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REVIEW ARTICLE

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Peri-operative management of percutaneous fetoscopic spina-bifida repair: a descriptive review of five cases from the United Kingdom, with focus on anaesthetic implications

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ABSTRACT
We present a case-based review of the first five percutaneous fetoscopic in-utero spina bifida repair procedures undertaken in the UK. Our focus is on implications of anaesthesia and analgesia for the mother and fetus, provision of uterine relaxation and fetal immobilisation while providing conditions conducive to surgical access. Minimising risks for fetal acidosis, placental and fetal hypoperfusion, maternal and fetal sepsis and maternal fluid overload were the foremost priorities. We discuss optimisation strategies undertaken to ensure fetal and maternal well-being under anaesthesia, shortcomings in the current approach, and possible directions for improvement.
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Keywords: Percutaneous fetoscopic spina-bifida repair; Transplacental anaesthesia; Fetal monitoring; Depth of anaesthesia; Uterine tocolysis

Introduction

Spina bifida results from abnormal development and incomplete closure of the neural tube and affects 33–48 per 100 000 live births globally.[1] Current practice is surgical repair within 1–2 days of birth. Recently, several animal and human reports have suggested that prenatal repair could offer better postnatal neurological function.[2,3] In 2011, the Management of Myelomeningocele Study (MOMS) compared open (hysterotomy) prenatal repair with the standard postnatal technique. They found reduced rates of neurosurgical intervention for hydrocephalus in a significant proportion of those treated prenatally and an improved composite score for mental development and motor function at 30 months.[4,5] However, it was associated with increased rates of preterm birth (13% before 30 weeks' gestation) and uterine dehiscence.

In the quest to reduce maternal and fetal complications, fetoscopic approaches have been adopted by many centres around the world with promising results.[6–8] There is no published guidance on optimal modes of anaesthesia. We report our first experiences of percutaneous fetoscopic spina bifida repair, including optimisation strategies undertaken to ensure fetal and maternal well-being under anaesthesia, shortcomings of the current approach and directions for improvement in the future.

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Case series

Eligibility

The MOMS trial criteria were used to determine eligibility for antenatal repair. All cases had fetal spina bifida recognised on antenatal ultrasound and confirmed by magnetic resonance imaging (MRI) early in the second

trimester. None of the fetuses had any other congenital abnormalities. The parents were counselled on the options available for repair and, following a multidisciplinary discussion, the percutaneous fetoscopic approach was offered. The parents gave consent and surgery was scheduled for the late second trimester.

Operative course

Extensive pre-operative planning was undertaken with advice from international experts. All team members participated in a simulation on the day of surgery.

Before surgery, the women were fasted, provided with standard antacid premedication and anti-thromboembolic stockings, and given rectal (PR) indomethacin 100 mg 12 h pre-operatively. Following pre-oxygenation, a rapid sequence induction was carried out with intravenous (IV) fentanyl 3 μg/kg, propofol 1.5 mg/kg and rocuronium 0.8 mg/kg. This generally achieved a bispectral index (BIS) of 25–30. Following intubation, positive-pressure ventilation was established with hyperventilation during intra-uterine carbon dioxide (CO_2) insufflation to maintain end-tidal CO_2 ($ETCO_2$) below 3.5 kPa. Antibiotic prophylaxis was administered at induction (cefuroxime 1.5 g in case 1 and clindamycin 600 mg in cases 2–5), with three further doses postoperatively.

Anaesthesia was maintained with sevoflurane at a minimum alveolar concentration (MAC) of 0.4–1, intravenous propofol infusion 2–3 mg/kg/h and remifentanil infusion 10 μg/kg/h adjusted to maintain cardiovascular stability. The depth of maternal anaesthesia was monitored using BIS and maintained at 40.[9] An arterial line was inserted to assist regular sampling and cardiovascular monitoring.

A phenylephrine infusion was titrated to maintain a target mean maternal blood pressure (65–70 mmHg in cases 1 and 2 and 80 mmHg in cases 3–5) during the procedure. Atropine 600 μg (cases 3–5) was given if the maternal heart rate fell below 60/min. A glyceryl trinitrate (GTN) infusion was available (50 mg/50 mL) to provide additional uterine relaxation. This was required in case 4 during which intermittent uterine contractions were observed following an intraperitoneal CO_2 leak during the procedure.

All women were placed in a semi-lithotomy/supine position, a urinary catheter inserted and PR indomethacin 100 mg given for uterine tocolysis. An 18-gauge needle was inserted into the uterus under ultrasound guidance and 500 mL of warm Ringer's lactate solution infused. Four percutaneous ports (in case 1) and three ports (in cases 2–5) were respectively inserted into the uterus under ultrasound guidance. Approximately 1 L of amniotic fluid was removed and humidified warm CO_2 insufflated. The uterine 'opening pressure' was measured and the maximum insufflation pressure set at 4 mmHg above it.[10] In cases 2–5, pressure was maintained at 2–3 mmHg above the opening pressure. We observed momentary drops in blood pressure during the insertion of trocars. Uterine insufflation with CO_2 seemed most stimulating for the mother, with a rise in blood pressure and BIS that was mitigated by IV morphine. The spinal defect was dissected by the neurosurgeon and repaired with a bio-cellulose patch placed over the neural placode (exposed open spinal cord), covered by an additional layer of a skin substitute (Nevelia®, Symatese, Montpelier, France) as needed (Fig. 1).

The uterine cavity was irrigated with warm (37 °C) Ringer's lactate solution, antibiotic instilled (cefuroxime 1.5 g in case 1, clindamycin 500 mg in cases 2–5) and the cavity re-filled with 1L Ringer's lactate solution or the drained amniotic fluid if not blood-stained.[11] Uterine tone was restored with termination of the GTN infusion and sevoflurane inhalation 5 min before removal of the trocars. Intravenous anaesthesia was maintained during uterine port-site haemostasis and closure of abdominal wounds. The duration of the procedure ranged from 4.0 to 5.5 h. Maternal temperature was monitored and maintained with a warm-air blanket. Women received IV paracetamol 1 g, IV metoclopramide 10 mg and PR indomethacin 100 mg. The maternal blood loss was approximately 150–200 mL and total fluids during the procedure limited to Hartmann's solution 1000–1500 mL. Following recovery from general anaesthesia, the mothers and fetuses were observed in the obstetric high dependency unit for 24–48 h. Adequate pain control was achieved with regular paracetamol and doses of oral morphine (0.15 mg/kg) except in case 2, for whom morphine patient controlled analgesia followed by epidural analgesia was required from days 2–4 because of intermittent shooting postoperative pain triggered by fetal movements impinging upon the uterine wounds. None of the women required a blood transfusion. There were no post-procedure placental abruptions or uterine dehiscences.

Fetal monitoring

Intra-operative fetal monitoring was obstetrician led. For case 1 this included pre- and postoperative ultrasound assessment of umbilical and middle cerebral artery blood flow and cardiotocogram (CTG), with visual monitoring of the umbilical cord pulsation intra-operatively. The uterine and middle cerebral artery blood flows were reported as normal before and after surgery. The beat-to-beat variation of the fetal heart on CTG was reduced postoperatively in case 1, although the baseline rate remained normal. Normal fetal movements were felt by the mother 48 h post-surgery.

In cases 2–5, additional intra-operative fetal monitoring was instituted every 15 min using a Doppler probe placed on the maternal flank under sterile conditions to gain umbilical artery signals from the umbilical cord, below the amniotic fluid level so as to avoid the CO_2

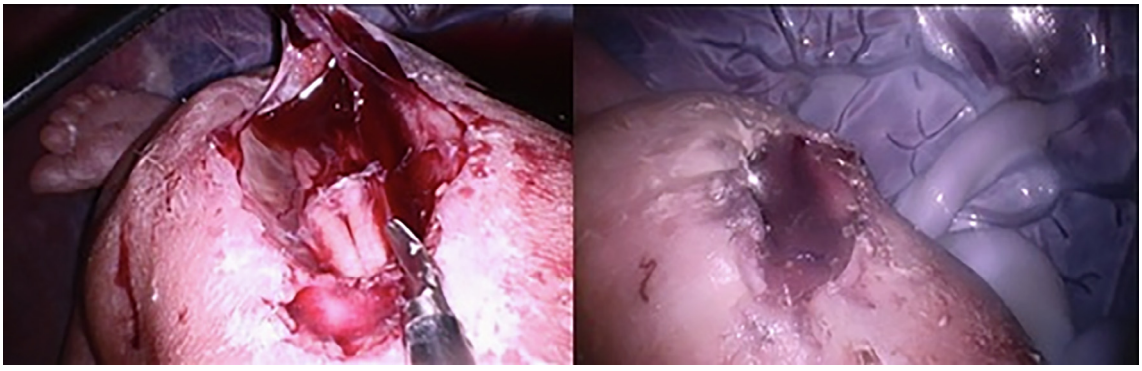

Fig. 1 Completed fetoscopic patch repair of the spina-bifida (case 1)

interface (Fig. 2). This fetal umbilical cord blood flow study was used to calculate the pulsatility index (PI), the systolic velocity-diastolic velocity/mean velocity, which is a measure of umbilical cord forward blood flow, and placental resistance.[12] The PI reduced with increasing gestation. A PI <1.0 was considered healthy and a rising value from baseline a cause for concern.

Fetal outcomes

A summary of fetal outcomes is shown in Table 1. Baby case 1 was born in a good condition, weighing 1.49 kg (<50th centile), but required intubation, surfactant and continuous positive-airway pressure for acute respiratory distress syndrome (ARDS) for 48 h. Haemoglobin concentration at birth was 101 g/L, platelet count 327×10^9/L, total white cell count 58.3×10^9/L, s. Na 134 mmol/L and s. K 5.0 mmol/L. The cranial ultrasound performed on day 1 showed subtle changes suspicious of periventricular leukomalacia and ventriculomegaly (Fig. 3). On neurological examination, the baby displayed good power and movement in all limbs and normal anal tone, and the bladder scan was within the normal range. At 48 h, there was renal impairment with the s. creatinine rising to a maximum of 289 μmol/L. This was managed without dialysis. There was no positive culture but sepsis was considered likely and treated. At two weeks of age, the baby developed a pulmonary haemorrhage and required mechanical ventilation and a course of antibiotics again. Ventricular index and occipito-frontal head circumference (OFC) increased in size, this being resolved by regular tapping initially and a ventriculo-peritoneal shunt (VP). His course continued to be complicated by respiratory issues. The baby died from complications of severe aspiration pneumonia at three months of age.

Babies 2–5 were born in good condition and their spinal wounds healed well. All were at home at the time of this review. The haemoglobin at birth in case 2 was

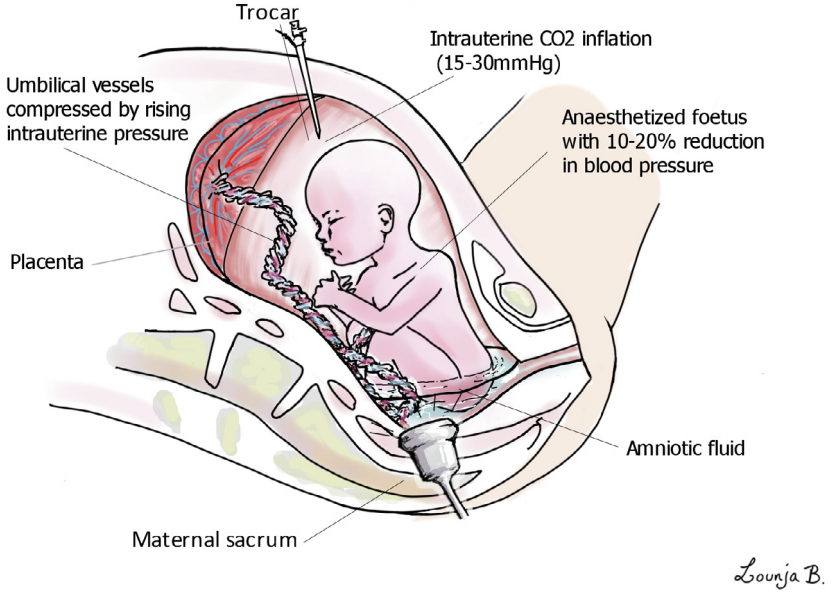

Fig. 2 An illustration outlining uterine CO_2 inflation during fetoscopy and umbilical cord blood flow monitoring

Table 1 Demographic outline of cases

Case number	Gestation at fetoscopic repair (weeks + days)	Onset of labour	Mode of delivery	Gestation at birth (weeks + days) Apgar scores at 1, 5 min	Infant age at this review (months, days) Current status
1	27 + 6	Spontaneous	Forceps	30 + 3 8, 10	VP-shunt Died at 3 months from complications of prematurity
2	27 + 3	Spontaneous	CS	32 + 5 2 ,9	7 months, 4 days VP shunt Well
3	29 + 3	Spontaneous	SVD	34 + 4 9, 10	3 months, 17 days Well
4	28 + 0	Spontaneous	CS	32 + 4 8, 10	1 month, 14 days Well Talipes
5	28 + 4	Spontaneous	CS	35 + 6 9, 10	1 month Well

CS: caesarean section; SVD: spontaneous onset vaginal delivery; VP: ventriculo-peritoneal.

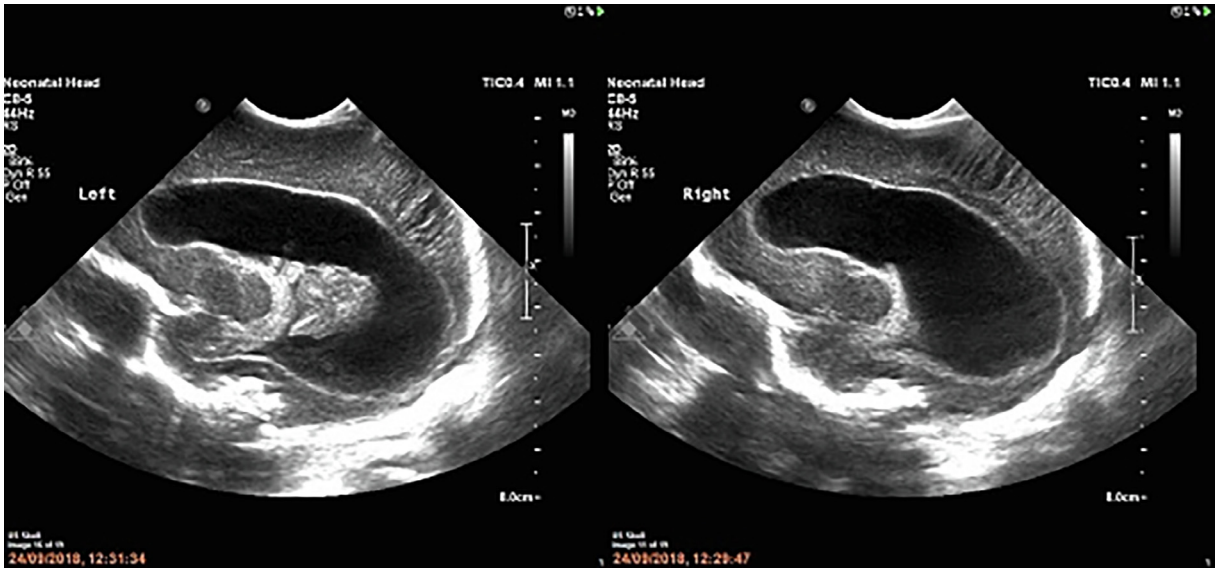

Fig. 3 Left and right neonatal cranial ultrasound images at birth (case 1)

152 g/L. All these babies are regularly monitored for hydrocephalus and two have required VP shunt insertion (Table 1).

Discussion

Experience in providing maternal and fetal anaesthesia has been gained from ex-utero intrapartum treatment (EXIT) procedures.[13] The aims of feto-maternal anaesthesia include fetal immobility, uterine relaxation and tocolysis, reducing the risk of sepsis, and preventing placental-fetal hypoperfusion and fetal acidosis.

Choice of anaesthetic

Inhalational agents, propofol, fentanyl and remifentanil given to the mother will all cross the placenta to provide anaesthesia and analgesia to the fetus.[13] If regional anaesthesia is used, separate provision of fetal anaesthesia and analgesia by direct fetal intramuscular injection is necessary. Drugs given to the fetus also have the potential to cross the placenta into the maternal circulation. Although the doses are significantly smaller, drug specific implications for the mother and fetal oxygenation have been reported.[14] Maternal hypotension is more common during regional anaesthesia and injudi-

cious over-infusion of IV fluid risks fluid overload and pulmonary oedema.[15–17] There is a further risk from absorption of amniotic and irrigating fluid through the myometrium and fluid retention due to tocolytic agents, especially beta-agonists, magnesium sulphate and atisoban, all of which contribute to maternal pulmonary oedema independent of anaesthetic technique. We opted for fluid-restrictive general anesthesia.[18–22]

We used a rapid sequence induction with cricoid pressure and tracheal intubation to reduce the risk of aspiration of gastric contents. General anaesthesia with controlled ventilation allowed manipulation of maternal $_{ET}CO_2$ (and hence fetal arterial CO_2) in response to uterine insufflation. Animal studies suggest that fetal acidosis may predispose to preterm delivery.[23] A study evaluating the consequences of a pneumoperitoneum on mid-term sheep fetuses reported that CO_2 inflation to 15 mmHg for 90–120 min induced fetal respiratory acidosis and correction via maternal hyperventilation was late and incomplete.[24] Acidosis was not demonstrated in umbilical venous blood in three human fetuses submitted to partial amniotic CO_2 inflation and CO_2 humidification,[25] but as umbilical venous blood is already equilibrated with maternal blood it may not give a reliable assessment of fetal acidosis. Umbilical arterial blood sampling is not feasible during fetoscopy because the sample would be contaminated by the pressurised CO_2 environment and because of the risk of CO_2 embolus.[26]

Multimodal balanced anaesthesia has been used in fetoscopic surgery to minimise the perceived risks of any one agent to the mother and fetus.[17,27–30] Incomplete myelination and synaptic activation make the fetus more sensitive to volatile agents and analgesics.[31] Animal studies suggest loss or death of brain cells and impaired neurocognitive function following anaesthetic exposure in neonates and late gestation fetuses.[32] Human studies in this area are limited and currently inconclusive. In 2016, the US Food and Drug Administration issued a warning regarding potential impaired brain development in children following exposure to inhalational agents (isoflurane, sevoflurane, desflurane) and intravenous agents (propofol, midazolam) in the third trimester of pregnancy, especially in procedures lasting >3 h.[33] The consequences of anaesthetic exposure in the second trimester when fetal surgical procedures are performed is unclear, although there is evidence that brief exposure is not associated with any long-term risk in humans.[33] Intravenous tocolytics for uterine relaxation may reduce the need for high concentrations of inhalational agents and hence reduce fetal exposure.[34] We used a remifentanil infusion to provide immobilisation of the fetus and analgesia.[35–37] The relatively high induction dose of fentanyl also contributed to fetal sedation. Total intravenous anaesthesia alone would have required higher cumulative doses of propofol that might induce fetal acidosis.[38] Maternal hypothermia has been associated with postoperative fetal bradycardia.[39] Maintenance of maternal normothermia via controlled active warming is essential. A prophylactic antibiotic that crosses the placenta was used as sepsis has been recognised as a cause of post-procedure fetal death.[11,40]

Tocolysis

We achieved adequate and reversible uterine relaxation with sevoflurane 0.5–1.0 MAC alone but also added GTN in case 4.[41] Uterine tone was restored at removal of trocars by terminating these agents at the end of the procedure. Indomethacin, a cyclo-oxygenase-2 inhibitor, was given to reduce the risk of postoperative contractions and preterm labour, although it has recognised fetal side effects such as renal failure, necrotising enterocolitis, intraventricular haemorrhage and closure of the ductus arteriosus[42,43] and maternal pulmonary oedema.[44]

We also had atosiban and magnesium sulphate available to supplement uterine relaxation. These were required in case 4 to mitigate contractions triggered by an intraperitoneal CO_2 leak. A non-randomised cohort study comparing magnesium sulphate versus atosiban during and after open fetal myelomeningocele repair reported similar short-term uterine outcomes without any serious maternal complications.[45] Beta-adrenergic agonists and calcium channel blockers are not ideal for this purpose[46] and new agents are sought.[47]

Fetal management and outcomes

Fetal oxygenation is dependent on maternal blood flow to the uteroplacental circulation, gas exchange across the placenta and fetal umbilical artery flow. Maternal hypotension, increased intra-uterine pressure, fetal bradycardia and hypovolaemia can cause fetal hypoxia.

We maintained maternal blood pressure with a phenylephrine infusion as its effects on placental blood flow are considered beneficial compared with ephedrine.[48] Compression of the aorta and inferior vena cava by the gravid uterus when the mother lies supine can reduce maternal blood pressure and hence placental flow, especially in the third trimester. We elected not to use a lateral tilt to assist surgical access, and momentary maternal hypotension was only observed during insertion of the trocars; this was assumed to be a result of aortocaval compression at this time.[49]

The fetal circulation is a relatively low-pressure system, with arterial systolic pressure of 45–50 mmHg in preterm neonates at 27 weeks' gestation.[50] Intrauterine pressure during contractions can reach 60 mmHg but this pressure occurs intermittently, allowing recovery of the circulation between contractions.[51,52] Continuous inflation of the uterus to a pressure of

15–30 mmHg for surgery compresses the umbilical cord circumferentially and may impede umbilical arterial blood flow.[53–55] Reduced umbilical vein flow will decrease fetal preload and blood pressure. Furthermore, umbilical artery compression may increase umbilical arterial resistance and create back pressure, promoting flow diversion to the pulmonary circulation through the ductus arteriosus, and increase desaturated blood admixture (Fig. 4).

Fetal intracranial pressure is most likely maintained in equilibrium with intra-uterine pressure via the open fontanelle and soft skull. High uterine inflation pressures, coupled with reduced fetal blood pressure, could also reduce cerebral perfusion. To minimise this effect, uterine inflation pressure was maintained just above 'opening' pressure, as this is reported to be safe.[11] Intermittent release of intra-uterine pressure may allow recovery of placental and cerebral blood flow.

Fetal cardiac output is maintained by a high heart rate rather than increased contractility.[56] Transplacental anaesthetic agents reduce fetal heart rate and myocardial contractility and can contribute to hypoperfusion.[57] Inhaled sevoflurane at a MAC of 2.4 has been shown to reduce umbilical flow during open fetal surgery[58] and we maintained a relatively low MAC in our cases. Fetal hypovolaemia can be easily overlooked. The fetal blood volume is approximately 120–160 mL/kg in the second trimester[59] and the haemoglobin range 115–125 g/L.[60] A 20 mL blood loss is a major haemorrhage in a fetus weighing 1.0 kg and with a 120 mL circulating blood volume. In addition, there is an increased bleeding tendency due to an immature coagulation system and high evaporative fluid losses.

During EXIT procedures or spina bifida repair with hysterotomy, direct access to the fetus allows monitoring with pulse oximetry, echocardiography, electrocardiography and umbilical blood gas analysis.[61,62] These monitors cannot be used practically during percutaneous fetoscopy and the ideal monitoring device is yet to be established.

Although cord blood gas analysis provides the best assessment of fetal oxygenation and acid-base status,[26,63] during fetoscopy this is less reliable because the CO_2 insufflation contaminates the sample. Venepuncture or cordocentesis risk CO_2 embolus into the fetal circulation.[25]

Umbilical artery flow pulsatility index (PI) and fetal heart rate assessed via umbilical artery doppler in cases 2–5 (Fig. 2) seemed superior to pre- and post-procedural ultrasound and intra-operative visual observation of cord pulsation. The images and dopplers obtained were of good quality but required a dedicated person to monitor PI during the procedure.[12] Monitoring of fetal heart rate and beat-to-beat variability may offer early indications of fetal distress but continuous CTG monitoring is impractical as the gaseous interface prevents beat capture.[64] Maternal transoesophageal echocardiography has been used to assess umbilical artery blood flow during maternal cardiac surgery and may be useful.[65] Since prolonged decreases in fetal heart rate or significant changes in umbilical artery flow, especially absent or reversed diastolic flow, are linked with increased perinatal morbidity and mortality,[66] immediate measures should be taken.

The aetiology of suspected cerebral periventricular leukomalacia in case 1 was largely unexplained but

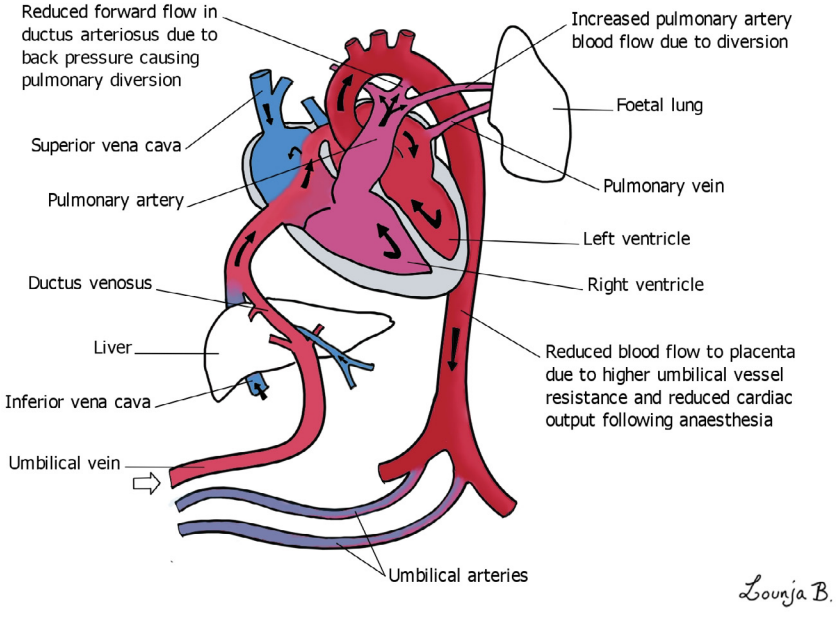

Fig. 4 An illustration outlining plausible effects of intra-uterine pressure and transplacental anaesthesia on fetal circulation during fetoscopic surgery

was in keeping with an undetected insult 2–3 weeks before birth, coinciding with the fetoscopic intervention or thereafter. Reduced cerebral and placental blood flow are the leading causes of hypoxic-ischaemic encephalopathy of the new-born,[67] hence our measures to increase maternal mean blood pressure from 65 to 70 mmHg in cases 1 and 2 to 80 mmHg in cases 3–5 by means of chronotropes (atropine) and vasopressors (phenylephrine). Neonatal sepsis was possible but the C-reactive protein of <0.2 mg/L at birth did not support this. Acute kidney injury in case 1 neonate was unanticipated. Antenatally, there was no renal dysplasia or bladder outflow tract obstruction. Acute kidney injury can result from indomethacin[68] or hypoperfusion during fetoscopic intervention (Fig. 4). Beta-lactams such as ceftriaxone have been shown to induce interstitial inflammation in animal fetal kidneys,[69] therefore we changed the antibiotic prophylaxis to clindamycin for cases 2–5.[70]

In case 1, the neonatal haemoglobin at birth was 101 g/L which was lower than expected for a premature neonate (mean 165 g/L)[71] and possibly due to blood loss at surgery or sepsis, but this was unlikely to have contributed to the kidney and cerebral injury. Babies born with lower haemoglobin levels following twin-to-twin transfusion syndrome have had preserved renal and cerebral function.[72]

Postoperative care

Following recovery from general anaesthesia the mothers were monitored in the obstetric high dependency unit for 24–48 h, with vital signs recorded every 4 h and CTG 12 hourly. Pain control was achieved with regular paracetamol and oral morphine as required, in order to minimise fetal and maternal stress-inducing preterm labour.[73] A single dose of indomethacin 100 mg was administered PR 6 h following surgery and progesterone 200 mg daily on discharge from hospital to reduce the risk of preterm labour. Indomethacin and atosiban were considered the least likely to be associated with serious adverse drug reactions in the mother.[74] Obstetric review occurred at one week postoperatively.

Team-working

The challenge of introducing a new procedure should not be underestimated for all staff involved.[75] We mitigated this by extensive pre-operative multidisciplinary planning.[76,77] The surgeons visited centres in Brazil and the USA, and the first three operations were attended by experienced fetal obstetric surgeons. There was extensive email correspondence between the UK and Brazilian anaesthetists about anaesthetic techniques. The UK anaesthetic and surgical teams met on several occasions before the procedures to ensure sharing of information and open discussion with the families about surgical and anaesthetic risks to both mother and baby, including image recording before obtaining informed consent.[78,79] The simulation with the full operating team on the day of surgery familiarised all personnel with the procedure, patient positioning, and laparoscopic and other equipment requirements.

In summary, percutaneous fetoscopic surgery poses many unique anaesthetic issues. These include inducing profound but reversible uterine relaxation, vigilance for maternal or fetal blood loss, transplacental anaesthesia, fetal immobilisation, fetal monitoring, maintenance of maternal mean blood pressure and a pro-active approach to fetal resuscitation. Postoperative measures to reduce the risk of premature delivery are required. The success of intra-uterine myelomeningocele repair relies on a well-coordinated multidisciplinary approach. Maintaining uterine CO_2 inflation pressure close to 'opening pressure' seems prudent.

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Declaration of interests

There are no conflicts of interest.

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