# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## INTERVENTIONAL PROCEDURES PROGRAMME

## Interventional procedure overview of open 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 open prenatal surgery can be done, through the mother's abdomen, an incision in the womb 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.

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# 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*

- Open prenatal repair for 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.



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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*

Open prenatal repair for open neural tube defects is typically done before 26 weeks of pregnancy. Using general anaesthesia, a low transverse laparotomy incision is done and the gravid uterus is exposed and exteriorised. The fetus and placenta are visualised by ultrasound and the fetus is manually positioned to allow a uterine incision (hysterotomy) over the centre of the myelomeningocele sac. The hysterotomy location is either anterior, fundal or posterior depending on the location of the placenta. The hysterotomy is made large enough to allow the neural tissue in the meningomyelocele to be dissected from surrounding tissue so that it can drop into the spinal canal. The defect is then closed. If there is insufficient dura or skin for closure, occasionally a biocellulose and dermal regeneration patch substitute may be used for repair. The uterine incision is closed and a sodium lactate solution with antibiotics is added to the uterus until the amniotic fluid index is normal. The maternal abdominal wound is then closed.

A number of variations to the procedure have been described and the technique is still evolving.

## Efficacy summary

#### Improvement in motor function of lower body

Prenatal repair compared with postnatal repair

A systematic review and meta-analysis of 2 studies (1 randomised controlled trial [RCT] and 1 prospective controlled study) compared infants with spina bifida aperta treated prenatally to the condition treated postnatally. It reported that independent ambulation at 30 months was seen in 38% (41/109) of children who had prenatal repair compared with 19% (21/111) of those who had postnatal repair (odds ratio [OR] 2.59, 95% confidence interval [CI] 1.39 to 4.86, p=0.003).[2]

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. It



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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% CI 49% to 89%) compared with 56% in open repair (95% CI 46T 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.[3]

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 the study.[4]

**Improvement in hindbrain herniation**

Prenatal repair compared with postnatal repair

A randomised controlled trial of 158 patients compared prenatal surgery (n=78) with postnatal surgery (n=80). It reported that prenatal surgery was associated with a significant decrease in the risk of moderate to severe hindbrain herniation at 12 months compared with postnatal surgery (25% compared with 67%, relative risk [RR] 0.56, 95% CI 0.38 to 0.81, p=0.0002). The proportion of infants who had no evidence of hindbrain herniation was higher in the prenatal surgery group (36%) than in the postnatal surgery group (4%). There were also lower rates of brain-stem kinking (20% compared with 48%, p<0.001), abnormal fourth-ventricle location (46% compared with 72%, p=0.002), and syringomyelia (39% compared with 58%, p=0.03) in the prenatal group compared to the postnatal group.[1]

The systematic review and meta-analysis of 2 studies (1 RCT and 1 prospective controlled study) compared infants with spina bifida aperta treated prenatally with the condition treated postnatally. It reported that no signs of hindbrain herniation were detected at first postnatal MRI in 32% (28/88) children who had prenatal repair compared with 4.5% (4/89) of those who had postnatal repair (OR 9.45, 95% CI 3.12 to 28.64, p<0.0001).[2]

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. This



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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 the fetoscopic data were combined with those of fetoscopic surgery through a maternal laparotomy (mean ES 69% [95% CI 39% to 93%] in modified fetoscopic repair compared with 54% [95% CI 21% to 86%] in open repair; p=0.52).[3]

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=0.163) 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.[4]

A retrospective case series of 237 pregnant women who had open fetal surgery for myelomeningocele reported that reversal of hindbrain herniation at birth occurred in 71.4% (168/237) of infants according to prenatal ultrasound follow up. Comparing results from the first 3 years of the case series with the last 3 years showed an increase in the rate of reversal of hindbrain herniation at birth (64.0 compared with 77.1%, p=0.042).[7]

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

Prenatal repair compared with postnatal repair

A randomised controlled trial of 158 patients compared prenatal surgery (n=78) with postnatal surgery (n=80). It reported that prenatal surgery was associated with a reduction in VP shunt placement compared with postnatal surgery (40% [31/78] compared with 82% [66/80], RR 0.48, 95% CI 0.36 to 0.64; p<0.001).[1]

The systematic review and meta-analysis of 2 studies (1 RCT and 1 prospective controlled study) compared infants with spina bifida aperta treated prenatally to the condition treated postnatally. This reported that the need for VP shunt placement at 1 year was lower in the prenatal group (41% [45/109]) than in the postnatal repair group (83% [93/112]); OR 0.14 (95% CI 0.08 to 0.26, p<0.0001).[2]

Open fetal repair compared with fetoscopic repair

The systematic review and meta-analysis of 11 observational studies compared fetoscopic approach with open surgical approach for fetal repair of



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myelomeningocele. It 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 fetoscopic data were combined with those of fetoscopic surgery through a maternal laparotomy (mean ES 42% [95% CI 33% to 52%] in modified fetoscopic repair compared with 40% [95%CI 32% to 49%] in open repair, p=0.73).[3]

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 VP shunt placement (assessed in 12 studies, 10 open surgery and 2 endoscopic surgery) was similar in infants followed for at least 12 months for both groups (40% [229/529], 95% CI 29% to 51%, p<0.0001, compared with 45% [35/78], 95% CI 34% to 56%, p=0.93).[4]

**Neurodevelopment impairment**

Prenatal repair compared with postnatal repair

A randomised controlled trial of 158 patients compared prenatal surgery (n=64) with postnatal surgery (n=70). It reported that prenatal surgery resulted in improvement in the child composite score for mental development and motor function at 30 months of age compared with postnatal surgery (148±57.5 compared with 122.6±57.2; p=0.007).[1] This was derived from the Bayley Mental Development Index (BMDI) (89.7±14.0 compared with 87.3±18.4, p=0.53) and the difference between motor function and anatomical levels (0.58±1.94 compared with 0.69±1.99, p=0.001). The mean Bayley Psychomotor Development Index was 64.0±17.4 compared with 58.3±14.8, p=0.03. Higher scores on BMDI indicate better performance, and positive values on the motor function indicate function that is better than expected.

Infants in the prenatal surgery group were more likely to have a level of function that was 2 or more levels better than expected according to the anatomical level (32% [20/62] compared with 12% [8/67], p=0.005). They were less likely to have a level of function that was 2 or more levels worse than the expected level (13% [8/62] compared with 28% [19/67], p=0.03) compared with those in the postnatal surgery group. Children in the prenatal surgery group were more likely than those in the postnatal surgery group to be able to walk without orthotics or devices (42% [26/62] compared with 21% [14/67], RR 2.01, 95% CI 1.16 to 3.48; p=0.01).

On the Peabody motor scales, the prenatal surgery group had better motor function than the postnatal surgery group. Parent-reported self-care and mobility, as measured by the Wee Functional Independence Measure for Children



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(WeeFIM) instrument, were significantly better in the prenatal surgery group (p=0.02, p=0.003). There were no significant between-group differences in cognitive scores (p=0.67).[1]

The systematic review and meta-analysis of 2 studies (1 RCT and 1 prospective controlled study) compared the neurological outcome of infants with spina bifida aperta. It reported that neurodevelopment impairment at 1 year was similar between children who had prenatal (23.8% [25/105]) and those who had postnatal (27.8% [30/108]) repair (OR, 0.82 [95% CI 0.43 to 1.56], p=0.54). This was assessed between 14 and 53 months of age by the Bayley Scales of Infant Development II (BSID-II) mental development index (MDI) for chronological age, with a cut-off of 70 or more (representing no more than 2 standard deviations below the mean). The RCT in this review also reported that the likelihood for impairment was similar between children in the prenatal surgery group who had shunt placement (18% [7/39]) and those who did not (8.3% [4/48], p=0.21).[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. It reported that the pooled rate of bladder dysfunction (assessed in 8 studies) was 72% (188/274), (95% CI 53% to 88%, 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.[4]

**Completion of surgery through the intended access**

Open fetal repair compared with fetoscopic repair

The systematic review and meta-analysis of 11 observational studies compared fetoscopic approach with open surgical approach for fetal repair of myelomeningocele. This 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 fetoscopic data were combined with those of fetoscopic surgery through a maternal laparotomy the difference between the groups was statistically significant. The mean ES was 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.[3]



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### Learning curve analysis of fetal surgery techniques

A systematic review and meta-analysis of learning curves of different techniques (open and fetoscopic approaches) for fetal spina bifida closure (in 17 studies) reported that outcomes significantly improved with experience irrespective of the approach used. Analysis of studies with different surgical techniques showed that all the techniques had comparable outcomes. Competency (defined by safety and efficacy) was achieved after 35 cases for standard hysterotomy, and competency was predicted to be achieved after more than 57 cases for mini-hysterotomy and other fetoscopic modifications.[6]

### Quality of life

A survey of 74 children who had had myelomeningocele repair (intrauterine or postnatal) assessed the quality of life of children who had intrauterine compared with postnatal repair. 23 patients' families responded to the survey. The study reported that children who had intrauterine repair (n=11) had better long-term psychosocial outcomes than those who had postnatal repair (n=12) (70.0 compared with 55.0, p=0.015). Improvement was consistent in all 3 domains of psychosocial health: emotional (80 compared with 65, p=0.040), social (80 compared with 55, p=0.048) and school functioning (60 compared with 37.5, p=0.028). There was no significant difference in physical health between the 2 groups (62.5 compared with 39.1; p=0.108).[9]

## 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 approach with open surgical approach for fetal repair of myelomeningocele. It 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 fetoscopic data were combined with those of fetoscopic surgery through a maternal laparotomy. The mean ES was 7% (95% CI 2% to 15%) in modified fetoscopic repair compared with 6% (95% CI 3% to 9%) in open repair, p=0.65.[3]

### Perinatal or neonatal death

Open fetal repair compared with fetoscopic repair



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A 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 perinatal death. This 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).[5]

Prenatal surgery compared with postnatal surgery

A randomised controlled trial of 158 patients compared prenatal surgery (n=78) compared with postnatal surgery (n=80). It reported no difference in perinatal or neonatal death in the prenatal surgery group compared with the postnatal surgery group. Perinatal death was 2% (2/78) compared with 2% (2/80), relative risk (RR) 1.03, 95% CI 0.14 to 7.10, p=1.00. Neonatal death was 1% (1/78) compared with 2% (2/80), RR 0.51, 95% CI, 0.05 to 5.54, p=0.58.[1]

**Premature birth/preterm delivery**

Prenatal repair compared with postnatal repair

A systematic review and meta-analysis of 2 studies (1 RCT and 1 prospective controlled study) compared infants with spina bifida aperta treated prenatally to the condition treated postnatally. This reported that the risk of prematurity (birth before 34 weeks) was higher in the prenatal repair group (52.6% [71/135]) than in the postnatal repair group (5.7% [7/122]); OR 17.62 [95% CI 7.60 to 40.87], p<0.0001).[2]

Open fetal repair compared with fetoscopic repair

The systematic review and meta-analysis of 11 observational studies compared fetoscopic approach with open surgical approach for fetal repair of myelomeningocele. This 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% (95% CI 88% to 100%) in fetoscopic repair compared with 81% (95% CI 66% to 92%) in open repair, p=0.04. When fetoscopic data were combined 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. The mean ES was 90% (95% CI 69% to 100%) in modified fetoscopic repair compared with 81% (95% CI 66% to 92%) in open repair, p=0.43.[3]

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,



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p=0.39. When fetoscopic data were combined 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.[3]

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 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).[5]

A retrospective case series of 237 pregnant women who had open fetal surgery for myelomeningocele reported preterm labour in 24% of cases.[7]

**Uterine dehiscence**

Open fetal repair compared with fetoscopic repair

The systematic review and meta-analysis of 11 observational studies compared fetoscopic approach with open surgical approach for fetal repair of myelomeningocele. This reported that the rate of uterine dehiscence was significantly higher in the open repair approach compared with the percutaneous fetoscopic approach. The mean ES was 11% (95% CI 5% to 20%) in open repair compared with 0% (95% CI 0% to 2%) in fetoscopic repair, p<0.01. When fetoscopic data were combined with those of fetoscopic surgery through a maternal laparotomy, the difference in the rates was 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.[3]

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 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).[5]

A retrospective case series of 237 pregnant women who had open fetal surgery for myelomeningocele reported dehiscence at the repair site in 2.5% of cases.[7]

**Premature rupture of membranes (PROM)**



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Prenatal repair compared with postnatal repair

A randomised controlled trial of 158 patients compared prenatal surgery (n=78) with postnatal surgery (n=80). This reported that prenatal repair was associated with an increased risk of the women experiencing preterm ruptured membranes (46% [36/78] compared with 8% [6/80], RR, 6.15 [95% CI 2.75 to 13.78], p<0.001) and subsequent preterm birth (both before 34 and 37 weeks).[1]

Open fetal repair compared with fetoscopic repair

The systematic review and meta-analysis of 11 observational studies compared fetoscopic approach 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 fetoscopic data were combined 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.[3]

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 premature rupture of membranes. This was lower in the open surgery group compared with endoscopic group (38%, 95% CI 26% to 50%, p=0.005 compared with 67%, 95% CI 12 to 100, p<0.0001).[5]

A retrospective case series of 237 pregnant women who had open fetal surgery for myelomeningocele reported premature rupture of membranes in 27% of cases.[7]

**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 39%, 95% CI 9 to 75, p=0.0001).[5]

**Chorioamniotic membrane separation**



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Open fetal repair compared with fetoscopic repair

The systematic review and meta-analysis of 11 observational studies compared fetoscopic approach 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 fetoscopic data were combined with those of fetoscopic surgery through a maternal laparotomy (mean ES 21% [95% CI 2 to 52] compared with 9% [95% CI 0 to 32], p=0.46).[3]

A retrospective case series of 237 pregnant women who had open fetal surgery for myelomeningocele reported that chorioamniotic membrane separation was detected by postoperative ultrasonography in 21% of cases.[7]

**Placental abruption**

Open fetal repair compared with fetoscopic repair

The systematic review and meta-analysis of 11 observational studies compared fetoscopic approach 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 fetoscopic data were combined with those of fetoscopic surgery through a maternal laparotomy (mean ES 3% [95% CI 0 to 17] compared with 3% [95% CI 1 to 5], p=0.85).[3]

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 placental abruption. There was no difference in the rate in the open surgery group compared with the endoscopic group (3%, 95% CI 0 to 8, p=0.02 compared with 2%, 95% CI 0 to 9, p=0.18).[5]

A retrospective case series of 237 pregnant women who had open fetal surgery for myelomeningocele reported placental abruption in 0.8% of cases.[7]

**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 approach with open surgical approach for fetal repair of myelomeningocele. It reported that the rate of CSF leakage or dehiscence



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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 fetoscopic data were combined 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).[3]

**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 rate 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 13, p=0.37).[5]

**Subsequent pregnancy outcomes**

A registry of 693 cases of open maternal fetal surgery for fetal myelomeningocele closure reported that 52 subsequent pregnancies progressed to more than 20 weeks. The overall live birth rate was 96% (51/52) delivering beyond 20 weeks gestational age and median gestational age at delivery of 37 weeks (range 36 to 37 weeks). The uterine rupture rate was 10% (5/52) in first subsequent pregnancy resulting in 4% (2/52) fetal deaths. Uterine dehiscence at the time of delivery was reported in 17% (9/52) cases but were asymptomatic. Placenta previa was noted in 1 subsequent pregnancy and placenta accreta was reported in 1 additional subsequent pregnancy but none needed hysterectomy.[8]

**Lethal pulmonary hypoplasia**

Lethal pulmonary hypoplasia after open fetal repair of myelomeningocele through a fundal hysterotomy at 24 weeks gestation was reported in a case report of 1 infant. The postoperative course for the mother was complicated by pulmonary oedema, abdominal pain, chronic oligohydramnios and preterm labour at 33 weeks gestation. The infant died from severe respiratory distress and cardiopulmonary arrest 9 hours after birth.[6]

## *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



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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 fetal surgery for myelomeningocele. 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 appendix C for details of 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.



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**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.<br>Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study.<br>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 | Open 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 3286 patients from 5 systematic reviews, 1 randomised controlled trial, 3 case series and 1 case report. There is an overlap of patients between the studies[1-5] 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.



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

## Study 1 Adzick S (2011)

**Details**

| | |
|---|---|
| Study type | Randomised controlled trial |
| Country | USA (3 centres) (Management of Myelomeningocele Study-MOMS) |
| Recruitment period | 2003 to 2010 |
| Study population and number | **n=183 foetuses or infants with a myelomeningocele**<br>**(91 prenatal [in-utero] repair** versus **92 postnatal repair [standard postnatal care])** |
| Age and sex | **Mean maternal age**: Prenatal repair:29.3 years; Postnatal repair: 28.8 years<br>**Gestational age at randomisation:** Prenatal repair: 23.6±1.4 weeks; Postnatal repair: 23.9±1.3 weeks<br>**Fetal sex female**: Prenatal repair 45% (35/78); Postnatal repair 64% (51/80) |
| Patient selection criteria | Inclusion criteria were a singleton pregnancy, myelomeningocele at level between T1 and S1, evidence of hindbrain herniation, gestational age of 19.0 to 25.9 weeks at randomisation, normal karyotype, US residency, maternal age ≥18 years.<br>Exclusion criteria included fetal anomaly unrelated to myelomeningocele, severe kyphosis, risk of preterm birth, placenta praevia or placental abruption, BMI ≥35, contraindication to surgery or general anaesthesia, insulin dependent pregestational diabetes, maternal HIV or Hepatitis B test positive, known Hepatitis C positive, maternal hypertension, uterine anomaly, previous spontaneous singleton delivery before 37 weeks, short cervix, history of incompetent cervix or cerclage, maternal-fetal Rh isoimmunization, lack of a support person. |
| Technique | **Prenatal surgery group:** maternal laparotomy and uterine incision (hysterotomy)was performed and then the lesion repaired using standardized techniques. Birth was by subsequent caesarean section at 37 weeks. Study involved multidisciplinary approach and participants remained near the center for the duration of pregnancy.<br>**Postnatal surgery group:** women and their infants in the standard care group underwent caesarean delivery at 37 weeks and then postnatal repair of MMC.<br>All surgeons used a stapling device with absorbable staples for uterine entry. The hysterotomy was closed in two layers. The first layer was incorporated with the absorbable staples and uterine membranes, and the second layer was tied with imbricating layer of suture. Patients were monitored closely postoperatively and the use of tocolytics was planned until 36$^{th}$ weeks of gestation. |
| Follow-up | **12 months, 30 months** |
| Conflict of interest/source of funding | Funded by the National Institute of Health (NIH). |

**Analysis**

**Follow-up issues**: Of 183 women, 158 randomised before July 2009 were included in the analysis for the primary outcome at 12 months and only 134 women randomised before December 2007 were included in the analysis at 30 months. 24 children were not included as they did not reach 30 months of age.

**Study design issues**: the methodological quality of the study was good, randomisation based on a computer-generated allocation sequence and a website for allocation concealment. Inclusion criteria were rigorous, blinding was not possible with participants and clinicians, but neurological outcome assessors were blinded. Selective reporting of data noted. Primary outcomes assessed were fetal/neonatal death and shunt placement at 12 months and the secondary primary outcome was neurodevelopment outcome at 30 months (a composite score of Mental Development Index [MDI] of the Bayley Scales of Infant Development II [BSID II] and the child motor function adjusted for the lesion level). The secondary outcomes included maternal, fetal and neonatal complications related to pregnancy and surgery, and neonatal morbidity and mortality.



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Intention-to-treat principle was used for analysis. Time to shunt placement or meeting shunt criteria were analysed using Kaplan-Meier survival curves. Four interim analyses were performed for each primary end point. For the first primary end point, 97.7% CI was used for reporting relative risk.

**Study population issues**: The postnatal group had higher proportion of fetuses with lesion level L3 or lower on ultrasonography compared to the prenatal group (84% vs 68%, p=0.02). The postnatal surgery group also had more female fetuses (64% vs 45%, p=0.02).

**Other issues**: The trial was stopped after the recruitment of 183 patients of planned 200 based on efficacy of the prenatal surgery. The study outcomes may not be reproducible outside a rigorous trial setting.

**Key efficacy and safety findings**

Efficacy

Number of patients analysed: **158 (prenatal = 78, postnatal= 80)**

**Primary outcomes**

| | **Prenatal surgery % (n=78)** | **Postnatal surgery % (n=80)** | **RR (95% CI)** | **P value** |
|---|---|---|---|---|
| | | | | |
| VP shunt placement | 40 (31/78) | 82 (66/80) | 0.48 (0.36 - 0.64) | <0.001 |
| No hindbrain herniation | 36 | 4 | | |
| Moderate to severe hindbrain herniation after birth | 25/78) | 67 (46/80) | 0.56 (0.38 - 0.81) | 0.0002 |
| Any hindbrain herniation | 64 (45/70) | 96 (66/69) | 0.76 (0.56 - 0.81) | <0.001 |
| Brainstem kinking (any degree) | 20(14/70) | 48 33/69) | 0.42 (0.25 - 0.71) | <0.001 |
| Abnormal location of fourth ventricle | 46 (32/70) | 72(49/68) | 0.63 (0.47 - 0.85) | 0.002 |
| Syringomyelia | 39 (27/69) | 58 (39/67) | 0.47-0.96) | 0.03 |

**Second Primary Outcomes**

Safety

**Maternal adverse events**

| | **Prenatal surgery % (n=78)** | **Postnatal surgery % (n=80)** | **RR (95% CI)** | **P value** |
|---|---|---|---|---|
| Maternal deaths | 0 | 0 | | |
| Chorioamniotic membrane separation | 26 (20/78) | 0 | NA | <0.001 |
| Pulmonary oedema | 6 (5/78) | 0 | NA | 0.03 |
| Oligohydramnios | 21 (16/78) | 4 (3/80) | 5.47 (1.66-18.04) | 0.001 |
| Placental abruption | 6 (5/78) | 0 | NA | 0.03 |
| Gestational diabetes | 5 (4/78) | 6 (5/80) | 0.82 (0.23-2.94) | 1.00 |
| Pre-eclampsia or hypertension | 4 (3/78) | 0 | NA | 0.12 |
| Chorioamnionitis | 3 (2/78) | 0 | NA | 0.24 |
| Preterm spontaneous membrane rupture | 46 (36/78) | 8 (6/80) | 6.15 (2.75-13.78) | <0.001 |
| Spontaneous labour | 38 (30/78) | 14 (11/80) | 2.80 (1.51-5.18) | <0.001 |
| Blood transfusion at delivery | 9 (7/78) | 1 (1/80) | 7.18 (0.90-57.01) | 0.03 |
| Hysterotomy site status | Intact 64 (49/76)<br>Very thin 25 (19/76)<br>Area of dehiscence 9 (7/76) | | | |



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| | Prenatal surgery % (n=64) | Postnatal surgery % (n=70) | RR (95% CI) | P value |
|---|---|---|---|---|
| Composite score for mental development and motor function at 30 months* | 148±57.5 | 122.6 ±57.2 | | 0.007 |
| BMDI | 89.7±14.0 | 87.3±18.4 | | 0.53 |
| Difference between motor function and anatomical levels | 0.58±1.94 | -0.69±1.99 | | 0.001 |
| Difference between motor function and anatomical level of lesion at 30 months -2 or more levels better | 32 (20/62) | 12 (8/67) | 0.005 | 0.005 |
| 2 or more levels worse | 13 (8/62) | 28 (19/67) | | 0.03 |
| Walking independently (on examination) | 42 (26/62) | 21 (14/67) | 2.01 (1.16 - 3.48) | 0.01 |
| Mean Bayley Psychomotor Development Index ^ | 64.0±17.4 | 58.3±14.8 | | 0.03 |

*derived from BMDI scores and the difference between motor function and anatomical levels. The higher scores indicate better outcomes.

^The scores are scaled to have a population mean(±SD) of 100±15, with a minimum score of 50 and maximum 150. Higher scores indicate better performance.

**Peabody Developmental Motor Scales (PDMS)^^**

| Scores | Prenatal | Postnatal | P value |
|---|---|---|---|
| Stationary | 7.4±1.1 | 7.0±1.2 | 0.04 |
| Locomotion | 3.0±1.8 | 2.1±1.5 | 0.002 |
| Object manipulation | 5.1±2.6 | 3.7±2.1 | <0.001 |

| | | | | |
|---|---|---|---|---|
| | Complete dehiscence 1 (1/76) | | | |

**Fetal/neonatal adverse events**

| | Prenatal surgery | Postnatal surgery | RR (95% CI) | P value |
|---|---|---|---|---|
| Perinatal death | 3 (2/78)<br>Still birth at 26 weeks<br>Neonatal death at 23 weeks | 2 (2/80)<br>Due to severe Chiari II malformation | 1.03 (0.14-7.10) | 1.00 |
| Neonatal death | 1 (1/78) | 2 (2/80) | 0.51 (0.05-5.54) | 0.58 |
| Deaths after 1 year | 1 (due to coxsackie septicaemia) | 1 (due to chemotherapy for choroid plexus carcinoma) | | |
| Fetal/neonatal bradycardia during surgery | 10 (8/78) | 0 | NA | 0.003 |
| Preterm birth before 37 weeks | (62/78) | (12/80) | 5.30 (3.11-9.04) | <0.00001 |
| Preterm birth before 34 weeks | (36/78) | (4/80) | 9.23 (3.45-24.71) | <0.00001 |
| Dehiscence at repair site | 13 (10/77) | 6 (5/80) | 2.05 (0.73-5.73) | 0.16 |
| Apnoea | 36 (28/77) | 22 (18/80) | 1.62 (0.98-2.67) | 0.06 |
| Pneumothorax | 1 (1/77) | 1 (1/80) | 1.05 (0.07-16.53) | 1.00 |
| Respiratory distress syndrome* | 21 (16/77) | 6 (5/80) | 3.32 (1.28-8.63) | 0.008 |
| Patient ductus arteriosus | 4 (3/77) | 0 | NA | 0.12 |
| Sepsis | 5 (4/77) | 1 (1/80) | 4.16 (0.48-36.36) | 0.20 |
| Necrotising enterocolitis^^ | 1 (1/77) | 0 | NA | 0.49 |



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^^the scores are reported in mean±SD and the minimum score is 0 and the maximum score is 20. Higher scores indicate better performance.

**WeeFIM Score****

| Scores | Prenatal | Postnatal | P value |
|---|---|---|---|
| Self-care | 20.5±4.2 | 19.0±4.2 | 0.02 |
| Mobility | 19.9±6.4 | 16.5±5.9 | 0.003 |
| Cognitive | 23.9±5.2 | 24.1±5.9 | 0.67 |

The degree of parent-reported disability is measured by the WeeFIM(Functional Independence Measure for Children) instrument. The score on the self-care measurement ranges from 8 to 56, on the mobility and cognitive measurements range from 5 to 35, with higher scores indicating greater independence.

| | | | | |
|---|---|---|---|---|
| Periventricular leukomalacia | 5 (4/77) | 2 (2/80) | 2.08 (0.39-11.02) | 0.44 |
| Foot deformity | 50 (39/78) | 45 (36/80) | 1.11(0.80-1.54) | 0.53 |
| Surgery for spinal tethered cord | 8 (6/77) | 1 (1/80) | 6.15 (0.76-50.00) | 0.06 |

*defined as a clinical diagnosis of type 1 distress syndrome and the need for oxygen therapy at 24 hours or more.

^defined as confirmed on blood culture, confirmed UTI, meningitis, or pneumonia.

**^^d**efined as a confirmed diagnosis of unequivocal presence of intramural air, perforation, erythema and induration of the abdominal wall, intraabdominal abscess, the formation of stricture after an episode of suspected necrotising enterocolitis at the time of surgery or autopsy.

There was no significant difference between groups in terms of identification of epidermoid cyst, Chiari decompression surgery and shunt infection.

Abbreviations used: CI, confidence interval; BMDI, Bayley Mental Development Index; NA, not available; RR, relative risk; SD, standard deviation; UTI= Urinary tract infection; VP, ventriculoperitoneal.



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## Study 2 Inversetti A (2019)

### Details

| | |
|---|---|
| Study type | Systematic review and meta-analysis |
| Country | 1 study in USA, 1 in Poland |
| Study period | Search period: Inception to March 2018; Databases searched: PubMed/MEDLINE, EMBASE, Web of Science and The Cochrane Central Register of Controlled Trials. Bibliography lists and topic-related reviews were also hand-searched. |
| Study population and number | **n= 213 children with Spina Bifida Aperta (SBA) in 2 studies**<br>**(1 RCT** [Farmer 2018] **and 1 prospective cohort study** [Zamlynski 2014])<br>**Prenatal repair (n=105) versus post-natal repair (n=108)** |
| Age and sex | Age of children at neurological evaluation: 14 to 53 months in cohort study and 30 months in the RCT.<br>Sex of the children not reported. |
| Study selection criteria | Randomized controlled trials and non-randomised prospective controlled studies comparing prenatal with post-natal repair of spina bifida in children (either through an open or fetoscopic approach), evaluating neurodevelopmental impairment after the age of 1 year, with large complete datasets in English language were included. The comparator/controls were SBA cases repaired in neonatal period.<br>Studies with duplicate records, lack of data, overlapping studies, reviews, book chapters, opinion papers, conference abstract, letters, animal model studies, non-English language studies, retrospective cohort studies and studies with only post-natal repair were excluded. |
| Technique | **Both studies in this systematic review used open repair technique for prenatal repair**. They were performed at gestational age between 19 and 27 weeks.<br>One study reported that postnatal repair was also performed 48 hours after birth. |
| Follow-up | **Varied (14 to 53 months after birth)** |
| Conflict of interest/source of funding | The authors received support and funding from Erasmus+ Programme of the European Commission, Innovative Engineering for Health award the Welcome Trust and Engineering and Physical Sciences Research Council, Great Ormond Street Hospital Charity Fund. |

### Analysis

**Follow-up issues**: The RCT study evaluated the neurodevelopment outcomes at 30 months of age. The prospective cohort studies evaluated the outcomes between 14 to 53 months of age.

**Study design issues**: Systematic review of the literature was done according to PRISMA guidelines, the protocol was registered with PROSPERO, comprehensive search strategy was used. High quality studies with limited number of patients were included. The risk of bias and the quality of the was assessed using the Cochrane Risk of Bias tool 2.0 for the RCT and the ROBINS-I tool for the cohort study. The Bayley Scales of Infant Development II (BSID-II) mental development index (MDI) was used to assess neurodevelopment outcomes in children. The secondary outcomes were preterm birth, need for ventriculoperitoneal shunts by 12 months age, absence of hindbrain herniation and motor functions in terms of independent ambulation.

The meta-analysis was performed for all variables and the incidence of the outcomes were calculated by pooling the number of events in the total number of cases. An estimated odds ratio (OR) for each outcome was reported with 95% CI, using random effects model. The heterogeneity among studies was tested using the $I^2$ test. The number needed to treat (NNT) or number needed to harm (NNH) was calculated when there are significant differences between the two groups. Sensitivity analysis was also performed to assess whether the effect was dependent on the study type or study quality.

**Study population issues**: Neurodevelopment impairment was compared between prenatal and post-natal group despite the prenatal group had higher rate preterm birth (OR 17.62, 95% CI 7.60 – 40.87, p<0.0001).

**Other issues:** There is an overlap of patients between the studies[1-5].



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**Key efficacy and safety findings**

Efficacy

Number of patients analysed: **213 (105 prenatal repair versus 108 post-natal repair)**

**Neurodevelopment impairment at 1 year or later (n=213)**

Assessed between 14 and 53 months of age, using BSID-II mental development index(MDI)[1] corrected for chronological age with cut-off of ≥70 (no more than 2 SD below the mean).

| Prenatal (n=105) | Post-natal (n=108) | OR (95% CI) | P |
|---|---|---|---|
| 23.8% (25/100) | 27.8% (30/108) | 0.82 (0.43-1.56) | 0.54 |

MDI evaluates cognition, language, memory, problem solving and social skills.

**Need for ventriculoperitoneal shunt placement by 1 year after birth**

| Prenatal (n=109) | Post-natal (n=112) | OR (95% CI) | P |
|---|---|---|---|
| 41.3% (45/109) | 83.0% (93/112) | 0.14 (0.08-0.26) | <0.0001 |

Every 2 foetuses operated prenatally, 1 required a shunt (NNT=2 [95% CI 1 to3]).

**Absence of signs of hindbrain herniation at MRI at 12 months**

| Prenatal (n=88) | Post-natal (n=89) | OR (95% CI) | P |
|---|---|---|---|
| 31.8% (28/88) | 4.5% (4/89) | 9.45 (3.12- 28.64) | <0.0001 |

For every 4 children operated prenatally, there was 1 additional child without signs of hindbrain herniation at first postnatal MRI evaluation (NNT=4).

**Independent ambulation at 30 months of age**

| Prenatal (n=109) | Post-natal (n=111) | OR (95% CI) | P |
|---|---|---|---|
| 37.6% (41/109) | 18.9% (21/111) | 2.59 (1.39-4.86) | 0.003 |

For every 5 babies operate prenatally, there was 1 additional baby that could walk independently (NNT=5 [95% ci 3 to 14]).

**Neurodevelopment impairment in prenatal group with or without shunt placement by 1 year (**only reported in the RCT)

Safety

**Incidence of preterm birth (n=257)**

(defined as birth before 34+6 weeks gestation)

| Prenatal n=135 | Post-natal n=122 | OR (95% CI) | P |
|---|---|---|---|
| 52.6% (71/135) | 5.7% (7/122) | 17.62 (7.60-40.87) | <0.0001 |

For every two foetuses operated prenatally, there was one additional premature birth (number needed to harm= 2 [95% CI 1-3]).



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| Prenatal with shunt (n=39) | Prenatal – no shunt (n=48) | RR (95% CI) | P |
|---|---|---|---|
| 17.9% (7/39) | 8.3% (4/48) | 0.90 (0.75-1.06) | 0.21 |

Abbreviations used: BSID-II, Bayley Scales of Infant Development II; CI, confidence interval; VP, ventriculoperitoneal; NNT, number needed to treat; OR, odds ratio; RCT, randomised controlled trial; RR= relative risk; SD, standard deviation.

## Study 3 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 foetuses with myelomeningocele in 11 retrospective or prospective observational studies**<br>**Fetoscopic repair (n=179 in 5 studies)** [Graf 2016, Pedreira 2016, Degenhardt 2014, Verbeek 2012, Belfort 2017],<br>**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.<br>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**:<br>**Fetoscopic repair** (in 5 studies) was done in two 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 mobilized 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.<br>In **fetoscopic repair via maternal laparotomy procedure (in 1 study)**, the primary closure was done by incorporating dura and skin.<br>**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



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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 | 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 and postnatal mortality)** | **9 (5, 14)** | **7 (2, 15)** | **6 (3,9)** | **0.20** | **0.65** |
| CSF leakage at the 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 |



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| | | | | | |
|---|---|---|---|---|---|
| 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 4 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**<br>(2 RCTs, 13 retrospective case series, 4 retrospective case-control studies)<br>**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.<br>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 following 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 to open repair. Some studies presented similar cases, but the outcomes assessed were different.



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**Other issues**: Authors state that results were not analysed according to short- and long-term follow-up periods and foetuses 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<br>$I^2$=84.73% |
| Endoscopic MMC repair (n=2 studies) | 45.0% (35/78) | 34.3 – 55.9 | P=0.930%<br>$I^2$ =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<br>$I^2$=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<br>$I^2$=89.27% |
| Endoscopic MMC repair (1 study) | N/A (6/7)[2] | N/A | N/A |

Safety

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



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[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<br>$I^2$=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 catheterization, abnormal video urodynamic, previous surgery for management of neurogenic bowel and bladder, video cystography showing vesicoureteral reflux.

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



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## Study 5 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**<br>(1 RCT, 11 retrospective cohort studies, 1 retrospective case-control study and 6 case reports)<br>**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<br>Mean gestational age at delivery – endoscopic: 32.0 weeks, open: 34.2 weeks<br>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.<br>Studies published before 1997, multiple publications and overlapping cases were excluded. |
| Technique | **Intra-uterine repair: endoscopic(fetoscopic) and open surgery.**<br>**Endoscopic surgery**: two studies from USA used carbon dioxide insufflation pressure of 12.0 to 12.5 mmHg and two studies from Germany used 14.1 to 15.6 mmHg pressure.<br>**Open surgery**: most of the studies used a method of closing hysterotomy in two layers but some studies reported using an inner running sutures and multiple interrupted outer sutures. For the two 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 following 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 two comparison groups (456 open surgeries, 84 endoscopic surgeries).



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**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 following 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 (%)** | **95% CI** | **P value, $I^2$** |
|---|---|---|---|---|



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| | | random effects | | |
|---|---|---|---|---|
| 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.



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## Study 6 Joyeux L (2019)

**Details**

| | |
|---|---|
| Study type | **Systematic review and meta-analysis** |
| Country | International |
| Study period | Search period: 1980 to 2018; Databases searched: Cochrane databases, PubMed, Medline Embase, Web of Science, Scopus and grey literature No restrictions applied on language and publication status. |
| Study population and number | **n= 548 cases in 17 studies on fetal open and endoscopic surgery for myelomeningocele**<br>standard hysterotomy (n=11 studies), mini-hysterotomy (n=1 study), fetoscopy [exteriorised uterus single layer] (n=1 study), percutaneous single layer (n=3 studies), percutaneous two-layer closure (n=1 study)<br>Standard hysterotomy in 347 cases, mini hysterotomy in 45 cases and fetoscopy in 156 cases. |
| Age and sex | Not reported |
| Study selection criteria | Studies on foetuses with an isolated spina bifida aperta in which in-utero closure was done, with follow-up of more than 12 months, reporting outcomes to measure learning curve, and with no language restrictions were included.<br>Studies with less than 5 cases, multiple publications, duplicates, conference abstracts, presentations, reviews and letters were excluded. |
| Technique | Studies in this systematic review used different access methods to perform fetal spina bifida aperta closure. Standard hysterotomy and mini hysterotomy done through maternal laparotomy and a large or mini hysterotomy.<br>Fetoscopic procedures were categorised based on where the cannulas were placed following exposure of the uterus through laparotomy (exteriorised uterus) or through a closed abdomen (percutaneous). |
| Follow-up | **Varied in studies** |
| 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 adhered to EQUATOR reporting guidelines, i.e. the PRISMA (preferred reporting items for systematic reviews and meta-analyses), GRADE (grading of recommendations, assessment, development and evaluation) and MOOSE (meta-analysis of observational studies in epidemiology) guidelines. Comprehensive search strategy was used, studies were screened and selected by 2 independent authors, quality assessed using standardised tools and categorised observations into blocks of 30 patients. Outcomes were compared to those in the MOMs trial as a reference experience. 2 complementary methods were used to determine the learning curve; the group splitting method (competency was defined when the procedure provided comparable results to the MOMs trial for 12 outcomes representing immediate, short term and long term outcomes) or the learning curve cumulative sum (LC CUSUM) analysis method (based on a composite binary outcome defining successful surgery).

Studies with moderate to low risk of bias were included. Meta-analysis was done using random effects model. Heterogeneity was assessed among studies by the $I^2$ statistic. Only outcomes for the standard hysterotomy meta-analysed.

**Other issues**: Learning curve of teams was assessed. Outcomes on fetoscopic approaches were not extracted as it is outside the scope of this overview.



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**Key efficacy and safety findings**

**Efficacy and safety**

Number of patients analysed: **12 studies standard hysterotomy 11 and mini hysterotomy 1)**

Overall outcomes improved with the number of cases.

Using the group splitting group, for standard hysterotomy, competency was achieved between 31 and 62 cases and remained stable afterwards.

For mini hysterotomy, competency was not achieved after 45 cases.

The operative times were longer in the mini-hysterotomy and fetoscopic approaches than the MOMs standard hysterotomy.

LC -CUSUM analyses predicted that competency for mini hysterotomy can occur after 57 cases and after 56 cases for percutaneous two-layer fetoscopy. Each failure resulted in 4 more cases needed to reach competency.

**Comparison of results from standard hysterotomy studies to the results of the MOMs trial**

| | **Reference MOMs trial (3 centres)** | **5 meta-analysed studies** | **Danzer 2010** | **3 centres from MOMs trial (4 studies)** | **2 meta-analysed studies** |
|---|---|---|---|---|---|
| Number of patients, block of experience | 91 | 85 block 1 | 28 block 2 | 30 block 3 | 143 block 4 |
| **Surgical outcomes** | | | | | |
| Maternal death % | 0 (0/91) | 0 | 0 | 0 | 0 |
| Postoperative death <7 days % | 2.2 (2/91) | 3.4 (3/85) | 0 | 2.2 (2/91) | 2.7 (4/142) |
| Mean operation time (min) | 105±22 | NS | NS | 105±22 | 78±12 |
| Technical failure | 0 (0/91) | 1.3 (1/85) | 0 | 0 | 1.1 (2/143) |
| PPROM <30±0 weeks % | NS | 18.9 (8/40) | 3.6 (1/28) | NS | 16.7 (16/96) |
| Delivery <30±0 weeks % | 11 (10/91) | 22.5 (19/85) | 7.1 (2/28) | 11 (10/91) | 8.4 (12/139) |
| **Short term neonatal neuroprotection** | | | | | |
| In utero complete reversal of HH % | NS | 41.4 (23/56) | 40.8 (11/27) | NS | 71.1 (59/83) |
| Any treatment at repair site % | 13 (10/77) | 3.7 (1/27) | 0 | 13 (10/77) | 5.4 (7/124) |
| Additional recoverage at repair site % | 2.6 (2/77) | 17.4 (6/35) | 0 | 2.6 (2/77) | 3.1 (4/124) |
| Improved motor function | NS | 59.2 (25/42) | 59.3 (16/27) | NS | 55 (44/80) |
| **Long term neuroprotection** | | | | | |
| Complete reversal of HH at 12 months | 35.7 (25/70) | NS | NS | 35.7 (25/70) | |



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| | | | | | |
|---|---|---|---|---|---|
| CSF diversion at 12 months | 44 (40/91) | 45.3 (9/17) | 48.1 (13/27) | 44 (40/91) | NS<br>35.3 (45/128) |
| Improved motor function at 30 months | 37.9 (33/87) | 52.9 (9/17) | 52.9 (9/17) | 37.9 (33/87) | NS |

**Comparison of results from mini hysterotomy studies to the results of the MOMs trial**

| | **Reference MOMs trial (3 centres)** | **Botelho 2017** | |
|---|---|---|---|
| Number of patients, block of experience | 91 | 30 block 1 | 15 block 2 |
| Maternal death % | 0 (0/91) | 0 | 0 |
| Postoperative death <7 days % | 2.2 (2/91) | 0 | 0 |
| Mean operation time (min) | 105±22 | 225±38 | 211±41 |
| Technical failure | 0 (0/91) | 0 | 0 |
| PPROM <30±0 weeks % | NS | 0 | 6.7 (1/15) |
| Delivery <30±0 weeks % | 11 (10/91) | 6.7 (2/30) | 0 |
| In utero complete reversal of HH % | NS | 36.7 (11/30) | 20 (3/15) |
| Any treatment at repair site % | 13 (10/77) | 10 (3/30) | 6.7 (1/15) |
| Additional recoverage at repair site % | 2.6 (2/77) | 10 (3/30) | 6.7 (1/15) |
| Improved motor function | NS | 43.3 (13/30) | 20 (3/15) |
| Complete reversal of HH at 12 months | 35.7 (25/70) | 36.7 (11/30) | 20 (3/15) |
| CSF diversion at 12 months | 44 (40/91) | 30 (10/30) | 57.1 (8/14) |
| Improved motor function at 30 months | 37.9 (33/87) | 43.3 (13/30) | NS |

Abbreviations used: CI, confidence interval; CSF, cerebrospinal fluid; LC CUSUM, HH, hindbrain herniation; learning curve cumulative sum; MMC myelomeningocele; PROM, preterm premature rupture of membranes; NS, not significant.



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## Study 7 Moron AF (2018)

### Details

| | |
|---|---|
| Study type | **Case series** |
| Country | Brazil |
| Study period | 2011-2017 |
| Study population and number | **n= 237 pregnant women carrying a fetus with an open spinal defect.**<br>Type of defect: myelomeningocele 74.6%, myeloschisis 25.4% |
| Age and sex | Maternal age: mean 30.9 years |
| Study selection criteria | Inclusion criteria: singleton pregnancy; maternal age 18 or more years of age; gestational age at surgery between 24 and 27 weeks; MMC with the upper boundary located between T1 and S1; evidence of hindbrain herniation; normal karyotype and absence of other fetal malformations; body mass index (BMI) <40 kg/m2.<br>Exclusion criteria: fetal kyphosis >30o, high risk for preterm deliveries (cervix length measurement by transvaginal ultrasound <25 mm and/or history of prematurity in a previous pregnancy); placenta praevia; uterine anomaly (fibroids and Mullerian abnormality); maternal conditions that would constitute an additional risk for maternal health (poorly controlled diabetes and hypertension, HIV, hepatitis B or C positivity); maternal-fetal Rh/Kell alloimmunisation or history of fetal neonatal alloimmune thrombocytopenia and maternal psychosocial limitations. |
| Technique | In utero open surgery for myelomeningocele repair. The technique was similar to MOMs trial but did not use surgical stapler. Sutures were used along the uterine incision. Surgery was performed between 24 and 27 weeks. |
| Follow-up | **Intra and post-operative** |
| Conflict of interest/source of funding | The authors declared no conflicts of interest. Study funded by institutional funds. |

### Analysis

**Study design issues**: large retrospective cohort study in 2 centres; all procedures were performed by the same specialist surgical team following the same protocol. The procedure was slightly modified compared to MOMs study.

### Key efficacy and safety findings

**Efficacy and safety**

Number of patients analysed: **237**

**Perinatal and surgical outcomes (n=237)**

| | |
|---|---|
| Total operative time, min | 119.7±7.6 |
| Gestational age at surgery | 25.2 ± 0.4 weeks |
| Gestational age at birth | 33.6 ±2.4 weeks |
| Delivery at less than 30 weeks | 6.8% |
| Delivery at more than 30 weeks | 47.9% |
| Chorioamniotic membrane separation | 20.8% |
| Premature rupture of Membranes (PROM) | 26.7% |
| Chorioamnionitis | 3 % |
| Oligohydramnios | 23.3% |
| Abruptio placentae during surgery (leading to fetal death in 1 and failure to perform fetal surgery in 1) | 0.8 (n=2) |
| Uterine scar dehiscence | 3.8 |
| Preterm labour (in all cases of uterine scar dehiscence) | 24.2% |



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| | |
|---|---|
| Blood transfusion at delivery (associated with uterine atony in 3 and uterine rupture in 2) | 2.1% (n=5) |
| Superficial dehiscence of the fetal repair (needed dressing changes during neonatal period) | 2.5% |
| Reversal of hindbrain herniation at birth (confirmed aby ultrasound and MRI) | 71.4% |
| Perinatal mortality | 2.1% (3 intrauterine deaths and 2 neonatal deaths) |
| Maternal deaths | 0 |

Comparing results from our study in the first 3 years with the last 3 years demonstrated significant improvement in the total surgical time (121.2 ± 6.4 versus 118.5 ± 8.2 minutes, p = 0.005), incidence of oligohydramnios (31.7 versus 16.7%, p = 0.010) and an increase in reversal of hindbrain herniation at birth (64.0 versus 77.1%, p = 0.042). Other variables showed an improvement in perinatal outcome but did not reach statistical significance. With experience outcome parameters improved in the 2 centres.

Abbreviations used:

## Study 8 Goodnight WH (2019)

### Details

| | |
|---|---|
| Study type | **Case series (fMMC registry data)** |
| Country | USA |
| Study period | 2010-2019 |
| Study population and number | **n= 693 pregnant women carrying a fetus with an open spinal defect.** |
| Age and sex | Age not reported |
| Patient selection criteria | Data on patients reporting maternal, obstetric, fetal/neonatal and subsequent pregnancy outcomes following open maternal fetal surgery for fetal myelomeningocele. |
| Technique | In utero open maternal surgery for myelomeningocele repair (method used in MOMs trial) |
| Follow-up | **Intra and post-operative** |
| Conflict of interest/source of funding | The authors declared no conflicts of interest. The registry (maintained by the fetal myelomeningocele consortium, sponsored by NAFTNet) is supported through funding by the Eunice Kennedy Shriver national institute for child health and human development. |

### Analysis

**Follow-up issues:** of 77 pregnancies, 15 are ongoing or missing outcome data so 62 pregnancies were analysed.

**Study design issues**: International multicentre prospective observational registry, data on subsequent pregnancies are collected by patient questionnaires and review of medical records. Investigators are blinded to study sites and patient identification information. This study reports only on a small sample of open maternal fetal surgery cases. Registry excludes MOMs trial patients.

### Key efficacy and safety findings

| **Efficacy and safety** | |
|---|---|
| Number of patients analysed: **693** | |
| Number of subsequent pregnancies | 77 (in 60 women)* |



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| | |
|---|---|
| Spontaneous pregnancy loss prior to 20 weeks | 13% (10/62) |
| Pregnancies that progressed beyond 20 weeks | 52 |
| Median gestational age at delivery | 37 weeks (range 36.3 to 37.1) |
| Overall live birth rate (all delivered by caesarean) | 96.2% (50/52) |
| Uterine rupture rate (all in first subsequent pregnancy) | 9.6% (n=5) |
| Fetal deaths (in uterine rupture cases) | 3.8% (n=2) |
| Uterine dehiscence at the time of delivery | 17.3% (n=9) |
| Maternal blood transfusion | 7.7 (n=4) |
| Placenta previa | 1.9 (n=1) |
| Placenta accrete | 1.9 (n=1) |
| preterm birth <32 weeks | 9.6% (n=5) |
| Preterm labour | 3.8 (n=2) |
| Preterm PROM | 1.9 (n=1) |

*45 women reported 1 subsequent pregnancy, 13 women reported 2 subsequent pregnancies and 2 women reported 3 subsequent pregnancies. 15 are ongoing or missing outcome data so 62 pregnancies were analysed.

Abbreviations used:

## Study 9 Mummareddy N (2019)

### Details

| | |
|---|---|
| Study type | **Case series** |
| Country | US |
| Study period | 1997 to 2003 |
| Study population and number | **n= 74 children who had had intrauterine or postnatal repair.** |
| Age and sex | Age: intrauterine versus postnatal group (median [IQR] 17 years [14 to 17 years] versus 15 years [14 to 19 years], p=0.926), sex (27.3% male versus 41.7% male, p=0.469). |
| Patient selection criteria | Children with myelomeningocele who had had intrauterine or postnatal closure were included. Intrauterine repair was done if lesion level was between T1 and S1 with hindbrain herniation, gestational age less than 25 weeks and 6 days, single pregnancy, and normal karyotype. |
| Technique | In utero open maternal surgery for myelomeningocele repair |
| Follow-up | **Intra and post-operative** |
| Conflict of interest/source of funding | No conflicts of interest; study was funded by a grant from NCATS/NIH |

### Analysis

**Follow-up issues:** 51 families did not respond to the survey (37 were unreachable and 9 did not have contact information, 4 were non English speaking and declined to participate).

**Study design issues**: small single centre study. Caregivers of children who had had intrauterine or postnatal closure were contacted to participate in the study. Patient information identified through medical records. QOL was measured by psychosocial and overall QOL metrics. The Pediatric Quality of Life Inventory (PedsQL 4.0) and a surgical history questionnaire were administered over the phone. Responses to the QOL survey were reverse scored and linearly transformed to a 0 to 100 scale, with a higher score indicating better QOL. The Mann-Whitney U-test was used to analyse differences in means.



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**Study population issues**: there were no significant differences in median age, sex, lesion level and functional level between patients who had the 2 types of repair.

**Other issues**: very low response rate and possible confounders (such as recall bias).

**Key efficacy and safety findings**

**Efficacy and safety**

Number of patients analysed: **23 (11 had intrauterine repair and 12 had postnatal repair)**

31% (23/74) of the patients' families responded to the PedsQL 4.0 questionnaire.

83% (19/23) families responded to the surgical history questionnaire.

**Surgical procedures needed**

| | Intrauterine repair (n=11) | Postnatal repair (n=12) | P value |
|---|---|---|---|
| % receiving neurosurgical procedures | 55.6% | 100% | 0.018 |
| Number of neurosurgical procedures, median (IQR) | 4 (2-10.5) | 2.5 (1.75-6.25) | 0.458 |
| % receiving non-neurosurgical procedures | 100% | 100% | >0.99 |

**Quality of life**

| | Intrauterine repair (n=11) Median (IQR) | Postnatal repair (n=12) Median (IQR) | P value | MCID |
|---|---|---|---|---|
| Physical health | 62.5 (37.5-78.1) | 39.1 (18.8-59.4) | 0.108 | 6.92 |
| Psychosocial health | 70.0 (56.7-83.3) | 55.0 (42.1-60.0) | 0.015 | 5.49 |
| Emotional | 80.0 (70.0-90.0) | 65.0 (51.3-80.0) | 0.040 | 7.79 |
| Social | 80.0(50.0-90.0) | 55.0 (46.3-63.8) | 0.048 | 8.98 |
| School | 60.0 (40.0-65.0) | 37.5 (25.0-50.0) | 0.028 | 9.67 |
| Total QOL score | 56.5 (55.4-81.5) | 49.5 (32.9-59.0) | 0.019 | 4.5 |

Abbreviations used: IQR, inter quartile range; MCID, minimal clinically important differences; PedsQL, paediatric quality of life inventory; QOL, quality of life.



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## Study 7 Lu GC (2001)

### Details

| | |
|---|---|
| Study type | Case report |
| Country | USA |
| Recruitment period | Not reported |
| Study population and number | n=**1 case of in utero open myelomeningocele repair** |
| Age and sex | Age of the woman not reported. Female infant born. |
| Patient criteria | Mild fetal ventriculomegaly, a Chiari type II malformation and a myelomeningocele with highest level of involvement at L5 noted at 20 weeks sonogram. |
| Technique | Open repair of myelomeningocele at 24 weeks gestation through fundal hysterotomy, closed in 2 layers. |
| Follow-up | **9 hours** |
| Conflict of interest/source of funding | none |

### Key efficacy and safety findings

| Safety |
|---|
| Number of patients analysed: **1**<br>**Pulmonary hypoplasia**<br>No intraoperative complications noted after in utero repair. Postoperative course was complicated by pulmonary oedema, abdominal pain, chronic oligohydramnios, persistent mild stable ventriculomegaly. At 33 weeks gestation infant was delivered by a caesarean delivery.<br>The postnatal course was complicated by severe respiratory distress syndrome caused by pulmonary hypoplasia at 9 hours after birth. Despite ventilatory support, infant died from cardiopulmonary arrest. |
| Abbreviations used: |



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## Validity and generalisability of the studies

- Prenatal repair of myelomeningocele was compared with postnatal repair in only 2 studies (1 RCT and a meta-analysis)[1,2]. The meta-analysis (of an RCT and prospective cohort study) assessed the neurodevelopment outcomes of children at 1-year follow-up[2].
- 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.
- 3 systematic reviews (with mainly observational studies) assessed the obstetrical, neonatal outcomes and complication rates after prenatal repair (by fetoscopic surgery and by open fetal surgery).[3-5]
- These two 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

- **Open maternal-fetal surgery for myelomeningocele repair** has been demonstrated to improve a number of important paediatric outcomes at the expense of procedure-associated maternal and fetal risks.
- This surgery should only be offered to carefully selected women with pregnancies complicated by fetal meningocele who meet established criteria for in utero repair. They should be counselled in nondirective fashion regarding all management options, including the possibility of open maternal-fetal surgery.
- Interested candidates for fetal myelomeningocele repair should be referred for further assessment and consultation to a fetal therapy center that offers this intervention and possesses the expertise, multidisciplinary team, services and facilities to provide detailed information regarding maternal-fetal surgery and the intensive care required for patients who choose to undergo open maternal-fetal surgery.[8]



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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.[9]

The MOMS Myelomeningocele Maternal-Fetal Management Task Force (MFMTF) in 2014 recommended standards for all fetal centres offering inutero repair of spina bifida. The criteria include: *fetal spina bifida repairs should only be performed in established centers that employ a multidisciplinary team approach; fetal surgery team must have experience working together and individual members must have a level of expertise in their field; the level of expertise demanded requires an adequate, annual volume of cases to maintain competency; new programs must receive guidance and training from established programs; MOMS protocol should be followed in all stages of care with few exceptions; ongoing care should be performed in multidisciplinary spina bifida clinics; counseling should be full disclosure and nondirective in nature, followed by a 24-hour reflective period; outcome data from all centers should be kept in a national registry with periodic review and a collaborative approach to reporting and research should be maintained; and close links between centers and community providers are essential.*[10]

# 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. Two Specialist Advisor Questionnaires for open prenatal repair for 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 was unable to gather patient commentary for this procedure.



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## *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
  - NCT01983345: Prenatal Surgical Repair of Fetal Myelomeningocele, non-randomised study, 50 participants, recruiting, start date July 2014, estimated completion date March 2022.



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# Appendix

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 |
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| 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 1200 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<br>RCT<br>N=183 women randomised (91 prenatal versus 92 postnatal surgery group)<br>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 to 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 to 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 & Therapy (42) 3 210-217. | Survey of 1200 specialists. | 57% responded. Compared to 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 subspecialists view prenatal closure favorably. These attitudes vary by specialty and risk tolerance. | Physician views |
| 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<br>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 | Parents perceptions regarding provider communication, treatment choices, and the family impact of having a child with MMC. |



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| | | frequently reported negative impacts concerned relational and financial strain. The vast majority of parents indicated that they would still undergo prenatal surgery. | |
| Barini R, Barreto, MW et al (2006). Abruptio placentae during fetal myelomeningocele repair. Fetal Diagnosis & Therapy (21) 1 115-7. | Case report<br>N=1 open prenatal surgical repair at L2. Hysterotomy closed in two layers. | Abruptio placentae and fetal death reported. | Included in systematic review added to table 2 (Junior A 2016). |
| 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<br>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 minimize 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 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. | Included in systematic review added to table 2 |
| Botelho RD, Imada V et al (2017). Fetal Myelomeningocele Repair through a Mini-Hysterotomy. Fetal Diagnosis & Therapy (42) 1 28-34. | Case series<br>N=45 women had fetal myelomeningocele repair through a mini hysterotomy. | There were no maternal, fetal or neonatal deaths. No maternal or fetal complications occurred until maternal hospital discharge. The average gestational age (GA) at surgery was 24.5 weeks. The median hysterotomy length was 3.05 cm. One patient (1/39; 2.6%) experienced chorioamniotic separation. Nine patients (9/39; 23.1%) had premature preterm rupture of membranes at a median GA of 34.1 weeks. The average GA at delivery was 35.3 weeks. Ninety-five percent (37/39) of our patients had an intact hysterotomy site at delivery. Ventriculoperitoneal shunt placement was necessary for 7.7% (3/39) of the neonates. | Modified open surgical approach though a mini hysterotomy. Included in systematic review added to table 2. |
| 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<br>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 - | 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 | Larger studies included in table 2. |



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| | S5 versus 4 fetuses with myelomeningocele had standard neurosurgical closure at 28-29 weeks' gestation. | 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. | |
| Bruner JP, Tulipan N et al (2004). Intrauterine repair of spina bifida: preoperative predictors of shunt-dependent hydrocephalus. American Journal of Obstetrics & Gynecology (190) 5 1305-12. | Case series (retrospective)<br>N=116<br>Open approach | This study suggests that, among fetuses who underwent operation in utero for spina bifida, fetuses with a ventricular size of <14 mm at the time of surgery, fetuses who had surgery at <or=25 weeks of gestation, and fetuses with defects that were located at <or=L4 were less likely to require ventriculoperitoneal shunting for hydrocephalus during the first year of life. | Study included in systematic review added to 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<br>N=10 patients undergoing hysterotomy for intrauterine repair of myelomeningocele were randomized 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. |
| Bruner JP, Tulipan N et al (1999). Fetal surgery for myelomeningocele and the incidence of shunt-dependent hydrocephalus. JAMA (282) 19 1819-25. | Case series<br>N=29 fetal MMC open surgery versus 23 matched controls.<br>Follow-up 6 months after delivery | Among study infants, the requirement for ventriculoperitoneal shunt placement was significantly decreased (59% vs 91%; P = .01). The median age at shunt placement was also older (50 vs 5 days; P = .006). Reduced incidence of hindbrain herniation (38% vs 95%; P<.001) reported. Following hysterotomy, study patients had an increased risk of oligohydramnios (48% vs 4%; P = .001) and admission to the hospital for preterm uterine contractions (50% vs 9%; P = .002). The estimated gestational age at delivery was earlier for study patients (33.2 vs 37.0 weeks; P<.001), and the birth weight of study neonates was less (2171 vs 3075 g; P<.001). | Larger studies included in 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<br>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. |
| Clayton DB, Tanaka ST et al (2011). Long-term urological impact of fetal myelomeningocele closure. Journal of Urology (186) 4 SUPPL. 1581-1585. | Retrospective case control<br>N=28 Open fetal myelomeningocele surgery<br>Follow-up mean 129.6 months | At a mean age of 9.6 years 23 used clean intermittent catheterization to manage the bladder, 24 required a bowel regimen to manage constipation and 6 underwent lower urinary tract reconstruction with enterocystoplasty and a catheterizable bladder channel. Videourodynamics performed in 14 patients at a mean age of 7.4 years revealed | Included in systematic review added to table 2. |



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| | Retrospective review and survey questionnaire -study were compared to 33 matched patients who had postnatal closure | decreased bladder capacity in 71%, detrusor overactivity in 35% and increased detrusor pressure in 25%. Compared to matched children who underwent postnatal closure no significant differences were noted in bladder management, urinary tract surgery or urodynamics. | |
| Carr, MC (2015). Urological results after fetal myelomeningocele repair in pre-MOMS trial patients at the Children's Hospital of Philadelphia. Fetal Diagnosis & Therapy (37) 3 211-8. | Retrospective case series<br>N=54 open fetal myelomeningocele surgery between 21 and 25 weeks' gestation.<br>Follow-up mean >12 months (5 years) | 4 fetal deaths occurred, and majority of patients followed up 5 years. 10 patients (18.5%) have successfully toilet-trained, while 2 patients have bowel continence and 1 had bladder continence but required enemas; 2 patients who successfully toilet-trained developed spinal dermoid cysts requiring surgical resection. | Included in systematic review added to table 2. |
| Corral E, Sepulveda W et al \|(2019). Use of plastic wound retractor at hysterotomy site in prenatal repair of myelomeningocele: a new technique. Journal of Maternal-Fetal & Neonatal Medicine 1-161. | Case series<br>N=16 cases of open surgery for prenatal repair of myelomeningocele using a new technique (use of a plastic wound retractor at hysterotomy site during prenatal repair of myelomeningocele to minimise surgical trauma). | When compared with MOMS trial, the use of the retractor was associated with a lower, rate of chorioamniotic membrane separation (20/78 (26%) versus 2/16 (13%), respectively), preterm rupture of membranes (36/78 (46%) versus 4/16 (25%), respectively), and persistent oligohydramnios (16/78 (21%) versus 1/16 (6%), respectively) as well as higher gestational age at delivery (34.1 weeks +/- 3.1 versus 36.0 weeks +/- 1.93, respectively) and birthweight (2383 g +/- 688 versus 2790 g +/- 529, respectively). There were no intra- or postoperative complications associated with the use of the device. | Modified open surgical approach in prenatal repair (preliminary study). |
| Brock JW, Carr MC et al (2015). Bladder Function After Fetal Surgery for Myelomeningocele. Pediatrics (136) 4 e906-13. | Retrospective case series-sub-study of MOMs study.<br>N=56 open fetal myelomeningocele surgery<br>Follow-up mean 12-30 months. | Prenatal surgery did not significantly reduce the need for clean intermittent catheterization (CIC) by 30 months of age but was associated with less bladder trabeculation and open bladder neck. The implications of these findings are unclear now but the need for long-term urologic follow-up of patients is needed. | Included in systematic review added to table 2. |
| Danzer E, Johnson MP et al (2004). Fetal head biometry following in-utero repair of myelomeningocele. Ultrasound in Obstetrics & Gynecology (24) 6 606-11. | Case series<br>N=50 fetuses had open fetal myelomeningocele repair | Preoperatively, the head circumference in fetuses with myelomeningocele was smaller than control values (186.4 vs. 198.8 mm, P = 0.0004). 8 weeks' postoperatively this difference had resolved (293 vs. 301.6 mm, P = 0.76). The mean increase in cortical index after repair was 20% (P = 0.02) compared with the predicted 51% in normal cases. The average increase in ventricular diameter was 3.9 mm (38.8%, P < 0.001). Mid-gestational repair of myelomeningocele alters fetal head growth. | Impact on fetal head biometry. |
| Danzer E, Johnson MP et al (2007). Fetal head biometry assessed by fetal magnetic resonance imaging following in utero myelomeningocele repair. Fetal Diagnosis & Therapy (22) 1 1-6. | Retrospective comparative study<br>N=22 myelomeningocele (MMC) foetuses with prenatal repair were compared to the pre- and postnatal | Mid-gestational repair of MMC promotes normalization of extra-axial cerebrospinal fluid (CSF) spaces. Due to progressive ventriculomegaly, brain thickness remains decreased in both prenatal repaired and age-matched non-repaired MMC patients when compared to age-matched normal values. Restoration of CSF volume in the posterior | Impact on fetal head biometry and CSF spaces. |



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| | 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). | fossa after in utero repair is indicative of reversal of hindbrain herniation. | |
| 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<br>N=54 patients underwent open fetoscopic MMC surgery<br>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, Gerdes M et al (2009). Lower extremity neuromotor function and short-term ambulatory potential following in utero myelomeningocele surgery. Fetal Diagnosis & Therapy (25) 1 47-53. | Retrospective case series<br>N=54 open fetal MMC surgery<br>Follow-up 66 months | We observed that fetoscopic MMC surgery in this highly selective population results in better than predicted Lower extremity neuromotor function at birth and short-term ambulatory status. However, fetoscopic MMC toddlers continue to demonstrate deficits in movement coordination that are characteristic for children with spina bifida. | 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 neurodevelopmental outcome following fetal myelomeningocele closure. Neuropediatrics (41) 3 140-3. | Retrospective review<br>N=54 children had fetoscopic MMC repair<br>databases and a parental questionnaire used. | 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 outcome. The occurrence of severe acquired intracranial injury and chronic epilepsy, however, appeared to be correlated with adverse neurocognitive outcome following fetoscopic MMC surgery. | Outcomes already reported in table 2. |
| Danzer E, Finkel RS et al (2008). Reversal of hindbrain herniation after maternal-fetal surgery for myelomeningocele subsequently impacts on brain stem function. Neuropediatrics (39) 6 359-62. | Retrospective case series (survey)<br>N=48 open fetal MMC surgery<br>Follow-up mean 72 months. | The majority of fetoscopic MMC children developed no or only mild brain stem dysfunction at follow-up. Our data support the hypothesis that neurodevelopmental deficits associated with MMC are at least partially acquired and that reversal of hindbrain herniation following fetoscopic MMC surgery may help to reduce the incidence and severity of brain stem dysfunction. | Included in systematic review added to table 2. |



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| 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<br>N=54 children underwent Fetoscopic MMC (fMMC) closure.<br>30 (56%) returned at 5 years of age for standardized 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. |
| Danzer E, Gerdes M et al (2011). Fetal myelomeningocele surgery: preschool functional status using the Functional Independence Measure for children (WeeFIM). Childs Nervous System (27) 7 1083-8. | Retrospective case series<br>N=26 open fetal MMC surgery<br>Follow-up 60 months | The majority of fMMC children achieved cognitive and mobility independence but continue to require significant assistance in self-care. Non-shunted and fMMC children with normal neurodevelopmental outcome were more likely to be independent in daily living activities. Better understanding of the extent of functional limitations following fMMC surgery will allow for more effective early interventions geared toward maximizing independence in everyday tasks in all environments. | Included in systematic review added to table 2. |
| Donepudi, R., Huynh, M., Moise, K. Jet al. (2019) Early Administration of Magnesium Sulfate during Open Fetal Myelomeningocele Repair Reduces the Dose of Inhalational Anesthesia. Fetal Diagnosis & Therapy (45) 3 192-196. | Prospective observational study Open fetal MMC repair magnesium sulfate at uterine closure (n=30) versus magnesium sulfate at maternal skin incision (n=21) | There was no difference in gestational age at intervention (24.92 +/- 0.62 vs. 25.22 +/- 0.47 weeks, p = 0.07) or at delivery (34.83 +/- 2.77 vs. 33.98 +/- 3.83 weeks, p = 0.38) between groups. The maximum MAC of sevoflurane was significantly lower in group 2 (1.84 +/- 0.25 vs. 1.05 +/- 0.28, p < 0.0001). There was no difference in the average dose of phenylephrine used.<br>Magnesium sulfate infusion initiated earlier in open fetal surgery reduces the total anesthetic exposure to the fetus. | Small study on use of magnesium sulfate |
| 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<br>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) | Hydrocephalus treatment outcomes |



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| | | 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. | |
| Friszer S, Dhombres, F et al (2016). Preliminary results from the French study on prenatal repair for fetal myelomeningoceles (the PRIUM study) (in French). Journal de Gynecologie Obstetrique et Biologie de la Reproduction (45) 7 738-744. | Prospective case series<br>N=3<br>Open prenatal surgery for MMC.<br>Follow-up:<1 year | Study suggests that only a limited number of couples will choose this procedure after specialized counselling in a reference centre. | Included in systematic review added to table 2. |
| Farmer DI, Thom EA, et al (2018). The Management of Myelomeningocele Study: full cohort 30-month pediatric outcomes. American journal of obstetrics and gynecology (218) 2 256.e1-256.e13. | RCT<br>N=183 with MMC<br><br>67/92 standard postnatal repair versus 62/91 prenatal open repair <26 weeks gestation<br><br>Follow-up 30 months | Prenatal repair improves the primary outcome composite score of mental development and motor function (199.4 ± 80.5 vs 166.7 ± 76.7, P = .004). Prenatal surgery also resulted in improvement in the secondary outcomes of independent ambulation (44.8% vs 23.9%, P = .004), WeeFIM self-care score (20.8 vs 19.0, P = .006), functional level at least 2 better than anatomic level (26.4% vs 11.4%, P = .02), and mean Bayley Scales of Infant Development, Second Edition, psychomotor development index (17.3% vs 15.1%, P = .03), but does not affect cognitive development at 30 months. The full cohort data of 30-month cognitive development and motor function outcomes validate in utero surgical repair as an effective treatment for fetuses with myelomeningocele. Current data suggest that outcomes related to the need for shunting should be counselled separately from the outcomes related to distal neurologic functioning. | Included in systematic review added to table 2. |
| Flanders, TM., Heuer, GG., Madsen, PJ et al. (2019) Detailed Analysis of Hydrocephalus and Hindbrain Herniation After Prenatal and Postnatal Myelomeningocele Closure: Report From a Single Institution. Neurosurgery (20) 20. | Retrospective study (subset of MOMS patients) who underwent fetal (n=119) /postnatal (n=62) MMC repair | In the postnatal group, 80.6% required CSF diversion compared to 38.7% fetal cases (P < .01). Hindbrain herniation resolution occurred in 81.5% fetal repairs compared to 32.6% postnatal (P < .01). In the fetal group, fetal/premature neonatal demise occurred in 6/119 (5.0%) patients. There was a 42.0% decrease (95% CI -55.2 to -28.8) and 48.9% increase (95% CI 33.7 to 64.1) in risk difference for CSF diversion and hindbrain herniation resolution, respectively, in the fetal group. On univariate analysis for both groups, prenatal atrial diameter, frontal-occipital horn ratio, and hindbrain herniation resolution were significantly associated with the absence of clinical hydrocephalus. The treatment of hydrocephalus was significantly delayed in the fetal group compared to the postnatal group (10 mo vs 13.8 d). | More comprehensive studies added to table 2. |
| Flanders, TM., Madsen, PJ., Pisapia, JM et al. (2019) Improved Postoperative Metrics with Modified | Retrospective study of a subset of post-MOMS patients (n=119) | Cerebrospinal fluid diversion was seen in 32 of 74 patients with the standard technique compared to 14 of 45 with the modified closure and was significantly decreased in post | Modified myofascial closure technique |



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| Myofascial Closure in Fetal Myelomeningocele Repair. Operative Neurosurgery (21) 21. | Fetal MMC repair - modified myofascial closure technique (compared pre and post modification groups) | modification when compared to that of the MOMS trial (P = .01). Hindbrain herniation resolution was significantly decreased in both the pre- and post-modification groups compared to that of the MOMS trial (P < .01). Prior to January 2015 with standard closure, 23 cysts required resection whereas no cysts required resection in the modified repair group (P < .01). Modified myofascial closure for fMMC closure is safe and feasible. | |
| 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.<br>N=71 fetuses which underwent minimally invasive fetoscopic patch coverage of SBA between 21 + 0 and 29 + 1 weeks of gestation.<br>Postnatal neurosurgical procedures were classified into two types: re-coverage of the SBA within the first 3 months following birth, and shunt placement as treatment of associated hydrocephalus within the first year.<br>Follow-up: 1 year | 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 seven (35%), adhesions with functional deterioration in three (15%), incomplete coverage in five (25%) and skin defect in five (25%) cases. Ventriculoperitoneal shunt placement within 1 year was required in 32 (45%) cases and was preceded by ventriculostomy in two. Three (4%) infants needed Chiari decompression surgery in the first 12 months following birth, because of syringomyelia or gait disturbance.<br>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 comparable to data of the Management of Myelomeningocele Study and lower compared with published data of patients with postnatal only coverage of SBA. | Included in systematic review added to table 2. |
| 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<br>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 normalized 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<br>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 (four 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. |
| Gomes Parizi, Joao Luiz, Leal da Cruz et al. (2019) A Comparative Analysis of Bladder Pattern of Patients that Underwent In Utero Versus Postnatal | Retrospective review fetal MMC surgery (n=88) and postnatal repair (86), postnatal repair patients below 12 months age (n=38). | In utero repair did not improve urological parameters when compared to patients operated in the postnatal period. | Similar studies included in systematic reviews |



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| Myelomeningocele Repair. Journal of Urology 101097JU0000000000000521 Sep 03, 2019. | | | |
| 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<br>N=95 infants who had intrauterine MMC repair.<br>(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<br>N=100 infants who had intrauterine MMC repair.<br>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 following IUMR and those associated with prematurity resulting from other causes. | Prematurity following prenatal MMC repair - outcomes already reported in table 2. |
| Hisaba WJ, Cavalheiro S et al (2012). Intrauterine myelomeningocele repair Postnatal results and follow-up at 3.5 years of age - Initial experience from a single reference service in Brazil. Child's Nervous System (28) 3 461-467. | Prospective case series<br>N=6 children who had open surgical repair of MMC between 26 and 27 weeks gestation.<br>Follow up 3.5 months. | Ventricular-peritoneal shunts were placed in 2cases. All 6 children are alive:5 have normal cognitive development and 1 has a neuropsychomotor developmental delay. 2 children had normal leg movements, a sacral functional level and are community ambulators. 3 children had upper lumbar anatomical level lesions and 1 had a lower thoracic level lesion at the time of fetal surgery. 1 child, with an L1-L2 anatomical level lesion, in no ambulatory and fully dependent on a wheelchair for mobility. | Included in systematic review added to table 2. |
| Hilton, SA., Hodges, MM., Dewberry, LC et al. (2019) MOMS Plus: Single-Institution Review of Outcomes for Extended BMI Criteria for Open Fetal Repair of Myelomeningocele. Fetal Diagnosis & Therapy 1-4 May 02. | Retrospective review Open fetal repair in women with BMI>35 N=11 | No adverse maternal outcomes associated with maternal obesity; however, the gestational age at delivery was 2 weeks earlier (average 32 weeks) compared to the MOMS trial. | Small study on a subgroup of patients with high BMI |
| 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)<br>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. |



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| Horst M, Mazzone L et al (2017). Prenatal myelomeningocele repair: Do bladders better? Neurourology & Urodynamics (36) 6 1651-1658. | Case series (prospective)<br>8 patients who had prenatal MMC closure with a postnatal follow-up of 2 years compared with eight 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. |
| Howley, LW., Chatterjee, D., Patel, S et al. (2019). Indomethacin dosing and constriction of the ductus arteriosus during open fetal surgery for myelomeningocele repair. Fetal Diagnosis and Therapy (45) 5 339-344. | Retrospective case series<br>N=42 women who had open fetal myelomeningocele repair | DA constriction was the most frequent and severe in the BID indomethacin group. QD indomethacin and greater magnesium sulfate dosing was associated with reduced DA constriction. Minimal fetal cardiac dysfunction (9.5%) and bradycardia (9.5%) were observed in all groups independent of indomethacin dosing. | Small study on use of perioperative tocolytic agents |
| 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 utilizes 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, Sutton, LN et al (2003). Fetal myelomeningocele repair: short-term clinical outcomes. American Journal of Obstetrics & Gynecology (189) 2 482-7. | Retrospective case series<br>Open approach<br>N=50<br>Level of lesion S1 or higher, lateral ventricle<17mm.<br>Hysterotomy closed in 2 layers. | Perinatal survival was 94% (47/50 fetuses). Mean age at delivery was 34 weeks 3 days. All fetuses demonstrated reversal of hindbrain herniation. Forty-three percent of the 50 fetuses have required ventriculoperitoneal shunting compared with 100% thoracic, 88% lumbar, and 68% sacral (85% overall) in 297 historic controls. Better-than-predicted leg function was seen in 57% of thoracic and lumbar level lesion patients. Early experience with fetal MMC repair suggests a decreased need for ventriculoperitoneal shunting, arrest or slowing of progressive ventriculomegaly, and consistent resolution of hindbrain herniation. | Included in systematic review added to table 2 |
| Johnson, MP, Bennett, KA, et al (2016).The Management of | Retrospective case series | prenatal surgery was associated with an increased risk for membrane separation, | Overlapping data with |



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| Myelomeningocele Study: obstetrical outcomes and risk factors for obstetrical complications following prenatal surgery. American journal of obstetrics and gynecology (215) 6 778.e1-778.e9. | 183 randomized (91 to prenatal and 92 to postnatal surgery)<br>Pregnancy outcomes were compared between the 2 surgery groups | 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 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). | MOMs trial (follow-up data of the MOMS study). |
| Johnson MP, Gerdes M et al (2006). Maternal-fetal surgery for myelomeningocele: neurodevelopmental outcomes at 2 years of age. American Journal of Obstetrics & Gynecology (194) 4 1145-50; discussion 1150-2. | Retrospective case series<br>N=30<br>Fetal MMC surgery - open approach<br>Mean follow-up= >12 months. | Overall shunt rate was 43% in this group. Neurodevelopmental testing found 67% with cognitive language and personal-social skills in the normal range, 20% with mild delays, and 13% with significant delays. Children with shunted hydrocephalus scored lower than those with unshunted ventriculomegaly. Children have characteristic neurodevelopmental deficits that do not appear worsened by fetal surgery, and developmental outcomes may be improved by decreasing the need for ventriculoperitoneal shunting. | 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 summarizes 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 |
| Kahr, Maike Katja, Winder, Franziska, Vonzun, Ladina, et al. (2019) Risk Factors for Preterm Birth following Open Fetal Myelomeningocele Repair: Results from a Prospective Cohort. Fetal Diagnosis & Therapy 1-9 May 17. | Retrospective case series<br>N=67 women had open fMMC repair. | Risk factors for preterm birth were preterm rupture of membranes (PPROM), chorioamniotic membrane separation (CMS), and placental abruption, whereas surgery duration did not influence outcome. the majority of women delivered at a gestational age >35 weeks. We conclude that the surgery technique should aim to minimize CMS and amniotic fluid leakage. | More comprehensive studies added to table 2. |
| Macedo, A Jr., Cavalheiro, S, Moron, A et al. (2019) Urinary and Fecal Continence in 5-Year-Old Patients Who Underwent in utero Myelomeningocele Repair: A Prospective Study. Fetal Diagnosis & Therapy 1-4 Mar 18. | Prospective case series<br>N=14 patients who had inutero MMC repair | The uro-dynamic class was high-risk in 6 (42.9%), incontinent in 4 (28.6%), hypocontractile in 1 (7.1%), normal in 3 (21.4%) patients. Three patients had undergone surgery. Twelve patients underwent clean intermittent catheterization (CIC) (85.7%). 3 (21.4%) patients had no urinary leakage. 11 patients (78.6%) used diapers. 8 patients (57.2%) underwent retrograde rectal irrigation and 11 (78.6%) complained of fecal loss. 11 patients (78.6%) did not report an impact on their self-esteem. Despite the use of CIC in | Similar studies included in systematic reviews |



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| | | 85.7% of the cases, the continence rate in MMC patients was low. | |
| 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.<br>n=19 patients<br>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 two 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 Catheterization 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<br>N=100 in utero myelomeningocoele (MMC) repair<br>Patients were categorised into four 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).<br>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 |
| Mohrlen, Ueli, Ochsenbein-Kolble, Nicole, Mazzone, et al. (2019) Benchmarking against the MOMS Trial: Zurich Results of Open Fetal Surgery for Spina Bifida. Fetal Diagnosis & Therapy 1-7 Jun 05. | Case series N=20 had open fetal surgery for spina bifida | There were only 3 favorable significant differences (gestational age at birth, hindbrain herniation, and psychomotor development). There were no statistically significant differences regarding any other parameters. Our findings confirm that rigorous apprenticeship, training, and comprehensive prospective data collection enable to achieve benchmark results. | More comprehensive studies added to table 2. |
| Mazzola, CA., Tyagi, R, Assassi, Nadege, B et al. (2019) Congress of Neurological Surgeons Systematic Review and Evidence-Based Guideline on the Incidence of Tethered Cord Syndrome in Infants With Myelomeningocele With Prenatal Versus Postnatal | Systematic review and guideline<br><br>prenatal closure versus postnatal closure. | There was Class II evidence from 1 study and Class III evidence from another 2 studies demonstrating that TCS develops in infants with prenatal MM closure at an equal or higher rate than with postnatal closure. There was an increased risk of development of inclusion cysts in infants who underwent in utero closure. Continued surveillance for TCS and/or the development of inclusion cysts in children with prenatal and postnatal closure of MM is | More comprehensive studies added to table 2. |



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| Repair. Neurosurgery (85) 3 E417-E419. | | indicated (Level II). Differences between prenatal and postnatal repair with respect to the development of TCS and/or inclusion cysts should be considered alongside other relevant maternal and fetal outcomes when deciding upon a preferred method for MM closure. | |
| Moldenhauer, JS. and Flake, AW (2019). Open fetal surgery for neural tube defects. Best Practice & Research in Clinical Obstetrics & Gynaecology (58) 121-132. | Review | This article will provide background to the scope of MMC, review the MOMS trial data, and highlight the current clinical status of open fMMC closure. | Review |
| Manrique S, Maiz, N et al (2018). Maternal anaesthesia in open and fetoscopic surgery of foetal open spinal neural tube defects: A 6-year observational study. European Journal of Anaesthesiology (30). | Retrospective cohort study<br>N=29 foetuses 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-operative tocolytic drugs [five of seven (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 (three drugs in all seven 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. | Anaesthetic management |
| Manrique S, Maiz N, Garcia I et al. (2019) Maternal anaesthesia in open and fetoscopic surgery of foetal open spinal neural tube defects: A retrospective cohort study. European Journal of Anaesthesiology (36) 3 175-184. | Retrospective cohort study prenatal open (n=7) versus fetoscopic (n=22) surgery | Open surgery was associated with more maternal haemodynamic changes and higher doses of halogenated anaesthetic and tocolytics agents than fetoscopic surgery. | Small study on use of anaesthesia |
| Nagaraj, UD., Bierbrauer, KS., Stevenson, CB et al. (2019) Prenatal and postnatal MRI findings in open spinal dysraphism following intrauterine repair via open versus fetoscopic surgical techniques. Prenatal Diagnosis (27) 27. | Retrospective analysis of fetal MRIs after prenatal repair of open spinal dysraphism by open hysterotomy (n=42) and fetoscopic approach (n=15) | Lateral ventricular size was significantly larger in the open (20.9 +/- 6.7 mm) versus the fetoscopic repair (16.1 +/- 4.9 mm) group (P = 0.01). This can likely be explained by initial selection criteria used for fetoscopic repair. Other postoperative imaging parameters on postnatal MRI (hindbrain herniation, spinal cord syrinx) were not significantly different between the two groups. | Small study assessing MRI findings |



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| Ochsenbein-Kolble, N., Brandt, S., Bode, P et al (2019) Clinical and Histologic Evaluation of the Hysterotomy Site and Fetal Membranes after Open Fetal Surgery for Fetal Spina Bifida Repair. Fetal Diagnosis & Therapy (45) 4 248-255. | Retrospective case series<br>N=36 women who had open fetal surgery | study provides evidence that the myometrium shows scarring with substantial thinning or dehiscence. Fetal membranes do not heal spontaneously. In order to prevent uterine rupture in subsequent pregnancies, we recommend the hysterotomy site to be completely excised after birth. | Histological analysis |
| 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<br>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 |
| Sanz Cortes, M., Davila, I., Torres, P et al. (2019) Does fetoscopic or open repair for spina bifida affect fetal and postnatal growth? Ultrasound in Obstetrics & Gynecology (53) 3 314-323. | Retrospective cohort study<br>Fetoscopic (n = 32) or open hysterotomy (n = 34) MMC repair in utero | Babies exposed to fetoscopic or open MMC repair in-utero did not show significant differences in fetal or postnatal growth parameters. These results support the safety of the use of CO2 gas for fetoscopic surgery. | Small study assessing biometrics |
| Sanz Cortes, Magdalena, Torres, Paola, Yepez, Mayel et al. (2019) Comparison of brain microstructure after prenatal spina bifida repair by either laparotomy assisted fetoscopic or open approach. Ultrasound in Obstetrics & Gynecology (20) 20. | Longitudinal retrospective cohort study<br>Prenatal Fetoscopic (n=27) or Open MMC (n=30) repair at 23-25.6 weeks of gestational age.<br>Follow-up 1 year (n=23, 5 fetoscopic and 18 open) | There were no differences in the degree of ventriculomegaly, GA at surgery, or GA/postnatal age at MRI between the groups. No differences in ADC values were seen between both groups. Additionally, there were no differences observed in the % change in ADC values either.<br>Fetoscopic MMC repair has no detectable effects on brain microstructure when compared to babies repaired by an open hysterotomy technique. Carbon dioxide insufflation of the uterine cavity during fetoscopy does not seem to have any isolated deleterious effects in fetal brain microstructure. | Small study assessing brain microstructure |
| Sacco, A, Ahmed, S, Deprest, J and David, AL (2019). A study to assess knowledge and acceptability of foetal surgery for spina bifida amongst healthcare professionals in the UK. Journal of Obstetrics & Gynaecology 1-7. | Survey on knowledge and acceptability of this treatment to healthcare professionals in the UK and Ireland (n=98). | Overall the majority of healthcare professionals agree with the concept that foetal surgery improves neonatal outcome in selected cases, but a variety of concerns exist, the most common being the lack of information regarding mid- to long-term effects on the child and mother. Other concerns included a lack of education, training and research; the specific risk of preterm birth following surgery; the evidence base for this procedure; effects on maternal choice and financial implications. | Survey |
| Sanz Cortes, Magdalena, Castro, Eumenia, Sharhan, Dina et al 2019. Amniotic membrane and placental histopathological findings after | Retrospective study<br>43 prenatally repaired spina bifida cases (17 fetoscopic and 26 open) | Fetoscopic surgery cases did not show significant differences in any of the studied parameters when compared against controls. No differences were detected either when compared with open repaired cases, except for | Small study on histological parameters |



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| open and fetoscopic prenatal neural tube defect repair. Prenatal Diagnosis (39) 4 269-279. | and 18 healthy controls were assessed. | lower proportion of pigmented laden macrophages in the fetoscopic group (11.8% vs 61.5%, P < 0.01). No associations between the duration of surgery or the duration of CO2 exposure and any of the quantitative histological parameters were detected. | |
| Tamber, Mandeep S., Flannery, Ann Marie, McClung-Smith, Catherine et al. (2019) Congress of Neurological Surgeons Systematic Review and Evidence-Based Guideline on the Incidence of Shunt-Dependent Hydrocephalus in Infants With Myelomeningocele After Prenatal Versus Postnatal Repair. Neurosurgery (85) 3 E405-E408. | Systematic review and guideline<br>Prenatal repair versus postnatal repair | Class I evidence from 1 study and class III evidence from 2 studies suggest that, in comparison to postnatal repair, prenatal surgery for MM reduces the risk of developing shunt-dependent hydrocephalus. Therefore, prenatal repair of MM is recommended for those fetuses who meet specific criteria for prenatal surgery to reduce the risk of developing shunt-dependent hydrocephalus (level I). Differences between prenatal and postnatal repair with respect to the requirement for permanent cerebrospinal fluid diversion should be considered alongside other relevant maternal and fetal factors when deciding upon a preferred method of MM closure. | More comprehensive studies added to table 2. |
| 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<br>N=183<br>91 women were randomized to prenatal surgery and 92 to postnatal repair.<br>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). |



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|---|---|---|---|
| Zamlynski, J, Horzelska, E et al (2017). Current views on fetal surgical treatment of myelomeningocele - the Management of Myelomeningocele Study (MOMS) trial and Polish clinical experience. Ginekologia Polska (88) 1 31-35. | Review | The main goal of fetal MMC repair is to improve development and life quality of children with Chiari II malformation. Management of 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). | Review |
| 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<br>N=55 fetouses (32 had open hysterotomy and 18 had fetoscopic repair).<br>Follow-up 1 year<br><br>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 treatment 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. |



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# Literature search strategy

| Databases | Date searched | Version/files |
|---|---|---|
| Cochrane Database of Systematic Reviews – CDSR (Cochrane Library) | 18/09/2019 | Issue 9 of 12, September 2019 |
| Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library) | 18/09/2019 | Issue 9 of 12, September 2019 |
| HTA database (CRD website) | 18/09/2019 | n/a |
| MEDLINE (Ovid) & MEDLINE In-Process (Ovid) | 18/09/2019 | 1946 to September 16, 2019 |
| Medline ePub ahead (Ovid) | 18/09/2019 | September 16, 2019 |
| EMBASE (Ovid) | 18/09/2019 | 1974 to 2019 September 17 |

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)



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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)
46 limit 45 to ed=20190101-20190930 (50)



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