NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of fetoscopic prenatal repair for open neural tube defects in the fetus

An open neural tube defect (open spina bifida) happens while the baby (fetus) is developing in the womb. Part of the spinal column does not form properly, leaving a gap that allows the spinal cord and nerves to develop outside the body. This may result in the baby being born with spina bifida and can cause lifelong disability. Up to 26 weeks of pregnancy keyhole (fetoscopic) surgery can be done, through the mother's abdomen, to close the gap in the baby's spine. The baby continues to grow and develop until birth. The aim is to prevent further damage to the brain, spinal cord and nerves.

Contents

Introduction

Description of the procedure

Efficacy summary

Safety summary

The evidence assessed

Validity and generalisability of the studies

Existing assessments of this procedure

Related NICE guidance

Additional information considered by IPAC

References

Additional relevant papers

Literature search strategy

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the

medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in June 2019.

Procedure name

- Fetoscopic prenatal repair of open neural tube defects in the fetus

Specialist societies

- Royal College of Paediatrics and Child Health (RCPCH)
- Royal College of Obstetricians and Gynaecologists (RCOG)
- Society of British Neurological Surgeons (SBNS)- paediatric neurosurgery
- British Maternal and Fetal medicine Society (BMFMS).

Description of the procedure

Indications and current treatment

Neural tube defects happen because the neural tube doesn’t fuse during early embryonic development. Open neural tube defects are those in which the affected region of the neural tube is exposed on the body’s surface. The most common neural tube defect is spina bifida where the defect is in the spine. Myelomeningocele (open spina bifida) is the most severe type of spina bifida, in which the baby's spinal canal remains open along several vertebrae in the back. The spinal cord and protective membranes around it push out and form a sac which is exposed on the baby's back. Children born with myelomeningocele may experience motor neurological deficits including muscle weakness and paralysis of the lower limbs, sensory deficit, bowel, bladder and sexual dysfunctions and learning difficulties. The condition can be associated with Chiari II malformation (hindbrain herniation) and hydrocephalus.

Conventional treatment for myelomeningocele (open spina bifida) is immediate surgical repair of the defect within days of birth to prevent further damage to nervous tissue and reduce the risk of central nervous system infection. The immediate management may also include ventricular-peritoneal shunt placement to relieve hydrocephalus. The condition can also be treated prenatally with the aim of decreasing morbidity in the child.

What the procedure involves

Fetoscopic prenatal repair is done before 26 weeks of pregnancy. It can be done using local, regional or general anaesthesia and with partial CO_2 insufflation of the uterine cavity. Under ultrasound guidance the paediatric laparoscopy set (a fetoscope/endoscope) is introduced through a port followed by the introduction of additional ports to allow the passage of instruments. Once the fetus is positioned adequately, the skin around the fetal neural placode/elements is dissected. A biocellulose patch is placed between the neural elements (defect) and the skin. The skin is sutured using interrupted stitches over the patch or, for a large defect, a dermal regeneration patch substitute can be used for repair.

A number of minor variations to the procedure have been described.

Efficacy summary

Improvement in motor function of lower body

Open fetal repair compared with fetoscopic repair

A systematic review and meta-analysis of 11 observational studies compared fetoscopic surgery with open surgery for fetal repair of myelomeningocele. This reported that both these surgical approaches were associated with comparable rates of motor response relative to myelomeningocele anatomical level. The mean effect size (ES) was 70% in fetoscopic repair (95% confidence interval [CI] 49% to 89%) compared with 56% in open repair (95% CI 46% to 67%); p=0.24. The outcomes were similar when fetoscopic data were combined with those of fetoscopic surgery through a maternal laparotomy. The mean ES was 72% in modified fetoscopic repair (95% CI 57% to 84%) compared with 56% in open repair (95% CI 46% to 67%); p=0.09.[1]

A systematic review and meta-analysis of 19 studies (n=908) compared fetal open and endoscopic surgery for myelomeningocele. It reported that the pooled rate of improvement of lower extremity function (walking independently without assistive appliances) assessed in 7 studies was 47% (161/315), (95% CI 30% to 64%) after open surgery. The pooled rate in the endoscopic surgery group (assessed in 1 small study) was 86% (6/7), (95% CI 49% to 97%). The authors noted that the estimate in this group is very imprecise because there were only 7 procedures in this study.[2]

Improvement in hindbrain herniation

Open fetal repair compared with fetoscopic repair

The systematic review and meta-analysis of 11 observational studies compared fetoscopic surgery with open surgery for fetal repair of myelomeningocele. It reported that both these surgical approaches were associated with comparable

rates of reversal of hindbrain herniation. The mean ES was 86%, (95% CI 53% to 100%) in fetoscopic repair, compared with 54% (95% CI 21% to 86%) in the open repair; p=0.18. The outcomes were similar when fetoscopic data were combined with those of fetoscopic surgery through a maternal laparotomy, with a mean ES of 69% (95% CI 39% to 93%) in modified fetoscopic repair compared with 54% (95% CI 21 to 86%) in open repair; p=0.52.[1]

The systematic review and meta-analysis of 19 studies (n=908) compared fetal open and endoscopic surgery for myelomeningocele. It reported that the pooled rate of hindbrain herniation reversal (assessed in 3 studies) was 34% (48/134), (95% CI 23% to 46%, p<0.0001) in the open surgery group. The pooled rate in the endoscopic surgery group (assessed in 1 small study of 7 procedures) was 86% (6/7), (95% CI 49% to 97%). The authors noted that the estimate in this group is very imprecise because there were only 7 procedures in the study.[2]

Ventriculoperitoneal (VP) shunt placement or ventriculostomy within 12 months of birth

Open fetal repair compared with fetoscopic repair

The systematic review and meta-analysis of 11 observational studies compared fetoscopic surgery with open surgical approach for fetal repair of myelomeningocele. This reported that there was no significant difference in the rate of VP shunt placement or ventriculostomy within 12 months of birth between fetoscopic and open repair approaches. The mean ES was 43% (95% CI 33% to 53%) in fetoscopic repair compared with 40% (95% CI 32% to 49%) in open repair, p=0.71. The outcomes were similar when combining the fetoscopic data with those of fetoscopic surgery through a maternal laparotomy, with a mean ES of 42% (95% CI 33% to 52%) in modified fetoscopic repair compared with 40% (95%CI 32% to 49%) in open repair, p=0.73.[1]

The systematic review and meta-analysis of 19 studies (n=908) compared fetal open and endoscopic surgery for myelomeningocele. It reported that the pooled rate of VP shunt placement (assessed in 12 studies, 10 open surgery and 2 endoscopic surgery) was similar in infants followed at least 12 months for both groups. This was 40% (229/529), 95% CI 29% to 51%, p<0.0001 compared with 45% (35/78), 95% CI 34% to 56%, p=0.93.[2]

Bladder and bowel function

Open fetal repair compared with fetoscopic repair

The systematic review and meta-analysis of 19 studies (n=908) compared fetal open and endoscopic surgery for myelomeningocele. This reported that the pooled rate of bladder dysfunction (assessed in 8 studies) was 72% (188/274), (95% CI 53% to 89%, p<0.0001) in the open surgery group. The pooled rate in the endoscopic surgery group (assessed in 1 small study) was 29% (2/7), (95%

CI 8% to 64%). The authors noted that the estimate in this group is very imprecise because there were only 7 procedures in the study.[2]

Completion of surgery through intended access

Open fetal repair compared with fetoscopic repair

The systematic review and meta-analysis of 11 observational studies compared fetoscopic surgery with open surgical approach for fetal repair of myelomeningocele. It reported that there was no significant difference in the rate of cases completed through the originally intended access between the fetoscopic and open approaches. The mean ES was 92% (95% CI 74% to 100%) in fetoscopic repair compared with 99.8% (95% CI 99% to 100%) in open repair, p=0.08. However, when combining the fetoscopic data with those of fetoscopic surgery through a maternal laparotomy the difference between the groups was statistically significant, with a mean ES of 90% (95% CI 72% to 99% in modified fetoscopic repair compared with 99.8% (95% CI 99% to 100%) in open repair, p=0.02.[1]

Safety summary

Combined fetal and postnatal mortality

Open fetal repair compared with fetoscopic repair

A systematic review and meta-analysis of 11 observational studies compared fetoscopic surgery with open surgical approach for fetal repair of myelomeningocele. This reported that there was no statistically significant difference in combined fetal and postnatal mortality between percutaneous fetoscopic and open repair approaches. The mean effect size (ES) was 9% (95% confidence interval [CI] 5% to 14%) in fetoscopic repair compared with 6% (95% CI 3% to 9%) in open repair, p=0.20. The outcomes were similar when combining the fetoscopic data with those of fetoscopic surgery through a maternal laparotomy, with a mean ES of 7% (95% CI 2% to 15%) in modified fetoscopic repair compared with 6% (95% CI 3% to 9%) in open repair, p=0.65.[1]

Perinatal or neonatal death

Open fetal repair compared with fetoscopic repair

A meta-analysis of procedure-related complications compared open fetal surgery (in 4 studies) with endoscopic fetal surgery (in 3 studies) for intrauterine myelomeningocele repair. This reported that the rate of death in the perinatal period was lower in the open surgery group compared with the endoscopic group (5%, 95% CI 3% to 8%, p=0.76 compared with 14%, 95% CI 1% to 38%, p=0.008).[3]

Premature birth/preterm delivery

Open fetal repair compared with fetoscopic repair

The systematic review and meta-analysis of 11 observational studies compared fetoscopic surgery with open surgical approach for fetal repair of myelomeningocele. It reported that the rate of preterm birth (less than 37 weeks gestational age) was significantly higher in the percutaneous fetoscopic approach compared with the open repair approach. The mean ES was 96% (5% CI 88% to 100%) in fetoscopic repair compared with 81% (95% CI 66% to 92%) in open repair, p=0.04. When combining the fetoscopic data with those of fetoscopic surgery through a maternal laparotomy, the difference in the rate of preterm birth was not statistically significant between the 2 approaches. There was a mean ES of 90% (95% CI 69% to 100%) in modified fetoscopic repair compared with 81% (95% CI 66% to 92%) in open repair, p=0.43.[1]

The systematic review also reported that the difference between fetoscopic and open approaches were not statistically significant for premature delivery at less than 30 weeks gestational age. The mean ES was 22% (95% CI 8% to 39%) in fetoscopic repair compared with 13% (95% CI 3% to 28%) in open repair, p=0.39. When combining the fetoscopic data with those of fetoscopic surgery through a maternal laparotomy, the difference in the rate of delivery at less than 30 weeks was also not statistically significant between the 2 approaches. The mean ES was 17% (95% CI 7% to 32%) in modified fetoscopic repair compared with 13% (95% CI 3% to 28%) in open repair, p=0.61.[1]

The meta-analysis of procedure-related complications in open fetal surgery (in 4 studies) compared with endoscopic fetal surgery (in 3 studies) for intrauterine myelomeningocele repair reported the rate of preterm delivery (at less than 34 weeks). This was lower in the open surgery group compared with the endoscopic group (45%, 95% CI 38% to 53%, p=0.21 compared with 80%, 95% CI 41% to 100%, p<0.0001).[3]

Uterine dehiscence

Open fetal repair compared with fetoscopic repair

The systematic review and meta-analysis of 11 observational studies compared fetoscopic surgery with open surgical approach for fetal repair of myelomeningocele. It reported that the rate of uterine dehiscence was significantly higher in the open repair approach compared with percutaneous fetoscopic approach. The mean ES was 11% (95% CI 5% to 20%) in fetoscopic repair compared with 0% (95% CI 0% to 2%) in open repair, p<0.01. When combining the fetoscopic data with those of fetoscopic surgery through a maternal laparotomy, the difference in the rates were also statistically significant between the 2 approaches. The mean ES was 11% (95% CI 5% to 20%) in

modified fetoscopic repair compared with 0% (95% CI 0% to 1%) in open repair, p<0.01.[1]

The meta-analysis of procedure-related complications in open fetal surgery (in 4 studies) compared with endoscopic fetal surgery (in 3 studies) for intrauterine myelomeningocele repair reported the rate of complete dehiscence, focal dehiscence and/or markedly thin hysterectomy scar. This was higher in the open surgery group compared with the endoscopic group (26%, 95% CI 12% to 42%, p<0.0001 compared with 1%, 95% CI 0% to 4%, p=0.84).[3]

Premature rupture of membranes (PROM)

Open fetal repair compared with fetoscopic repair

The systematic review and meta-analysis of 11 observational studies compared fetoscopic surgery with open surgical approach for fetal repair of myelomeningocele. It reported that the rate of premature rupture of membranes was significantly higher in the percutaneous fetoscopic approach compared with open repair approach. The mean ES was 91% (95% CI 74% to 99%) in fetoscopic repair compared with 36% (95% CI 24% to 49%) in open repair, p<0.01. When combining the fetoscopic data with those of fetoscopic surgery through a maternal laparotomy, the difference in the rates were also statistically significant between the 2 approaches. The mean ES was 79% (95% CI 40% to 99%) in modified fetoscopic repair compared with 36% (95% CI 24% to 49%) in open repair, p=0.04.[1]

The meta-analysis of procedure-related complications in open fetal surgery (in 4 studies) compared with endoscopic fetal surgery (in 3 studies) for intrauterine myelomeningocele repair reported the rate of premature rupture of membranes. This was lower in the open surgery group compared with the endoscopic group (38%, 95% CI 26% to 50%, p=0.005 compared with 67%, 95% CI 12% to 100%, p<0.0001).[3]

Oligohydramnios

Open fetal repair compared with fetoscopic repair

The meta-analysis of procedure-related complications of open fetal surgery (in 4 studies) compared with endoscopic fetal surgery (in 3 studies) for intrauterine myelomeningocele repair reported the rate of oligohydramnios. This was lower in the open surgery group compared with the endoscopic group (14%, 95% CI 7% to 24%, p=0.004 compared with 29%, 95% CI 9% to 75%, p=0.0001).[3]

Chorioamniotic membrane separation

Open fetal repair compared with fetoscopic repair

The systematic review and meta-analysis of 11 observational studies compared fetoscopic surgery with open surgical approach for fetal repair of myelomeningocele. It reported that there was no significant difference in the rate of chorioamniotic membrane separation between percutaneous fetoscopic and open repair approaches. The mean ES was 17% (95% CI 0% to 61%) compared with 9% (95% CI 0% to 32%), p=0.70. The outcomes were similar when combining the fetoscopic data with those of fetoscopic surgery through a maternal laparotomy, with a mean ES of 21% (95% CI 2% to 52%) compared with 9% (95% CI 0% to 32%), p=0.46.[1]

Placental abruption

Open fetal repair compared with fetoscopic repair

The systematic review and meta-analysis of 11 observational studies compared fetoscopic surgery with open surgical approach for fetal repair of myelomeningocele. It reported that there was no significant difference in the rate of placental abruption between percutaneous fetoscopic and open repair approaches. The mean ES was 2% (95% CI 0% to 18%) compared with 3% (95% CI 1% to 5%), p=0.83. The outcomes were similar when combining the fetoscopic data with those of fetoscopic surgery through a maternal laparotomy, with a mean ES of 3% (95% CI 0% to 17%) compared with 3% (95% CI 1% to 5%), p=0.85.[1]

The meta-analysis of procedure-related complications of open fetal surgery (in 4 studies) compared with endoscopic fetal surgery (in 3 studies) for intrauterine myelomeningocele repair reported that there was no difference in the rate of placental abruption in the open surgery group compared with endoscopic group (3%, 95% CI 0% to 8%, p=0.02 compared with 2%, 95% CI 0% to 9%, p=0.19).[3]

Cerebrospinal fluid (CSF) leakage needing postnatal treatment of repair site

Open fetal repair compared with fetoscopic repair

The systematic review and meta-analysis of 11 observational studies compared fetoscopic surgery with open surgical approach for fetal repair of myelomeningocele. This reported that the rate of CSF leakage or dehiscence needing postnatal operative revision or nonoperative treatment at the repair site was significantly higher in the percutaneous fetoscopic approach compared with the open repair approach. The mean ES was 28% (95% CI 19% to 38%) compared with 7% (95% CI 2% to 13%), p<0.01. When combining the fetoscopic data with those of fetoscopic surgery through a maternal laparotomy, the difference in the rates were also statistically significant between the 2 approaches (mean ES 30% [95% CI 21% to 39%] compared with 7% [95% CI 2% to 13%], p<0.01).[1]

Chorioamnionitis

Open fetal repair compared with fetoscopic repair

The meta-analysis of procedure-related complications of open fetal surgery (in 4 studies) compared with endoscopic fetal surgery (in 3 studies) for intrauterine myelomeningocele repair reported the rate of chorioamnionitis. There was no difference in the open surgery group compared with the endoscopic group (3%, 95% CI 2% to 6%, p=0.44 compared with 6%, 95% CI 2% to 12%, p=0.37).[3]

Iatrogenic flank hernia

Iatrogenic bilateral flank hernia after fetoscopic repair of myelomeningocele (myeloschisis defect) using lateral relaxing incisions for a water-tight closure was reported in a case report of 1 baby. These defects were repaired, and the patient was discharged after 8 days.[4]

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, specialist advisers listed the following anecdotal adverse events: bleeding, wound infection, and amniotic fluid leakage through the port insertion into the maternal abdomen. They considered that the following were theoretical adverse events: hysterectomy, haemorrhage, complications related to general anaesthesia and maternal death.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to fetoscopic prenatal repair of open neural tube defects in the fetus. The following databases were searched, covering the period from their start to 01.02.2019: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Fetus with open neural tube defects (open spina bifida/myelomeningocele).
Intervention/test	Fetoscopic prenatal surgical repair.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 346 patients from 3 systematic reviews and 1 case reports. There is an overlap of patients between the studies[1-3] included in the overview.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) are listed in the appendix.

Table 2 Summary of key efficacy and safety findings on fetoscopic prenatal repair of open neural tube defects in the fetus

Study 1 Kabagambe 2018

Details

Study type	Systematic review and meta-analysis
Country	4 studies in USA, 3 in Germany, 2 in Brazil, 1 in France and 1 in Poland.
Study period	Search period 2011 to 2016. Databases searched: Pubmed and Embase. One further study on fetoscopic MMC repair published in 2017 was also added after completion of the systematic review.
Study population and number	**n= 436 fetuses with myelomeningocele in 11 retrospective or prospective observational studies** **Fetoscopic repair (n=179 in 5 studies)** [Graf 2016, Pedreira 2016, Degenhardt 2014, Verbeek 2012, Belfort 2017], **Open fetal repair (n=257 in 6 studies)** [Danzer 2016, Friszer 2016, Moldenhauer 2015, Zamlynski 2014, Bennet 2014, Hisaba 2012]).
Age and sex	Maternal age, gestational age at the time of repair and sex of the fetuses were not reported.
Study selection criteria	English or French studies (of all types) that report fetal, obstetrical, or post-natal outcomes of the prenatal repair of myelomeningocele published since January 2011(MOMS), with varied follow-up periods were included. Studies focusing on the postnatal repair or medical management of myelomeningocele, and prenatal diagnosis, summary and review of myelomeningocele and its treatment, summary of perioperative care, management of urological mobility, ethical issues surrounding fetal surgery, epidemiology and translational research were excluded. Editorial articles t and duplicate studies were excluded. One case report of prenatal repair using cryopreserved umbilical vein was also excluded.
Technique	**Prenatal repair of myelomeningocele**: **Fetoscopic repair** (in 5 studies) was done in 2 different approaches; percutaneous fetoscopic repair and fetoscopic repair via maternal laparotomy. The percutaneous fetoscopic technique was varied by centre to centre; some used collagen/Teflon patch to cover the spinal cord and mobilised skin to cover free edges of the patch. At least 3 studies used this technique. Others used a bio cellulose patch over the cord and performed closure of the skin over the patch. One study from Brazil used this technique. In **fetoscopic repair via maternal laparotomy procedure (in 1 study)**, the primary closure was done by incorporating dura and skin. **Open fetal repair** (in 6 studies) also slightly varied by centre.
Follow-up	**Varied in studies (0 to 10 years)**
Conflict of interest/source of funding	The authors declared no conflicts of interest.

Analysis

Follow-up issues: Follow-up varied in studies. Only short-term follow-up reported.

Study design issues: comprehensive search strategy was used; data was extracted into a database. Two authors reviewed and analysed the data. The risk of bias and the quality of the studies (retrospective and prospective observational studies) were assessed using the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0. Studies were heterogenous and varied in surgical techniques by centre, with selective reporting of outcomes within each study and incomplete outcome data from some studies making comparison difficult to interpret. The analysis also included a more recent modified percutaneous fetoscopic approach via maternal laparotomy and combined the outcomes of both fetoscopic approaches. There is no standardised approach used in the studies. A sub analysis of the studies conducted since 2010 was also done to account for the impact of recent advances in both open and fetoscopic technique. Statistical heterogeneity was observed among the studies.

Study population issues: The selected studies were mainly observational studies from different countries. Each centre used only one surgical approach; therefore, it is not possible to compare fetoscopic vs open repair within a centre. There is an overlap of patients between the studies[1-5].

Key efficacy and safety findings

Efficacy and safety

Number of patients analysed: **436 (179 fetoscopic repair 257 open fetal repair)**

The outcomes for fetoscopic and open repair were compared after a weighted proportion for each outcome was obtained for all studies based on the sample size.

Outcomes	Percutaneous fetoscopic repair mean ES % (95% CI)[1]	Percutaneous fetoscopic +via maternal laparotomy mean ES% (95% CI)	Open fetal repair mean ES % (95% CI)	P value (with maternal laparotomy)	P value (without maternal laparotomy)
VP shunt placement or ventriculostomy within 12 months of birth	**43 (33, 53)**	**42 (33, 52)**	**40 (32, 49)**	**0.71**	**0.73**
Function vs anatomic level[2]	70 (49,89)	72 (57,84)	56(46,67)	0.24	0.09
Completion via intended access	92(74, 100)	90(72, 99)	99.8 (99, 100)	0.08	0.02
Reversal of hindbrain herniation	86(53,100)	69(39,93)	54(21,86)	0.18	0.52

2 Proportion of better motor response relative to lesion level

Adverse events

Complications	Fetoscopic repair mean ES % (95% CI)[1]	Percutaneous fetoscopic +via a maternal laparotomy mean ES% (95%CI)	Open fetal repair Mean ES % (95% CI)	P value (with maternal laparotomy)	P value (without maternal laparotomy)
Mortality (combined fetal, postnatal mortality)	**9 (5, 14)**	**7 (2, 15)**	**6 (3,9)**	**0.20**	**0.65**
CSF leakage at MMC repair site (needing postnatal treatment)	28(19, 38)	30(21, 39)	7(2,13)	<0.01	<0.01
Delivery <30 weeks GA	22 (8, 39)	17 (7, 32)	13 (3, 28)	0.39	0.61
Preterm birth (<37 weeks)	96 (88, 100)	90 (69, 100)	81 (66, 92)	0.04	0.43
PROM	91 (74, 99)	79 (40, 99)	36 (24, 49)	<0.01	0.04
CA membrane separation	17 (0, 61)	21 (2, 52)	9 (0, 32)	0.70	0.46
Placental abruption	2 (0, 18)	3 (0, 17)	3 (1, 5)	0.83	0.85
Uterine dehiscence	0 (0, 2)	0 (0, 1)	11 (5, 20)	<0.01	<0.01

Abbreviations used: CA, chorioamniotic; CI, confidence interval; ES, effect size; GA, gestational age; PROM, premature rupture of membranes; MMC, myelomeningocele; VP, ventriculoperitoneal.

Study 2 Junior E (2016)

Details

Study type	**Systematic review and meta-analysis**
Country	15 studies in USA, 2 in Brazil, 1 in Germany, 1 in Poland.
Study period	Search period: 2003 to October 2015; Databases searched: Cochrane Central Register of Controlled Trials, Literatura Latino-American e do Caribe em Ciencias da Saude (LILACS), PubMed and SCOPUS. No restrictions applied on language and publication status.
Study population and number	**n= 908 infants in 19 studies for fetal open and endoscopic surgery for myelomeningocele** (2 RCTs, 13 retrospective case series, 4 retrospective case-control studies) **Open fetal surgery (n=827 in 17 studies), Endoscopic fetal surgery (n=81 in 2 studies)**
Age and sex	Maternal age, gestational age at the time of surgery and delivery, and sex of the fetuses were not reported in this systematic review.
Study selection criteria	Randomised controlled trials and observational studies (with at least 10 cases) on treatment of myelomeningocele by endoscopic or open fetal surgery techniques, with follow-up of more than 12 months were included. Studies with less than 10 cases, multiple publications and overlapping cases were excluded.
Technique	All studies in this systematic review are fetal repair of myelomeningocele: 827 women had open fetal MMC surgery and 81 women had endoscopic fetal MMC surgery.
Follow-up	**Varied in studies (range 12 to 129.6 months)**
Conflict of interest/source of funding	The authors declared no conflicts of interest.

Analysis

Follow-up issues: Follow-up varied in studies, but all studies had minimum of 12 months follow-up.

Study design issues: Systematic review was registered with the prospective register of systematic reviews (PROSPERO). comprehensive search strategy was used, studies were screened and selected by 2 authors, data was extracted into a standardised form. Two authors assessed the risk of bias of observational studies using Newcastle-Ottawa Scale. The quality of evidence was evaluated after the GRADE Working group recommendation. Except for the 2 RCTs, the evidence was considered of low quality because of serious limitations and inconsistencies in the studies. High heterogeneity in studies was reported so it was difficult to interpret results. The primary outcome assessed was ventriculoperitoneal shunt placement rate, and secondary outcomes were hindbrain hernia reversal, lower extremity function and bladder dysfunction. Meta-analysis was done using MEdCalc version 12.7, using random effects model. Heterogeneity was assessed among studies by the I^2 statistic.

Study population issues: Sample size was significantly smaller for endoscopic surgery groups compared with open repair. Some studies presented similar cases, but the outcomes assessed were different.

Other issues: Authors state that results were not analysed according to short- and long-term follow-up periods and fetuses were not separated according the fetal upper level of MMC which could have potentially interfered with the outcomes. There is an overlap of patients between the studies[1-5].

Key efficacy and safety findings

Efficacy

Number of patients analysed: **908 (827 open fetal surgery versus 81 endoscopic fetal surgery)**

Ventriculoperitoneal shunt placement rate (n=607 [12 studies])

Procedure	Pooled proportion % random effects (n)	95% CI	P value, I^2
Open MMC repair (n=10 studies)	39.8% (229/529)	29.0 – 51.1	P<0.0001 I^2=84.73%
Endoscopic MMC repair (n=2 studies)	45.0% (35/78)	34.3 – 55.9	P=0.930% I^2 =0%

Hindbrain herniation reversal[3] (n=141 [4 studies])

Procedure	Pooled proportion % random effects (n)	95% CI	P value, I^2
Open MMC repair(n=3 studies)	34.0 % (48/134)	23.2 – 45.6	P=0.163 I^2=44.73%
Endoscopic MMC repair (n=1)	N/A (6/7)[2]	N/A	N/A

[2] Meta-analysis was not done due to <10 cases

[3] considered as total absence of hindbrain herniation in MRI examination.

Lower extremity function[3] (n=322 [8 studies])

Procedure	Pooled proportion % random effects (n)	95% CI	P value, I^2
Open MMC repair (7 studies)	46.8% (161/315)	30.4 – 63.5	P<0.0001 I^2=89.27%
Endoscopic MMC repair (1 study)	N/A (6/7)[2]	N/A	N/A

[2] Meta-analysis was not done due to <10 cases

[3] only children walking independently without assistive appliances were considered.

Bladder dysfunction[3] (n=281 [9 studies])

Procedure	Pooled proportion % random effects (n)	95% CI	P value, I^2
Open MMC repair (n=8 studies)	72.4% (188/274)	52.5 – 88.5	P<0.0001 I^2=91.54%
Endoscopic MMC repair (n=1 study)	N/A (2/7)[2]	N/A	N/A

[2] Meta-analysis was not done due to <10 cases

[3] assessed using at least one of the following parameters: clean intermittent catheterisation, abnormal video urodynamic, previous surgery for management of neurogenic bowel and bladder, video cystography showing vesicoureteral reflux.

Safety

One study with endoscopic repair (n=10) reported 1 fetal death and 2 technical failures.

Abbreviations used: CI, confidence interval; MMC myelomeningocele; NA, not available.

Study 3 Junior E (2016)

Details

Study type	Systematic review and meta-analysis
Country	9 studies in USA, 4 in Brazil, 2 in Germany, 2 in Switzerland, 1 in Spain and 1 in Poland
Study period	Search period: 1997 to April 2015, Databases searched: PubMed and SCOPUS.
Study population and number	**n= 541 cases in 19 studies on intra-uterine repair of spina bifida** (1 RCT, 11 retrospective cohort studies, 1 retrospective case-control study and 6 case reports) **open fetal surgery (n=456 cases in 13 studies), endoscopic surgery (n=84 cases in 5 studies), combined technique (n=1 in 1 study)**
Age and sex	Mean gestational age at surgery – endoscopic: 24.2 weeks, open: 23.9 weeks Mean gestational age at delivery – endoscopic: 32.0 weeks, open: 34.2 weeks Maternal age and sex of the babies were not reported.
Study selection criteria	Randomised controlled trials and observational studies evaluating endoscopic and/or open fetal surgery techniques for spina bifida, in all languages were included. For meta-analysis, only studies with ≥10 cases that were published in or after 2010 were included. Studies published before 1997, multiple publications and overlapping cases were excluded.
Technique	**Intra-uterine repair: endoscopic(fetoscopic) and open surgery.** **Endoscopic surgery**: 2 studies from USA used carbon dioxide insufflation pressure of 12.0 to 12.5 mmHg and 2 studies from Germany used 14.1 to 15.6 mmHg pressure. **Open surgery**: most of the studies used a method of closing hysterotomy in 2 layers but some studies reported using an inner running sutures and multiple interrupted outer sutures. For the 2 layers method, one study from USA reported using amnio-patch in 4 cases, and a study from Spain reported using collagen. One study from USA closed hysterotomy with closely placed full-thickness running locked sutures supplemented with figure-of-eight interrupted sutures.
Follow-up	**Intra and post-operative**
Conflict of interest/source of funding	The main author received a grant from the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and a postdoctoral fellowship from the Department of Obstetrics and Fetal Therapy, Leiden University Medical Centre, The Netherlands.

Analysis

Follow-up issues: only intra and post-operative period outcomes were assessed. Short term and long-term outcomes were not assessed.

Study design issues: Systematic review was registered with the prospective register of systematic reviews (PROSPERO). comprehensive search strategy was used, data extraction was done in a standardised manner. Authors contacted the study authors for missing data. Two authors assessed the risk of bias of the observational studies using Newcastle-Ottawa Scale. The quality of evidence for the main outcomes was evaluated after the GRADE Working group recommendation. The primary outcomes assessed were complete dehiscence, focal dehiscence and/or markedly this hysterotomy scar, preterm delivery and mean gestational age at delivery. The secondary outcomes were oligohydramnios, premature rupture of membranes, placental abruption, chorioamnionitis and perinatal death.

For summary measures, the pooled proportions of the evaluated outcomes (with 95% CI) were reported by separating studies according to types of surgery (open versus endoscopic). Meta-analysis was conducted using MEdCalc version 12.7, using random effects model. Heterogeneity was assessed among studies by the I^2 statistic.

Study population issues: There was a significant difference in sample sizes between the 2 comparison groups (456 open surgeries, 84 endoscopic surgeries).

Other issues: only one RCT comparing prenatal open surgery with postnatal open surgery was included in the meta-analysis. Other studies included were of low quality and inconsistent due to high heterogeneity among studies. There is an overlap of patients between the studies[1-5].

Key efficacy and safety findings

Efficacy

Number of patients analysed: **342 (77 Endoscopic versus 265 Open surgery) in meta-analysis**

(The single case of combined open and endoscopic surgery was part of endoscopic surgery group in the meta-analysis).

Duration of surgery

	Minutes (mean ±SD)
Open surgery (n=224)	113.3±32.1
Endoscopic surgery (n=77)	267.4 ±38.2

Safety

Procedure related complications

Uterine dehiscence rate

(includes complete dehiscence, focal dehiscence and/or markedly thin hysterotomy scar after surgery).

Type of surgery	**n**	**Total proportion (%) random effects**	**95% CI**	**P value, I^2**
Endoscopic surgery (3 studies)	77	0.85	0.03-4.02	P=0.84 I^2=0%
Open surgery (4 studies)	265	25.07	12.49-41.71	P<0.0001 I^2=87%

Rate of preterm Delivery (defined as delivery at <34 weeks of gestational age).

Type of surgery	**n**	**Total proportion (%) random effects**	**95% CI**	**P value, I^2**
Endoscopic surgery (3 studies)	77	79.86	41.33-99.66	P<0.0001 I^2=90.4%
Open surgery (4 studies)	265	45.34	38.01-52.77	P=0.21 I^2=32.6%

Rate of oligohydramnios

Type of surgery	**n**	**Total proportion (%) random effects**	**95% CI**	**P value, I^2**
Endoscopic surgery (3 studies	77	27.66	18.24-38.80	P=0.0001 I^2=88.9%
Open surgery (4 studies)	265	14.31	6.55-24.43	P=0.0042 I^2=77.3%

Rate of premature rupture of membranes (PROM)

Type of surgery	**n**	**Total proportion (%) random effects**	**95% CI**	**P value, I^2**
Endoscopic surgery (3 studies)	77	66.62	11.95-99.98	P<0.0001 I^2=95.6%
Open surgery (4 studies)	265	37.75	25.94-50.34	P=0.005 I^2=76.6%

Rate of placental abruption

Type of surgery	n	Total proportion (%) random effects	95% CI	P value, I^2
Endoscopic surgery	77	2.20	0.01-9.17	P=0.187 I^2=40.35%
Open surgery	265	3.19	0.49-8.13	P=0.02 I^2=68%

Rate of chorioamnionitis

Type of surgery	n	Total proportion (%) random effects	95% CI	P value, I^2
Endoscopic surgery (3 studies)	77	5.69	1.72-11.79	P=0.37 I^2=0%
Open surgery (4 studies)	265	3.37	1.55-5.85	P=0.44 I^2=0%

1 case of chorioamnionitis occurred in the combined endoscopic and open surgery.

Rate of perinatal death

Type of surgery	n	Total proportion (%) random effects	95% CI	P value, I^2
Endoscopic surgery (3 studies)	77	14.42	1.33-37.93	P=0.008 I^2=78.8%
Open surgery (4 studies)	265	5.08	2.78-8.01	P=0.76 I^2=0%

1 case of combined open and endoscopic surgery ended in perinatal death.

Abbreviations used: CI, confidence interval; SD, standard deviation.

Study 4 Ewing DC (2019)

Details

Study type	Case report
Country	USA
Recruitment period	Not reported
Study population and number	n=**1 case of in utero fetoscopic myelomeningocele (myeloschisis) repair**
Age and sex	28-year old mother, male infant born
Patient selection criteria	Prenatal course complicated by Chiari II malformation, myelomeningocele and ventriculomegaly status
Technique	Fetoscopic repair of myelomeningocele done at 24 weeks gestation. Due to the size of the skin defect and concern about tissue tension upon primary closure, fasciocutaneous advancement flaps were made by lateral relaxing incisions in the flanks to achieve a water-tight closure. Relaxing incisions (donor sites) were left to heal secondarily.
Follow-up	**8 days**
Conflict of interest/source of funding	Authors report no conflicts of interest.

Key efficacy and safety findings

Safety
Number of patients analysed: **1** **Iatrogenic flank hernia after fetoscopic myelomeningocele repair** Mother had an uncomplicated spontaneous vaginal delivery at 39 weeks gestation. Upon delivery a right flank hernia (with exposed retroperitoneal contents) through the relaxing incision in addition to delayed healing of the left relaxing incision were noted in the neonate. Both skin defects were repaired in layers with wide subcutaneous undermining and retroperitoneal domain was re-established with imbrication of the overlying muscle on the right side. During post-operative course the neonate was neurologically intact with preserved motor function in the lower extremities and patellar and ankle reflexes. Ventriculomegaly was also noted to be stable. The patient was discharged after 8 days.
Abbreviations used:

Validity and generalisability of the studies

- Two types of prenatal repair (fetoscopic and open techniques) were reported in many observational studies (with large to small cohorts and varied follow-up periods). There are no RCTs comparing open fetal surgery with endoscopic fetal surgery.
- There were 3 systematic reviews done (with mainly observational studies) to assess the obstetrical outcomes, neonatal outcomes and complication rates after prenatal repair (by fetoscopic surgery and by open fetal surgery).[3 to 5]
- These 2 techniques evolved over time, reported some heterogeneity in clinical practice in different countries and variation in outcomes. Studies also reported that in some cases with large defects, different materials have been used for closure of the defect.
- There is limited data on long-term outcomes.

Existing assessments of this procedure

The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine recommend that

- Active research is ongoing into minimally invasive Fetoscopic approaches to myelomeningocele repair. **Fetoscopic fetal myelomeningocele repair** cannot be recommended outside of an institutional board approved investigational setting at a centre with an appropriate level of expertise, resources and research oversight.[5]

- The Society of Obstetricians and Gynaecologists of Canada clinical practice guideline (2014) recommends that 'following the detection of an isolated open/closed neural tube defect, families should be offered a choice of 3 obstetrical care management options after diagnostic and genetic testing results are available as part of informed consent process. Options should include information about *prenatal* myelomeningocele repair and prognosis (if there are no maternal or fetal contraindications for prenatal repair at 20–26 weeks' gestation), *postnatal* myelomeningocele surgical repair and prognosis, and *pregnancy termination* with autopsy.[6]

Related NICE guidance

There is currently no NICE guidance related to this procedure.

Additional information considered by IPAC

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to

represent the view of the society. The advice provided by Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Four Specialist Adviser Questionnaires for fetoscopic prenatal repair of open neural tube defects in the fetus were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme will seek patient organisation submissions instead of patient commentary as the procedure was done only in very few cases.

Company engagement

There is no specific device used for this procedure other than those normally used in surgical procedures. If there is insufficient dura or skin to complete the closure, then a patch substitute (single layer dermal regeneration template) is used for repair. These products are not CE marked for use in this procedure/indication. They are mainly considered as off label use. Therefore, no structured information requests were sent to companies.

Issues for consideration by IPAC

- Ongoing studies
  - NCT02390895: Prenatal Endoscopic Repair of Fetal Spina Bifida, single group assignment, 75 participants, recruiting. start date: May 2017, estimated completion date: March 2023.
  - NCT02230072: Fetoscopic Meningomyelocele Repair Study (fMMC), single group assignment, 64 participants, recruiting, start date: June 2014, estimated completion date: January 2021.
  - NCT03315637: Fetal Endoscopic Surgery for Spina Bifida, single group assignment, 50 participants, recruiting, start date: January 2015, estimated completion date: December 2024.
  - NCT03090633: Fetoscopic Repair of Isolated Fetal Spina Bifida, single group assignment, 10 participants, recruiting. Start date: May 2017, estimated completion date: April 2027.

References

1. Kabagambe SK, Jensen GW et al (2018). Fetal Surgery for Myelomeningocele: A Systematic Review and Meta-Analysis of Outcomes in Fetoscopic versus Open Repair. Fetal Diagnosis & Therapy (43) 3 161-174.
2. Araujo Junior E, Tonni E, Gabriele and Martins, et al (2016). Outcomes of infants followed-up at least 12 months after fetal open and endoscopic surgery for meningomyelocele: a systematic review and meta-analysis. Journal of Evidence-based Medicine (9) 3 125-135.
3. Araujo Junior E, Eggink AJ, van den Dobbelsteen J et al (2016). Procedure-related complications of open vs endoscopic fetal surgery for treatment of spina bifida in an era of intrauterine myelomeningocele repair: systematic review and meta-analysis. Ultrasound in Obstetrics & Gynecology (48) 2 151-60.
4. Ewing DC, Dempsey R et al (2019). An unreported complication after fetoscopic myelomeningocele closure. The Journal of Craniofacial Surgery, 30 (2) 578-580.
5. American College of Obstetricians and Gynecologists. ACOG Committee opinion no. 720: maternal-fetal surgery for myelomeningocele. Obstet Gynecol. 2017; https://www.acog.org/-/media/Committee-Opinions/Committee-on-Obstetric-Practice/co720.pdf?dmc=1&ts=20190624T1048186597
6. Wilson RD, Wilson RD, Audibert F, et al (2014). SOGC Genetics Committee, Special Contributors, Society of Obstetricians and Gynaecologists of Canada. Prenatal screening, diagnosis, and pregnancy management of fetal neural tube defects. J Obstet Gynaecol Can; 36(10): 927–942.

Additional relevant papers

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Alatas I, Canaz H et al (2015). Percutaneous minimally invasive fetoscopic surgery for spina bifida Aperta: First cases of Turkey. Child's Nervous System (31) 10 1905.	Case series N=2 fetuses with L5 and L4 lesions Percutaneous minimally invasive fetoscopic approach done at 25+2 and 25+4 weeks of gestation. Fetuses were delivered respectively at 31+1 and 31+3 weeks of gestation Follow-up: short term	Neural cords were covered although in small areas skin closure was incomplete but occurred within 4 to 6 weeks. Both neonates showed reversal of hindbrain herniation, near-normal leg function, and satisfactory bladder and bowel function. Ventriculoperitoneal shunt insertion was not required.	Larger studies included in table 2.
Alatas I, Canaz H and Ozel K (2016). First year neurologic outcome after fetal surgery. Child's Nervous System (32) 10 1958.	Case series N=4 patients who had percutaneous fetoscopic patch closure for myelomeningocele. Follow-up: 1 year	Shunting was not needed. Overactive detrussor and detrussor sphincter dyssynergia occurred in all patients but clean transient catheterisation was needed in only 1 patient. In 1 patient, clonus occurred at 6 months and tethered cord releasing operation was performed.	Larger studies included in table 2.
Antiel RM, Collura CA et al (2017). Physician views regarding the benefits and burdens of prenatal surgery for myelomeningocele. Journal of Perinatology (37) 9 994-998.	Survey of 1,200 specialists.	57% responded, most disagreed that open fetal surgery places an unacceptable burden on women and their families. Most agreed that denying the benefits of open maternal-fetal surgery is unfair to the future child. Most (94%) would recommend prenatal fetoscopic over open or postnatal closure for a hypothetical fetoscopic technique that had similar shunt rates (40%) but decreased maternal morbidity.	Physicians views
Antiel RM, Adzick NS et al (2016). Impact on family and parental stress of prenatal vs postnatal repair of myelomeningocele. American journal of obstetrics and gynaecology (215) 4 522.e1-522.e6.	MOMS study RCT N=183 women randomised (91 prenatal versus 92 postnatal surgery group) 171 women completed the Impact on Family Scale and 172 completed the Parenting Stress Index at both 12 and 30 months.	The prenatal surgery group had significantly lower revised 15-item Impact on Family Scale scores as well as familial-social impact subscale scores compared with the postnatal surgery group (P =.02 and 0.004, respectively). There was no difference in total parental stress between the 2 groups (P = .89) or in any of the Parenting Stress Index Short Form subscales. The overall negative family impact of caring for a child with spina bifida, up to 30 months of age, was significantly lower in the prenatal surgery group compared with the postnatal surgery group. Ambulation status and family resources were predictive of impact on family and parental stress.	Impact on family and parental stress
Antiel RM, Flake AW et al (2017). Specialty-Based Variation in Applying Maternal-Fetal Surgery Trial Evidence. Fetal Diagnosis &	Survey of 1,200 specialists.	57% responded. Compared with postnatal closure, 33% viewed prenatal closure as "very favorable" and 60% as "somewhat favorable." Most physicians reported being more likely to recommend prenatal surgery (69%), while 28% were less likely to recommend pregnancy termination. The vast majority of pediatric	Physician views

Therapy (42) 3 210-217.		subspecialists view prenatal closure favorably. These attitudes vary by specialty and risk tolerance.	
Antiel RM, Janvier A et al (2018). The experience of parents with children with myelomeningocele who underwent prenatal surgery. Journal of Pediatric Rehabilitation Medicine (11) 4 217-225.	Mixed methods study 109 parents of children with myelomeningocele (MMC) completed questionnaires	Parents were well informed, after a diagnosis, most learned about options from obstetrician, although one-third were not told about the option of prenatal surgery. About one-fourth of these parents felt pressure to undergo one particular option. Half of parents said that having a child with MMC has had a positive impact on them and their family, while the other half indicated that having a child with MMC has had both positive and negative impacts. The most commonly noted positive impacts were changes in parental attitudes, as well as having new opportunities and relationships. The most frequently reported negative impacts concerned relational and financial strain. The vast majority of parents indicated that they would still undergo prenatal surgery.	Parents perceptions regarding provider communication, treatment choices, and the family impact of having a child with MMC.
Belfort MA, Whitehead WE, et al (2015). Fetoscopic Repair of Meningomyelocele. Obstetrics & Gynecology (126) 4 881-4 Oct.	Case report N=1 patient with a fetus with a L3-S1 meningomyelocele underwent a laparotomy and fetoscopic repair using a two-port, in-CO_2 approach at 23 weeks of gestation. Carbon dioxide insufflation pressure 12mmHg.	The neonate was delivered at 30 weeks of gestation by lower segment caesarean delivery and required no further surgery, has not needed a shunt (5 months), and has normal, age-appropriate neurologic function.	Larger studies included in table 2.
Belfort MA, Whitehead WE et al (2017). Fetoscopic open neural tube defect repair: Development and refinement of a two-port, carbon dioxide insufflation technique. Obstetrics and Gynecology (129) 4 734-743.	Retrospective cohort study N=28 patients with open spina bifida. Two-port fetoscopic repair in the exteriorised, carbon dioxide-filled uterus (15 iterative approach and 13 standardised approach). Follow up less than 1 year.	gestational age (24.8 weeks) was similar, but delivery occurred at 35.9 weeks of gestation with the iterative technique compared with 39 weeks of gestation with the standard technique (P<.01). Complication rates, preterm rupture of membranes rates, and vaginal delivery rates (were not statistically different between the techniques. there was leakage of cerebrospinal fluid from the repair site at birth In 6 of 12 (50%) compared with 1 of 10 (10%), respectively (P=.07). Management of Myelomeningocele Study criteria for hydrocephalus-death at discharge were met in 9 of 12 (75%) and 3 of 10 (30%), respectively.	Included in systematic review added to table 2
Bennett KA, Carroll M A et al (2014). Reducing perinatal complications and preterm delivery for patients undergoing in utero closure of fetal myelomeningocele: further modifications to the multidisciplinary surgical technique. Journal of Neurosurgery. Pediatrics. (14) 1 108-14.	Case series N=43 patients who had in utero myelomeningocele closure compared with data for 78 patients who had undergone fetal repair as part of MOMS (the MOMS cohort). For the study cohort, no uterine trocar was used, and uterine entry, manipulation, and closure were modified to minimise separation of the amniotic membrane.	The incidence of premature rupture of membranes (22% vs 46%, p = 0.011) and chorioamnion separation (0% vs 26%, p < 0.001) were lower for the study cohort than for the MOMS cohort. Incidence of oligohydramnios did not differ between the cohorts. The mean (+/- SD) gestational age of 34.4 (+/- 6.6) weeks for the study cohort was similar to that for the MOMS cohort (34.1 +/- 3.1 weeks). However, the proportion of infants born at term (37 weeks or greater) was significantly higher for the study cohort (16 of 41; 39%) than for the MOMS cohort (16 of 78; 21%) (p = 0.030). Compared with 10 (13%) of 78 patients in the MOMS cohort, only 2 (4%) of 41 infants in the study cohort were delivered earlier than 30 weeks of gestation (p = 0.084, approaching	Included in systematic review added to table 2

		significance). For the study cohort, 2 fetal deaths were attributed to the intervention, and both were believed to be associated with placental disruption; one of these mothers had previously unidentified thrombophilia. Mortality rates did not statistically differ between the cohorts.	
Bruner JP, Tulipan NB et al (2000). In utero repair of myelomeningocele: a comparison of endoscopy and hysterotomy. Fetal Diagnosis & Therapy (15) 2 83-8.	Retrospective comparative case series N=4 fetuses with isolated myelomeningocele had endoscopic coverage of the defect with a maternal split-thickness skin graft at 22-24 weeks' gestation T12 - S5 versus 4 fetuses with myelomeningocele had standard neurosurgical closure at 28-29 weeks' gestation.	The mean operating time for endoscopic procedures was 297 +/- 69 min. Two fetal losses occurred as a result of chorioamnionitis and placental abruption, respectively. A third baby delivered at 28 weeks' gestation after prolonged disruption of the membranes. The 2 survivors required standard closure of the myelomeningocele after delivery. The mean operating time for the hysterotomy procedures was 125 +/- 8 min. No mortality occurred, and all the infants delivered between 33 and 36 weeks with well-healed myelomeningocele scars. The functional levels of all infants approximate the anatomical levels of the lesions. In utero repair through a hysterotomy appears to be technically superior to procedures performed endoscopically.	Larger studies included in table 2.
Bruner JP, Boehm, FH and Tulipan, N (1999). The Tulipan-Bruner trocar for uterine entry during fetal surgery. American journal of obstetrics and gynecology (181) 5 Pt 1 1188-1191.	Case series N=10 patients undergoing hysterotomy for intrauterine repair of myelomeningocele were randomised to initial uterine entry with electrocautery or with the Tulipan-Bruner trocar.	The time required for initial uterine entry with electrocautery was 231 +/- 63 seconds compared with 146 +/- 51 seconds with the trocar (P <.05). The total blood loss for all 10 cases was <50 mL, but the presence of blood in the wound was judged much more inconvenient when electrocautery was used. Electrocautery required 2 surgical assistants, whereas the trocar was readily placed with only a single assistant. The Tulipan-Bruner trocar provides quicker, less traumatic uterine entry during creation of a hysterotomy, as compared with electrocautery.	More comprehensive studies added to table 2.
Canaz H, Alatas I et al (2018). Comparison of percutaneous minimally invasive fetoscopic surgery and open fetal surgery: Single center experience. Child's Nervous System (34) 5 1034.	Comparative case series N=4 fetosopic surgery cases versus 3 open fetal surgery cases.	Although short term results are similar in both techniques, there are some differences in surgical management, anesthesiology, postoperative and postnatal care.	Larger studies added to table 2.
Degenhardt, J., Schurg, R et al (2014). Percutaneous minimal-access fetoscopic surgery for spina bifida aperta. Part II: maternal management and outcome. Ultrasound in Obstetrics & Gynecology (44) 5 525-31.	Retrospective study N=51 women undergoing minimal-access fetoscopic surgery for spina bifida aperta (T1-S1), at a mean gestational age of 24 weeks. Carbon dioxide insufflation pressure 15.6mmHg. Follow-up: less than 1 year.	Chorioamniotic membrane separation occurred in one patient, mild pulmonary edema occurred in one and oligohydramnios occurred in 7. All fetuses survived surgery, but there was one very early preterm delivery 1 week after the procedure and this neonate died immediately, from early postoperative chorioamnionitis. Amniotic fluid leakage occurred in 43 patients, at a mean gestational age of 29.7 weeks; 2 of these patients developed chorioamnionitis. Duration of maternal hospitalisation after surgery was 7.2 days. Mean gestational age at delivery was 33 weeks. All abdominal and uterine trocar insertion sites healed well.	Included in systematic review added to table 2.
Danzer E, Johnson MP et al (2007). Fetal head biometry assessed by	Retrospective comparative study	Mid-gestational repair of MMC promotes normalisation of extra-axial cerebrospinal fluid (CSF) spaces. Due to progressive	Impact on fetal head biometry

fetal magnetic resonance imaging following in utero myelomeningocele repair. Fetal Diagnosis & Therapy (22) 1 1-6.	N=22 myelomeningocele (MMC) fetuses with prenatal repair were compared with the pre- and postnatal measurements of patients who had MMC repair after birth (n = 16) and a cohort of age-matched control patients (prenatal, n = 52; postnatal, n = 9).	ventriculomegaly, brain thickness remains decreased in both prenatal repaired and age-matched non-repaired MMC patients when compared with age-matched normal values. Restoration of CSF volume in the posterior fossa after in utero repair is indicative of reversal of hindbrain herniation.	and CSF spaces.
Danzer E, Adzick, NS et al (2008). Intradural inclusion cysts following in utero closure of myelomeningocele: clinical implications and follow-up findings. Journal of Neurosurgery. Pediatrics. (2) 6 406-13.	Retrospective analysis N=54 patients who had fetoscopic myelomeningocele (MMC) closure Median follow-up of 36 months (range 12-63 months)	Cutaneously derived intradural inclusion cysts (ICs) can develop following fetoscopic MMC surgery. Deterioration of bladder function, risk of recurrence, and loss of lower-extremity function appear to be the most important long-term complications of IC in children with fetoscopic MMCs. The ongoing NIH-sponsored MOMS may help determine whether children with fetoscopic MMC are at increased risk of IC development compared with children treated with postnatal MMC closure. Parents seeking fetoscopic MMC closure should be informed about the possibility of IC formation and the potential clinical consequences.	Fetoscopic MMC and intradural inclusion cysts
Danzer E, Ernst LM et al (2009). In utero meconium passage in fetuses and newborns with myelomeningocele. Journal of Neurosurgery. Pediatrics. (3) 2 141-6.	Case series 54 fetuses had fetoscopic MMC repair 46 sacs were pathologically examined and compared with 53 MMC sacs from postnatally repair.	Compared with postnatal MMCs (79%), meconium histiocytosis was less prevalent in fetoscopic MMC sacs (57%; p=0.017). Meconium staining was completely absent in 43% of the fetoscopic MMC sacs. Mild meconium histiocytosis was found in 35% fetoscopic MMC and 61% postnatal MMC sacs (p=0.035). There was no statistical difference between groups with moderate and severe meconium histiocytosis.	Intrauterine meconium exposure
Danzer E, Thomas NH et al (2016). Long-term neurofunctional outcome, executive functioning, and behavioral adaptive skills following fetal myelomeningocele surgery. American Journal of Obstetrics & Gynecology (214) 2 269.e1-269.e8.	Retrospective case series N=54 patients underwent open fetoscopic MMC surgery Median follow-up 10 years.	33 (79%) are community ambulators, 3 (9%) are household ambulators, and 6 (14%) are wheelchair dependent. Preschool ambulation was predictive of long-term ambulation (P < .01), whereas the need for tethered cord surgery was associated with persistent deterioration of ambulatory status (P = .007). Normal bladder function was found in 26%. Although the majority scored within the average range for the Behavioral Regulation Index, Metacognition Index, and Global Executive Composite indices, significantly more children who had fMMC surgery had deficits in EF in all 3 BRIEF indices compared with the population norms. The general adaptive composite scores were also more likely to fall below average following fMMC surgery. Normal early neurodevelopmental outcomes were predictive of normal EF and BAS (P < .01). Need for shunting was associated with a significant impairment of BAS 26/54 (P = .02).	Included in systematic review added to table 2.
Danzer E, Finkel R et al (2010).The relationship of seizure activity and chronic epilepsy in early infancy and short-term	Retrospective review N=54 children had fetoscopic MMC repair	The incidence of seizures in fetoscopic MMC children was similar to previously reported data of postnatally repaired MMC patients. Seizure activity alone without chronic epilepsy was not associated with a worse neurocognitive	Outcomes already reported in table 2.

neurodevelopmental outcome following fetal myelomeningocele closure. Neuropediatrics (41) 3 140-3.	databases and a parental questionnaire used.	outcome. The occurrence of severe acquired intracranial injury and chronic epilepsy, however, appeared to be correlated with adverse neurocognitive outcome following fetoscopic MMC surgery.	
Danzer E, Gerdes M et al (2010). Preschool neurodevelopmental outcome of children following fetal myelomeningocele closure. American Journal of Obstetrics & Gynecology (202) 5 450.e1-9.	Retrospective case series N=54 children underwent Fetoscopic MMC (fMMC) closure. 30 (56%) returned at 5 years of age for standardised neurocognitive examination.	Mean verbal intelligence quotient (VIQ), performance intelligence quotient (PIQ), and full intelligence quotient (FIQ) scores were within normal population range. High-average or average scores for VIQ, PIQ, FIQ, and processing speed were found in 93%, 90%, 90%, and 60%, respectively. Mean FIQ and processing speed of nonshunted children were significantly higher than for those who required shunt placement (P=.02 and P=.01, respectively). Mean VIQ and PIQ tended to be higher in nonshunted fMMC children (P=.05). The majority of fMMC children in this highly selective population had average preschool neurodevelopmental scores. fMMC children who did not require shunt placement were more likely to have better scores.	Included in systematic review.
Elbabaa, SK, Gildehaus, AM et al (2017). 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 Nervous System (33) 7 1157-1168.	Case series retrospective N=60 fetal MMC inutero repairs at 20- 26 weeks using standard hysterotomy method	30 infants and toddlers underwent treatment of hydrocephalus (25 ETV and VPS groups). 25 patients underwent ETV (24 primary ETV and 1 after shunt failure). Nineteen patients underwent shunt placements (6 primary/13 after ETV failure). Mean GA at time of MMC repair for the ETV group was 24 + 6/7 weeks (range 22 + 4/7 to 25 + 6/7). Mean follow-up for patients who had a successful ETV was 17.25 months (range 4-57 months). Bayley neurodevelopmental testing results were examined pre- and post-ETV. Overall ETV success rate was 11/24 (45.8%) at the time of this study. The total number of patients who underwent shunt placement was 19/55 (34.5%), while shunting rate was 40% in the MOMS trial. young age (less than 6 months) and late GA at time of fetal MMC repair (after 23 weeks GA) were predictors for ETV failure, while in-utero stability of ventricular size (less than 4 mm) and in-utero ventricular size post-repair <=15.5 mm were predictors for ETV success.	Hydrocephalus treatment outcomes
Graf K, Kohl T et al (2016). Percutaneous minimally invasive fetoscopic surgery for spina bifida aperta. Part III: neurosurgical intervention in the first postnatal year. Ultrasound in Obstetrics & Gynecology (47) 2 158-61.	Retrospective cohort study. N=71 fetuses which underwent minimally invasive fetoscopic patch coverage of SBA between 21 + 0 and 29 + 1 weeks of gestation. Postnatal neurosurgical procedures were classified into 2 types: re-coverage of the SBA within the first 3 months following birth, and shunt placement as treatment of associated	20/71 (28%) patients underwent early postnatal neurosurgical intervention by means of re-coverage of the SBA. This was performed because of cerebrospinal fluid leakage in 7 (35%), adhesions with functional deterioration in 3 (15%), incomplete coverage in 5 (25%) and skin defect in 5 (25%) cases. Ventriculoperitoneal shunt placement within 1 year was required in 32 (45%) cases and was preceded by ventriculostomy in 2. Three (4%) infants needed Chiari decompression surgery in the first 12 months following birth, because of syringomyelia or gait disturbance. Fetoscopic patch coverage of SBA may require postnatal re-coverage in some cases. In most cases, conservative wound treatment shows good results, without requiring neurosurgical intervention. The low 1-year-shunt rate is	Included in systematic review added to table 2.

	hydrocephalus within the first year. Follow-up: 1 year	comparable to data of the Management of Myelomeningocele Study and lower compared with published data of patients with postnatal only coverage of SBA.	
Grant RA, Heuer GG et al (2011). Morphometric analysis of posterior fossa after in utero myelomeningocele repair. Journal of Neurosurgery. Pediatrics. (7) 4 362-8.	Retrospective analysis N=29 patients who had in utero MMC repair, 24 who had postnatal MMC repair and 1114 fetal and paediatric controls without defects.	Myelomeningocele was associated with tonsillar herniation and a smaller PF than in control fetuses. Antenatal surgical repair corrected both abnormalities. The CSO angle began significantly more acutely in patients with MMC, but normalised with development regardless of when surgery was performed. Determining the clinical effects of antenatal repair requires further follow-up.	Morphometric changes in posterior fossa.
Grivell, RM, Andersen C and Dodd JM (2014). Prenatal versus postnatal repair procedures for spina bifida for improving infant and maternal outcomes. Cochrane Database of Systematic Reviews 10 CD008825 Oct 28.	Cochrane review Randomised controlled trials comparing prenatal and postnatal repair of meningomyelocele for fetuses with spina bifida and different types of prenatal repair.	Included 1 trial Adzick 2011 (4 reports) involving 158 women, examined the effect of prenatal repair versus postnatal repair. This review is based one small well-conducted study. There is insufficient evidence to recommend drawing firm conclusions on the benefits or harms of prenatal repair as an intervention for fetuses with spina bifida. Current evidence is limited by the small number of pregnancies that have been included in the single conducted randomised trial to date.	More comprehensive systematic reviews included in table 2.
Gine C, Arevalo S et al (2018). Fetoscopic two-layer closure of open neural tube defects. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology (52) 4 452-457 2018.	Case series N=5 pregnant women with a fetus with a NTD, including 3 cases of myelomeningocele and 2 cases of myelocele, were operated on using a fetoscopic two-layer closure technique.	Surgery was successful in all cases, without any intraoperative complications. In terms of obstetric complications, 3 cases of premature rupture of membranes and one case of chorioamnionitis were recorded. Fetoscopic two-layer closure of NTD may improve the quality of the tissue covering the defect, diminishing the need for postnatal surgical revision, and preserving the well-documented beneficial effects of prenatal closure on the neural tissue and hindbrain herniation. However, this technique may not be appropriate for those cases with wide diastasis of the myofascial layer or with a low quantity of available tissue.	Minor modification.
Hamdan AH, Walsh W et al (2002). Gestational age at intrauterine myelomeningocele repair does not influence the risk of prematurity. Fetal Diagnosis & Therapy (17) 2 66-8.	Retrospective case series N=95 infants who had intrauterine MMC repair. (group 1 n=51, >/=25 weeks gestation age, group 2 n=44, <25 weeks).	Group 1 median gestational age at delivery was 34.4 weeks (range 32.6-35.3). Group 2 the median gestational age at delivery was 34 weeks (range 31.6-35.3; p = 0.88). Early intrauterine myelomeningocele repair before 25 week's gestation does not decrease the gestational age at delivery when compared with repair after 25 weeks.	Effect of gestational age during repair on duration of pregnancy.
Hamdan AH, Walsh W et al (2004). Intrauterine myelomeningocele repair: effect on short-term complications of prematurity. Fetal Diagnosis & Therapy (19) 1 83-6.	Retrospective study N=100 infants who had intrauterine MMC repair. 44 infants were born <34 weeks gestation. 74 matched controls were studied.	11 infants from the IUMR group and 23 infants from the control group developed respiratory distress syndrome (29.7 vs. 31.1%; p = 0.8). Six infants from the IUMR group and 13 infants from the control group developed chronic lung disease (16.2 vs. 17.5%; p = 0.9). The length of stay was 28 (range 2-82) days for the IUMR group and 24 (range 1-99) days (p = 0.09) for the control group. There was also no significant difference between groups with regard to intraventricular haemorrhage and days on ventilators. There is no difference between short-term complications of prematurity	Prematurity following prenatal MMC repair - outcomes already reported in table 2.

		following IUMR and those associated with prematurity resulting from other causes.	
Holmes NM, Nguyen HT et al (2001). Fetal intervention for myelomeningocele: effect on postnatal bladder function. Journal of Urology (166) 6 2383-6.	Case series (retrospective review) N=6 had prenatal surgical repair of myelomeningocele before 24 weeks gestation.	Patients treated in utero appear to have the same changes in urodynamic parameters and anatomical abnormalities in the urinary tract as other children with spinal defects who have undergone standard postnatal care. The long-term effects on bladder function in the fetus after in utero repair of myelomeningocele remain unknown.	Larger studies included in table 2.
Horst M, Mazzone L et al (2017). Prenatal myelomeningocele repair: Do bladders better? Neurourology & Urodynamics (36) 6 1651-1658.	Case series (prospective) 8 patients who had prenatal MMC closure with a postnatal follow-up of 2 years compared with 8 patients after postnatal MMC repair.	The level of the bony spinal defect was similar in both groups. Urological evaluation at 2 years revealed normal bladder function in 50% after prenatal repair. Neurogenic bladder dysfunction requiring CIC and anticholinergic therapy was seen in 50% in the prenatal and in 100% in the postnatal group. Significant bladder wall thickening was found in 37.5% and 87.5%, respectively. Febrile UTIs occurred in 37.5% in the prenatal and 62.5% in the postnatal group during the observation period. Our data suggest a positive effect of prenatal MMC closure on lower urinary tract function.	Larger studies included in table 2.
Huang GO, Belfort MA et al (2017). Early postnatal bladder function in fetoscopic myelomeningocele repair patients. Journal of Pediatric Rehabilitation Medicine (10) 3-4 327-333.	Case series N=14 urologic assessment of patients undergoing fetoscopic MMC repair	No patients had hydronephrosis or bladder thickening. Detrusor overactivity was observed in 9 (64.3%) patients. Impaired compliance was seen in 8 (57.1%) patients. No patients had a detrusor leak point pressure of > 40 cm H2O or evidence of detrusor sphincter dyssynergia. 3 (21.4%) patients had vesicoureteral reflux, 7 (50.0%) had an open bladder neck, and none had trabeculated bladders.	Larger studies included in table 2.
Joyeux L, Engels AC et al (2016). Fetoscopic versus Open Repair for Spina Bifida Aperta: A Systematic Review of Outcomes. Fetal Diagnosis & Therapy (39) 3 161-71.	Systematic review on fetoscopic spina bifida aperta repair (FSBAR) with the results of the open approach (OSBAR) as in the Management Of Myelomeningocele Study (MOMS) (n=78)). Inclusion criteria were studies of spina bifida aperta patients who underwent FSBAR and were followed for >=12 months. 5 studies included.	Statistical analysis was on 2 overlapping case series (n = 51 and 71). In those, FSBAR was technically different from OSBAR, had comparable perinatal mortality (7.8 vs. 2.6%, p = 0.212) and shunt rate at 12 months (45 vs. 40%, p = 0.619), longer operation time (223 vs. 105 min, p < 0.001), higher preterm prelabor membrane rupture rate (84 vs. 46%, p < 0.001), earlier gestational age at birth (32.9 vs. 34.1 weeks, p = 0.03), higher postnatal reoperation rate (28 vs. 2.56%, p < 0.001) and absence of uterine thinning or dehiscence (0 vs. 36%, p < 0.001). Functional outcomes were not available. FSBAR utilises a different neurosurgical technique, takes longer to complete, induces more prematurity, requires additional postnatal procedures, yet has a comparable shunt rate and is not associated with uterine thinning or dehiscence. Long-term functional data are awaited.	More comprehensive systematic reviews included in table 2.
Johnson, MP, Bennett, KA, et al (2016).The Management of Myelomeningocele Study: obstetrical outcomes and risk factors for obstetrical complications following prenatal surgery. American journal of obstetrics and	Retrospective case series 183 randomised (91 to prenatal and 92 to postnatal surgery) Pregnancy outcomes were compared between the 2 surgery groups	prenatal surgery was associated with an increased risk for membrane separation, oligohydramnios, spontaneous membrane rupture, spontaneous onset of labor, and earlier gestational age at birth. In multivariable logistic regression of the prenatal surgery group adjusting for clinical center, earlier gestational age at surgery and chorioamniotic membrane separation were associated with increased risk of spontaneous membrane rupture (odds ratio, 1.49; 95% confidence interval, 1.01-2.22; and	Overlapping data with MOMs trial (follow-up data of the MOMS study).

gynecology (215) 6 778.e1-778.e9.		odds ratio, 2.96, 95% confidence interval, 1.05-8.35, respectively). Oligohydramnios was associated with an increased risk of subsequent preterm delivery (odds ratio, 9.21; 95% confidence interval, 2.19-38.78). Nulliparity was a risk factor for nonintact hysterotomy (odds ratio, 3.68; 95% confidence interval, 1.35-10.05).	
Kohl, T (2014). Percutaneous minimally invasive fetoscopic surgery for spina bifida aperta. Part I: surgical technique and perioperative outcome. Ultrasound in Obstetrics & Gynecology (44) 5 515-24.	Case series N=51 human fetuses at 21.0-29.1 weeks of gestation had percutaneous fetoscopic closure of SBA.	Percutaneous minimal-access fetoscopic closure of SBA was performed with a high rate of technical success, regardless of placental or fetal position. All fetuses survived surgery, but there was 1 very early preterm delivery 1 week after the procedure and this neonate died immediately, from early postoperative chorioamnionitis. Of the 50 surviving fetuses, 44 (88%) were delivered at or beyond 30 weeks and 25 (50%) at or beyond 34 weeks of gestation. There was 1 neonatal death from an uinsuspected case of trisomy 13 and two infant deaths from Chiari-II malformation.	Patients overlap with those reported by Dangerhardt 2014 (included in systematic review added to table 2).
Kohl T, Hering R et al (2006). Percutaneous fetoscopic patch coverage of spina bifida aperta in the human - Early clinical experience and potential. Fetal Diagnosis and Therapy (21) 2 185-193.	Case series N=3 Percutaneous fetoscopic patch coverage of spina bifida aperta in 3 human fetuses between 23 + 4 and 25 + 3 weeks of gestation	Patch detached in the first case 3 weeks after the procedure, it covered the exposed neural tissue in the 2 other fetuses beyond their delivery. Two of the 3 children survived, but 1 unexpectedly died from a ventilation problem in its 3rd week of life. In 1 of the 2 survivors, ventriculoperitoneal shunt insertion was delayed	Larger studies included in table 2.
Kohl T, Tchatcheva, K et al (2010). Partial amniotic carbon dioxide insufflation (PACI) during minimally invasive fetoscopic surgery: early clinical experience in humans. Surgical Endoscopy (24) 2 432-44.	Case series N=37 fetoscopic procedures between 17 + 5 and 33 + 2 weeks of gestation Partial amniotic carbon dioxide insufflation (PACI) during fetoscopic surgery	PACI could successfully be instituted in 36 of the 37 procedures. In one case, when in the presence of increased uterine tone the opening pressure exceeded the maximum insufflation pressure of the insufflator, the strategy was abandoned. In all cases where PACI could be instituted successfully, the approach offered far superior visualisation of the fetoscopic procedure than would have been possible within amniotic fluid. Acute or chronic maternal or fetal complications were observed in only one case (intraoperative membrane rupture). PACI greatly improves fetal visualisation during fetoscopic interventions when fetoscopy within fluid meets with difficulties. Continued assessment of its benefits, risks, and safety margins at specialist centers is required.	Patients overlap with those reported by Verbeek 2014 (included in systematic review added to table 2).
Kabagambe, SK., Chen, YJ. and Farmer, DL (2017). Fetal surgery for myelomeningocele: current clinical practice and translational research. Minerva Pediatrica (69) 1 59-65.	This review summarises the trends in fetoscopic and open fetal repair of MMC.	The fetoscopic approach to fetal MMC repair is a promising alternative to the open approach if preterm birth and persistent CSF leakage can be overcome.	Review
Kohn JR, Rao V et al (2018). Management of Labor and Delivery After Fetoscopic Repair of an Open Neural	Retrospective cohort study. patients with completed second-trimester fetoscopic neural tube	34 patients had fetoscopic repair, followed by 17 vaginal deliveries (50%, 95% CI 32-68%). Median gestational age was 38 1/7 weeks at vaginal delivery (range 26 0/7-40 2/7 weeks of gestation) and 37 1/7 weeks of gestation at	Larger studies included in table 2.

Tube Defect. Obstetrics & Gynecology (131) 6 1062-1068.	defect repair followed by standardised management of labor and delivery at our institution.	caesarean delivery (range 25 5/7-40 5/7 weeks of gestation); 62% of deliveries occurred at term. Eight patients had prelabor caesarean delivery: 3 nonurgent and 5 urgent (for nonreassuring fetal heart tracings). 26 patients labored;6 were induced and 20 labored spontaneously. Of the latter, 5 were augmented. Of 26 laboring patients, 17 delivered vaginally and 9 underwent urgent caesarean delivery (35%, 95% CI 17-56%; 7 nonreassuring fetal heart tracings and 2 breech). There were no cases of uterine rupture or dehiscence. Most (94%, 95% CI 80-99%) had normal 5-minute Apgar scores; one neonate (3%, 95% CI 0-15%) had acidosis but normal Apgar scores. data regarding trial of labor, use of low-dose oxytocin, and vaginal delivery after prenatal fetoscopic neural tube defect repair are reassuring.	
Macedo A, Jr, Leal M et al (2015). Urological evaluation of patients that had undergone in utero myelomeningocele closure: A prospective assessment at first presentation and early follow-up. Do their bladder benefit from it? Neurourology & Urodynamics (34) 5 461-4.	in utero myelomeningocele (MMC) closure at 25 weeks gestation age. n=19 patients follow-up=5.4 months	Birth occurred at a mean gestational age of 31.8 weeks 26-36. Hyperactive bladder was observed in 89.5% 17/19. Bladder compliance was normal in 2 cases (10.5%), was markedly reduced in 10 patients (52.6%) and not possible to be determined due to urinary leakage in 7 patients (36.8%). We observed normal bladder capacity in 8 patients (42.1%), reduced in 11 (57.9%), and detrusor-sphincter dyssynergia in 9 patients (47.4%). Underactive bladder was diagnosed in one case. Clean Intermittent Catheterisation was initiated by 11 patients (57.9%) mostly in association with anticholinergics 10/11. Vesicoureteral reflux was found in 5 patients (26.3%) and 9 had pyelonephritis at a mean follow-up of 5.4 months 2-17.	Urodynamic study.
Macedo, A., Ottoni, SL et al (2019). In utero myelomeningocoele repair and urological outcomes: the first 100 cases of a prospective analysis. Is there an improvement in bladder function? BJU International.	Case series N=100 in utero myelomeningocoele (MMC) repair Patients were categorised into 4 groups: normal, high risk (overactive bladder with a detrusor leak-point pressure >40 cm H2O and high filling pressures also >40 cm H2O), incontinent, and underactivity (underactive bladder with post-void residual urine). Follow-up mean 5.8 months	Patients classified as high risk in 52.6%, incontinent in 27.4%, with underactive bladder in 4.2%, and only 14.7% had a normal bladder profile. Clean intermittent catheterisation was initiated in 57.3% of the patients and anticholinergics in 52.6%. Antibiotic prophylaxis was initiated in 19.1% of the patients presenting with vesico-ureteric reflux.	Urodynamic evaluation
Manrique S, Maiz, N et al (2018). Maternal anaesthesia in open and fetoscopic surgery of fetal open spinal neural tube defects: A 6-year observational	Retrospective cohort study N=29 fetouses had myelomeningocele repair (7 open approach and 22 fetoscopic approach).	There were no significant differences in maternal doses of opioids or neuromuscular blocking agents. Open surgery was associated with higher dose of halogenated anaesthetic agents [maximum medium alveolar concentration (MAC) sevoflurane 1.90 vs. 1.50%, P = 0.01], higher need for intra-	Anaesthetic management

study. European Journal of Anaesthesiology (30).		operative tocolytic drugs [5 of 7 (71.4%) and two of 22 (9.1%) required nitroglycerine, P = 0.001], higher volume of colloids (500 vs. 300 ml, P = 0.036) and more postoperative tocolytic drugs (3 drugs in all 7 cases (100%) of open and in one of 21 (4.76%) of fetoscopic surgery, P < 0.001). Median mean arterial pressure was lower in open than in fetoscopic surgery. SBP, DBP and mean blood pressure decreased during uterine exposure, and this descent was more acute in open surgery. Use of vasoconstrictor drugs was related to the time of uterine exposure, but not to surgical technique. Blood gas analysis was not affected by CO2 insufflation during fetoscopic surgery. Open surgery was associated with more maternal haemodynamic changes and higher doses of halogenated anaesthetic and tocolytics agents than fetoscopic surgery.	
Pedreira, D, Zanon, N et al (2016). Endoscopic surgery for the antenatal treatment of myelomeningocele: the CECAM trial. American journal of obstetrics and gynecology (214) 1 111.e1-111.e11.	Case series prospective N=10 pregnancies with lumbosacral OSB Fetoscopic surgery done percutaneously under general anaesthesia with 3 ports and partial carbon dioxide insufflation. Biocellulose patch placed over the lesion. Follow-up 1 year.	The median gestational age at the time of surgery was 27 weeks (range 25-28 weeks). Endoscopic repair was completed in 8 of 10 fetuses. Two cases were unsuccessful due to loss of uterine access. The mean gestational age at birth was 32.4 weeks with a mean latency of 5.6 weeks between surgery and delivery (range 2-8 weeks). There was 1 fetal and 1 neonatal demise, and 1 unsuccessful case underwent postnatal repair. Of the 7 infants available for analysis, complete reversal of hindbrain herniation occurred in 6 of 7 babies. Three babies required ventriculoperitoneal shunting or third ventriculostomy. Functional motor level was the same or better than the anatomical level in 6 of 7 cases. There was no significant maternal morbidity and no evidence of myometrial thinning or dehiscence. However, surgeries were complicated by premature rupture of membrane and prematurity.	Included in systematic review added to table 2.
Pastuszka, A, Bohosiewicz, J et al (2018). Prenatal myelomeningocele repair improves urinary continence and reduces the risk of constipation. Neurourology & Urodynamics (37) 8 2792-2798.	Comparative case series n-72 patients with MMC (36 prenatal surgery versus 36 postnatal surgery).	Urodynamic and imaging studies showed no differences between the test groups. Children from the prenatally operated group showed statistically significant lower number of urinary tract infections, better urine continence, and less frequent constipation. Time of MMC repair does not statistically influence the urodynamic tests results and the urodynamic parameters are not the prognostic elements to assess the social urinary continence possibility in patients with the neurogenic bladder.	Similar studies included in systematic reviews
Lapa Pedreira, DA, Acacio, GL et al(2018). Percutaneous fetoscopic closure of large open spina bifida using a bilaminar skin substitute. Ultrasound in Obstetrics & Gynecology (52) 4 458-466.	Case series N=47 fetuses Fetoscopic surgical approach for MMC (modified technique using a bilaminar skin substitute or biocellulose patch to close large defects)	Preterm prelabor rupture of membranes (PPROM) occurred in 36 of the 45 (80%) cases. the mean gestational age at delivery was 32.8 +/- 2.5 weeks. A bilaminar skin substitute was required in 13/45 (29%) cases; in the remaining 32 cases, direct skin-to-skin suture was feasible. There were 12 cases of myeloschisis, of which 10 were in the two-patch group. 5 of the 13 (38.5%) cases in the two-patch group, additional postnatal repair was needed. In the remaining cases, the silicone layer detached spontaneously from the dermal	Modified technique

		matrix (on average, 25 days after birth), and the lesion healed by secondary intention. mean operating time was 193 (range, 83-450) min. Complete reversal of hindbrain herniation occurred in 68% of the 28 single-patch cases and 33% of the 12 two-patch cases (P < 0.05). In 4 cases there was no reversal; half of these occurred in myeloschisis cases.	
Tulipan, N, Wellons, JC, et al (2015). Prenatal surgery for myelomeningocele and the need for cerebrospinal fluid shunt placement. Journal of neurosurgery. Pediatrics (16) 6 613-620.	RCT N=183 91 women were randomised to prenatal surgery and 92 to postnatal repair. Follow up 1 year.	The primary outcome occurred in 73% of infants in the prenatal surgery group and in 98% in the postnatal group (p < 0.0001). Actual rates of shunt placement were only 44% and 84% in the 2 groups, respectively (p < 0.0001). The authors revised the most commonly met criterion to require overt clinical signs of increased intracranial pressure, defined as split sutures, bulging fontanelle, or sunsetting eyes, in addition to increasing head circumference or hydrocephalus. Using these modified criteria, only 3 patients in each group met criteria but did not receive a shunt. For the revised composite outcome, there was a difference between the prenatal and postnatal surgery groups: 49.5% versus 87.0% (p < 0.0001). There was also a significant reduction in the number of children who had a shunt placed and then required a revision by 1 year of age in the prenatal group (15.4% vs 40.2%, relative risk 0.38 [95% CI 0.22-0.66]). In the prenatal surgery group, 20% of those with ventricle size < 10 mm at initial screening, 45.2% with ventricle size of 10 up to 15 mm, and 79.0% with ventricle size ≥ 15 mm received a shunt, whereas in the postnatal group, 79.4%, 86.0%, and 87.5%, respectively, received a shunt (p = 0.02). Lesion level and degree of hindbrain herniation appeared to have no effect on the eventual need for shunting (p = 0.19 and p = 0.13, respectively). Similar results were obtained for the revised outcome.	Overlapping data with MOMs study (follow-up outcomes of the MOMS).
Verbeek, RJ, Heep, A et al (2012). Fetal endoscopic myelomeningocele closure preserves segmental neurological function. Developmental Medicine & Child Neurology (54) 1 15-22.	Prospective case series N=19 fetous with MMC Fetoscopic repair of MMC matched each successfully treated fSBA infant with another nSBA infant of the same age and level of lesion, resulting in 13 matched pairs (mean age 14 mo) .	Three procedures resulted in fetal death, 3 procedures were interrupted by iatrogenic haemorrhages and 13 procedures were successful. the fSBA group were born at a lower gestational age than the nSBA group (median 32 wks [range 25-34 wks] vs 39 wks [34-41 wks]; p=0.001) and experienced more complications (chorioamnionitis, premature rupture of the amniotic membranes, oligohydramnios, and infant respiratory distress syndrome necessitating intermittent positive-pressure ventilation). Neurological function was better preserved after fSBA than after nSBA (median motor and sensory gain of 2 segments; better preserved knee-jerk [p=0.006] and anal [p=0.032] reflexes). The dMUD was smaller in fSBA than in nSBA infants (mean difference 24, 95% confidence interval [CI] 15-33; p<0.05), which was associated with better preserved segmental muscle function.	Included in systematic review added to table 2.
Zamlynski, J, Horzelska, E et al (2017). Current views	Review	The main goal of fetal MMC repair is to improve development and life quality of children with Chiari II malformation. Management of	Review

on fetal surgical treatment of myelomeningocele - the Management of Myelomeningocele Study (MOMS) trial and Polish clinical experience. Ginekologia Polska (88) 1 31-35.		Myelomeningocele Study (MOMS) which was published in 2011 clearly confirmed effectiveness of prenatal surgery. In this paper we compare MOMS results with our own clinical experience (n=71).	
Zarutskie, A, Guimaraes, C et al (2019). Prenatal brain imaging for predicting postnatal hydrocephalus treatment in fetuses that had neural tube defect repair. Ultrasound in Obstetrics & Gynecology (08) 08.	Prospective cohort study N=55 fetouses (32 had open hysterotomy and 18 had fetoscopic repair). Follow-up 1 year Pre and post surgical brain images assessed.	Persistence of hindbrain herniation on MRI 6 weeks after prenatal neural tube defect repair independently predicted the need for postnatal hydrocephalus tretament better than any ultrasound or MRI-derived measurements of ventricular characteristics. These results will aid in prenatal counseling and add support to the hypothesis that hindbrain herniation is a significant driver of hydrocephalus in myelomeningocele patients.	Imaging results for predicting postnatal treatment.

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	01/02/2019	Issue 2 of 12, February 2019
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	01/02/2019	Issue 2 of 12, February 2019
HTA database (CRD website)	01/02/2019	n/a
MEDLINE (Ovid)	31/01/2019	1946 to January 30, 2019
MEDLINE In-Process (Ovid) & MEDLINE ePubs ahead of print (Ovid)	31/01/2019	January 30, 2019
EMBASE (Ovid)	31/01/2019	1974 to 2019 January 30
BLIC	01/02/2019	n/a

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1 Meningomyelocele/ (3896)
2 MENINGOCELE/ (2629)
3 Meningomyelocel*.tw. (911)
4 Meningocel*.tw. (1512)
5 Neural Tube Defects/ (7396)
6 (open* adj4 neural* adj4 tube* adj4 defect*).tw. (363)
7 ONTD*.tw. (41)
8 Myelomeningocel*.tw. (3101)
9 Spinal Dysraphism/ (5819)
10 (Spinal adj4 dysraph*).tw. (1049)
11 Spina Bifida Cystica/ (267)
12 (Spina* adj4 bifida* adj4 cystic*).tw. (241)
13 (Spina* adj4 bifida adj4 apert*).tw. (176)
14 (Spina* adj4 bifida adj4 manifest*).tw. (22)
15 ((Congenital* or famil* or open*) adj4 spina* adj4 bifida*).tw. (492)
16 OSB.tw. (153)
17 Arnold-Chiari Malformation/ (3219)
18 ((Arnold-Chiari or "Arnold Chiari") adj4 Malformation*).tw. (776)
19 (("type II" or "type 2" or type-II or type-2) adj4 Chiari adj4 malformation*).tw. (166)
20 ANENCEPHALY/ (3017)
21 Anencephal*.tw. (2714)
22 Cephalocel*.tw. (223)
23 HYDROCEPHALUS/ and FETUS/ (257)
24 (Hydrocephal* adj4 (prenatal or fetal or f?etus* or "in uter*" or in-uter* or "intra uterin*" or intrauterin* or intra-uterin*)).tw. (532)
25 "fluid* on the brain".tw. (5)
26 or/1-25 (26323)

27 ((prenatal or fetal or f?etus* or "in uter*" or in-uter* or "intra uterin*" or intrauterin* or intra-uterin*) adj4 (surgical* or surger* or repair* or interven*)).tw. (4890)
28 (open* adj4 (surger* or surgical* or repair*)).tw. (41157)
29 Fetoscopy/ (1645)
30 Endoscopy/ (49167)
31 ((endoscop* or fetoscop*) adj4 repair*).tw. (1269)
32 Hysterotomy/ (227)
33 hysterotom*.tw. (905)
34 (("in uter*" or in-uter* or "intra uterin*" or intrauterin* or intra-uterin* or prematur*) adj4 closure*).tw. (1068)
35 Duragen*.tw. (25)
36 Allogen.tw. (44)
37 (Biodesign adj4 Duroplasty).tw. (0)
38 Duraform.tw. (7)
39 (DePuy adj4 Synthes).tw. (53)
40 (Alloderm adj4 LifeCell).tw. (78)
41 or/27-40 (97469)
42 26 and 41 (787)
43 animals/ not humans/ (4508736)
44 42 not 43 (702)
45 limit 44 to english language (622)