Unanswered	1	1.0
Country of Practice	England	80	81.6
	Channel Islands	6	6.1
	Republic of Ireland	4	4.1
	Scotland	4	4.1
	Wales	4	4.1

Knowledge and Attitudes Regarding Spina Bifida

Results of questions pertaining to knowledge and opinions of responders regarding spina bifida are shown in Figure 3.7. Paediatric neurosurgeons were most likely to rate their knowledge of spina bifida as “expert”; MFM clinicians, obstetricians and neonatologists most commonly described theirs as “good” and midwives “limited”. Paediatric neurosurgeons, MFM clinicians and neonatologists were most likely to be moderately or very familiar with managing patients with spina bifida; general obstetricians and midwives were “slightly” or “not at all” familiar with this. Most respondents agreed that spina bifida was associated with significant disability, and that babies having postnatal repair generally do not have a normal quality of life, although 19.4% of respondents were unsure regarding this latter point.

Knowledge and Attitudes Regarding Fetal Surgery

Knowledge about fetal surgery was rated highest in MFM clinicians, with most other groups rating their knowledge as “limited” (Figure 3.8). Most respondents (72.4%) had no experience performing or counselling about fetal surgery. Familiarity with the MOMS trial was highest amongst MFM clinicians and paediatric neurosurgeons and the “two-hit” hypothesis was generally well-known. Around 70% of respondents agreed with the concept that fetal surgery improved the outcome in selected cases, although this was lower in the group of paediatric neurosurgeons (41%).

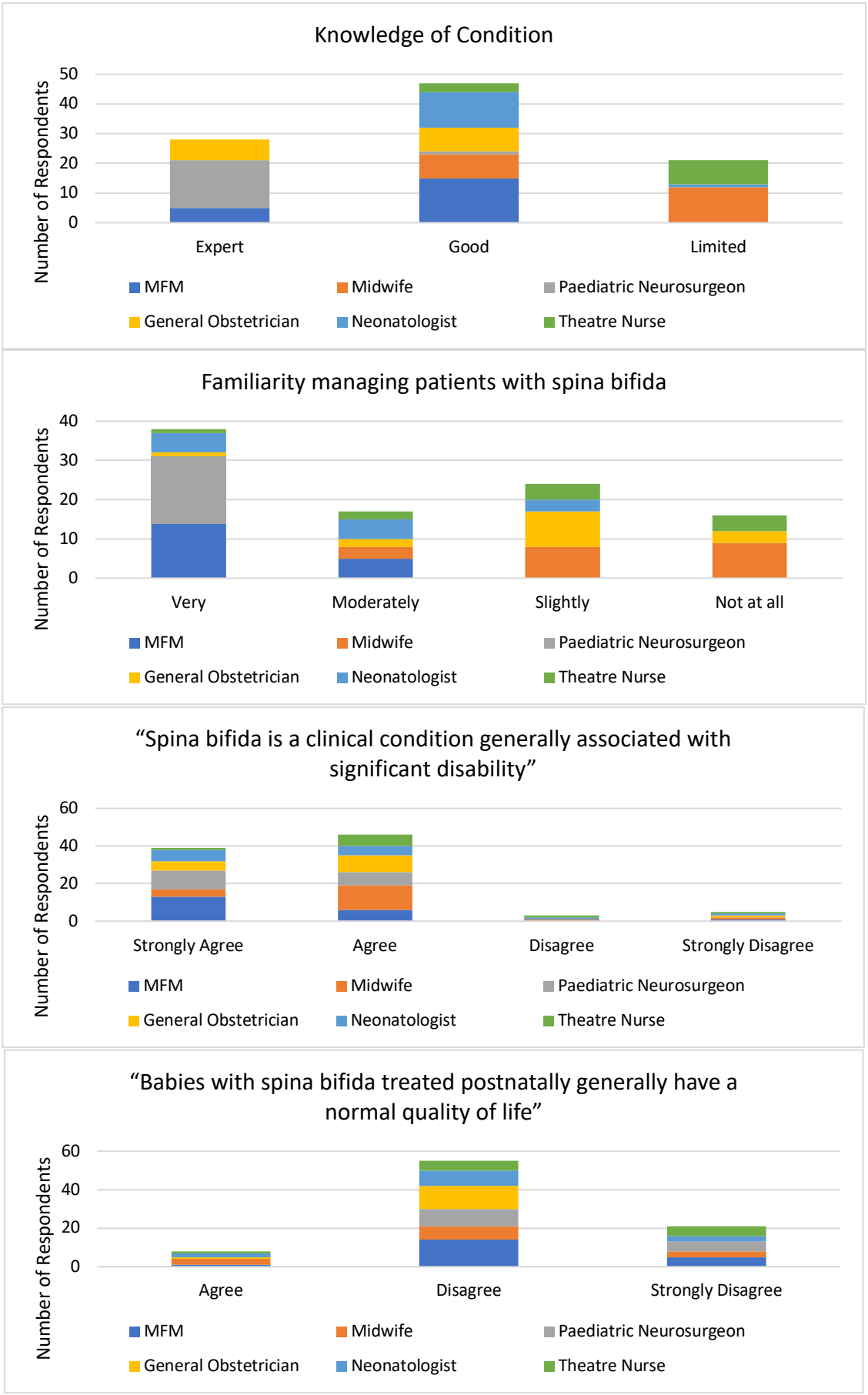

Figure 3.7: Knowledge and Opinions Regarding Spina Bifida

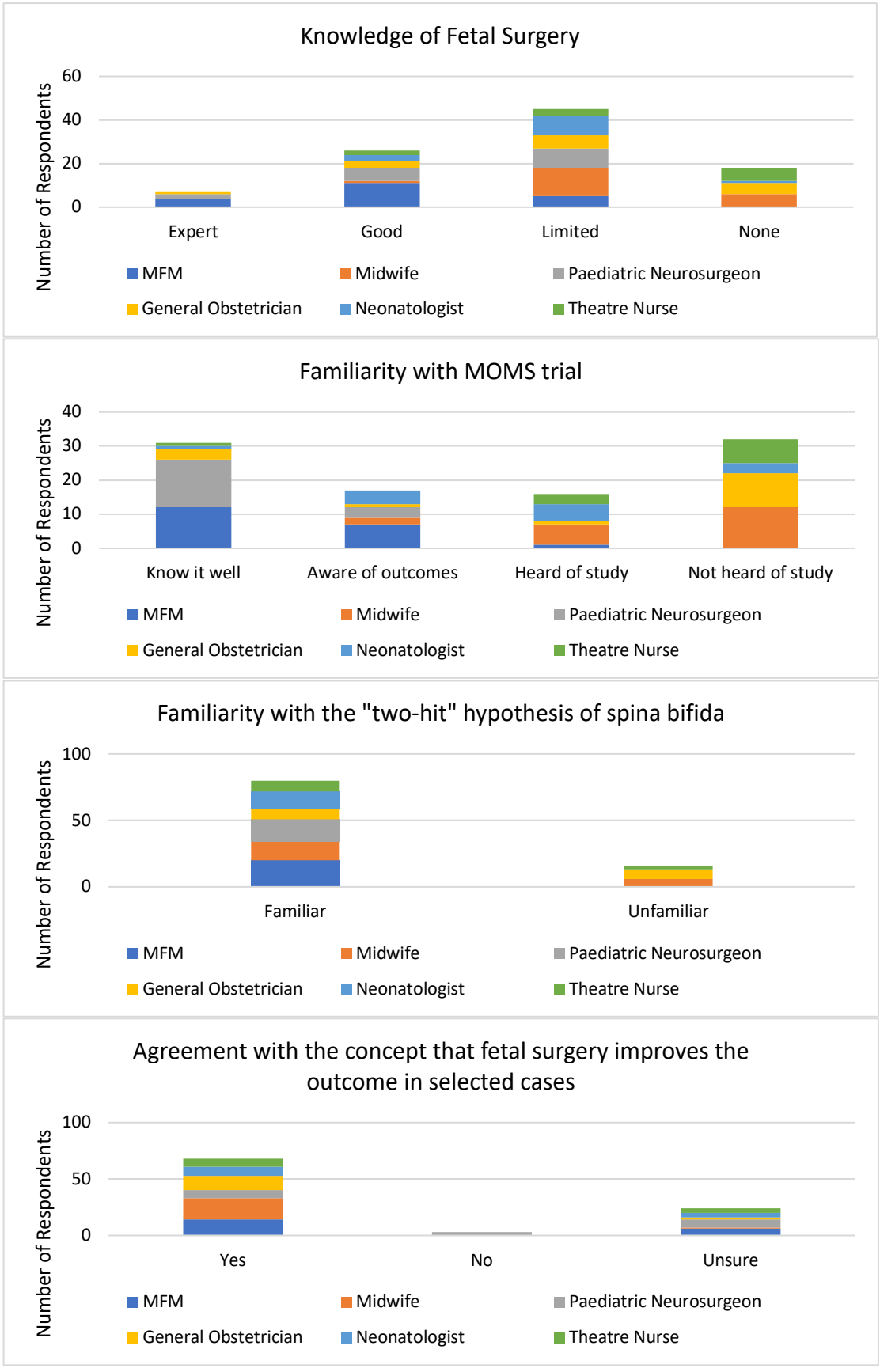

Figure 3.8: Knowledge and Opinions Regarding Fetal Surgery

Concerns Regarding Fetal Surgery

There were a variety of concerns raised regarding fetal surgery, the most common being the lack of mid-to long-term information regarding the effects on the child and mother. The ten commonest concerns are shown in Figure 3.9.

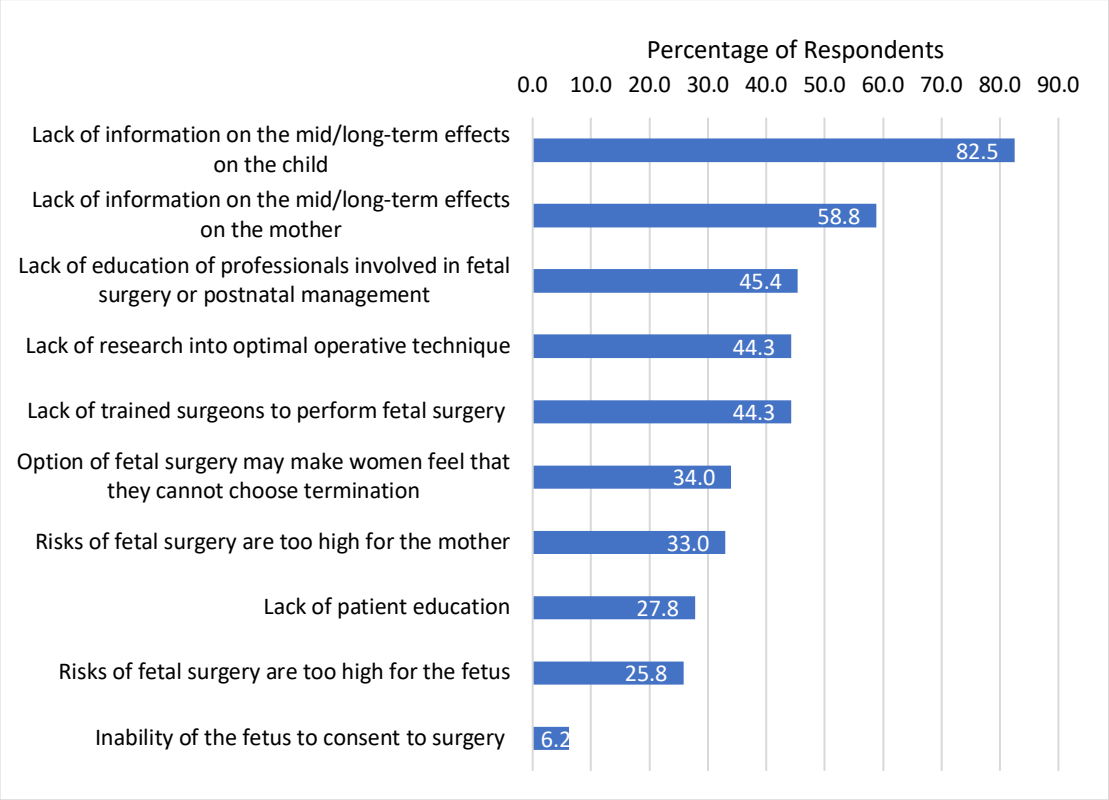

Figure 3.9: Concerns Regarding Fetal Surgery

Free Text Responses

Responders were given the opportunity to leave free text comments in the questionnaire. These are reported below, grouped by topic.

Prematurity

- “Some improvement in outcomes must be balanced against the risks of prematurity.” - Fetal Medicine Consultant
- “[Lack of] evidence as to the relative benefits of fetal surgery versus the potential long-term complications of pre-term birth on baby and family and maternal complications.” - Midwife
- “The risk of preterm delivery following fetal surgery with its consequent co morbidities need to be highlighted.” - Neonatologist

Evidence base/ outcomes

- “Several studies in Europe now suggest expectant management is associated with better outcomes than the experimental arm in MOMS. In that respect MOMS was unusual as outcomes in the control group were worse than we would expect.” - Fetal Medicine Consultant
- “I am aware of a small number of surgeons offering in utero surgery for MMC in Europe. I know from colleagues who have treated some of these in utero repair cases post-op that serious complications from in-utero surgery go unreported, and this sends a misleading message to expectant parents regarding the safety of in-utero surgery. My concern about a small number of lone practitioners doing in-utero surgery is that they have an

inherent bias towards the procedure and become zealous proponents." - Paediatric Neurosurgeon

- "I take issue fundamentally with the concept that surgical repair in utero can reduce lifelong disability, versus postnatal repair." - Paediatric Neurosurgeon
- "There is no evidence anywhere that laparoscopic surgery for spina bifida improves outcomes." - Fetal Medicine Consultant

Maternal choice and information

- "Mothers may feel compelled to have a treatment that could adversely affect all their future pregnancies and result in net harm over the mother's reproductive life course." - Fetal Medicine Consultant
- 'I would love to see more research into this technique and am pleased we are going to offer it in the UK.' – Fetal Medicine Midwife
- "If the existence of your service caused even a small number of parents to choose not to terminate (and have a healthy replacement baby) the net harm would be considerable." - Fetal Medicine Consultant
- "[There is] evidence of historical poor or less than optimal consent processes for reproductive technologies both in research and clinical practice i.e. consenting in one consultation, not ensuring time for consideration and clarification." - Midwife
- "Both maternal and neonatal outcomes must be balanced." - Midwife

Financial Implications

- “In an NHS struggling to resource basic care, while this is exciting stuff, is the balance of needs being appropriately considered?” - Fetal Medicine Consultant
- “[I am concerned about] distribution of finances in difficult economic times.” - General Obstetrician

3.5.4 Discussion

In this study we assessed the attitudes of healthcare professionals in the UK to fetal surgery for spina bifida. The level of knowledge and experience of spina bifida and fetal surgery was relatively high, reflecting the expertise of the professional groups that we surveyed. We targeted MFM clinicians and midwives, paediatric neurosurgeons and neonatologists who were most likely to be referred women whose fetus has spina bifida and who might be considering fetal surgery. Familiarity with the “two-hit hypothesis” and the MOMS trial was also high and in general over two-thirds of respondents agreed with the concept that fetal surgery improved outcomes in selected cases. However, there were concerns expressed regarding this surgery, particularly about the safety and efficacy long term for both the mother and her child, the risk of preterm birth, the implications for maternal choice and cost.

We sought opinions from a range of healthcare professionals involved in the care of patients considering fetal surgery, such as obstetric anaesthetists and theatre staff, rather than concentrating only on MFM clinicians or paediatric neurosurgeons. Although we received between 11 and 20 responses per

healthcare group, we believe that the opinions expressed are likely to be similar to those held by other healthcare professionals. A recent transcript of a scientific conference of patients and healthcare professionals convened by SHINE, a UK spina bifida charity, had similar consensus findings after a review of the literature concerning fetal surgery for spina bifida[327]. Attendees agreed that further data was required regarding long-term neonatal outcomes following open fetal surgery (currently being collected as part of the MOMS2 trial), and the long-term maternal outcome including the impact on future pregnancies. A recent study showed no impact of open fetal surgery on future fertility[109]. There was also a call for standardised reporting of postnatal surgery outcomes to allow comparison with fetal surgery. Finally there was agreement that pregnant women whose fetus is known to have spina bifida should be counselled that fetal surgery is an option in specific circumstances.

The legality and ethics of fetal surgery, particularly regarding the status of the mother and the fetus, have been debated extensively[328 329 330]. Some countries have now adopted guidelines to support providing information to parents on the option of fetal spina bifida repair and prognosis if there are no maternal or fetal contraindications for prenatal repair at 20–26 weeks' gestation.

The findings and concerns expressed in this study and the above conference have guided the establishment of the first open fetal surgery clinical service in the UK, and have informed the recently approved NHS Specialist Commissioning Service specification. Collecting data on both short and long-term outcomes is an absolute requisite to enable the quality of a new clinical service to be evaluated. This will require outcome data to be provided not only by MFM clinicians and neonatologists who manage the care of the mother and neonate in the short term, but also long term engagement from the paediatric neurosurgical and

neurological teams who manage the child growing up. As knowledge about fetal surgery for spina bifida increases amongst patients and healthcare professionals, aided by media reports and social media, the provision of a UK clinical service in a strictly regulated and transparent manner will provide NHS patients with the best possible care.

3.5.5 Conclusion

This study highlights the opinions of healthcare professionals in the UK regarding fetal surgery. The majority of respondents agree with the concept of fetal surgery but have concerns, particularly regarding long-term effects. In offering this new service it is important that healthcare professionals are cognisant of existing concerns and address them as far as possible by applying internationally accepted criteria, emphasising patient choice and collecting and evaluating long-term data.

3.5.6 Contributions

The work in Chapter 3.5 was produced in collaboration with: Dr Shahanaz Ahmed (University College London), Professor Jan Deprest (KU Leuven, Belgium) and Professor Anna David (University College London).

Chapter 4 **Patient Cohort**

4.1 Summary of cases

In line with international best practice guidance for fetal surgery[304], we created a database and kept records of all patients referred to our service. Referrals began by word of mouth before our service was fully set up, and initially required cross-site working with Leuven, Belgium until our service was fully operational in London. At that point we sent information to all fetal medicine units in the UK and placed an announcement on the British Maternal and Fetal Medicine Society (BMFMS) website. Clinical details of all cases assessed to date (January 2018 - January 2019) are shown in Table 4.1.

Table 4.1: Overview of Fetal Surgery Referrals seen at UCLH Jan 2018-Jan 2019

Patient number	Referral from (regional FMU)	Lesion level	Eligible for surgery	Exclusion reason	Parents' decision	Maternal complications	Pregnancy complications	Delivery gestation (weeks + days)	Neonatal
1	Self/London	S2	No	S2 level	Expectant			37+0	No VP shunt yet
2	Belfast	L1	No	Cri du Chat	Expectant			32+0	Neonatal death <24hrs
3	Belfast	L4	Yes		Fetal surgery (Leuven)	Wound infection, psychological distress		37+0	Wound infection No VP shunt yet
4	Bristol	L4	Yes		Termination				
5	Belfast	L3	Yes		Fetal surgery (Leuven)		PTL 35 weeks	35+2	No VP shunt yet
6	Birmingham	L1	No	Kyphosis	Expectant			38+1	VP shunt day 1
7	Birmingham	T11	Yes		Fetal surgery (London)	Buttock cellulitis, seroma, PPH at delivery, post-CS haematoma	APH 32 weeks, PROM 33 weeks	33+5	VP shunt day 4
8	Dublin	L4	Yes		Fetal surgery (Leuven)		PROM 35 weeks	35+3	No VP shunt yet
9	Belfast	L5	No	Cortical folding	Expectant			Unknown	Unknown
10	Birmingham	L4	No	Brain + limb abnormalities	Expectant			Unknown	Unknown

Patient number	Referral from (regional FMU)	Lesion level	Eligible for surgery	Exclusion reason	Parents' decision	Maternal complications	Pregnancy complications	Delivery gestation (weeks + days)	Neonatal
11	Self/London	S2	No	S2 level	Expectant			37+4	VP shunt 2-3 weeks
12	Luton	L3	No	Cortical folding	Expectant			37+6	No VP shunt yet
13	Manchester	T7	No	Kyphosis	Expectant			38+3	Undiagnosed CDH VP shunt 2 weeks
14	Belfast	L4	Yes		Fetal surgery (London)		PROM 31 weeks, PTL 33 weeks	33+3	No VP shunt yet
15	Belfast	L4	No	Brain + limb abnormalities	Expectant		Premature delivery due to VM	34+6	VP shunt day 2
16	London	T12	No	Kyphosis	Expectant			Unknown	Unknown
17	Dundee	L1	Yes		Fetal surgery (Leuven)	Seroma	PROM 32 weeks	33+0	Skin graft 3 weeks of age; ETV 11 weeks
18	Kent	S1	Yes		Fetal surgery (London)		?CMS - oligo 26wks, PTL 28 weeks	28+6	No VP shunt yet
19	Devon	L3	Yes		Fetal surgery (Leuven)		CMS 26 weeks, PROM 28 weeks	34+0	No VP shunt yet
20	Cambridge	L3	Yes		Fetal surgery (Leuven)	Pulmonary oedema	?CMS 30 weeks	Still pregnant	
21	Dublin	L4	Yes		Fetal surgery (Leuven)			Still pregnant	
22	Manchester	T12	No	Kyphosis	Expectant			Still pregnant	

Patient number	Referral from (regional FMU)	Lesion level	Eligible for surgery	Exclusion reason	Parents' decision	Maternal complications	Pregnancy complications	Delivery gestation (weeks + days)	Neonatal
23	London	L4	Yes		Fetal surgery (London)	Wound infection		Still pregnant	
24	Manchester	L2	Yes		Fetal surgery (Leuven)			Still pregnant	
25	Southampton	L3	Yes		Fetal surgery (London)	Seroma		Still pregnant	
26	Manchester	T10	Yes		Termination				
27	London	S1	Yes		Termination				

Grey: fetal surgery cases. APH: antepartum haemorrhage, CMS: chorionic membrane separation, PPH: postpartum haemorrhage, PROM: preterm rupture of membranes, PTL: preterm labour, VP: ventriculoperitoneal,

4.2 Patients excluded

To date, 11 out of 27 patients (41%) assessed for fetal surgery were not offered surgery as one or more exclusion criteria were judged to be present. Exclusion criteria in this group were: additional abnormalities (4), spinal kyphosis (4), lesion level too low (2) and genetic anomalies (1). At our institution, such cases are discussed in multi-disciplinary meetings and images (both US and MR) are shared for second and third opinions if needed. All women not offered surgery continued the pregnancy and had/ plan for postnatal surgery. Out of the 16 patients offered surgery, 13 accepted and proceeded with this and three declined and opted to terminate the pregnancy. The rate of termination of pregnancy seen in our patient cohort is therefore low (11%, 3/27) which is not representative of the group of women with spina bifida as a whole[60 76]. We believe this is because women and families who wish to end the pregnancy have already made this decision after counselling at their local or regional hospital, and that the patients who attend our unit are therefore self-selected as those likely to continue the pregnancy regardless of whether they qualify for surgery or not.

4.3 Imaging

Two patients referred to us were judged to have lesion levels lower than previously assessed which made them unsuitable for surgery. In our discussions following these cases, it was apparent that ambiguity existed regarding where one judges the defect to start on US - according to the first bony disruption, the first clear bone absence, the skin and soft tissue abnormality or a combination of the above? Additionally, should the defect be assessed in sagittal or transverse

planes? On reviewing the literature, it appeared that there are no clear guidelines on this, and it is common to experience inter-observer variability of one to two levels. As the anatomical level does not exactly correspond with function[331], and as parental decision to terminate does not seem to only relate to lesion level[76], it seemed to us that up until this point complete accuracy and agreement regarding lesion level has not been required in antenatal counselling. However, now that fetal surgery contains strict criteria regarding lesion level it is evident that accurately labelling the lesion level, and agreement on that level between experts, is critically important. The radiology team at Children's Hospital of Philadelphia (CHOP) have described how they label spinal levels when assessing patient's considering fetal surgery[332], taking into account the level of the first bony disruption in both the sagittal and transverse planes. We agreed to follow this, and to discuss all cases between our two teams to establish agreement. The same paper describes measurement of the spinal angle in kyphosis, which appears to us less variable.

In our experience so far, we have found that it is not always clear if other abnormalities encountered are additional to the diagnosis of spina bifida or part of the spectrum. In two cases there have been multiple anomalies of the brain and limbs and so these cases were excluded without too much difficulty. In some cases we have found other abnormalities which can be part of the spina bifida spectrum but can also be independent anomalies - for example, absence of the cavum septi pellucidi, dysgenesis of the corpus callosum or abnormal cerebral cortical folding[333] [334] [335] [336]. When encountering these abnormalities we have considered the reports of both US and MR and made a decision after discussion based on what we feel the likelihood is that the abnormality seen is part of the spectrum of spina bifida.

4.4 Ethical Issues

One patient was found to fulfil criteria and underwent an uncomplicated fetal repair in Leuven. On waking from anaesthetic she expressed regret at having the procedure and requested termination of pregnancy; this desire to end the pregnancy continued for the next few days. Her regret seemed to focus around her feelings that she did not want to have a baby affected by spina bifida, however "mild" or improved; that she did not want a child with urological difficulties (which is likely even with fetal surgery as bladder innervation is from a much lower spinal level); she felt that her baby would have a poor quality of life and would have a negative effect on her existing child. She acknowledged that she had been aware of all these issues prior to having fetal surgery, and that she had made the decision to proceed freely and without coercion, but when she felt unwell herself following surgery this highlighted to her that she did not want a child which was unwell.

This case raised many ethical concerns, which we discussed and considered extensively. In the short-term the team in Belgium felt unable to offer termination in such circumstances. It was discussed that medical termination of pregnancy would not be possible so soon after a hysterotomy, and so surgical removal, probably by re-opening the hysterotomy, would be required. Counselling and support was arranged for her and she reported gradually "coming to terms" with the situation. She returned home and engaged with local care; on review three months after the baby was born she reported being happy with the situation. We reviewed our counselling around fetal surgery and felt that in this case, as in all others, we provided the option of fetal surgery with evidence of likely risks and

benefits, but in no way sought to persuade the patient to choose this path. We had equally explored the option of termination of pregnancy beforehand with the patient and had made steps to see if it was possible to arrange this in our hospital if that is what she chose. There had been no psychiatric or psychological concerns prior to surgery. This case reinforced our commitment to non-directive counselling and allowing patients time for reflection.

Another case that raised some ethical concerns was the referral of a patient who spoke no English and had newly arrived in the UK from Pakistan in order to marry a British Pakistani man. The partner and his family were present at her initial consultation, and all spoke fluent English; they were very keen for the patient to proceed with fetal surgery in order to give any benefit possible to the baby. We spoke to the patient privately via an interpreter and she said that she did not want to end the pregnancy but it was difficult to ascertain how much she wanted surgery and whether she was being coerced into this. On ultrasound scan the patient was found not to be eligible (brain and limb anomalies) and so we did not proceed further with decision-making. We discussed the case in a multi-disciplinary team meeting and agreed that if further cases with concerns regarding maternal autonomy presented we would assess the patient at least twice alone, using interpreters as necessary, and decide each on a case-by-case basis.

4.5 Maternal, Pregnancy and Neonatal Outcomes

Thus far our maternal and pregnancy outcomes have appeared approximately in line with the MOMS trial, although there have still only been small numbers of women operated on overall. The average gestational age at delivery has been 33 weeks and there has been no maternal mortality or major morbidity. As all children born are still under 12 months of age, it is still very early to assess neonatal outcomes but thus far there have been no serious complications of prematurity and one ventriculoperitoneal shunt placed (14%) which is encouraging. We will be following outcomes closely in the future.

4.6 Patient Acceptability

Patient's experience of our service and attitude towards the proposed treatment is of vital importance when setting up any service, particularly one as new and complex as this. We therefore are undertaking a continuous survey study of patient feedback as they come through our unit.

4.6.1 Methods

We developed an electronic questionnaire aimed at patients reviewed in our unit for the possibility of fetal surgery. The questionnaire was divided into sections assessing the responders background knowledge of spina bifida and fetal surgery, opinions about fetal surgery, reasons for their choice of whether to have

surgery or not if it was offered and experience of the service. We asked as many qualitative or free-text questions as possible in order to capture patient's thoughts and opinions. No question box was mandatory. The survey was reviewed by the patient charity SHINE[301] for readability and acceptability. The survey was sent to all patients after they had been assessed at UCLH, and after surgery if this occurred, but before delivery of the baby.

4.6.2 Results

The response rate was 19 out of 27 (70.3%)

Initial diagnosis/ referring unit

Eighteen out of 19 patients (94.7%) had seen a fetal medicine specialist prior to assessment at our unit and 12 (63.2%) had seen paediatric surgeon. The option of termination of pregnancy had been discussed in all cases. Five patients (26.3%) had fetal surgery discussed at the time of initial diagnosis; eight (42.1%) had it discussed at the time of discussion of the options of postnatal surgery and termination of pregnancy, one patient (5.3%) had it discussed once they had decided to continue the pregnancy and five (26.3%) had not had fetal surgery discussed with them but had found out themselves in another way.

Patient feedback:

- "We felt uninformed when our first hospital gave us the diagnosis, but as soon as we transferred to UCLH we were given all the information we needed/asked for. We appreciated how team were happy to

spend time thoroughly explaining things to us and we were able to ask as many questions as we liked."

- "We have been lucky enough to have had it explained by many knowledgeable Consultants & Doctors at UCLH & our local hospital, alongside the charity Shine, who have been most helpful in our understanding."
- "It [fetal surgery] had been mentioned in passing with our Fetal Medicine team, but it was brushed over and not explained fully, so we weren't aware that it could be an option for us at that point, more a ground-breaking idea, that would develop in the future. We then went on to find out more about the process through watching a BBC Horizon documentary by complete chance, which happened to be on TV the week of our diagnosis. We followed up by calling UCLH the next morning and enquiring about the process, things moved quickly from there, and we asked our hospital to refer us, which they did promptly."
- "At UCL this [fetal surgery] was discussed fully and in detail, however limited knowledge was known at our local hospital at the time of diagnosis through ultrasound."
- "Yes it [termination] was [mentioned], it came up very quickly after having made the discovery in my 20 week scan, which came as a massive blow and definitely sent us to an incredibly difficult place emotionally."

Assessment at UCLH

All patients (100%) felt that fetal surgery had been adequately explained to them.

Patient feedback:

- “All aspects have been covered.”
- “Yes [adequately explained], once we got in contact with Adalina at UCLH.”
- “[Explained] extremely clearly.”
- “Before we transferred to UCLH, our previous hospital gave us no information about it and when we asked if anything could be done before birth, they just told us to research it ourselves because they couldn't help. We went ahead and researched fetal surgery ourselves, found Prof Deprest and spoke to him. He put us in touch with Adalina and from this point onwards, everyone we have come into contact with has been extremely helpful in explaining fetal surgery and everything we needed to know about it. The counselling at UCLH and in Belgium was excellent. We can't thank Adalina and the team enough.”
- “When we first got the diagnosis, we felt frustrated that there was (supposedly!) nothing we could do to improve the life of our child and we would have to wait out the pregnancy knowing that damage was being done before baby was born. Following our research, the counselling we received from Prof Deprest/the UCLH team/Dominic Thompson and reading the MOMs trial, we believed the benefits of the surgery outweighed the risks. We felt that going ahead with it

aligned with our determination to do all we can to improve our child's life and we hoped we could prevent some of the damage done in the third trimester by having the operation as early as possible. We also had a huge amount of respect for the team who counselled us and felt encouraged by their belief in the surgery."

Opinion on fetal surgery for spina bifida

Patient feedback:

- "If we had the option, this is definitely the route we would have taken for our child. Potential benefits outweigh the risks by far, especially in the case of lower smaller lesions. I would not hesitate in recommending anyone to speak to the team for assessment. From a practical perspective, it would definitely be an advantage for anyone from NI to have the surgery in London."
- "It is amazing. Doing this before birth and improving children's lives and giving hope to parents is fantastic. It is a big commitment though and parents have to be committed. The benefit to the child has to be significant. So it was good we were told what our scan results meant even though it wasn't good news for us."
- "Despite the surgery not going ahead in the end, we would make the same decision if we found ourselves in this situation again. We think that every parent who gets the diagnosis should have the experience we had at UCLH in order to be fully informed and be able to consider fetal surgery as an option."

- “It gave us back some hope for our baby and has left us feeling optimistic about our baby's overall outcome.”
- “It should be offered to more people.”
- “I think it is a brilliant opportunity for parents to have.”
- “With all due respect, it’s a mirage of hope. We were so happy to hear that we had some hope of helping our child before he’s born. We travelled halfway across the country to see the specialist and we was then told our son was not eligible for the surgery because he was unfit for the procedure. So please don’t get your hopes up too much God forbid if any of you went through what we did it will definitely break you down even more. I’m sorry.”
- “We think it is a truly incredible and ground breaking surgery that offers hope and assistance to your baby at a point when you do feel quite helpless as a parent. I would do anything for my baby and if fetal surgery was going to improve their outlook then I definitely would have opted for it. Unfortunately we fell below the criteria, but we do not regret investigating this option in the slightest, as we learnt so much throughout the process and feel so much more equipped now to deal with the postnatal surgery and life for our child beyond that.”
- “Requirements for surgery are set to high very limited people are offered the surgery due to these requirements.”

- “It is an option I was grateful to have and I think it is an amazing surgery in benefit of the baby and mother. It's just a shame that not many people know or have adequate understanding of it.”
- “Utterly incredible - it still leaves us in awe that such procedures are available and offered. We couldn’t be more grateful.“
- “It is a fantastic medical development which is hopefully going to improve the quality of life for the patients who qualify.”
- “I think it is a vital service. Evidence has shown it has improved patient outcomes.”
- “We see the risks associated with both pre and postnatal surgery, and found the benefits of prenatal closure for the baby outweighed those risks.”
- “We wish we could have it done but sadly can’t.”
- “It gives the baby more of a fighting chance to lessen the effects”
- “I think it is amazing and gives hope to parents whose babies are given diagnosis of Spina Bifida. It is so important that our society wants to care for children that aren’t perfect and need extra care.”
- “It's a step in the right direction and we think it's a viable option but the additional risks that it introduces need to be reduced.”
- “That it should be discussed at every hospital if this diagnosis is found. That more needs to be done to showcase this surgery and that it can be positive for the unborn baby. I'm in total awe of this surgery and think it's incredible.”

Other things which would have been helpful

Patient feedback:

- “Reports from UCHL/Leuven sent to me as well as referring consultant”
- “I would suggest a follow-up list for patients who do not undergo surgery (and as a reminder to the referring consultant) for completeness and in case they need access to the following:
    - Official USS / MRI report - including images - our neuroradiologist was reluctant to comment without images
    - Appointment with neurosurgeon if wishes
    - Appointment with neonatal/paediatric SB team if wishes
    - Discussion about options”
- “I think mothers need to be made aware of how much they can or cannot do physically after, possibly given a contact of a woman who has been through it if possible. I joined a facebook group and there was a lot of support there. I think when patients are discharged back to their regions they need to feel like someone is taking over their care so they feel a continuation of care. We didn't get that far, but I remember worrying about after surgery care locally.”
- “I believe it would have been helpful to have someone explain to me what to expect when baby is born. In terms of how long baby will

have to spend in hospital even if he is born at full term (37 weeks) and is not required to have a shunt fitted."

- "I would have love to have been pointed the direction of support groups in my area that can help me and maybe even other parents."
- "Specifics on why it is that the CSF is unable to drain from the ventricles."
- "More information on the future implications of gross hydrocephalus. There maybe isn't a lot of studies on this."
- "Genetic chances before second pregnancy as [I was] led to believe it was from lack of folic acid."
- "Shine charity website and other mums that have Spina Bifida children."

Other comments

- "Very helpful to have had the most up to date evidence/research made available by Adalina prior to the assessment meeting at UCHL. Entire team very accommodating and professional. Good to have all parts of assessment in one unit. Prof Deprest a very knowledgeable and compassionate person, full explanation of condition, surgery, risks, realistic & honest about outcomes."
- "We would like to take this opportunity to say thank you to Adalina, Prof Deprest, Fred, Prof Peebles and the rest of the UCLH team. Adalina in particular has been more wonderful than she realises! The service the team provided has been professional, supportive and

faultless during one of the most emotionally difficult times we have ever been through. Our families are hugely grateful to you all too."

- "We felt very well looked after by all the professionals that we have encountered and felt that they really cared for us and wanted to do their best for us."
- "I was looked after brilliantly at UCLH. They were attentive, compassionate and very informative. They were also very thorough with their check-ups."
- "We'd like to thank all the Doctors and Consultants at UCLH for their time and care throughout this tumultuous time for us as parents to be. Dr Adalina Sacco has been incredibly kind and informative throughout and we really would like to offer her our thanks for helping us progress though our diagnosis to a position of acceptance and understanding. We would have no issue in recommending the team, hospital and surgery option to others in the same position. We felt very well looked after and understood the possible outcomes and consequences. We are so glad that UCLH & GOSH are now offering this as possibility and hope it will go from strength to strength as more operations take place. Wishing you all the best."
- "Our experience with the staff at UCL has been incredible, we really couldn't have been more grateful for the guidance, knowledge, treatment and care from all those within the team. They changed our mindset from a very dark period at the time of diagnosis, to that of very optimistic and positive towards the life we can give out little girl.

We will forever be grateful to all those involved within the Fetal medicine Team and the Antenatal Care Unit."

- "My partner and I are very grateful to have had the team review our case and consider us for the surgery. The team at UCLH were very knowledgeable and compassionate."
- "I was very happy with the service offered and it provided us with vital information to inform our decisions."
- "We had such a lovely experience with everyone we encountered; we couldn't fault it at all. From initial contact to our appointment in London, what we thought would be an arduous journey was made so easy by everyone involved. We can't thank Adalina enough!"
- "Many thanks to Adalina and the other doctors who saw us down in London."
- "Many thanks for the team that looked after us with such knowledge and skill."
- "Service was amazing. All the doctors and surgeons explained everything clearly and gave us the time to ask as many questions we needed to. They couldn't have been any nicer and were always available via email and phone."
- "Every single one of them were amazing. Adalina, Fred, Rewan, George and Prof Deprest are the most incredible people I have ever met. I can't physically remember everyone else but these people stick out. The only improvement I can think of is educating COB

about the surgery, post op pain and management, and that we haven't had our babies yet."

4.6.3 Conclusion

So far, our service has received a positive response and patients report being well-informed and do not seem pressurised into fetal surgery. We have taken on board patient feedback and suggestions for improvement and have worked on these. We will continue asking for patient feedback with all patients we see.

Chapter 5 Developing Practices and Techniques in Fetal Surgery

5.1 First Trimester Diagnosis of Spina Bifida

5.1.1 Introduction

Detection of fetal spina bifida usually occurs during the second trimester (anomaly) ultrasound scan at 18+0 to 20+6 weeks' gestation[337]. Diagnostic signs include a "lemon" shaped skull, a "banana" shaped cerebellum and visualisation of the spinal lesion. Detection of spina bifida at an earlier gestation would be beneficial for several reasons: firstly, there is evidence that in cases of significant abnormalities, parents prefer to be informed as early as possible in the pregnancy[338]. Secondly, if termination of pregnancy is the ultimate choice of the couple it is safer and more easily performed at earlier gestations[339]. Thirdly, in cases where in-utero closure is an option, earlier diagnosis allows time for detailed counselling and assessment in a specialist centre. Randomised control trial evidence has found that open fetal surgery to close spina bifida between 19+0 to 25+6 weeks' gestation improves motor outcomes and reduces postnatal ventriculoperitoneal shunt rates compared to postnatal repair[94] and this is now available in a number of centres worldwide[340].

A number of sonographic signs have been described in the last decade to aid early detection of spina bifida, although they have yet to become well established in clinical practice. Most evidence has been derived from retrospective reviews;

prospective evaluation of first trimester signs of spina bifida, particularly in a low risk population routinely scanned by sonographers, is lacking. The most extensively researched first trimester sonographic signs of spina bifida are the intracranial translucency[341], brainstem diameter[342], brainstem-occipital bone (BSOB) distance[343], aqueduct of Sylvius (AOS) to occiput distance[344] and frontomaxillary facial angle[345]. Rather than pattern recognition, these markers all involve taking measurements, which may add significant time to the scan.

We describe here a new first trimester ultrasound sign – the "crash sign" – and its evaluation in a cohort of pregnant women whose fetus was suspected to have spina bifida at 11-13+6 weeks of gestation, and who were referred to a fetal medicine specialist for evaluation. The crash sign is based entirely on pattern recognition and not measurements, and therefore has the potential to be easily performed and adopted during a first trimester scan.

5.1.2 **Methods**

Crash sign

The "crash sign" described here was first detected by one of the authors (FU) following reviews of stored first trimester brain 3D ultrasound volumes from fetuses with spina bifida. It is the posterior displacement and deformation of the mesencephalon against the occipital bone in the axial view (Figure 5.1). It is so named as it resembles the back of a car which has crashed into a wall; additionally, the moving image of a car reversing into a wall is a good aide memoir

for the hindbrain herniation which occurs in spina bifida[346], making the sign easily memorable.

In order to assess for crash sign, the standard axial view of the head in the first trimester[347] (11-14+1 weeks of gestation) is taken at the level of the mesencephalon. In the normally developed fetus, the mesencephalon is visualised as a semi-circular structure in the posterior brain and appears as a continuation of the thalami. It contains a round echolucent structure centrally, which represents the cerebral aqueduct of Sylvius. The mesencephalon is surrounded by the fluid filled arachnoid space which separates it from the occipital bone. In open spina bifida, the arachnoid space is no longer fluid-filled and the mesencephalon sits directly against the occipital bone. Narrowing of the aqueduct of Sylvius may also occur, and in some cases it may no longer be visible. The crash sign can be readily recognised on axial sonographic views by using both transabdominal and transvaginal approaches.

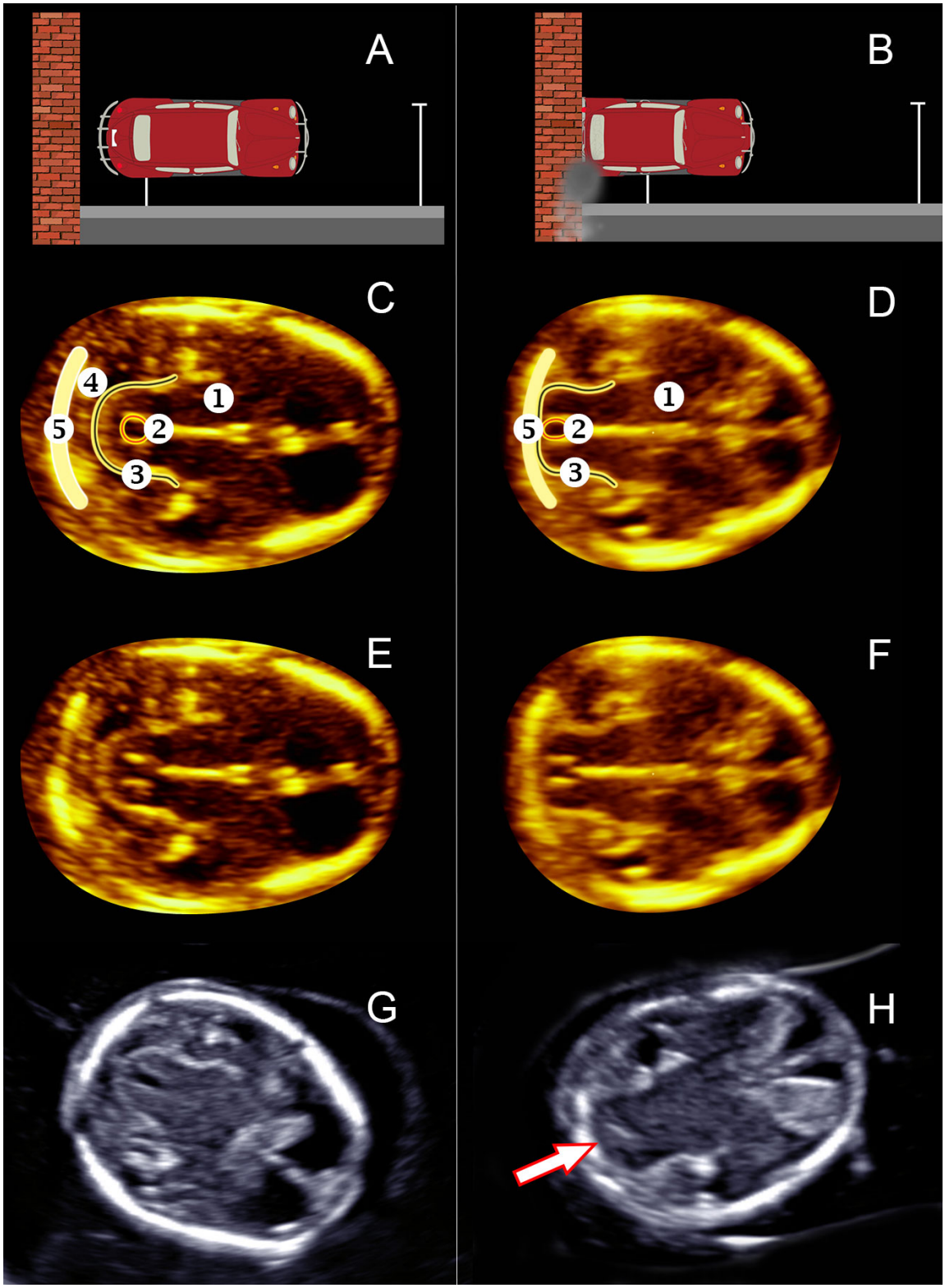

Figure 5.1: 12-13 weeks ultrasound images of the mesencephalon in a normal fetus (left, C,E,G) and its posterior displacement and deformation against the occipital bone in a fetus with open spina bifida (right, D,F,H): the “crash sign”. C,D,E and F represent 3D reconstructed images of monochorionic twins, discordant for spina bifida. G represents a normal case; H shows the crash sign (arrow) in another fetus with spina bifida.
1) thalami, 2) aqueduct, 3) mesencephalon, 4) arachnoid space, 5) occipital bone.
Reproduced with permission of UCLH, London

Study participants

This was a retrospective observational study from three large fetal medicine referral centres (University College London Hospital, London; Moscow Regions Research Institute of Obstetrics and Gynaecology; and Emergency University Hospital of Craiova, Romania). Women who were referred for a fetal medicine ultrasound scan between January 2012 and December 2015 due to concerns regarding fetal spina bifida were included. In these centres, a detailed anatomical examination of the fetus was routinely performed at 11+0 to 14+1 weeks' gestation according to last menstrual period or crown rump length, if there was a discrepancy of more than 5 days between the dates. The scan assessed viability, gestational age, multiple pregnancy and nuchal translucency. The protocol included examining the fetal brain in axial and sagittal views, as well as obtaining axial and longitudinal vertebral views of the spine with assessment of the overlying skin. The transvaginal approach was used in cases where the transabdominal route was unable to produce an image of adequate quality or was impossible due to fetal position. Of note, patients were referred to the fetal medicine units following a suspicion of spina bifida for any reason - e.g. brain changes, spinal appearance - and not necessarily because the primary operator detected the crash sign.

Experienced fetal medicine specialists performed all examinations on the following models of Voluson Ultrasound Scanners: 730, E8 and E10 (GE Healthcare, United States). The patient underwent ultrasound examination of the brain and spine by one of the authors, including 3D neurosonography in the majority of cases. All findings were video archived. A prenatal diagnosis of spina bifida was made by visualisation of the myelomeningocele and spinal defect by

at least two independent fetal medicine experts; if findings were inconclusive a repeat ultrasound scan was scheduled for 10-14 days later. All women with a diagnosis of spina bifida were offered chorionic villus sampling (CVS) to check for chromosomal abnormalities. In cases where the pregnancy was terminated or natural pregnancy loss occurred, post-mortem examination was offered to confirm the ultrasound findings.

Cases of spina bifida suspected in the first trimester were collated and images retrospectively reviewed by one author (FU) for the presence of crash sign.

5.1.3 **Results**

During the four-year period of this study there were 62 suspected cases of spina bifida at 11 to 13 weeks, based on the appearance of the brain and spine. Figure 5.2 outlines the study participants and their outcomes. Nine cases were excluded from our analyses as the patients were lost to follow up and the diagnosis of spina bifida could not be confirmed. Figure 5.3 represents images of 15 consecutive cases of spina bifida from one hospital (UCLH).

Of the 53 cases with known outcome, all were confirmed to have spina bifida present. Forty-eight of these were confirmed by sonography only as described above and five were also subsequently confirmed by fetal post-mortem. There were 37 cases of myelomeningocele and 16 cases of rachischisis.

In the 53 cases of spina bifida, 48 had crash sign present and five did not (Figure 5.2). Of the 48 patients with spina bifida and positive crash sign, 27 (56.3%) had isolated spina bifida whereas 21 (43.7%) had other associated anomalies. Of the five patients with spina bifida who were crash sign negative, one (20.0%) had isolated spina bifida and four (80.0%) had other associated anomalies. Associated anomalies were as follows: trisomy 18 (10), trisomy 13 (2), triploidy (4), omphalocele-exstrophy-imperforate anus-spinal (OEIS) complex (5) and structural anomalies in other organ systems (4).

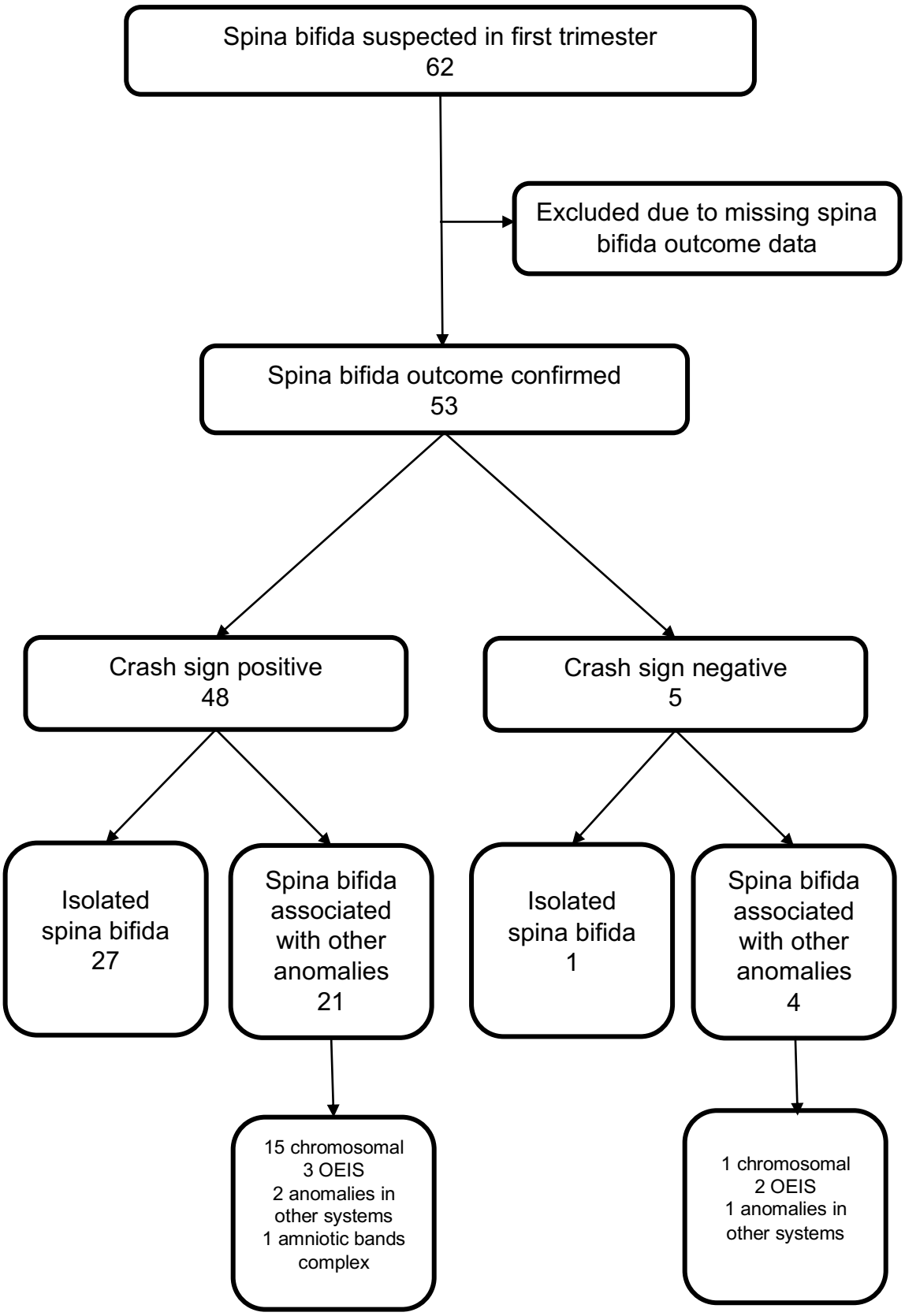

Figure 5.2: Study participants and outcomes according to presence of crash sign

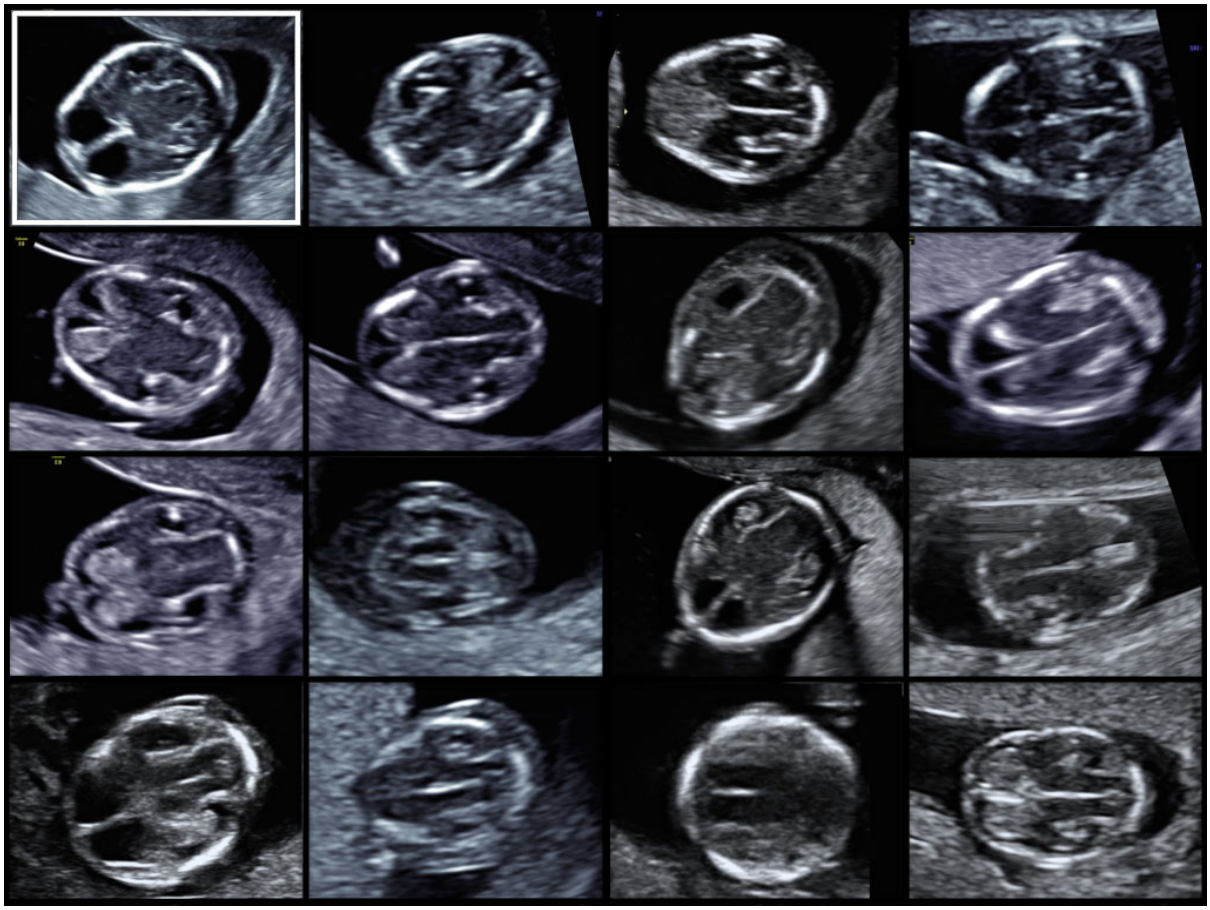

Figure 5.3: Crash sign in 15 consecutive cases of spina bifida from one hospital (UCLH). For comparison normal case in the left upper corner (white outline)

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5.1.4 **Discussion**

In this study we describe the crash sign, a new sonographic marker of spina bifida for use in the first trimester. We have retrospectively evaluated its presence in cases of spina bifida detected at 11-14+1 weeks' gestation, and found that 90.6% (48/53) of confirmed cases displayed this sign on retrospective review. The crash sign is based on the changes that develop in the mesencephalon as a result of the reduced intracranial pressure associated with spina bifida. In normal early

development, the fetal skull is soft due to incomplete ossification, and the shape of the head is therefore a function of the intracranial pressure. Intracranial pressure is created by cerebrospinal fluid (CSF) production within the large choroid plexuses in the lateral, third and fourth ventricles. In the normal fetus there is constant CSF flow in the caudal direction of the spinal cord within a closed system. In the case of an open spinal defect however, CSF leaks out with consequent reduction in intracranial pressure. This in turn causes collapse of the skull with the appearance of reduced fluid or a "shrivelled" brain. In human fetuses this process would explain the reduction in frontomaxillary facial angle[343] as well as the findings of reduced biparietal diameter and the ventricular system changes seen in the first trimester fetuses with spina bifida[348].

Unidirectional leakage of the fluid towards the open spinal defect results from a pressure gradient between the 'high' pressure choroid filled ventricles and the 'low' pressure spinal cord. This produces posterior and caudal displacement of the mesencephalon. During this process the mesencephalon meets the only firm cranial structure on its way, the occipital bone, and is compressed against it. The resulting deformation of the mesencephalon represents the crash sign which we have evaluated in our study.

The strength of our study is that it was multicentre, meaning that the findings are likely to be generalisable. However, this study was conducted by retrospective review of images and by fetal medicine specialists experienced in neurosonography. Therefore there may be a bias in the diagnostic ability of the crash sign to prospectively detect spina bifida. In addition, not all fetuses with

confirmed spina bifida were crash sign positive. All scans were performed by sonographers and fetal medicine specialists with considerable expertise and experience in first trimester anomaly scanning where transvaginal ultrasound was available if necessary. However, the thalamic plane is advisable as a good practice point for head biometry in the first trimester[347], and it theoretically could be possible for all practitioners (usually sonographers) performing screening ultrasound scans at 11-14+1 weeks' gestation to evaluate the posterior fossa for the crash sign. At present there is no national guideline for routine anatomy scanning at the dating scan, but it is likely there will be in the future and evaluation of the posterior fossa may be part of this. Certainly in situations where a first trimester anomaly scan is being performed for suspected fetal abnormalities, we believe that proper evaluation of the fetal mesencephalon is important. Posterior displacement and deformation of the mesencephalon against the occipital bone in the axial view of the brain should prompt the specialist to carefully examine the spine for a defect.

5.1.5 Conclusion

We have described the use of a new sonographic marker, the crash sign, for diagnosing spina bifida in the first trimester. Our results show that first trimester detection of spina bifida is possible using this sign, but further prospective evaluation is needed to determine its value in a clinical setting.

5.1.6 Contributions

The work in Chapter 5.1 was produced in collaboration with: Dr Fred Ushakov (University College London Hospital), Dr Elena Andreeva (Moscow Regions Research Institute of Obstetrics and Gynecology, Russia), Dr Stefania Tudorache (Emergency University Hospital of Craiova, Romania), Dr Thomas Everett (University College London Hospital), Professor Anna David (University College London) and Mr Pranav Pandya (University College London Hospital).

5.2 Fetoscopic Repair of Spina Bifida

5.2.1 Introduction

As discussed in chapter 1.2, the first case of fetal spina bifida repair was performed by minimal access (fetoscopic) surgery in 1994[89]. This procedure had a high mortality rate and so was temporarily abandoned; the first open repair was performed in 1998 and experience with this technique grew rapidly from then. However, the interest in fetoscopic repair has never gone away. Within all surgical fields there has been a general shift towards less invasive techniques over the last 20 to 30 years, enabled by technological advances. Within fetal surgery, the potential that the risks to the mother of a hysterotomy - including scar dehiscence or rupture and the need to have a caesarean delivery in all pregnancies - and to the fetus - of ruptured membranes and premature labour - may be reduced by minimal access surgery has kept interest in this technique alive.

In 2000, four cases of fetoscopic spina bifida repair were described[157]. Two of the fetuses died and the other two required standard closure of the defect after delivery. The authors concluded that repair through a hysterotomy “with current technology… appears technically superior”. In 2003, a series of 13 cases of fetoscopic spina bifida[93] reported the death of four patients, the need to convert to a “limited maternal hysterotomy” in ten cases, a mean gestational age of 31 weeks and the need for a ventriculoperitoneal shunt in five out of nine surviving cases. The authors noted that this technique “does not yet yield optimal surgical

results". In 2006 another three cases of fetoscopic repair[349] was published, in which there was one death and ventriculoperitoneal shunt was "delayed in one of the two survivors". Again, these results were not entirely encouraging but the authors noted that fetoscopic repair is feasible and substantially reduces maternal trauma.

In the last ten years, evidence for fetoscopic spina bifida repair by several groups around the world has accumulated. Before analysing their results further, it is worth noting that the "fetoscopic repairs" described are a mixture of different techniques. Open repair of fetal spina bifida developed in a similar fashion across centres and, following the MOMs trial[94] which included a standardised repair technique, has continued to be performed in the same way in centres offering this service, with some small local modifications. Conversely, from the beginning fetoscopic repair has varied between centres in terms of maternal abdominal entry, uterine entry, insufflation and the repair technique itself. These will be described further below, before exploring the results reported from groups performing fetoscopic surgery.

5.2.2 Techniques

Uterine entry

The uterus can be reached through the maternal abdomen by laparotomy, followed by port insertion into the uterus, or by ports inserted through the maternal abdomen and then into the uterus, usually described as the

"percutaneous" method. The number of ports used to access the uterus has varied from one to five, and the size of ports varies between centres.

Insufflation

Visibility and access within the uterus was initially achieved via amniotic fluid exchange, although this allowed poor visualisation of the fetus. Carbon dioxide insufflation was suggested as an alternative[350] which allows greater visualisation, and is now the most common method used in fetoscopic repair.

There is theoretical concern that carbon dioxide insufflation of the uterus can lead to fetal acidosis based on animal models[351 352]. Animal experiments of fetoscopic surgery using carbon dioxide insufflation have not shown evidence of harm[353], although these experiments have themselves been criticised as unrepresentative of the conditions used for human fetoscopic surgery[354]. So far, the centres using carbon dioxide have not reported any evidence of acute fetal acidosis (such as persistent heart rate or function changes), neonatal acidosis (such as hypoxic ischaemic brain injury) or maternal harm (such as respiratory or haemodynamic changes)[271].

Repair technique

The repairs described include patch coverage of the dura, patch coverage of the skin, fetoscopic suturing of the fetal skin and combinations of these methods. Patches which have been used for this surgery are diverse and include polytetrafluorethylene (Teflon), collagen, biosynthetic cellulose and porcine small-bowel submucosa.

5.2.3 Results from Individual Centres

The CECAM (Cirurgia Endoscópica para Correção Antenatal da Meningomielocele) prospective cohort trial of ten cases of fetoscopic repair by Dr Pedreira's group in Brazil reported in 2016[119]. The procedure involved percutaneous access, carbon dioxide insufflation and the insertion of three ports (sizes 11, 11 and 14 French, approximately 3.6mm and 4.6mm). The repair was performed by neuroplacode circumcision, biocellulose patch and skin closure by continuous suture. The procedure was performed at an average gestation of 27 weeks, which is later than open surgery is performed. Endoscopic repair was completed in 8 out of 10 cases. The mean gestational age at birth was 32.4 weeks. There was one fetal and one neonatal death, and one unsuccessful case underwent postnatal repair. Six of the seven infants analysed had MRI reversal of hindbrain herniation postnatally, and three of the seven required ventriculoperitoneal shunting. All cases were delivered by caesarean section and all port sites were well healed.

An update by this group has recently been accepted for publication[355]; this describes 47 cases of repair as described above with a description of a new technique of bilaminar skin substitute for larger lesions. The average gestational age reported is 32.8 weeks, with premature preterm rupture of membranes occurring in 84% of patients.

Professor Kohl's group in Germany has published several papers, including most recently a retrospective cohort study of 71 fetoscopic spina bifida repairs in 2016[122]. The procedure was performed by a percutaneous approach with the

insertion of three or four ports (5mm), followed by carbon dioxide insufflation. The repair was performed by lesion dissection and coverage with one or more collagen or Teflon patches. The surgery was performed between 21 and 29 weeks' gestation and all deliveries were by caesarean section. The average gestational age at delivery was 32+2 weeks. There were no fetal deaths but five deaths occurred in the first year due to: Chiari II complications (2), prematurity (2) and trisomy 13 (1). Postnatal neurosurgical treatment was required by 61%, and 45% required ventriculoperitoneal shunting.

A retrospective cohort study by Professor Belfort's group in Texas reported in 2017[118]. This described 28 attempted fetoscopic cases, of which 22 were performed fetoscopically (four were completed as hybrid-open procedures and two were abandoned). Results were split into two cohorts of patients: the first 15 treated with an "iterative technique" which was developing and the latter 13 with a "standardised technique" which remained constant. The standardised technique consisted of a maternal laparotomy, insertion of two uterine ports (12 French, approximately 4.0mm), carbon dioxide insufflation and repair by a single layer continuous suture involving both the skin and dura.

The average gestation at delivery was 35.9 weeks with the iterative technique and 39.0 weeks with the standardised technique. The average duration of surgery was 267 minutes for the iterative technique and 246 minutes for the standardised technique. Vaginal delivery occurred in five out of 12 iterative and 6 out of ten standard procedures and in those women who had caesarean section for obstetric reasons all port sites appeared well healed. The average gestational

age at preterm rupture of membranes (PROM) was 34 weeks in both groups. In the iterative group, 75% of neonates reached criteria for ventriculoperitoneal shunt placement, whereas in the standardised group 30% did. The paper was published before longer-term findings, such as ambulation, could be established.

5.2.4 Results from Systematic Reviews

A systematic review of fetoscopic versus open repair of spina bifida was published in 2016[114]. This included five reports from two centres (those of Professor Kohl and Dr Pedreira as described above) and analysis was restricted to two overlapping case series due to bias and heterogeneity. A distinction was made between the first 30 (early) cases, during which time a learning curve was presumed, and later cases.

After the early cases, it was found that fetoscopic repair had a comparable mortality rate to open repair, as well as comparable incomplete closure rates, placental abruption, ventriculoperitoneal shunting or Chiari II malformation decompression at 12 months. On the negative side, fetoscopic repair was found to have a longer operating duration, earlier gestational age at birth (32.9 vs 34.1 weeks), higher PPROM rate (84 vs 46%) and a ten times higher need for additional postnatal surgery (28 vs 2.6%). On the positive side, fetoscopic surgery was found to have a lower rate of chorioamniotic membrane separation; no cases of maternal haemorrhage requiring transfusion at delivery and no cases of uterine thinning or dehiscence occurred. Outcomes were not available for complete

reversal of Chiari II malformation at 1 year, and neurological or motor function at 2.5 years.

A second systematic review of fetoscopic versus open surgery for spina bifida was published in 2017[115]. Five studies of fetoscopic closure were included; these were the publications of Professor Kohl and Dr Pedreira's groups as above, with the later publication from Professor Belfort's group added. This review also found no difference in mortality or ventriculoperitoneal shunting rates between the two groups. Additionally, no differences were found in reversal of hindbrain herniation, motor response relative to the anatomical level, preterm birth (under 30 weeks' gestation), chorioamniotic membrane separation, and placental abruption.

On the negative side, fetoscopic repair was associated with higher rates of dehiscence or cerebrospinal fluid leakage from the repair site requiring postnatal treatment, and higher rates of PROM (79 vs. 36%). There was a lower number of cases completed via the route intended (90% vs 99.8%). On the positive side, the rate of uterine dehiscence was lower with fetoscopic repair (0% vs 11%). When looking at for differences between percutaneous surgery and fetoscopic repair via a maternal laparotomy, there was no difference in the rate of preterm birth.

5.2.5 Discussion

As the evidence presented above shows, to date there has been no randomised comparisons between open and fetoscopic surgery for spina bifida. Fetoscopic data has mostly come from retrospective cohort studies and, with the exception of the group in Texas, most units offer either open or fetoscopic repair and not both.

There have been several concerns voiced regarding fetoscopic repair. Poorer fetal outcomes due to inadequate spinal repair techniques and higher rates of prematurity are the main issues discussed[356]. There have also been accusations of selective publishing of results.[354]

The time taken to complete fetoscopic surgery is much longer than the open procedure (78.5 +/- 11mins[98]) in all centres offering this, and the length of exposure to carbon dioxide remains a concern as discussed above. Longer-term outcomes from all groups performing fetoscopic surgery are awaited.

Given the ongoing debate and concern regarding fetoscopic surgery, one would expect further studies and, ideally, a randomised trial in the future. However, first a standardised technique would need to be agreed and willingness from institutions currently "committed" to a certain procedure would be needed. In the meantime, the topic remains a source of debate in the fetal surgery community. In 2017 the American College of Obstetricians and Gynaecologists (ACOG) Committee Opinion on maternal-fetal surgery for myelomeningocele[112] stated: "At

this time, fetoscopic fetal myelomeningocele repair cannot be recommended outside of an institutional review board-approved investigational setting at a center with an appropriate level of expertise, resources, and research oversight."

5.2.6 Mini-hysterotomy

Another less-invasive alternative to the open surgical method is the use of a "mini-hysterotomy" i.e. a uterine opening less than 4cm as opposed to the 6-8cm opening commonly used[155]. Through this a standard multi-layer microsurgical repair is done. In a case series of 45 patients, there was a reduced PPROM rate (23%), a slightly higher gestational age at delivery (35 weeks) and a 95% intact hysterotomy site at delivery. Outcomes were only given until discharge from hospital, but given that the same technique is used, one could hope that longer follow up will provide evidence of benefit for this technique.

5.3 Future Fetal Treatment of Spina Bifida

5.3.1 Instrument Development

Our research teams at UCL and KU Leuven have been developing this technology and instruments for use in fetal surgery, and are currently training on high fidelity in-vivo models, exploring the extent to which a layered watertight neurosurgical repair can be performed. The GIFT-Surg project, with funding of the Wellcome foundation, are working on a single orifice miniature access robot for endoscopic closure of spina bifida lesions.

5.3.2 Stem Cell Therapy

Neural stem cells are multipotent stem cells with the potential to differentiate into neurons, astrocytes and oligodendrocytes. Their therapeutic potential is currently being explored in a wide range of conditions, including spina bifida. Although most research in this field involves postnatal treatment, a number of studies regarding the potential for spinal cord repair in-utero have been published. In animal models of spina bifida, neural stem cells have been shown to engraft into areas of damaged spinal cord, produce neurotrophic factors and reduce apoptosis[357] [358]. Neural stem cells could potentially be combined with a prenatal scaffold or patch[359] or simply injected into the amniotic cavity[360] in order to promote spinal cord repair in fetal spina bifida.

Chapter 6 **Conclusion**

Throughout two years of working on the implementation of fetal surgery for spina bifida in the UK, I have developed my knowledge and understanding of the condition and treatment. I have researched what is already available in this field globally, and produced a large systematic review summarising the maternal risks of this and other fetal surgery, an aspect which appears to be often neglected. I have systematically and thoroughly contributed to the set-up of this new service, the first in the UK, and have been instrumental in its success. I have researched cost-effectiveness and healthcare acceptability, and in the year that it has been running our fetal surgery service has been well-received, with more patient referrals than anticipated. I have monitored our patient cohort for eligibility, complications, outcomes and acceptability and will continue to do this as the children born having had this surgery grow. I would like to see earlier diagnosis of this condition, for patient decision-making, preparedness and surgical planning, and have worked with colleagues in developing a technique for doing so. In the future I expect that a single fetoscopic surgical technique will be developed and shown to have equal fetal benefit with reduced maternal morbidity to the open technique, at which point I believe all centres should offer this. I have experienced multiple challenges in setting up this service, and believe that this project has equipped me well for developing services and implementing change in the NHS in the future.

References

1. Wilson PK. *Childbirth: Reproductive Science, Genetics, and Birth Control*. Volume 4. Garland Publishing; 1996.

2. Jancelewicz T, Harrison MR. A History of Fetal Surgery. *Clin Perinatol*. 2009;36(2):227-236. doi:10.1016/j.clp.2009.03.007.

3. Jost A. Sur la diffe renciation sexuelle de l'embryon de lapin. I: Remarques au su- jet de certaines operations chirurgicales sur l'embryon. II: Experiences de para- boise. *C R Seances Soc Biol Fil*. 1946;140:461.

4. Louw J, Barnard C. Congenital intestinal atresia; observations on its origin. *Lancet*. 1955;269:1065.

5. Liley A. Intrauterine transfusion of fetus in haemolytic disease. *BMJ*. 1963;2:1107–1109.

6. Adamsons K. Fetal surgery. *N Engl J Med*. 1966;275(4):204-206.

7. Woo J. A Short History of the Development of Ultrasound in Obstetrics and Gynecology. British Medical Ultrasound Society.

8. Donald I. Investigation of abdominal masses by pulsed ultrasound. *Lancet*. 1958;271(7032):1188-1195.

9. Deprest JA, Flake AW, Gratacos E, et al. The making of fetal surgery. *Prenat Diagn*. 2010;30(7):653-667. doi:10.1002/pd.2571.

10. Harrison M, Filly R, MS G. Fetal treatment. *N Engl J Med*. 1982;307:1651.

11. Manning FA, Harrison MR, Rodeck C. Catheter shunts for fetal hydronephrosis and hydrocephalus. Report of the International Fetal Surgery Registry. *N Engl J Med*. 1986;315(5):336-340. http://gateway.proquest.com/openurl?ctx_ver=Z39.88-2004&res_id=xri:pqm&req_dat=xri:pqil:pq_clntid=50325&rft_val_fmt=ori/fmt:kev:mtx:journal&genre=article&issn=0028-4793&volume=315&issue=5&spage=336.

12. Estes J, MacGillvray T, Hedrick M, Adzick N, Harrison M. Fetoscopic surgery for the treatment of congenital anomalies. *J Pediatr Surg*. 1992;27(8):950-954.

13. Deprest J. *Endoscopy in Fetal Medicine. The EUROFOETUS and EuroTwin2Twin*

Group. 3rd ed. Endo:Press, GmbH, Germany; 2015.

14. Harrison M, Globus M, Filly R. Management of the fetus with a correctable congenital defect. *JAMA*. 1981;246(7):774-777.

15. Morris R, Malin G, Khan K, Kilby M. Systematic review of the effectiveness of antenatal intervention for the treatment of congenital lower urinary tract obstruction. *BJOG*. 2010;117:382-390.

16. Morris R. Percutaneous vesicoamniotic shunting versus conservative management for lower urinary tract obstruction (PLUTO): a randomised trial. *Lancet*. 2013;382:1496-1506.

17. Morris R, Ruano R, Kilby M. Effectiveness of fetal cystoscopy as a diagnostic and therapeutic intervention for lower urinary tract obstruction: a systematic review. *Ultrasound Obs Gynecol*. 2011;37:629-637.

18. Harrison M, Adzick N, Flake A. Successful repair in utero of a fetal diaphragmatic hernia after removal of herniated viscera from the left thorax. *N Engl J Med*. 1990;322:1582-1584.

19. Hendrick M, Estes J, Sullivan K. Plug the lung until it grows (PLUG): a new method to treat congenital diaphragmatic hernia in utero. *J Pediatr Surg*. 1994;29:612-617.

20. Deprest J, Gratacos E, Nicolaides KH, Group FT. Fetoscopic tracheal occlusion (FETO) for severe congenital diaphragmatic hernia: evolution of a technique and preliminary results. *Ultrasound Obstet Gynecol*. 2004;24(2):121-126. http://onlinelibrary.wiley.com/doi/10.1002/uog.1711/full.

21. Harrison M, Keller R, Hawgood S. A randomized trial of fetal endoscopic tracheal occlusion for severe fetal congential diaphragmatic hernia. *N Engl J Med*. 2003;349:1916-1924.

22. Jani JC, Nicolaides KH, Gratacós E, et al. Severe diaphragmatic hernia treated by fetal endoscopic tracheal occlusion. *Ultrasound Obstet Gynecol*. 2009;34(3):304-310. doi:10.1002/uog.6450.

23. TOTAL Trial. https://www.totaltrial.eu.

24. Hedrick H, Flake A, Crombleholme T, et al. Sacrococcygeal teratoma: prenatal assessment, fetal intervention, and outcome. *J Pediatr Surg*. 2004;39(3):430-438.

25. Adzick NS. Management of fetal lung lesions. *Clin Perinatol*. 2009;36(2):363. doi:10.1016/j.clp.2009.03.001.

26. Wilson R, Baxter J, Johnson M. Thoracoamniotic shunts: fetal treatment of pleural effusions and congenital cystic adenomatoid malformations. *Fetal Diagn Ther*. 2004;19:413-420.

27. Ohye R, Sleeper L, Mahony L. Pediatric heart networkinvestigators. Comparison of shunt types in the Norwood procedure forsingle-ventricle lesions. *N Engl J Med*. 2010;362:1980-1992.

28. Maxwell D, Allan L, Tynan M. Balloon dilatation of the aortic valve in the fetus: a report of two cases. *Br Heart J*. 1991;65(5):256-258.

29. Oepkes D, Moon-Grady A, Wilkins-Haug L, Tworetzky W, Arzt W, Devlieger R. 2010 Report from the ISPD Special Interest Group fetaltherapy: fetal cardiac interventions. *Prenat Diagn*. 2011;31:249-251.

30. Donofrio MT, Moon-Grady AJ, Hornberger LK, et al. Diagnosis and treatment of fetal cardiac disease: a scientific statement from the American Heart Association. *Circulation*. 2014;129(21):2183-2242. doi:10.1161/01.cir.0000437597.44550.5d.

31. Friedman K, Sleeper L, Freud L, Marshall A. Improved Technical Success, Postnatal Outcomes and Refined Predictors of Outcome for Fetal Aortic Valvuloplasty. *Ultrasound Obstet Gynecol*. 2017;Epub ahead. doi:doi: 10.1002/uog.17530.

32. De Vore G, Dixon J, Hobbins J. Fetoscope-directed Nd : YAG laser: a potential tool for fetal surgery. *Am J Obstet Gynecol*. 1983;143:379-380.

33. De Lia JE, Cruikshank DP, Keye WR. Fetoscopic neodymium:YAG laser occlusion of placental vessels in severe twin-twin transfusion syndrome. *Obstet Gynecol*. 1990;75(6):1046-1053. https://go.openathens.net/redirector/nhs?url=http%3A%2F%2Fovidsp.ovid.com%2Fovidweb.cgi%3FT%3DJS%26PAGE%3Dfulltext%26NEWS%3DN%26CSC%3DY%26D%3Dovft%26SEARCH%3D0029-

7844.is%2Band%2B75.vo%2Band%2B6.ip%2Band%2B1046.pg.

34. Ville Y, Hyett J, Hecher K, Nicolaides K. Preliminary experience with endoscopic laser surgery for severe twin-twin transfusion syndrome. *N Engl J Med*. 1995;332(4):224-227. http://gateway.proquest.com/openurl?ctx_ver=Z39.88-2004&res_id=xri:pqm&req_dat=xri:pqil:pq_clntid=50325&rft_val_fmt=ori/fmt:kev:mtx:journal&genre=article&issn=0028-4793&volume=332&issue=4&spage=224.

35. Senat M, Deprest J, Boulvain M. A randomized trial of endoscopic laser surgery versus serial amnioreduction for severe twin-to-twin transfusion syndrome at midgestation. *N Engl J Med*. 2004;351:136-144.

36. Khoshnood B, Loane M, de Walle H, et al. Long term trends in prevalence of neural tube defects in Europe: population based study. *BMJ*. 2015;351:h5949. doi:10.1136/bmj.h5949.

37. Department of Health and Social Care. Fortifying flour with folic acid: government to consult. https://www.gov.uk/government/news/fortifying-flour-with-folic-acid-government-to-consult.

38. Cochrane DD, Wilson RD, Steinbok P, et al. Prenatal spinal evaluation and functional outcome of patients born with myelomeningocele: information for improved prenatal counselling and outcome prediction. *Fetal Diagn Ther*. 1996;11(3):159-168.

39. de Jong TP, Chrzan R, Klijn AJ, Dik P. Treatment of the neurogenic bladder in spina bifida. *Pediatr Nephrol*. 2008;23:889-896. doi:10.1007/s00467-008-0780-7.

40. Velde S Vande, Biervliet S Van, Renterghem K Van, Laecke E Van, Hoebeke P, Winckel M Van. Achieving Fecal Continence in Patients With Spina Bifida : A Descriptive Cohort Study. 2007;178(December):2640-2644. doi:10.1016/j.juro.2007.07.060.

41. Verhoef M, Barf HA, Vroege JA, et al. Sex Education , Relationships , and Sexuality in Young Adults With Spina Bifida. *Arch Phys Med Rehabil*. 2005;86(5):979-987. doi:10.1016/j.apmr.2004.10.042.

42. Teo C, Jones R. Management of Hydrocephalus by Endoscopic Third Ventriculostomy in Patients with Myelomeningocele. *Pediatr Neurosurg*. 1996;25:57-63.

43. Tomlinson P, Sugarman I. Complications with shunts in adults with spina bifida. *BMJ*. 1995;311:286.

44. Roach JW, Short BF, Saltzman HM. Adult Consequences of Spina Bifida: A Cohort Study. *Clin Orthop Relat Res*. 2011;469(5):1246-1252.

45. Oakeshott P, Hung G, Poulton A, Reid F. Expectation of life and unexpected death in open spina bifida: a 40-year complete, non-selective, longitudinal cohort study. *Dev Med Child Neurol*. 2010;52(8):749-753.

46. Vermaes IPR, Janssens JMAM, Bosman AMT, Gerris JRM. Parents' psychological adjustment in families of children with Spina Bifida : a meta-analysis. *BMC Pediatr*. 2005;5(32):1-13. doi:10.1186/1471-2431-5-32.

47. Bellin MH, Bentley KJ, Sawin KJ, et al. Adjustment of Siblings of Youths With Spina Bifida. *Fam Syst Heal*. 2009;27(1):1-15. doi:10.1037/a0014859.

48. Shields N, Taylor NF, Dodd KJ. Self-concept in children with spina bifida compared with typically developing children. *Dev Med Child Neurol*. 2008;50(10):733-743. doi:10.1111/j.1469-8749.2008.03096.x.

49. Buran CF, Sawin KJ, Brei TJ, Fastenau PS. Adolescents with myelomeningocele : activities , beliefs , expectations , and perceptions. *Dev Med Child Neurol*. 2004;46(04):244-252.

50. Frey L, Hauser WA. Epidemiology of Neural Tube Defects. *Epilepsia*. 2003;44(3):4-13. doi:10.1002/ajmg.c.30057.

51. Imbard A, Benoist JF, Blom HJ. Neural tube defects, folic acid and methylation. *Int J Environ Res Public Health*. 2013;10(9):4352-4389. doi:10.3390/ijerph10094352.

52. Hall JG, Solehdin F. Genetics of neural tube defects. *Ment Retard Dev Disabil Res Rev*. 1998;281:269-281.

53. Wide K, Winbladh B, Kallen B. Major malformations in infants exposed to antiepileptic drugs in utero , with emphasis on carbamazepine and valproic acid : a nation-wide , population-based register study. *Acta Paediatr*. 2004;93(2):174-176. doi:10.1080/08035250310021118.

54. Northrup H, Volcik KA. Spina bifida and other neural tube defects. *Curr Probl Pediatr*. 2000;30(10):313-332.

55. Stothard KJ, Tennant PWG, Bell R. Maternal Overweight and Obesity and the Risk of Congenital Anomalies. 2015;301(6).

56. Group MVSR. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. MRC Vitamin Study Research Group. *Lancet*. 1991;338(8760):131-137.

57. World Health Organisation. Standards for maternal and neonatal care. *Integr Manag pregnancy childbirth*. 2007;Chapter 1.

58. Bestwick JP, Huttly WJ, Morris JK, Wald NJ. Prevention of neural tube defects: A cross-sectional study of the uptake of folic acid supplementation in nearly half a million women. *PLoS One*. 2014;9(2). doi:10.1371/journal.pone.0089354.

59. Kancherla V, Wagh K, Johnson Q, Oakley GP. A 2017 global update on folic acid-preventable spina bifida and anencephaly. *Birth Defects Res*. 2018;110(14):1139-1147. doi:10.1002/bdr2.1366.

60. Morris JK, Rankin J, Draper ES, et al. Prevention of neural tube defects in the UK: A missed opportunity. *Arch Dis Child*. 2016;101(7):604-607. doi:10.1136/archdischild-2015-309226.

61. Brock DJ, Sutcliffe RG. Alpha-fetoprotein in the antenatal diagnosis of anencephaly and spina bifida. *Lancet*. 1972;300(7770):197-199. doi:https://doi.org/10.1016/S0140-6736(72)91634-0.

62. Allan LD, Sweet EM, Donald IAN, Gibson AAM. Amniotic-fluid alpha-fetoprotein in the antenatal diagnosis of spina bifida. *Lancet*. 1973;302(7828):522-525.

63. Brock DJH, Bolton AE, Scrimgeour JB. Prenatal Diagnosis of Spina Bifida and Anencephaly Through Maternal Plasma-Alpha-Fetoprotein Measurement. *Lancet*. 1974;303(7861):767-769. doi:10.1016/S0140-6736(74)92839-6.

64. Wald NJ, Brock DJH, Bonnar J. Prenatal diagnosis of spina bifida and anencephaly by maternal serum-alpha-fetoprotein measurement. A controlled study. *Lancet*.

1974;303(7861):765-767. doi:10.1016/S0140-6736(74)92838-4.

65. Wald NJ, Cuckle H, Brock JH, Peto R, Polani PE, Woodford FP. Maternal serum-alpha-fetoprotein measurement in antenatal screening for anencephaly and spina bifida in early pregnancy. Report of U.K. collaborative study on alpha-fetoprotein in relation to neural-tube defects. *Lancet (London, England)*. 1977;1(8026):1323-1332. http://www.hlisd.org/LibraryDetail.aspx?LibraryID=3866.

66. Michell R, Bradley-Watson P. The Detection of Fetal Meningocoele By Ultrasound B Scan. *BJOG An Int J Obstet Gynaecol*. 1973;80(12):1100-1101. doi:10.1111/j.1471-0528.1973.tb02986.x.

67. Campbell S, Pryse-Davies J, Coltart T, Seller M, Singer J. Ultrasound in the diagnosis of spina bifida. *Lancet*. 1975;305(7915):1065-1068.

68. Wald N, Cuckle H, Boreham J, Stirrat G. Small Biparietal Diameter of Fetuses With Spina Bifida: Implications for Antenatal Screening. *BJOG An Int J Obstet Gynaecol*. 1980;87(3):219-221. doi:10.1111/j.1471-0528.1980.tb04522.x.

69. Hibbard BM, Roberts EE, Robertson IB. Diagnostic effectiveness of ultrasound in detection of neural tube defect. The South Wales experience of 2509 scans (1977-1982) in high-risk mothers. *Lancet*. 1983;322(8358):1068-1069.

70. Nicolaides KH, Gabbe SG, Campbell S, Guidetti R. Ultrasound Screening for Spina Bifida: Cranial and Cerebellar Signs. *Lancet*. 1986;328(8498):72-74. doi:10.1016/S0140-6736(86)91610-7.

71. Campbell J, Gilbert WM, Nicolaides KH, Campbell S. Ultrasound screening for spina bifida: cranial and cerebellar signs in a high-risk population. *Obstet Gynecol*. 1987;70(2):247-250. https://go.openathens.net/redirector/nhs?url=http%3A%2F%2Fovidsp.ovid.com%2Fovidweb.cgi%3FT%3DJS%26PAGE%3Dfulltext%26NEWS%3DN%26CSC%3DY%26D%3Dovft%26SEARCH%3D0029-7844.is%2Band%2B70.vo%2Band%2B2.ip%2Band%2B247.pg.

72. Nadel A, Green J, Holmes L, Frigoletto F, Benacerraf B. Absence of need for amniocentesis inpatients with elevated levels of maternal serum alpha-fetoprotein and

normal ultrasonographic examinations. *N Engl J Med*. 1990;323(9):557-561.

73. Boyd P, Wellesley D, De Walle H, et al. Evaluation of the prenatal diagnosis of neural tube defects by fetal ultrasonographic examination in different centres across Europe. *J Med Screen*. 2000;7(4):169-174. doi:10.1136/jms.7.4.169.

74. Wald NJ, Cuckle HS, Haddow JE, Doherty RA, Knight GJ, Palomaki GE. Sensitivity of Ultrasound in Detecting Spina Bifida. *N Engl J Med*. 1991;324(11):769-772.

75. NHS. NHS Fetal Anomaly Screening Programme Handbook Valid from August 2018. 2018;(August):133. www.facebook.com/PublicHealthEngland.

76. Ovaere C, Eggink A, Richter J, et al. Prenatal diagnosis and patient preferences in patients with neural tube defects around the advent of fetal surgery in Belgium and Holland. *Fetal Diagn Ther*. 2015;37(3):226-234. doi:10.1159/000365214.

77. Thompson D. Postnatal management and outcome for neural tube defects including spina bifida and encephalocoeles. *Prenat Diagn*. 2009;29:412-419.

78. Tolcher M, Shazly S, Shamshirsaz A, et al. Neurological outcomes by mode of delivery for fetuses with open neural tube defects: A systematic review and meta-analysis. *BJOG An Int J Obstet Gynaecol*. 2018:1-6. doi:10.1111/1471-0528.15342.

79. Sival D, Begeer J, Staal-Schreinemachers A. Perinatal motor behaviour and neurological outcome in spina bifida aperta. *Early Hum Dev*. 1997;50(1):27-37.

80. Meuli M, Meuli-Simmen C, Yingling CD, et al. Creation of myelomeningocele in utero: a model of functional damage from spinal cord exposure in fetal sheep. *J Pediatr Surg*. 1995;30(7):1028.

81. Heffez D, Aryanpur J, Hutchings G, Freeman J. The paralysis associated with myelomeningocele: clinical and experimental data implicating a preventable spinal cord injury. *Neurosurgery*. 1990;26(6):987-992.

82. Villablanca J, Hovda D. Developmental neuroplasticity in a model of cerebral hemispherectomy and stroke. *Neuroscience*. 2000;95(3):625-637.

83. Michejda M. Intrauterine treatment of spina bifida: primate model. *Z Kinderchir*. 1984;39(259-61).

84. Heffez D, Aryanpur J, Rotellini N, Hutchins G. Intrauterine repair of experimental surgically created dysraphism. *Neurosurgery*. 1993;32(6):1005-1010.

85. Danzer E, Johnson MP, Adzick NS. Fetal surgery for myelomeningocele: progress and perspectives. *Dev Med Child Neurol*. 2012;54(1):8-14. doi:10.1111/j.1469-8749.2011.04049.x.

86. Meuli M, Meuli-Simmen C, Hutchins G. In utero surgery rescues neurological function at birth in sheep with spina bifida. *Nat Med*. 1995;1(4):342-347.

87. Bouchard S, Davey M, Rintoul N. Correction of hindbrain herniation and anatomy of the vermis following in utero repair of myelomeningocele in sheep. *J Pediatr Surg*. 2003;38:451-458.

88. Paek B, Farmer D, Wilkinson C. Hindbrain her- niation develops in surgically created myelomeningocele but is absent after repair in fetal lambs. *Am J Obstet Gynecol*. 2000;183:1119-1123.

89. Bruner JP, Tulipan NE, Richards WO. Endoscopic coverage of fetal open myelomeningocele in utero. *Am J Obstet Gynecol*. 1997;176(1):256-257. http://www.hlisd.org/LibraryDetail.aspx?LibraryID=3866.

90. Adzick NS, Sutton LN, Crombleholme TM, Flake AW. Successful fetal surgery for spina bifida. *Lancet (London, England)*. 1998;352(9141):1675-1676. http://gateway.proquest.com/openurl?ctx_ver=Z39.88-2004&res_id=xri:pqm&req_dat=xri:pqil:pq_clntid=50325&rft_val_fmt=ori/fmt:kev:mtx:journal&genre=article&issn=0140-6736&volume=352&issue=9141&spage=1675.

91. Sutton LN, Adzick NS, Bilaniuk LT, Johnson MP, Crombleholme TM, Flake AW. Improvement in hindbrain herniation demonstrated by serial fetal magnetic resonance imaging following fetal surgery for myelomeningocele. *JAMA*. 1999;282(19):1826-1831. http://www.hlisd.org/LibraryDetail.aspx?LibraryID=3866.

92. Tulipan N, Bruner JP, Hernanz-Schulman M, et al. Effect of intrauterine myelomeningocele repair on central nervous system structure and function. *Pediatr Neurosurg*. 1999;31(4):183-188. http://gateway.proquest.com/openurl?ctx_ver=Z39.88-2004&res_id=xri:pqm&req_dat=xri:pqil:pq_clntid=50325&rft_val_fmt=ori/fmt:kev:mtx:jour

nal&genre=article&issn=1016-2291&volume=31&issue=4&spage=183.

93. Farmer DL, von Koch CS, Peacock WJ, et al. In utero repair of myelomeningocele: experimental pathophysiology, initial clinical experience, and outcomes. *Arch Surg*. 2003;138(8):872-878. http://www.hlisd.org/LibraryDetail.aspx?LibraryID=3866.

94. Adzick NS, Thom EA, Spong CY, et al. A randomized trial of prenatal versus postnatal repair of myelomeningocele. *N Engl J Med*. 2011;364(11):993-1004. doi:10.1056/NEJMoa1014379.

95. Johnson MP, Bennett KA, Rand L, et al. The Management of Myelomeningocele Study: obstetrical outcomes and risk factors for obstetrical complications following prenatal surgery. *Am J Obstet Gynecol*. 2016;215(6):778. doi:10.1016/j.ajog.2016.07.052.

96. Tulipan N, Wellons JC, Thom EA, et al. Prenatal surgery for myelomeningocele and the need for cerebrospinal fluid shunt placement. *J Neurosurg Pediatr*. 2015;16(6):613-620. doi:10.3171/2015.7.PEDS15336.

97. Zamlynski J, Olejek A, Tomasz K. Comparison of prenatal and postnatal treatments of spina bifida in Poland – a non-randomized, single-center study. *J Matern Neonatal Med*. 2014;27(14):1409-1417.

98. Moldenhauer JS, Soni S, Rintoul NE, et al. Fetal myelomeningocele repair: the post-MOMS experience at the Children's Hospital of Philadelphia. *Fetal Diagn Ther*. 2015;37(3):235-240. doi:10.1159/000365353.

99. Wille DA, Klein A, Mazzone L, et al. Preliminary Results in Children with Myelomeningocele after Fetal Surgery: Data from the Zurich Cohort. *Neuropediatrics*. 2016;47:FV01-09.

100. Moron A, Barbosa M, Milani H, et al. Perinatal outcomes after open fetal surgery for myelomeningocele repair: a retrospective cohort study. *BJOG An Int J Obstet Gynaecol*. 2018;[Epub ahea. doi:10.1111/1471-0528.15312.

101. Soni S, Moldenhauer JS, Spinner SS, et al. Chorioamniotic membrane separation and preterm premature rupture of membranes complicating in utero myelomeningocele repair. *Am J Obstet Gynecol*. 2016;214(5):647. doi:10.1016/j.ajog.2015.12.003.

102. Antiel RM, Adzick NS, Thom EA, et al. Impact on family and parental stress of prenatal vs postnatal repair of myelomeningocele. *Am J Obstet Gynecol*. 2016;215(4):522. doi:10.1016/j.ajog.2016.05.045.

103. Danzer E, Gerdes M, Bebbington MW, Zarnow DM, Adzick NS, Johnson MP. Preschool neurodevelopmental outcome of children following fetal myelomeningocele closure. *Am J Obstet Gynecol*. 2010;202(5):450. doi:10.1016/j.ajog.2010.02.014.

104. Danzer E, Gerdes M, Bebbington MW, Koh J, Adzick SN, Johnson MP. Fetal myelomeningocele surgery: preschool functional status using the Functional Independence Measure for children (WeeFIM). *Childs Nerv Syst*. 2011;27(7):1083-1088. doi:10.1007/s00381-011-1388-y.

105. Danzer E, Gerdes M, Bebbington MW, Koh J, Adzick NS, Johnson MP. Preschool neurobehavioral outcome following fetal myelomeningocele surgery. *Fetal Diagn Ther*. 2011;30(3):174-179. doi:10.1159/000330048.

106. Danzer E, Thomas NH, Thomas A, et al. Long-term neurofunctional outcome, executive functioning, and behavioral adaptive skills following fetal myelomeningocele surgery. *Am J Obstet Gynecol*. 2016;214(2):269. doi:10.1016/j.ajog.2015.09.094.

107. Danzer E, Adzick NS, Rintoul NE, et al. Intradural inclusion cysts following in utero closure of myelomeningocele: clinical implications and follow-up findings. *J Neurosurg Pediatr*. 2008;2(6):406-413. doi:10.3171/PED.2008.2.12.406.

108. Carr MC. Urological results after fetal myelomeningocele repair in pre-MOMS trial patients at the Children's Hospital of Philadelphia. *Fetal Diagn Ther*. 2015;37(3):211-218. doi:10.1159/000362932.

109. Wilson RD, Lemerand K, Johnson MP, et al. Reproductive outcomes in subsequent pregnancies after a pregnancy complicated by open maternal-fetal surgery (1996-2007). *Am J Obstet Gynecol*. 2010;203(3):209. doi:10.1016/j.ajog.2010.03.029.

110. Kett JC, Woodrum DE, Diekema DS. A survey of fetal care centers in the United States. *J Neonatal Perinatal Med*. 2014;7(2):131-135. doi:10.3233/NPM-14814005.

111. NAFTNet Website. https://www.naftnet.org.

112. ACOG Committee Opinion. Maternal-Fetal Surgery for Myelomeningocele. 2017;(Number 720):130:e164-7.

113. Moon-Grady A, Baschat A, Cass D. Fetal Treatment 2017: The Evolution of Fetal Therapy Centers – A Joint Opinion from the International Fetal Medicine and Surgical Society (IFMSS) and the North American Fetal Therapy Network (NAFTNet). *Fetal Diagn Ther*. 2017;42:241-248.

114. Joyeux L, Engels AC, Russo FM, et al. Fetoscopic versus Open Repair for Spina Bifida Aperta: A Systematic Review of Outcomes. *Fetal Diagn Ther*. 2016;39(3):161-171. doi:10.1159/000443498.

115. Kabagambe S, Jensen G, Chen YJ. Fetal Surgery for Myelomeingocele: A Systematic Review and Meta-Analysis of Outcomes in Fetoscopic versus Open Repair. *Fetal Diagn Ther*. 2017;Epub prior. doi:10.1159/000479505.

116. ISPD Website. https://ispdhome.org.

117. ISPD Fetal Surgery Map. https://ispdhome.org/ISPD/SIGs/Fetal_Therapy_Map.aspx.

118. Belfort MA, Whitehead WE, Shamshirsaz AA, et al. Fetoscopic Open Neural Tube Defect Repair: Development and Refinement of a Two-Port, Carbon Dioxide Insufflation Technique. *Obstet Gynecol*. 2017;129(4):734-743. doi:10.1097/AOG.0000000000001941.

119. Pedreira DAL, Zanon N, Nishikuni K, et al. Endoscopic surgery for the antenatal treatment of myelomeningocele: the CECAM trial. *Am J Obstet Gynecol*. 2016;214(1):111. doi:10.1016/j.ajog.2015.09.065.

120. Kohl T. Percutaneous minimally invasive fetoscopic surgery for spina bifida aperta. Part I: surgical technique and perioperative outcome. *Ultrasound Obstet Gynecol*. 2014;44(5):515-524. doi:10.1002/uog.13430.

121. Degenhardt J, Schürg R, Winarno A, et al. Percutaneous minimal-access fetoscopic surgery for spina bifida aperta. Part II: maternal management and outcome. *Ultrasound Obstet Gynecol*. 2014;44(5):525-531. doi:10.1002/uog.13389.

122. Graf K, Kohl T, Neubauer BA, et al. Percutaneous minimally invasive fetoscopic surgery

for spina bifida aperta. Part III: neurosurgical intervention in the first postnatal year. *Ultrasound Obstet Gynecol*. 2016;47(2):158-161. doi:10.1002/uog.14937.

123. Elbabaa SK, Gildehaus AM, Pierson MJ, Albers JA, Vlastos EJ. First 60 Fetal In-Utero Myelomeningocele Repairs at Saint Louis Fetal Care Institute in the Post-Moms Trial Era: Hydrocephalus Treatment Outcomes (Endoscopic Third Ventriculostomy Versus Ventriculo-Peritoneal Shunt). *Childs Nerv Syst*. 2017;33(7):1157-1168.

124. Meuli M, Moehrlen U. Fetal surgery for myelomeningocele is effective: a critical look at the whys. *Pediatr Surg Int*. 2014;30(7):689-697. doi:10.1007/s00383-014-3524-8.

125. Morris RK, Selman TJ, Harbidge A, Martin WI, Kilby MD. Fetoscopic laser coagulation for severe twin-to-twin transfusion syndrome: factors influencing perinatal outcome, learning curve of the procedure and lessons for new centres. *BJOG*. 2010;117(11):1350-1357. doi:10.1111/j.1471-0528.2010.02680.x.

126. Farrell JA, Albanese CT, Jennings RW, Kilpatrick SJ, Bratton BJ, Harrison MR. Maternal fertility is not affected by fetal surgery. *Fetal Diagn Ther*. 1999;14(3):190-192. http://gateway.proquest.com/openurl?ctx_ver=Z39.88-2004&res_id=xri:pqm&req_dat=xri:pqil:pq_clntid=50325&rft_val_fmt=ori/fmt:kev:mtx:journal&genre=article&issn=1015-3837&volume=14&issue=3&spage=190.

127. Golombeck K, Ball RH, Lee H, et al. Maternal morbidity after maternal-fetal surgery. *Am J Obstet Gynecol*. 2006;194(3):834-839. http://www.hlisd.org/LibraryDetail.aspx?LibraryID=3866.

128. Merz W, Tchatcheva K, Gembruch U, Kohl T. Maternal complications of fetoscopic laser photocoagulation (FLP) for treatment of twin-twin transfusion syndrome (TTTS). *J Perinat Med*. 2010;38(4):439-443. doi:10.1515/JPM.2010.061.

129. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Int J Surg*. 2010;8(5):336-341. doi:10.1016/j.ijsu.2010.02.007.

130. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240(2):205-213. doi:10.1097/01.sla.0000133083.54934.ae.

131. Higgins J, Green S. Assessing risk of bias in included studies. *Cochrane Handb Syst Rev Interv*. 2008:187-241.

132. Wells G, Shea B, O'Connell D, Peterson J, Welcho V, Losos M. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. *Ottawa Heal Res Inst*. 2011.

133. National Institutes of Health: Study Quality Assessment Tools. www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools. Published 2014.

134. Barthod G, Teissier N, Bellarbi N, et al. Fetal airway management on placental support: limitations and ethical considerations in seven cases. *J Obstet Gynaecol*. 2013;33(8):787-794. doi:10.3109/01443615.2013.823924.

135. Cass DL, Olutoye OO, Cassady CI, et al. EXIT-to-resection for fetuses with large lung masses and persistent mediastinal compression near birth. *J Pediatr Surg*. 2013;48(1):138-144. doi:10.1016/j.jpedsurg.2012.10.067.

136. Chen XY, Yang JX, Zhang HY, et al. Ex utero intrapartum treatment for giant congenital omphalocele. *World J Pediatr*. 2018;(0123456789):1-5. doi:10.1007/s12519-018-0129-7.

137. Dahlgren G, Törnberg DC, Pregner K, Irestedt L. Four cases of the ex utero intrapartum treatment (EXIT) procedure: anesthetic implications. *Int J Obstet Anesth*. 2004;13(3):178-182.

138. Flake AW, Crombleholme TM, Johnson MP, Howell LJ, Adzick NS. Treatment of severe congenital diaphragmatic hernia by fetal tracheal occlusion: clinical experience with fifteen cases. *Am J Obstet Gynecol*. 2000;183(5):1059-1066. http://www.hlisd.org/LibraryDetail.aspx?LibraryID=3866.

139. George RB, Melnick AH, Rose EC, Habib AS. Case series: Combined spinal epidural anesthesia for Cesarean delivery and ex utero intrapartum treatment procedure. *Can J Anaesth*. 2007;54(3):218-222. http://gateway.proquest.com/openurl?ctx_ver=Z39.88-2004&res_id=xri:pqm&req_dat=xri:pqil:pq_clntid=50325&rft_val_fmt=ori/fmt:kev:mtx:journal&genre=article&issn=0832-610X&volume=54&issue=3&spage=218.

140. Hedrick HL. Ex utero intrapartum therapy. *Semin Pediatr Surg*. 2003;12(3):190-195.

141. Hedrick HL, Flake AW, Crombleholme TM, et al. The ex utero intrapartum therapy procedure for high-risk fetal lung lesions. *J Pediatr Surg*. 2005;40(6):1038-1044. doi:10.1016/j.jpedsurg.2005.03.024.

142. Kern C, Ange M, Morales, Peiry B, Pfister RE. Ex utero intrapartum treatment (EXIT), a resuscitation option for intra-thoracic foetal pathologies. *Swiss Med Wkly*. 2007;137(19-20):279-285.

143. Kornacki J, Szydłowski J, Skrzypczak J, et al. Use of ex utero intrapartum treatment procedure in fetal neck and high airway anomalies – report of four clinical cases. *J Matern Neonatal Med*. 2017;0(0):1-5. doi:10.1080/14767058.2017.1390740.

144. Kunisaki SM, Barnewolt CE, Estroff JA, et al. Ex utero intrapartum treatment with extracorporeal membrane oxygenation for severe congenital diaphragmatic hernia. *J Pediatr Surg*. 2007;42(1):98. https://auth.elsevier.com/ShibAuth/institutionLogin?entityID=https://idp.eng.nhs.uk/openathens&appReturnURL=https%3A%2F%2Fwww.clinicalkey.com%2Fcontent%2FplayBy%3Fissn%3D0022-3468%26vol%3D42%26issue%3D1%26pgfirst%3D98.

145. Laje P, Johnson MP, Howell LJ, et al. Ex utero intrapartum treatment in the management of giant cervical teratomas. *J Pediatr Surg*. 2012;47(6):1208-1216. doi:10.1016/j.jpedsurg.2012.03.027.

146. Laje P, Howell LJ, Johnson MP, Hedrick HL, Flake AW, Adzick NS. Perinatal management of congenital oropharyngeal tumors: the ex utero intrapartum treatment (EXIT) approach. *J Pediatr Surg*. 2013;48(10):2005-2010. doi:10.1016/j.jpedsurg.2013.02.031.

147. Laje P, Peranteau WH, Hedrick HL, et al. Ex utero intrapartum treatment (EXIT) in the management of cervical lymphatic malformation. *J Pediatr Surg*. 2015;50(2):311-314. doi:10.1016/j.jpedsurg.2014.11.024.

148. Lazar DA, Olutoye OO, Moise KJ, et al. Ex-utero intrapartum treatment procedure for giant neck masses--fetal and maternal outcomes. *J Pediatr Surg*. 2011;46(5):817-822. doi:10.1016/j.jpedsurg.2011.02.006.

149. Noah MMS, Norton ME, Sandberg P, Esakoff T, Farrell J, Albanese CT. Short-term

maternal outcomes that are associated with the EXIT procedure, as compared with cesarean delivery. *Am J Obstet Gynecol*. 2002;186(4):773-777. http://www.hlisd.org/LibraryDetail.aspx?LibraryID=3866.

150. Pellicer M, Pumarola F, Peiró JL, et al. [EXIT procedure in the management of severe foetal airway obstruction. the paediatric otolaryngologist's perspective]. *Acta Otorrinolaringol Esp*. 2007;58(10):487-490.

151. Stoffan AP, Wilson JM, Jennings RW, Wilkins-Haug LE, Buchmiller TL. Does the ex utero intrapartum treatment to extracorporeal membrane oxygenation procedure change outcomes for high-risk patients with congenital diaphragmatic hernia? *J Pediatr Surg*. 2012;47(6):1053-1057. doi:10.1016/j.jpedsurg.2012.03.004.

152. Tuncay Ozgunen F, Kucukgoz Gulec U, Evruke I., Agcabay C, Kadayifci T., Ozcan K. Fetal orofarengeal tumorler ve EXIT islemine dogum hekimi acisindan bakis [The point of view by obstetricians to fetal oropharengal tumors and EXIT procedure: Case report]. *Turkiye Klin Jinekoloji Obstet*. 2010;20(4):247-251.

153. Zamora IJ, Ethun CG, Evans LM, et al. Maternal morbidity and reproductive outcomes related to fetal surgery. *J Pediatr Surg*. 2013;48(5):951-955. doi:10.1016/j.jpedsurg.2013.02.010.

154. Bennett KA, Carroll MA, Shannon CN, et al. Reducing perinatal complications and preterm delivery for patients undergoing in utero closure of fetal myelomeningocele: further modifications to the multidisciplinary surgical technique. *J Neurosurg Pediatr*. 2014;14(1):108-114. doi:10.3171/2014.3.PEDS13266.

155. Botelho R, Imada V, Rodrigues da Costa K, Watanabe L, R RJ. Fetal Myelomeningocele Repair through a Mini-Hysterotomy. *Fetal Diagn Ther*. 2017;42(1):28-34.

156. Bruner JP, Tulipan N, Paschall RL, et al. Fetal surgery for myelomeningocele and the incidence of shunt-dependent hydrocephalus. *JAMA*. 1999;282(19):1819-1825. http://www.hlisd.org/LibraryDetail.aspx?LibraryID=3866.

157. Bruner JP, Tulipan NB, Richards WO, Walsh WF, Boehm FH, Vrabcak EK. In utero repair of myelomeningocele: a comparison of endoscopy and hysterotomy. *Fetal Diagn Ther*. 2000;15(2):83-88. http://gateway.proquest.com/openurl?ctx_ver=Z39.88-

2004&res_id=xri:pqm&req_dat=xri:pqil:pq_clntid=50325&rft_val_fmt=ori/fmt:kev:mtx:journal&genre=article&issn=1015-3837&volume=15&issue=2&spage=83.

158. Friszer S, Dhombres F, Di Rocco F, et al. [Preliminary results from the French study on prenatal repair for fetal myelomeningoceles (the PRIUM study)]. *J Gynecol Obstet Biol Reprod (Paris)*. 2016;45(7):738-744. doi:10.1016/j.jgyn.2015.09.002.

159. Marenco ML, Márquez J, Ontanilla A, et al. [Intrauterine myelomeningocele repair: experience of the fetal medicine and therapy program of the Virgen de Rocío University Hospital]. *Rev Esp Anestesiol Reanim*. 2013;60(1):47-53. doi:10.1016/j.redar.2012.07.011.

160. Ochsenbein-Kölble N, Krähenmann F, Hüsler M, et al. Tocolysis for in utero Surgery: Atosiban Performs Distinctly Better than Magnesium Sulfate. *Fetal Diagn Ther*. 2017. doi:10.1159/000478261.

161. Sinskey JL, Rollins MD, Whitlock E, et al. Incidence and Management of Umbilical Artery Flow Abnormalities during Open Fetal Surgery. *Fetal Diagn Ther*. 2017. doi:10.1159/000477963.

162. Harrison MR, Langer JC, Adzick NS, et al. Correction of congenital diaphragmatic hernia in utero, V. Initial clinical experience. *J Pediatr Surg*. 1990;25(1):47.

163. Harrison MR, Adzick NS, Flake AW, et al. Correction of congenital diaphragmatic hernia in utero: VI. Hard-earned lessons. *J Pediatr Surg*. 1993;28(10):1411.

164. Harrison MR, Mychaliska GB, Albanese CT, et al. Correction of congenital diaphragmatic hernia in utero IX: fetuses with poor prognosis (liver herniation and low lung-to-head ratio) can be saved by fetoscopic temporary tracheal occlusion. *J Pediatr Surg*. 1998;33(7):1017.

165. Adzick NS, Flake AW, Crombleholme TM. Management of congenital lung lesions. *Semin Pediatr Surg*. 2003;12(1):10-16.

166. Hedrick HL, Flake AW, Crombleholme TM, et al. Sacrococcygeal teratoma: prenatal assessment, fetal intervention, and outcome. *J Pediatr Surg*. 2004;39(3):430.

167. Longaker MT, Golbus MS, Filly RA, Rosen MA, Chang SW, Harrison MR. Maternal

outcome after open fetal surgery. A review of the first 17 human cases. *JAMA*. 1991;265(6):737-741. http://www.hlisd.org/LibraryDetail.aspx?LibraryID=3866.

168. Aboudiab MS, Chon AH, Korst LM, Llanes A, Ouzounian JG, Chmait RH. Management of twin–twin transfusion syndrome with an extremely short cervix. *J Obstet Gynaecol (Lahore)*. 2018;38(3):359-362. doi:10.1080/01443615.2017.1330324.

169. Baschat AA, Barber J, Pedersen N, Turan OM, Harman CR. Outcome after fetoscopic selective laser ablation of placental anastomoses vs equatorial laser dichorionization for the treatment of twin-to-twin transfusion syndrome. *Am J Obstet Gynecol*. 2013;209(3):234. doi:10.1016/j.ajog.2013.05.034.

170. Chalouhi GE, Quibel T, Benzina N, Bernard J-P, Essaoui M, Ville Y. [Outcome of triplet pregnancies managed for twin-to-twin transfusion syndrome: A single center experience]. *J Gynecol Obstet Biol Reprod (Paris)*. 2016;45(8):929-935. doi:10.1016/j.jgyn.2015.08.006.

171. Chang J, Tracy TF, Carr SR, Sorrells DL, Luks FI. Port insertion and removal techniques to minimize premature rupture of the membranes in endoscopic fetal surgery. *J Pediatr Surg*. 2006;41(5):905-909.

172. Chang Y-L, Chao A-S, Chang S-D, et al. Outcome of twin-twin transfusion syndrome treated by laser therapy in Taiwan's single center: Role of Quintero staging system. *Taiwan J Obstet Gynecol*. 2016;55(5):700-704. doi:10.1016/j.tjog.2015.05.006.

173. Chmait RH, Korst LM, Llanes A, Mullin P, Lee RH, Ouzounian JG. Perioperative characteristics associated with preterm birth in twin-twin transfusion syndrome treated by laser surgery. *Am J Obstet Gynecol*. 2013;209(3):264. doi:10.1016/j.ajog.2013.05.025.

174. Chmait RH, Kontopoulos E V., Chon AH, Korst LM, Llanes A, Quintero RA. Amniopatch treatment of iatrogenic preterm premature rupture of membranes (iPPROM) after fetoscopic laser surgery for twin–twin transfusion syndrome. *J Matern Neonatal Med*. 2017;30(11):1349-1354. doi:10.1080/14767058.2016.1214123.

175. Crombleholme TM, Shera D, Lee H, et al. A prospective, randomized, multicenter trial of amnioreduction vs selective fetoscopic laser photocoagulation for the treatment of severe twin-twin transfusion syndrome. *Am J Obstet Gynecol*. 2007;197(4):396.

https://auth.elsevier.com/ShibAuth/institutionLogin?entityID=https://idp.eng.nhs.uk/openathens&appReturnURL=https%3A%2F%2Fwww.clinicalkey.com%2Fcontent%2FplayBy%2Fdoi%2F%3Fv%3D10.1016%2Fj.ajog.2007.07.020.

176. De Lia JE, Kuhlmann RS, Harstad TW, Cruikshank DP. Fetoscopic laser ablation of placental vessels in severe previable twin-twin transfusion syndrome. *Am J Obstet Gynecol*. 1995;172(4):1202. http://www.hlisd.org/LibraryDetail.aspx?LibraryID=3866.

177. De Lia JE, Kuhlmann RS, Lopez KP. Treating previable twin-twin transfusion syndrome with fetoscopic laser surgery: outcomes following the learning curve. *J Perinat Med*. 1999;27(1):61-67.

178. De Lia JE, Worthington D, Carr MH, Graupe MH, Melone PJ. Placental laser surgery for severe previable feto-fetal transfusion syndrome in triplet gestation. *Am J Perinatol*. 2009;26(8):559-564. doi:10.1055/s-0029-1220789.

179. Deprest JA, Van Schoubroeck D, Van Ballaer PP, Flageole H, Van Assche FA, Vandenberghe K. Alternative technique for Nd: YAG laser coagulation in twin-to-twin transfusion syndrome with anterior placenta. *Ultrasound Obstet Gynecol*. 1998;11(5):347-352. http://onlinelibrary.wiley.com/doi/10.1046/j.1469-0705.1998.11050347.x/full.

180. Draga E, Janiak K, Bielak A, et al. Fetal therapy- laser therapy of twin-to-twin transfusion syndrome /TTTS/. *Polish Gynaecol*. 2016;87(02):104-110. doi:10.17772/gp/61328.

181. Duron VD, Watson-Smith D, Benzuly SE, et al. Maternal and fetal safety of fluid-restrictive general anesthesia for endoscopic fetal surgery in monochorionic twin gestations. *J Clin Anesth*. 2014;26(3):184-190. doi:10.1016/j.jclinane.2013.10.010.

182. Ek S, Kublickas M, Bui T-H, et al. Establishing a national program for fetoscopic guided laser occlusion for twin-to-twin transfusion syndrome in Sweden. *Acta Obstet Gynecol Scand*. 2012;91(10):1196-1200. doi:10.1111/j.1600-0412.2012.01447.x.

183. Habli M, Bombrys A, Lewis D, et al. Incidence of complications in twin-twin transfusion syndrome after selective fetoscopic laser photocoagulation: a single-center experience. *Am J Obstet Gynecol*. 2009;201(4):417. doi:10.1016/j.ajog.2009.07.046.

184. Has R, Kalelioglu I, Corbacioglu Esmer A, et al. Stage-related outcome after fetoscopic

laser ablation in twin-to-twin transfusion syndrome. *Fetal Diagn Ther*. 2014;36(4):287-292. doi:10.1159/000362385.

185. Hecher K, Diehl W, Zikulnig L, Vetter M, Hackelöer BJ. Endoscopic laser coagulation of placental anastomoses in 200 pregnancies with severe mid-trimester twin-to-twin transfusion syndrome. *Eur J Obstet Gynecol Reprod Biol*. 2000;92(1):135-139.

186. Hernández-Andrade E, Guzmán-Huerta M, Benavides-Serralde JA, et al. [Laser ablation of the placental vascular anastomoses for the treatment of twin-to-twin transfusion syndrome]. *Rev Invest Clin*. 2011;63(1):46-52.

187. Huber A, Baschat AA, Bregenzer T, et al. Laser coagulation of placental anastomoses with a 30 degrees fetoscope in severe mid-trimester twin-twin transfusion syndrome with anterior placenta. *Ultrasound Obstet Gynecol*. 2008;31(4):412-416. doi:10.1002/uog.5283.

188. Ishii K, Nakata M, Wada S, Hayashi S, Murakoshi T, Sago H. Perinatal outcome after laser surgery for triplet gestations with feto-fetal transfusion syndrome. *Prenat Diagn*. 2014;34(8):734-738. doi:10.1002/pd.4357.

189. Ishii K, Nakata M, Wada S, Murakoshi T, Sago H. Feasibility and preliminary outcomes of fetoscopic laser photocoagulation for monochorionic twin gestation with selective intrauterine growth restriction accompanied by severe oligohydramnios. *J Obstet Gynaecol Res*. 2015;41(11):1732-1737. doi:10.1111/jog.12827.

190. Lanna MM, Faiola S, Consonni D, Rustico MA. Increased risk of placental abruption after solomon laser treatment of twin-twin transfusion syndrome. *Placenta*. 2017;53:54-56. doi:10.1016/j.placenta.2017.03.018.

191. Lecointre L, Sananès N, Weingertner AS, et al. Photocoagulation laser par fœtoscopie pour syndrome transfuseur-transfusé : analyse d'une série consécutive unicentrique de 200 cas. *J Gynecol Obstet Hum Reprod*. 2017;46(2):175-181. doi:10.1016/j.jogoh.2016.10.004.

192. Malshe A, Snowise S, Mann LK, et al. Preterm delivery after fetoscopic laser surgery for twin-twin transfusion syndrome: etiology and risk factors. *Ultrasound Obstet Gynecol*. 2017;49(5):612-616. doi:10.1002/uog.15972.

193. Martínez JM, Eixarch E, Crispi F, Puerto B, Gratacós E. Tratamiento por fetoscopia de la transfusión feto-fetal: Resultados en 500 casos consecutivos. *Diagnostico Prenat*. 2012;23(3):102-108. doi:10.1016/j.diapre.2012.06.010.

194. Middeldorp JM, Sueters M, Lopriore E, et al. Fetoscopic laser surgery in 100 pregnancies with severe twin-to-twin transfusion syndrome in the Netherlands. *Fetal Diagn Ther*. 2007;22(3):190-194. http://gateway.proquest.com/openurl?ctx_ver=Z39.88-2004&res_id=xri:pqm&req_dat=xri:pqil:pq_clntid=50325&rft_val_fmt=ori/fmt:kev:mtx:journal&genre=article&issn=1015-3837&volume=22&issue=3&spage=190.

195. Miyadahira M, Brizot M, Carvalho M, et al. Type II and III Selective Fetal Growth Restriction: Perinatal Outcomes of Expectant Management and Laser Ablation of Placental Vessels. *Clinics*. 2018;73:1-5. doi:10.6061/clinics/2018/e210.

196. Molina García FS, Zaragoza García E, Carrillo Badillo MP, Fernández de Santos AG, Calpena García A, Montoya Ventoso F. Implementación de la terapia láser endoscópica para las complicaciones de gestaciones gemelares monocoriales. *Progresos en Obstet y Ginecol*. 2009;52(6):313-319. doi:10.1016/S0304-5013(09)71466-9.

197. Müllers SM, McAuliffe FM, Kent E, et al. Outcome following selective fetoscopic laser ablation for twin to twin transfusion syndrome: an 8 year national collaborative experience. *Eur J Obstet Gynecol Reprod Biol*. 2015;191:125-129. doi:10.1016/j.ejogrb.2015.05.019.

198. Nakata M, Ishii K, Sumie M, et al. A prospective pilot study of fetoscopic laser surgery for twin-to-twin transfusion syndrome between 26 and 27 weeks of gestation. *Taiwan J Obstet Gynecol*. 2016;55(4):512-514. doi:10.1016/j.tjog.2016.06.002.

199. Nguyen HK, Cheng YW, Lee H, et al. 446: Recent experience with twin-twin transfusion syndrome: 2005-2011. *Am J Obstet Gynecol*. 2012;206(1):S205. doi:10.1016/j.ajog.2011.10.464.

200. Ozawa K, Sugibayashi R, Wada S, et al. Fetoscopic laser photocoagulation for amniotic fluid discordance bordering on twin–twin transfusion syndrome: Feasibility, perinatal and long-term outcomes. *J Obstet Gynaecol Res*. 2017;43(8):1256-1262. doi:10.1111/jog.13349.

201. Papanna R, Johnson A, Ivey RT, Olutoye OO, Cass D, Moise KJ. Laparoscopy-assisted fetoscopy for laser surgery in twin-twin transfusion syndrome with anterior placentation. *Ultrasound Obstet Gynecol*. 2010;35(1):65-70. doi:10.1002/uog.7495.

202. Papanna R, Habli M, Baschat AA, et al. Cerclage for cervical shortening at fetoscopic laser photocoagulation in twin-twin transfusion syndrome. *Am J Obstet Gynecol*. 2012;206(5):425. doi:10.1016/j.ajog.2012.02.022.

203. Peeters SHP, Stolk TT, Slaghekke F, et al. Iatrogenic perforation of intertwin membrane after laser surgery for twin-to-twin transfusion syndrome. *Ultrasound Obstet Gynecol*. 2014;44(5):550-556. doi:10.1002/uog.13445.

204. Persico N, Fabietti I, D'Ambrosi F, Riccardi M, Boito S, Fedele L. Postnatal survival after endoscopic equatorial laser for the treatment of twin-to-twin transfusion syndrome. *Am J Obstet Gynecol*. 2016;214(4):533. doi:10.1016/j.ajog.2015.10.020.

205. Quintero RA, Comas C, Bornick PW, Allen MH, Kruger M. Selective versus non-selective laser photocoagulation of placental vessels in twin-to-twin transfusion syndrome. *Ultrasound Obstet Gynecol*. 2000;16(3):230-236. http://onlinelibrary.wiley.com/doi/10.1046/j.1469-0705.2000.00265.x/full.

206. Quintero RA, Bornick PW, Allen MH, Johson PK. Selective laser photocoagulation of communicating vessels in severe twin-twin transfusion syndrome in women with an anterior placenta. *Obstet Gynecol*. 2001;97(3):477-481. https://go.openathens.net/redirector/nhs?url=http%3A%2F%2Fovidsp.ovid.com%2Fovidweb.cgi%3FT%3DJS%26PAGE%3Dfulltext%26MODE%3Dovid%26CSC%3DY%26NEWS%3DN%26D%3Dovft%26SEARCH%3D%252210.1016%2FS0029-7844(00)01172-8%2522.di.

207. Rossi AC, Kaufman MA, Bornick PW, Quintero RA. General vs local anesthesia for the percutaneous laser treatment of twin-twin transfusion syndrome. *Am J Obstet Gynecol*. 2008;199(2):137. doi:10.1016/j.ajog.2007.12.008.

208. Ruano R, Brizot M de L, Liao AW, Zugaib M. Selective fetoscopic laser photocoagulation of superficial placental anastomoses for the treatment of severe twin-twin transfusion syndrome. *Clinics (Sao Paulo)*. 2009;64(2):91-96.

http://europepmc.org/search?query=(DOI:%2210.1590/S1807-59322009000200005%22).

209. Rüegg L, Hüsler M, Krähenmann F, Natalucci G, Zimmermann R, Ochsenbein-Kölble N. Outcome after fetoscopic laser coagulation in twin–twin transfusion syndrome – is the survival rate of at least one child at 6 months of age dependent on preoperative cervical length and preterm prelabour rupture of fetal membranes? *J Matern Neonatal Med*. 2018;0(0):1-9. doi:10.1080/14767058.2018.1506441.

210. Rustico MA, Lanna MM, Faiola S, et al. Fetal and maternal complications after selective fetoscopic laser surgery for twin-to-twin transfusion syndrome: a single-center experience. *Fetal Diagn Ther*. 2012;31(3):170-178. doi:10.1159/000336227.

211. Said S, Flood K, Breathnach F, et al. Fetoscopic laser treatment of twin-to-twintransfusion syndrome (TTTS). *Ir Med J*. 2008;101(6):191-193.

212. Senat M-V, Deprest J, Boulvain M, Paupe A, Winer N, Ville Y. Endoscopic laser surgery versus serial amnioreduction for severe twin-to-twin transfusion syndrome. *N Engl J Med*. 2004;351(2):136-144. http://gateway.proquest.com/openurl?ctx_ver=Z39.88-2004&res_id=xri:pqm&req_dat=xri:pqil:pq_clntid=50325&rft_val_fmt=ori/fmt:kev:mtx:journal&genre=article&issn=1533-4406&volume=351&issue=2&spage=136.

213. Sepulveda W, Wong AE, Dezerega V, Devoto JC, Alcalde JL. Endoscopic laser surgery in severe second-trimester twin-twin transfusion syndrome: a three-year experience from a Latin American center. *Prenat Diagn*. 2007;27(11):1033-1038. https://go.openathens.net/redirector/nhs?url=http%3A%2F%2Fonlinelibrary.wiley.com%2Fdoi%2F10.1002%2Fpd.1829%2Ffull.

214. Shamshirsaz AA, Javadian P, Ruano R, et al. Comparison between laparoscopically assisted and standard fetoscopic laser ablation in patients with anterior and posterior placentation in twin-twin transfusion syndrome: a single center study. *Prenat Diagn*. 2015;35(4):376-381. doi:10.1002/pd.4552.

215. Slaghekke F, Lopriore E, Lewi L, et al. Fetoscopic laser coagulation of the vascular equator versus selective coagulation for twin-to-twin transfusion syndrome: an open-label randomised controlled trial. *Lancet (London, England)*. 2014;383(9935):2144-2151.

doi:10.1016/S0140-6736(13)62419-8.

216. Taniguchi K, Sumie M, Sugibayashi R, Wada S, Matsuoka K, Sago H. Twin anemia-polycythemia sequence after laser surgery for twin-twin transfusion syndrome and maternal morbidity. *Fetal Diagn Ther*. 2015;37(2):148-153. doi:10.1159/000365812.

217. Tchirikov M, Oshovskyy V, Steetskamp J, Falkert A, Huber G, Entezami M. Neonatal outcome using ultrathin fetoscope for laser coagulation in twin-to-twin-transfusion syndrome. *J Perinat Med*. 2011;39(6):725-730. doi:10.1515/JPM.2011.091.

218. Teoh M, Walker S, Cole S, Edwards A. "A problem shared is a problem halved": success of a statewide collaborative approach to fetal therapy. Outcomes of fetoscopic laser photocoagulation for twin-twin transfusion syndrome in Victoria. *Aust N Z J Obstet Gynaecol*. 2013;53(2):108-113. doi:10.1111/ajo.12062.

219. Thia E, Thain S, Yeo G. Fetoscopic laser photocoagulation in twin-to-twin transfusion syndrome: experience from a single institution. *Singapore Med J*. 2017;58(6):321-326. doi:10.11622/smedj.2016067.

220. Ville Y, Van Peborgh P, Gagnon A, Frydman R, Fernandez H. [Surgical treatment of twin-to-twin transfusion syndrome: coagulation of anastomoses with a Nd:YAG laser, under endosonographic control. Forty four cases]. *J Gynecol Obstet Biol Reprod (Paris)*. 1997;26(2):175-181.

221. Ville Y, Hecher K, Gagnon A, Sebire N, Hyett J, Nicolaides K. Endoscopic laser coagulation in the management of severe twin-to-twin transfusion syndrome. *Br J Obstet Gynaecol*. 1998;105(4):446-453.

222. Weingertner A-S, Kohler A, Mager C, et al. [Fetoscopic laser coagulation in 100 consecutive monochorionic pregnancies with severe twin-to-twin transfusion syndrome]. *J Gynecol Obstet Biol Reprod (Paris)*. 2011;40(5):444-451. doi:10.1016/j.jgyn.2011.04.001.

223. Wilson I, Henry A, Hinch E, et al. Audit of immediate outcomes for MCDA twins following laser therapy for twin-twin transfusion syndrome at the NSW Fetal Therapy Centre. *Aust N Z J Obstet Gynaecol*. 2016;56(3):289-294. doi:10.1111/ajo.12464.

224. Yamamoto M, El Murr L, Robyr R, Leleu F, Takahashi Y, Ville Y. Incidence and impact

of perioperative complications in 175 fetoscopy-guided laser coagulations of chorionic plate anastomoses in fetofetal transfusion syndrome before 26 weeks of gestation. *Am J Obstet Gynecol*. 2005;193(3):1110-1116. http://www.hlisd.org/LibraryDetail.aspx?LibraryID=3866.

225. Yang X, Leung TY, Ngan Kee WD, Chen M, Chan LW, Lau TK. Fetoscopic laser photocoagulation in the management of twin-twin transfusion syndrome: local experience from Hong Kong. *Hong Kong Med J = Xianggang yi xue za zhi*. 2010;16(4):275-281.

226. Zaretsky M V, Tong SH, Lagueux M, et al. North American Fetal Therapy Network: Indications for delivery following laser ablation for twin-twin transfusion syndrome. *Am J Obstet Gynecol*. 2018;218(1):S316-S316. doi:10.1016/j.ajog.2017.11.055.

227. Zhao D, Cohen D, Middeldorp JM, et al. Histologic Chorioamnionitis and Funisitis After Laser Surgery for Twin-Twin Transfusion Syndrome. *Obstet Gynecol*. 2016;128(2):304-312. doi:10.1097/AOG.0000000000001469.

228. Bebbington MW, Danzer E, Moldenhauer J, Khalek N, Johnson MP. Radiofrequency ablation vs bipolar umbilical cord coagulation in the management of complicated monochorionic pregnancies. *Ultrasound Obstet Gynecol*. 2012;40(3):319-324. doi:10.1002/uog.11122.

229. Berg C, Holst D, Mallmann MR, Gottschalk I, Gembruch U, Geipel A. Early vs late intervention in twin reversed arterial perfusion sequence. *Ultrasound Obstet Gynecol*. 2014;43(1):60-64. doi:10.1002/uog.12578.

230. Delabaere A, Favre N, Velemir L, et al. Suivi pédiatrique de 30 grossesses gémellaires monochoriales consécutives traitées par fœticide sélectif. *Gynecol Obstet Fertil*. 2013;41(2):85-89. doi:10.1016/j.gyobfe.2012.12.007.

231. Deprest JA, Audibert F, Van Schoubroeck D, Hecher K, Mahieu-Caputo D. Bipolar coagulation of the umbilical cord in complicated monochorionic twin pregnancy. *Am J Obstet Gynecol*. 2000;182(2):340-345. doi:10.1016/S0002-9378(00)70221-3.

232. Gallot D, Laurichesse H, Lemery D. Selective feticide in monochorionic twin pregnancies by ultrasound-guided umbilical cord occlusion. *Ultrasound Obstet Gynecol*.

2003;22(5):484-488. doi:10.1002/uog.917.

233. Gouverneur M, Klumper F, Loproire E, Vandenbussche F, Oepkes D. Selectieve foeticide door navelstrengcoagulatie bij afwijkende monochoriale meerlingen. *Ned Tijdschr Geneeskd*. 2009;153(19):906-911.

234. Gül A, Güngördük K, Yildirim G, et al. Bipolar cord coagulation in monochorionic twins discordant for major fetal anomalies. *J Turkish Ger Gynecol Assoc*. 2008;9(1):24-28.

235. Has R, Kalelioglu I, Esmer AC, et al. Bipolar cord coagulation in the management of complicated monochorionic twin pregnancies. *Fetal Diagn Ther*. 2014;36(3):190-195. doi:10.1159/000360853.

236. He ZM, Fang Q, Yang YZ, et al. Fetal reduction by bipolar cord coagulation in managing complicated monochorionic multiple pregnancies: Preliminary experience in China. *Chin Med J (Engl)*. 2010;123(5):549-554. doi:10.3760/cma.j.issn.0366-6999.2010.05.008.

237. Ilagan JG, Wilson RD, Bebbington M, et al. Pregnancy outcomes following bipolar umbilical cord cauterization for selective termination in complicated monochorionic multiple gestations. *Fetal Diagn Ther*. 2008;23(2):153-158. doi:10.1159/000111598.

238. Jelin E, Hirose S, Rand L, et al. Perinatal outcome of conservative management versus fetal intervention for twin reversed arterial perfusion sequence with a small acardiac twin. *Fetal Diagn Ther*. 2010;27(3):138-141. doi:10.1159/000295176.

239. King JR, Conturie CL, Ouzounian JG, Korst LM, Llanes A, Chmait RH. Umbilical Cord Occlusion via Laser Coagulation in Monochorionic Multifetal Gestations before and after 20 Weeks of Gestation. *Fetal Diagn Ther*. 2017;42(1):9-16. doi:10.1159/000448948.

240. Lanna MM, Rustico MA, Dell'Avanzo M, et al. Bipolar cord coagulation for selective feticide in complicated monochorionic twin pregnancies: 118 consecutive cases at a single center. *Ultrasound Obstet Gynecol*. 2012;39(4):407-413. doi:10.1002/uog.11073.

241. Lee H, Bebbington M, Crombleholme TM. The North American fetal therapy network registry data on outcomes of radiofrequency ablation for twin-reversed arterial perfusion sequence. *Fetal Diagn Ther*. 2013;33(4):224-229. doi:10.1159/000343223.

242. Lewi L, Gratacos E, Ortibus E, et al. Pregnancy and infant outcome of 80 consecutive

cord coagulations in complicated monochorionic multiple pregnancies. *Am J Obstet Gynecol*. 2006;194(3):782-789. http://www.hlisd.org/LibraryDetail.aspx?LibraryID=3866.

243. Moise KJKY, Johnson A, Nickeleit V, et al. Radiofrequency ablation for selective reduction in the complicated monochorionic gestation. *Am J Obstet Gynecol*. 2008;198(2):198.e1-198.e5. doi:10.1016/j.ajog.2007.07.043.

244. Nobili E, Paramasivam G, Kumar S. Outcome following selective fetal reduction in monochorionic and dichorionic twin pregnancies discordant for structural, chromosomal and genetic disorders. *Aust N Z J Obstet Gynaecol*. 2013;53(2):114-118. doi:10.1111/ajo.12071.

245. Paramasivam G, Wimalasundera R, Wiechec M, Zhang E, Saeed F, Kumar S. Radiofrequency ablation for selective reduction in complex monochorionic pregnancies. *BJOG An Int J Obstet Gynaecol*. 2010;117(10):1294-1298. doi:10.1111/j.1471-0528.2010.02624.x.

246. Peng R, Xie HN, Lin MF, et al. Clinical Outcomes after Selective Fetal Reduction of Complicated Monochorionic Twins with Radiofrequency Ablation and Bipolar Cord Coagulation. *Gynecol Obstet Invest*. 2016;81(6):552-558. doi:10.1159/000445291.

247. Quintero RA, Romero R, Reich H, et al. In utero percutaneous umbilical cord ligation in the management of complicated monochorionic multiple gestations. *Ultrasound Obstet Gynecol*. 1996;8(1):16-22. http://onlinelibrary.wiley.com/doi/10.1046/j.1469-0705.1996.08010016.x/full.

248. Quintero RA, Chmait RH, Murakoshi T, et al. Surgical management of twin reversed arterial perfusion sequence. *Am J Obstet Gynecol*. 2006;194(4):982-991. doi:10.1016/j.ajog.2005.10.195.

249. Roman A, Papanna R, Johnson A, et al. Selective reduction in complicated monochorionic pregnancies: Radiofrequency ablation vs. bipolar cord coagulation. *Ultrasound Obstet Gynecol*. 2010;36(1):37-41. doi:10.1002/uog.7567.

250. Schou K V., Jensen LN, Jørgensen C, Søgaard K, Tabor A, Sundberg K. Ultrasound-Guided Bipolar Umbilical Cord Occlusion in Complicated Monochorionic Pregnancies: Is There a Learning Curve. *Fetal Diagn Ther*. 2018;44(1):65-71. doi:10.1159/000479104.

251. Sugibayashi R, Ozawa K, Sumie M, Wada S, Ito Y, Sago H. Forty cases of twin reversed arterial perfusion sequence treated with radio frequency ablation using the multistep coagulation method: A single-center experience. *Prenat Diagn*. 2016;36(5):437-443. doi:10.1002/pd.4800.

252. Takano M, Murata S, Fujiwara M, Hirata H, Nakata M. Experience of fetoscopic laser photocoagulation and cord transection for twin-reversed arterial perfusion sequence. *J Obstet Gynaecol Res*. 2015;41(9):1326-1329. doi:10.1111/jog.12720.

253. Taylor MJO, Shalev E, Tanawattanacharoen S, et al. Ultrasound-guided umbilical cord occlusion using bipolar diathermy for Stage III/IV twin-twin transfusion syndrome. *Prenat Diagn*. 2002;22(1):70-76. https://go.openathens.net/redirector/nhs?url=http%3A%2F%2Fonlinelibrary.wiley.com%2Fdoi%2F10.1002%2Fpd.256%2Ffull.

254. Tsao KJ, Feldstein VA, Albanese CT, et al. Selective reduction of acardiac twin by radiofrequency ablation. *Am J Obstet Gynecol*. 2002;187(3):635-640. doi:10.1067/mob.2002.125242.

255. Zhang ZT, Yang T, Liu CX, Li N. Treatment of twin reversed arterial perfusion sequence with radiofrequency ablation and expectant management: A single center study in China. *Eur J Obstet Gynecol Reprod Biol*. 2018;225:9-12. doi:10.1016/j.ejogrb.2018.03.046.

256. Deprest J, Jani J, Gratacos E, et al. Fetal intervention for congenital diaphragmatic hernia: the European experience. *Semin Perinatol*. 2005;29(2):94-103.

257. Jani J, Gratacós E, Greenough A, et al. Percutaneous fetal endoscopic tracheal occlusion (FETO) for severe left-sided congenital diaphragmatic hernia. *Clin Obstet Gynecol*. 2005;48(4):910-922. https://go.openathens.net/redirector/nhs?url=http%3A%2F%2Fovidsp.ovid.com%2Fovidweb.cgi%3FT%3DJS%26PAGE%3Dfulltext%26MODE%3Dovid%26CSC%3DY%26NEWS%3DN%26D%3Dovft%26SEARCH%3D%252210.1097%2F01.grf.0000184774.02793.0c%2522.di.

258. Jani JC, Nicolaides KH, Gratacós E, Vandecruys H, Deprest JA, Group FT. Fetal lung-to-head ratio in the prediction of survival in severe left-sided diaphragmatic hernia

treated by fetal endoscopic tracheal occlusion (FETO). *Am J Obstet Gynecol*. 2006;195(6):1646-1650. https://auth.elsevier.com/ShibAuth/institutionLogin?entityID=https://idp.eng.nhs.uk/openathens&appReturnURL=https%3A%2F%2Fwww.clinicalkey.com%2Fcontent%2FplayBy%2Fdoi%2F%3Fv%3D10.1016%2Fj.ajog.2006.04.004.

259. Jiménez JA, Eixarch E, DeKoninck P, et al. Balloon removal after fetoscopic endoluminal tracheal occlusion for congenital diaphragmatic hernia. *Am J Obstet Gynecol*. 2017;217(1):78. doi:10.1016/j.ajog.2017.02.041.

260. Kosinski P, Wielgos M. Foetoscopic endotracheal occlusion (FETO) for severe isolated left-sided congenital diaphragmatic hernia: single center Polish experience. *J Matern Neonatal Med*. 2018;31(19):2521-2526. doi:10.1080/14767058.2017.1344969.

261. Manrique S, Munar F, Andreu E, et al. [Fetoscopic tracheal occlusion for the treatment of severe congenital diaphragmatic hernia: preliminary results]. *Rev Esp Anestesiol Reanim*. 2008;55(7):407-413.

262. Peralta CFA, Sbragia L, Bennini JR, et al. Fetoscopic endotracheal occlusion for severe isolated diaphragmatic hernia: Initial experience from a single clinic in Brazil. *Fetal Diagn Ther*. 2011;29(1):71-77. doi:10.1159/000314617.

263. Persico N, Fabietti I, Ciralli F, et al. Fetoscopic Endoluminal Tracheal Occlusion in Fetuses with Severe Diaphragmatic Hernia: A Three-Year Single-Center Experience. *Fetal Diagn Ther*. 2017;41(3):215-219. doi:10.1159/000448096.

264. Ruano R, da Silva MM, Campos JADB, et al. Fetal pulmonary response after fetoscopic tracheal occlusion for severe isolated congenital diaphragmatic hernia. *Obstet Gynecol*. 2012;119(1):93-101. doi:10.1097/AOG.0b013e31823d3aea.

265. Ruano R, Yoshisaki CT, da Silva MM, et al. A randomized controlled trial of fetal endoscopic tracheal occlusion versus postnatal management of severe isolated congenital diaphragmatic hernia. *Ultrasound Obstet Gynecol*. 2012;39(1):20-27. doi:10.1002/uog.10142.

266. Ruano R, Peiro JL, da Silva MM, et al. Early fetoscopic tracheal occlusion for extremely severe pulmonary hypoplasia in isolated congenital diaphragmatic hernia: preliminary

results. *Ultrasound Obstet Gynecol*. 2013;42(1):70-76. doi:10.1002/uog.12414.

267. Arens C, Koch C, Veit M, et al. Anesthetic Management for Percutaneous Minimally Invasive Fetoscopic Surgery of Spina Bifida Aperta: A Retrospective, Descriptive Report of Clinical Experience. *Anesth Analg*. 2017;125(1):219-222. doi:10.1213/ANE.0000000000001896.

268. Kohn J, Rao V, Sellner A, et al. Management of labor and delivery after fetoscopic repair of an open neural tube defect. *Obs Gynecol*. 2018;0(0):1-7. doi:10.1097/AOG.0000000000002577.

269. Pedreira DAL, Zanon N, de Sá RAM, et al. Fetoscopic single-layer repair of open spina bifida using a cellulose patch: preliminary clinical experience. *J Matern Fetal Neonatal Med*. 2014;27(16):1613-1619. doi:10.3109/14767058.2013.871701.

270. Verbeek RJ, Heep A, Maurits NM, et al. Fetal endoscopic myelomeningocele closure preserves segmental neurological function. *Dev Med Child Neurol*. 2012;54(1):15-22. doi:10.1111/j.1469-8749.2011.04148.x.

271. Ziemann M, Fimmers R, Khaleeva A. Partial amniotic carbon dioxide insufflation (PACI) during minimally invasive fetoscopic interventions on fetuses with spina bifida aperta. *Surg Endosc*. 2018;Epub ahead. doi:doi: 10.1007/s00464-018-6029-z.

272. Morris RK, Malin GL, Quinlan-Jones E, et al. Percutaneous vesicoamniotic shunting versus conservative management for fetal lower urinary tract obstruction (PLUTO): A randomised trial. *Lancet*. 2013;382(9903):1496-1506. doi:10.1016/S0140-6736(13)60992-7.

273. Ruano R, Duarte S, Bunduki V, Giron AM, Srougi M, Zugaib M. Fetal cystoscopy for severe lower urinary tract obstruction--initial experience of a single center. *Prenat Diagn*. 2010;30(1):30-39. doi:10.1002/pd.2418.

274. Welsh A, Agarwal S, Kumar S, Smith RP, Fisk NM. Fetal cystoscopy in the management of fetal obstructive uropathy: Experience in a single European centre. *Prenat Diagn*. 2003;23(13):1033-1041. doi:10.1002/pd.717.

275. Cavalheiro S, Moron AF, Almodin CG, et al. Fetal hydrocephalus. *Childs Nerv Syst*. 2011;27(10):1575-1583. doi:10.1007/s00381-011-1539-1.

276. Mallmann MR, Graham V, Rösing B, et al. Thoracoamniotic Shunting for Fetal Hydrothorax: Predictors of Intrauterine Course and Postnatal Outcome. *Fetal Diagn Ther*. 2017;41(1):58-65. doi:10.1159/000446110.

277. Kohl T, Hering R, Van de Vondel P, et al. Analysis of the stepwise clinical introduction of experimental percutaneous fetoscopic surgical techniques for upcoming minimally invasive fetal cardiac interventions. *Surg Endosc*. 2006;20(7):1134-1143. http://gateway.proquest.com/openurl?ctx_ver=Z39.88-2004&res_id=xri:pqm&req_dat=xri:pqil:pq_clntid=50325&rft_val_fmt=ori/fmt:kev:mtx:journal&genre=article&issn=1432-2218&volume=20&issue=7&spage=1134.

278. Kohl T, Tchatcheva K, Weinbach J, et al. Partial amniotic carbon dioxide insufflation (PACI) during minimally invasive fetoscopic surgery: early clinical experience in humans. *Surg Endosc*. 2010;24(2):432-444. doi:10.1007/s00464-009-0579-z.

279. Nivatpumin P, Pangthipampai P, Jirativanont T, Dej-Arkom S, Triyasunant N, Tempeetikul T. Anesthetic Techniques and Incidence of Complications in Fetoscopic Surgery. *J Med Assoc Thai*. 2016;99(5):602-610.

280. Peralta CFA, Sbragia L, Corrêa-Silva EP de B, et al. [Maternal complications following endoscopic surgeries in fetal Medicine]. *Rev Bras Ginecol Obstet*. 2010;32(6):260-266.

281. E.A. T. Maternal reproductive outcomes after in-utero repair of myelomeningocele. *Am J Obstet Gynecol*. 2016;214(1). http://www.hlisd.org/LibraryDetail.aspx?LibraryID=3866.

282. Gregoir C, Engels AC, Gomez O, et al. Fertility, pregnancy and gynecological outcomes after fetoscopic surgery for congenital diaphragmatic hernia. *Hum Reprod*. 2016;31(9):2024-2030. doi:10.1093/humrep/dew160.

283. Le Lous M, Mediouni I, Chalouhi G, et al. Impact of laser therapy for twin-to-twin transfusion syndrome on subsequent pregnancy. *Prenat Diagn*. 2018;38(4):293-297. doi:10.1002/pd.5227.

284. Vergote S, Lewi L, Gheysen W, De Catte L, Devlieger R, Deprest J. Subsequent fertility, pregnancy, and gynecologic outcomes after fetoscopic laser therapy for twin-twin transfusion syndrome compared with normal monochorionic twin gestations. *Am J Obstet Gynecol*. 2018;218(4):447.e1-447.e7. doi:10.1016/j.ajog.2018.01.013.

285. Mascarenhas MN, Flaxman SR, Boerma T, Vanderpoel S, Stevens GA. National, Regional, and Global Trends in Infertility Prevalence Since 1990: A Systematic Analysis of 277 Health Surveys. *PLoS Med*. 2012;9(12):1-12. doi:10.1371/journal.pmed.1001356.

286. Wilcox A, Weinber C, O'Connor J, Baird D. Incidence of Early Pregnancy Loss. *N Engl J Med*. 1988;319(4):189-194.

287. Andersen AN, Wohlfahrt J, Christens P, Olsen J, Melbye M, Nybo A. Maternal age and fetal loss: population based register linkage study. *BMJ*. 2000;320(June):1708-1712.

288. Herbert D, Lucke J, Dobson A. Pregnancy Losses In Young Australian Women. Findings from the Australian Longitudinal Study on Women's Health. *Women's Heal Issues*. 2009;19(1):21-29. doi:10.1016/j.whi.2008.08.007.

289. Blencowe H, Cousens S, Oestergaard MZ, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: A systematic analysis and implications. *Lancet*. 2012;379(9832):2162-2172. doi:10.1016/S0140-6736(12)60820-4.

290. Tanne JH. Preterm and low weight births rise again in the US. *BMJ*. 2017;3311:j3311. doi:10.1136/bmj.j3311.

291. National Institute for Health and Care Excellence. Preterm labour and birth. 2015. nice.org.uk/guidance/ng25.

292. Greene RA, Fitzpatrick C, Turner MJ. What are the maternal implications of a classical caesarean section? *J Obstet Gynaecol (Lahore)*. 1998;18(4):345-347. doi:10.1080/01443619867083.

293. Shavit C, Rollins M, Ferschl M. Maternal convulsion during high-dose sevoflurane anaesthesia for open foetal surgery. *Br J Anaesth*. 2017;118(4):634-635.

294. Gratacós E, Deprest J. Current experience with fetoscopy and the Eurofoetus registry for fetoscopic procedures. *Eur J Obstet Gynecol Reprod Biol*. 2000;92(1):151-159.

295. Bliton MJ. Parental hope confronting scientific uncertainty: a test of ethics in maternal-fetal surgery for spina bifida. *Clin Obstet Gynecol*. 2005;48(3):595-607. https://go.openathens.net/redirector/nhs?url=http%3A%2F%2Fovidsp.ovid.com%2Fovid

web.cgi%3FT%3DJS%26PAGE%3Dfulltext%26MODE%3Dovid%26CSC%3DY%26NEWS%3DN%26D%3Dovft%26SEARCH%3D%252210.1097%2F01.grf.0000169660.80698.a8%2522.di.

296. Fry JT, Frader JE. “We want to do everything”: How parents represent their experiences with maternal-fetal surgery online. *J Perinatol*. 2018;38(3):226-232. doi:10.1038/s41372-017-0040-4.

297. Abraham RJ, Sau A, Maxwell D. A review of the EXIT (Ex utero Intrapartum Treatment) procedure. *J Obstet Gynaecol*. 2010;30(1):1-5. doi:10.3109/01443610903281656.

298. Peters T, Waterman R, Phillips J. *The Seven S Model - a Managerial Tool for Analyzing and Improving Organizations*. London; 2006. doi:NCCDSO.

299. Monkhouse S, Burgess P. Setting up a new service. BMJ Careers.

300. NHS England. *Planning, Assuring and Delivering Service Change for Patients*.; 2015.

301. Shine website. https://www.shinecharity.org.uk.

302. Lamont R. Setting up a preterm prevention clinic: a practical guide. *BJOG An Int J Obstet Gynaecol*. 2006;113(Suppl. 3):86-92.

303. Tupper C, Andrews SS. Setting up an outpatient service for early medical termination. *J Fam Plan Reprod Heal Care*. 2007;33(3):199-202.

304. Cohen AR, Couto J, Cummings JJ, et al. Position statement on fetal myelomeningocele repair. *Am J Obstet Gynecol*. 2014;210(2):107-111. doi:10.1016/j.ajog.2013.09.016.

305. UCL Hospitals NHS Foundation Trust. *New Interventional Procedures: Introduction to UCLH. Policy & Procedure.*; 2014.

306. Department of Health. *The Interventional Procedures Programme: Working with the National Institute for Clinical Excellence to Promote Safe Clinical Innovation*.; 2003.

307. National Institute for Health and Care Excellence. NICE Public Board Meeting.

308. Sykes M, Gillespie BM, Chaboyer W. Surgical Team Mapping:Implications for Staff Allocation and Coordination. *AORN J*. 2015;101(238-248).

309. Xiao Y, Jones A, Zhang B. Team Consistency and Occurrences of Prolonged Operative

Time, Prolonged Hospital Stay, and Hospital Readmission: A Retrospective Analysis. *World J Surg*. 2015;39(4):890-896.

310. The Royal College of Surgeons of England. The High Performing Surgical Team - A Guide to Best Practice. *Prof Stand*. 2014.

311. World Health Organisation. WHO Guidelines for Safe Surgery: Safe Surgery Saves Lives. 2009.

312. Darzi A, Smith S, Taffinder N. Assessing operative skill. *BMJ*. 1999;318:887-888.

313. Vincent C, Moorthy K, Sarker S. Systems approaches to surgical quality and safety: from concept to measurement. *Ann Surg*. 2004;239(4):475-482.

314. NHS England. *Human Factors in Healthcare: A Concordat from the National Quality Board*.; 2013.

315. Aggarwal R, Undre S, Moorthy K. The simulated operating theatre: comprehensive training for surgical teams. *Qual Saf Heal Care*. 2004;13(Suppl 1):i27-i32.

316. National Patient Safety Alliance. WHO surgical safety checklist: for maternity cases only. http://www.nrls.npsa.nhs.uk/resources/?EntryId45=83972.

317. Reinebrant HE, Pileggi-Castro C, Romero CL. Cyclo-oxygenase (COX) inhibitors for treating preterm labour. *Cochrane Database Syst Rev*. 2015.

318. Nassr A, Whitehead W, H E. Effects of indomethacin therapy for short course tocolysis in the perioperative period on fetuses undergoing neural tube defect repair: a single center experience. *Prenat Diagn*. 2017;37:79-80.

319. Bowles D, Wasiak R, Kissner M. Economic burden of neural tube defects in Germany. *Public Health*. 2014;128:274-281.

320. Werner E, Han C, Burd I. Evaluating the cost-effectiveness of prenatal surgery for myelomeningocele: a decision analysis. *Ultrasound Obs Gynecol*. 2012;40:158-164.

321. Sing Au K, Ashley-Koch A, Northrup H. Epidemiologic and genetic aspects of spina bifida and other neural tube defects. *Dev Disabil Res Rev*. 2010;16(1):6-15.

322. Sekhon M, Cartwright M, Francis JJ. Acceptability of healthcare interventions: an

overview of reviews and development of a theoretical framework. *BMC Health Serv Res*. 2017;17:88.

323. Bil JP, Hoorneborg E, Prins M. The Acceptability of Pre-Exposure Prophylaxis: Beliefs of Health-Care Professionals Working in Sexually Transmitted Infections Clinics and HIV Treatment Centers. *Front Public Heal*. 2018;6(5).

324. Gucciardo L, De Koninck P, Verfaillie C. Perception and Knowledge About Stem Cell and Tissue Engineering Research: A Survey Amongst Researchers and Medical Practitioners in Perinatology. *Stem Cell Rev Reports*. 2014. doi:DOI 10.1007/s12015-014-9506-3.

325. Deprest J, Toelen J, Debyser Z. The fetal patient – ethical aspects of fetal therapy. *Facts, Views Vis Obs*. 2011;3(3):221-227.

326. R.M. A, A.W. F, M.P. J, et al. Specialty-Based Variation in Applying Maternal-Fetal Surgery Trial Evidence. *Fetal Diagn Ther*. 2017;42(3):210-217.

327. Shanmuganathan M, Sival DA, Eastwood KA, et al. Prenatal surgery for spina bifida: a therapeutic dilemma. Proceedings of the SHINE conference, Belfast. *Ir J Med Sci*. 2018;187(3):713-718. doi:10.1007/s11845-017-1709-6.

328. Rodrigues HCML, van den Berg PP, Düwell M. Dotting the I's and crossing the T's: autonomy and/or beneficence? The "fetus as a patient" in maternal-fetal surgery. *J Med Ethics*. 2013;39(4):219-223. doi:10.1136/medethics-2012-100781.

329. Cao KX, Booth A, Ourselin S, David AL, Ashcroft R. The legal frameworks that govern fetal surgery in the United Kingdom, European Union, and the United States. *Prenat Diagn*. 2018. doi:10.1002/pd.5267.

330. Chervenak FA, McCullough LB. Ethical dimensions of the fetus as a patient. *Best Pract Res Clin Obstet Gynaecol*. 2017;43:2-9. doi:10.1016/j.bpobgyn.2016.12.007.

331. Rintoul NE, Sutton LN, Hubbard AM, et al. A new look at myelomeningoceles: functional level, vertebral level, shunting, and the implications for fetal intervention. *Pediatrics*. 2002;109(3):409-413. https://doi.org/10.1542/peds.109.3.409.

332. Coleman BG, Langer JE, Horii SC. The diagnostic features of spina bifida: the role of

ultrasound. *Fetal Diagn Ther*. 2015;37(3):179-196. doi:10.1159/000364806.

333. Just M, Schwarz M, Ludwig B, E J, T M. Cerebral and spinal MR-findings in patients with postrepair myelomeningocele. *Pediatr Radiol*. 1990;(20):262-266.

334. Hannay HJ, Dennis M, Kramer L, Blaser S, Fletcher JM. Partial agenesis of the corpus callosum in spina bifida meningomyelocele and potential compensatory mechanisms. 2009;31(2):180-194. doi:10.1080/13803390802209954.

335. Juranek J, Salman MS. Anomalous development of brain structure and function in spina bifida myelomeningocele. *Dev Disabil Res Rev*. 2010;16(1):23-30.

336. Gilbert JN, Jones KL, Rorke LB, Chernoff GF, James HE. Central Nervous System Anomalies Associated with Meningomyelocele, Hydrocephalus, and the Arnold-Chiari Malformation: Reappraisal of Theories Regarding the Pathogenesis of Posterior Neural Tube Closure Defects. *Neurosurgery*. 1986;18(5):559-564.

337. Ghi T, Pilu G, Falco P, et al. Prenatal diagnosis of open and closed spina bifida. *Ultrasound Obstet Gynecol*. 2006;28(7):899-903. http://onlinelibrary.wiley.com/doi/10.1002/uog.3865/full.

338. Mulvey S, Wallace E. Women's knowledge of and attitudes to first and second trimester screening for Down's syndrome. *BJOG An Int J Obstet Gynaecol*. 2000;107(10):1302-1305.

339. Bartlett L, Berg C, Shulman H. Risk factors for legal induced abortion-related mortality in the United States. *Obstet Gynecol*. 2004;103(4):729-737.

340. Sacco A, Simpson L, Deprest J, David A. A Study to Assess Global Availability of Fetal Surgery for Myelomeningocele. *Prenat Diagn*. 2018;Epub ahead. doi:10.1002/pd.5383.

341. Fong KW, Toi A, Okun N, Al-Shami E, Menezes RJ. Retrospective review of diagnostic performance of intracranial translucency in detection of open spina bifida at the 11-13-week scan. *Ultrasound Obstet Gynecol*. 2011;38(6):630-634. doi:10.1002/uog.8994.

342. Chaoui R, Benoit B, Heling K. Prospective detection of open spina bifida at 11-13 weeks by assessing intracranial translucency and posterior brain. *Ultrasound Obstet Gynecol*. 2011;38:722-726.

343. Lachmann R, Chaoui R, Moratalla J, Picciarelli G, Nicolaides KH. Posterior brain in fetuses with open spina bifida at 11 to 13 weeks. *Prenat Diagn*. 2011;31(1):103-106. doi:10.1002/pd.2632.

344. Finn M, Sutton D, Atkinson S. The aqueduct of Sylvius: a sonographic landmark for neural tube defects in the first trimester. *Ultrasound Obstet Gynecol*. 2011;38:640-645.

345. Lachmann R, Picciarelli G, Moratalla J. Frontomaxillary facial angle in fetuses with spina bifida at 11-13 weeks' gestation. *Ultrasound Obstet Gynecol*. 2010;36:268-271.

346. Ultrasound LS of. Crash sign: Diagnosis of Spina Bifida at 11-13 weeks. https://www.youtube.com/watch?v=k6Vy4PKJekM.

347. ISUOG Practice Guidelines: performance of first-trimester fetal ultrasound scan. *Ultrasound Obstet Gynecol*. 2013;41:102-113.

348. Loureiro T, Ushakov F, Montenegro N, Gielchinsky Y, Nicolaides KH. Cerebral ventricular system in fetuses with open spina bifida at 11-13 weeks' gestation. *Ultrasound Obstet Gynecol*. 2012;39(6):620-624. doi:10.1002/uog.11079.

349. Kohl T, Hering R, Heep A, et al. Percutaneous fetoscopic patch coverage of spina bifida aperta in the human--early clinical experience and potential. *Fetal Diagn Ther*. 2006;21(2):185-193. http://gateway.proquest.com/openurl?ctx_ver=Z39.88-2004&res_id=xri:pqm&req_dat=xri:pqil:pq_clntid=50325&rft_val_fmt=ori/fmt:kev:mtx:journal&genre=article&issn=1015-3837&volume=21&issue=2&spage=185.

350. Kohl T, Tchatcheva K, Berg C, Geipel A, Van de Vondel P, Gembruch U. Partial amniotic carbon dioxide insufflation (PACI) facilitates fetoscopic interventions in complicated monochorionic twin pregnancies. *Surg Endosc*. 2007;21(8):1428-1433. http://gateway.proquest.com/openurl?ctx_ver=Z39.88-2004&res_id=xri:pqm&req_dat=xri:pqil:pq_clntid=50325&rft_val_fmt=ori/fmt:kev:mtx:journal&genre=article&issn=1432-2218&volume=21&issue=8&spage=1428.

351. Gratacos E, Wu J, Devlieger R. Effects of amniodistention with carbon dioxide on fetal acid-base status during fetoscopic surgery in a sheep model. *Surg Endosc*. 2001;15:368-372.

352. Kuks F, Deprest J, Marcus M. Carbon dioxide pneumoamnios causes acidosis in fetal

lamb. *Fetal Diagn Ther*. 1994;9:105-109.

353. Kohl T, Ziemann M, Weinbach J. Partial amniotic carbon dioxide insufflation during minimally invasive fetoscopic interventions seems safe for the fetal brain in sheep. *J Laparoendosc Adv Surg Tech*. 2010;20:651-653.

354. A. F. Percutaneous minimal-access fetoscopic surgery for myelomeningocele - not so minimal! *Ultrasound Obstet Gynecol*. 2014;44(5):499-500. http://onlinelibrary.wiley.com/doi/10.1002/uog.14673/full.

355. Lapa A, Acacio G, Goncalves R. Percutaneous fetoscopic closure of large open spina bifida using a bilaminar skin substitute. *Ultrasound Obstet Gynecol*. 2018;Epub ahead. doi:10.1002/uog.19001.

356. Mazzone L, Meuli M. Re: Fetoscopic repair of spina bifida: safer and better? *Ultrasound Obstet Gynecol*. 2016;48(6):802.

357. Fauza DO, Jennings RW, Teng YD, Snyder EY. Neural stem cell delivery to the spinal cord in an ovine model of fetal surgery for spina bifida. *Surgery*. 2008;144(3):367-373. doi:10.1016/j.surg.2008.05.009.

358. Li H, Gao F, Ma L, et al. Therapeutic potential of in utero mesenchymal stem cell (MSCs) transplantation in rat foetuses with spina bifida aperta. *J Cell Mol Med*. 2012;16(7):1606-1617. doi:10.1111/j.1582-4934.2011.01470.x.

359. Saadai P, Wang A, Nout YS, et al. Human induced pluripotent stem cell-derived neural crest stem cells integrate into the injured spinal cord in the fetal lamb model of myelomeningocele. *J Pediatr Surg*. 2013;48(1):158-163. doi:10.1016/j.jpedsurg.2012.10.034.

360. Dionigh B, Ahmed A, Ill JB, Connors P, Zurakowski D, Fauza D. Partial or complete coverage of experimental spina bifida by simple intra-amniotic injection of concentrated amniotic mesenchymal stem cells. *J Pediatr Surg*. 2014;50(1):69-73.