**Prenatal Predictors of Need for CSF Diversion in Infants Following Prenatal Repair of Open Spina Bifida; Systematic Review and Meta-analysis**

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**Condensation:** In prenatally repaired OSB, the gestational age at the time of surgery and preoperative LV diameter appeared to be strongly associated with the need for CSF diversion by 12 months of age, in which both GA at fetal surgery ≥25 weeks and preoperative LV diameter>15 mm lesion more than quadrupled that risk. Similarly, lesion level at L2 or higher and Myeloschisis type of lesion were strong associations in which they more than doubled that risk. Of all these significant associations, gestational age at the time of the repair is a modifiable factor; therefore, we recommend earlier repair to decrease the incidence of shunt-dependent hydrocephalus.

**Short title:** Prenatal repair of meningomyelocele and cerebrospinal fluid diversion

**AJOG at Glance**

**Why was this study conducted?**

To investigate prenatal predictors of the need for cerebrospinal fluid (CSF) diversion in infants with the prenatal repair of open spina bifida (OSB).

**Key findings:**

In pregnancies undergoing prenatal repair of open spina bifida, preoperative factors that predict the need for CSF diversion during the first year of life were gestation at surgery of 25 weeks or beyond, preoperative posterior horn of lateral ventricles measuring 15 mm or more, Myeloschisis type of lesion, and preoperative lesion level above L3.

**What does this add to what is known?**

This study provides pertinent counseling points regarding the postnatal need for CSF fluid diversion in fetuses with open spina bifida considered for prenatal repair.

**Abstract**

**Objectives:** We aimed to investigate prenatal predictors of the need for cerebrospinal fluid (CSF) diversion in infants following prenatal repair of open spina bifida (OSB).

**Data sources:** A systematic search was performed to identify relevant studies published from inception until Jun 2022 in the English language using the databases PubMed, Scopus, and Web of Science.

**Study eligibility**: We included retrospective and prospective cohort studies as well as randomized controlled trials reporting on the prenatal repair of open spina bifida (OSB).

**Study appraisal and synthesis methods:** The random-effect model was used to pool the mean differences or odds ratios (OR) and the corresponding 95% confidence intervals (CIs). Heterogeneity was assessed using the I2 value.

**Results:** A total of nine studies, including 948 pregnancies undergoing prenatal repair of OSB, were included in the final analysis. Prenatal factors that were significantly associated with the need for postnatal CSF diversion were gestational age (GA) at surgery≥25 weeks (OR:4.2, 95% CI 1.8, 9.9; I2=54%; P=0.001), Myeloschisis (OR:2.2;95% CI 1.1, 4.1; I2 =0.0%, P=0.02), preoperative lateral ventricle (LV) width ≥15 mm (OR:4.5, 95% CI 2.9, 6.9; I2 = 0.0%; P<0.0001), predelivery LV width (mm) (MD: 8.3, 95% CI 6.4, 10.2; I2= 0.0%; P<0.0001), and preoperative lesion level at T12-L2 (OR 2.5; 95% CI 1.03, 6.3; I2 = 68%, P=0.04). Factors that significantly reduced the need for postnatal shunt placement were GA at surgery<25 weeks (OR 0.3, 95% CI 0.15, 0.6; I2 67%; P=0.001) and preoperative LV width <15 mm (OR 0.3, 0.2, 0.4; I2 =0.0%; P<0.0001).

**Conclusion:** This study demonstrated that among fetuses that underwent surgical OSB repair, those with GA at surgery at or beyond 25 weeks, preoperative LV width of 15 mm or more, Myeloschisis type of lesion, and preoperative lesion level above L3 were predictive of the need for CSF diversion during the first year of life.

**Introduction**

Spina bifida is a congenital anomaly of the neural tube associated with neurological complications, loss of bowel and bladder function, and deterioration of lower extremity motor control. There are approximately 1,500 newborns with spina bifida each year in the United States1.

Myelomeningocele (MMC) is the most severe form of open spina bifida (OSB) in which there is a defect in the vertebral column with a sac-like protrusion of the meninges and spinal cord. It occurs due to the failure of caudal neuropore fusion during embryogenesis, leading to chronic exposure of the neural placode to the hostile uterine environment with ongoing mechanical and chemical destruction. This two-step injury is commonly known as the two-hit theory 2. In addition, chronic CSF leaking through the defect results in progressive hindbrain herniation and obliteration of the cisterna magna, a condition known as Chiari II malformation. This herniation is associated with a substantial risk of subsequent injury to various brainstem functions and worsening hydrocephalus 2, which is seen in 80-90% of individuals with MMC 3.

Despite prompt postnatal repair, OSB is linked to an increased mortality rate ranging from 14% to 35% in the first five years of life, the highest among those with brainstem dysfunction secondary to chronic herniation 4. In addition, survivors with (OSB) can suffer lifelong morbidity related to hydrocephalus, shunt complications, motor impairment, and sphincteric dysfunction. 4

The value of prenatal repair is to decrease the disease implication by interrupting the second hit mentioned earlier. In 2011, a multicenter, randomized controlled trial known as the management of myelomeningocele trial (MOMS trial) demonstrated a 50% reduction in shunt rates at 12 months of age with actual rates of shunt placement were 40% in the prenatal-surgery group and 82% in the postnatal-surgery group (P<0.001), reduced fetal and neonatal death (68% of the infants in the prenatal-surgery group and in 98% of those in the postnatal-surgery group, P<0.001), and resulted in improvement in the motor function at 30 months (P=0.007).5 Even though the MOMs trial concluded that prenatal repair reduced the need for shunting, more data is needed to evaluate predictors of postnatal shunt placement. Therefore, in this study, we aimed to systematically investigate prenatal predictors of CSF diversion in the first year of life in infants following prenatal repair of OSB.

**Methods**

### **Search Strategy and information resources**

This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines 6. The study protocol of this systematic review was registered in the PROSPERO international prospective register of systematic reviews (Registration number CRD42022333562)

PubMed, Web of Science, and Scopus were searched from inception to June 2022. Initially, selected studies were reviewed for eligibility by two independent authors (SN and SG), and conflicts were resolved by consulting the third investigator (HJM). A search was conducted using combinations of the relevant medical subject heading (MeSH) terms, keywords, and word variants for ("meningomyelocele" OR "neural tube defect" OR "spina bifida" OR "ventriculomegaly" OR "hydrocephalus") AND ("outcome" OR "sequala" OR "morbidity"). References of relevant articles were manually reviewed, and eligible studies were added to the results from the electronic literature search. Search strategies are reported in Supplementary Data Table S1.

### **Eligibility criteria and study selection**

### Inclusion criteria were randomized control trials (RCT), cohort, case-control, or case series studies evaluating infants following prenatal repair of OSB and reporting on the need for shunt or ventriculostomy for CSF diversion. Studies were included regardless of the technique of closure, whether open or fetoscopic, based on recent evidence reporting on 300 fetoscopic repairs and showed no difference in fetal or infant outcomes including need for CSF diversion between open or fetoscopic repair approach aside from maternal outcomes such as uterine dehiscence and cesarean section rates.7 Exclusion criteria included studies reporting on pregnancies not undergoing prenatal repair, studies not reporting on the need for CSF diversion, narrative review articles, systematic reviews, and conference abstracts. In addition, we limited this search to articles published in the English language.

### **Data extraction**

All the extracted studies were transferred into Rayyan, an automated web application designed to screen the papers for systematic reviews 8. After removing the duplicates, records were included for title/abstract screening by two independent reviewers (SG, SN), and the third reviewer (HJM) evaluated the conflicting results (Figure 1). The following variables were extracted from the full-text of included records: year of publication, country of the study, case numbers, type of prenatal repair, age at follow-up, type of OSB, level of lesion, lateral ventricle diameter, degree of hindbrain herniation, sac size and diameter, gestational age at diagnosis, foot malposition, gestational age at delivery, and postnatal outcomes including the need for CSF diversion via shunt or endoscopic ventriculostomy. LV diameter included measurements done via ultrasonography of the widest LV diameter of the posterior horn. In case of overlap which was determined by evaluating the institution, the study period, and the investigated variables, the study with the larger sample size was included for review. Overlap of the population was assessed according to the authors and institution where the study was performed and the year of publication. If overlapped studies reported on different variables, then they were not excluded.

### **Assessment of risk of bias**

### We used the Newcastle-Ottawa Scale (NOS) to evaluate the quality of included cohort or case-control studies and the risk of bias. NOS comprises "participant selection," "comparability of study groups," and "assessment of outcome or exposure." A score above seven is considered high quality 9. No studies were excluded based on quality assessment results. The risk of bias tool for randomized trials (ROB2) was used to assess the included RCTs.10

**Data synthesis and Statistical Analysis**

Statistical analysis was performed using the Review Manager (Version 5.4; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen). Variables that were reported in the median with range or interquartile range were converted to mean and standard deviation by using the Wan formula11. We used the Mantel-Haenszel method to calculate the pooled mean or proportions and their 95% confidence intervals. Variables that were reported in at least two studies were included in the analysis. The heterogeneity of the included studies was assessed using the I2 test. Based on the heterogeneity of the included studies, a random-effects model was used instead of the fixed (common)-effects model. Publication bias was assessed graphically by creating funnel plots.

# Results

**Study selection and characteristics**

As shown in the PRISMA flow chart (Figure 1), a total of 1281 articles were retrieved from three databases. Of those articles, 654 were excluded for duplication. The remaining 629 studies were screened for eligibility. Title and abstract screening resulted in 42 potentially eligible studies. After a full-text assessment was performed, nine studies encompassing 948 pregnancies that underwent prenatal repair of OSB were included 12-20. Study characteristics are presented in Table 1. Included studies were published between 2002 and 2021. Five studies were conducted in the USA12, 13, 15, 17, 18; one was an international multicenter16, one was in Germany14, and two were in Switzerland; even though they overlapped, they were both included given that they reported different variables.19, 20 Six were retrospective cohorts,12, 13, 15, 17, 19, 20 two were prospective cohorts,14, 16, and one was RCT.18 Regarding the technique for intrauterine entry for the OSB repair, six studies were open repair 12, 15, 17-20, two studies were fully percutaneous fetoscopic repair14, 16, and one study included both open and laparotomy-assisted fetoscopic repair21.

**Risk of bias of included studies**

There was no evidence of small study effects on any outcome. The risk of bias using NOS for cohort and case control showed a minimum score of 7, and ROB2 for the RCT showed low concern (total score in Table 1, details of scoring in Table S2).

**Synthesis of results**

We evaluated prenatal predictors of the need for CSF diversion via shunt or endoscopic ventriculostomy in the first year of life. Table 1 presents the list of the included variables in the analysis. Prenatal factors that were significantly associated with the need for postnatal CSF diversion were gestational age (GA) at surgery≥25 weeks (OR 4.2, (95% CI 1.8, 9.9), I2 54%, P=0.001), Myeloschisis (OR 2.2, 95% CI 1.1, 4.1; I2 = 0.0%, P=0.02), preoperative lateral ventricle (LV) ≥15 mm (OR 4.5, 95% CI 2.9, 6.9; I2 =0.0%, P<0.0001), predelivery LV width (mm) (MD 8.3, 95% CI 6.4, 10.2; I2 =0.0%, P<0.0001), and preoperative lesion level at T12-L2 (OR 2.5, 95% CI 1.03, 6.3; I2 =68%, P=0.04). Factors that significantly reduced the need for postnatal shunt placement were GA at surgery<25 weeks (OR 0.3, 95% CI 0.15, 0.6; I2 =67%, P=0.001) and preoperative LV<15 mm (OR 0.3, 0.2, 0.4; I2 =0.0%, P<0.0001), (Figures 2-11). Neither the prenatal findings of talipes (p=0.11), preoperative hindbrain herniation (p=0.37), or gestational age at birth (p=0.21) were significantly associated with the need for CSF diversion in infants following prenatal repair of OSB.

**Comment**

***Main Findings***

This study identified antenatal predictors of CSF diversion by 12 months of age in infants following prenatal repair of OSB. Both GA at fetal surgery ≥25 weeks and preoperative LV diameter>15 mm were significantly associated with more than quadrupling the risk of shunt placement, while lesion level at L2 or higher and Myeloschisis type of lesion more than doubled that risk. Neither the prenatal finding of talipes, preoperative severe hindbrain herniation, or gestation at birth were significantly associated with the need for CSF diversion in infants following prenatal repair of OSB.

***Strengths and limitations:***

The strengths of our review are the comprehensive and extensive search criteria in three major databases (PubMed, Web of Science, and Scopus) to retrieve as many studies as possible. Moreover, most studies used uniform inclusion criteria similar to the MOMs trial except for a few differences, like a BMI of 40 Kg/m2 (two studies: Vonzun et al19andDiehl et al14) and not excluding mothers with treated medical conditions less likely to affect the perinatal outcomes.

We acknowledge our limitations; the retrospective nature of most of the included studies comes with its inherited limitations of bias and confounding factors. Moreover, as known with any surgical intervention studies**,** there is significant heterogeneity in surgical approaches or techniques between different studies, which may even differ within the same cohort or institution. Similarly, the CSF diversion surgery including ETV or Shunt is a neurosurgeon dependent decision, and so that this outcome can experience great variability among different centers and providers. Whether the selection of the surgical approach was affected by the severity of hydrocephalus or not is unknown, and further investigation of this outcome is warranted

***Comparison with existing literature***

Our study identified early GA at surgery, particularly <25 weeks, as a predictor of a lower need for shunt postnatally. This finding could be explained by the two-hit mechanism that has been hypothesized for the neurological damage in MMC: it assumes that the functionally normal, yet dysraphic (first "hit") exposed spinal cord is progressively damaged during intrauterine life by trauma and toxic effect of the amniotic fluid (second "hit"). A study investigating MMC natural history utilizing postmortem pathology of terminated pregnancies showed that the exposed spinal cord is significantly damaged early in pregnancy and that spinal injury extends cranially with a significant reduction in motor neurons in the adjacent cord right above the defect, which worsens with advancing gestation at a rate of 16% per week.22 Another study identified that LV diameter increases with advancing gestation, which will result in further neurological injury and worsening hindbrain herniation and hence hydrocephalus that would increase chances of the need for postnatal shunt.15 . Therefore, we would advocate prompt antenatal repair sooner after the diagnosis is made in order to optimize fetal neurological outcomes. This recommendation is feasible since OSB is frequently diagnosed at mid-gestation anatomical survey around 20 weeks gestation. In addition, prompt referral to an experienced fetal center and completion of genetic and imaging workup could be accomplished in less than two weeks, allowing surgical intervention at around 24 weeks of gestation. In the MOMs trial, where an open approach with a hysterotomy was performed, the average GA at surgery was 23 weeks, with the average delivery at 34 weeks, similar to the fetoscopic group. 23. Therefore, regardless of the surgical approach, the risk of extreme prematurity is unlikely to change if the GA of repair is aimed at around 24 weeks gestation. Since repair is usually done at 24-26 weeks in most centers and given lack of studies investigating earlier repair, authors cannot present data on how early repair is feasible or should be done. A study by Miled et al 2020 showed that significant neuronal loss is present at ≤16 weeks and proposed that early prenatal repair at <16 weeks could prevent Chiari II malformation in 69.3% of cases, rescue the 17% remaining motor neurons in the exposed cord, and prevent the extension to the upper spinal cord.24

The level of disruption and the severity of hydrocephalus are two essential factors in determining the outcome of prenatal repair. This review shows that lesion levels at L2 and above can predict diversion-dependent hydrocephalus within the first year of life. The association between the defect level and the need for postnatal CSF diversion was established early on and explained by increased CSF leaking in higher-level lesions, leading to the progression of herniation, with subsequent worsening of the hydrocephalus and the need for postnatal diversion. 3. Understanding this pathological process, it is clear that the severity of hydrocephalus is another critical factor determining the need for postnatal shunt surgery. In this meta-analysis, we found that an LV diameter of 15 mm or more is predictive of requiring postnatal shunting. Similarly, a retrospective cohort investigating prenatal predictors of diversion-dependent hydrocephalus in the postnatal repair group showed that prenatal LV diameter predicts postnatal shunting in the postnatal repair group 25. As a result, dilated lateral ventricles are predictors of shunt-dependent hydrocephalus, whether repaired prenatally or postnatally. This conclusion does not contradict the MOMS report of reduced shunting in prenatally repaired cases 5. It does, however, revise expectations in this subset of fetuses with higher-level lesions and severely dilated ventricles, which is essential information beneficial in the preoperative counseling of expecting parents.

***Conclusion and implications***

In prenatally repaired OSB, the GA at the time of surgery and preoperative LV diameter appeared to be significantly associated with the need for CSF diversion by 12 months of age, in which both GA at fetal surgery ≥25 weeks and preoperative LV diameter>15 mm lesion more than quadrupled that risk. Similarly, lesion level at L2 or higher and Myeloschisis type of lesion were also significantly associated, which more than doubled that risk. While GA at the time of the repair at <25 weeks appears to be associated with less need for CSF diversion, issues related to prematurity and previable delivery need to be considered.

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| Study ID  **Table 1.** Characteristics of the studies included in the systematic review | Author | Publication year | Study period | Country | Institute | Study design | Inclusion criteria | Exclusion criteria | Type of repair | Total number of cases and number per group | Risk of bias score\* |
| 3 | Tulipan18 | 2015 | 2003-2010 | USA | Children's Hospital of Philadelphia, Vanderbilt University, and the University of California, San Francisco | RCT | MOMS criteria26 | MOMS criteria26 | Open | N=183, CSF diversion N=40, no diversion N=51 | Low concern |
| 9 | Vonzun19 | 2018 | 2010-2017 | Switzerland | Zürich Center for Fetal Diagnosis and Therapy, Zürich, Switzerland | Retrospective cohort | The inclusion criteria for fetal MMC repair were the MOMS trial criteria: a singleton pregnancy, MMC with the upper level between T1 and S1, evidence of hindbrain herniation, a gestational age (GA) of 19 – 25.9 weeks, a normal karyotype, and maternal age of at least 18 years. The only modification was a BMI < 40 (MOMS<35 weeks) | The exclusion criteria were additional fetal malformations unrelated to MMC, severe kyphosis > 30°, short cervix or previous preterm birth, placenta previa, former placental abruption, maternal HIV or hepatitis B/C positivity, uterine abnormality, previous hysterotomy in the active uterine segment, psychosocial problems, and other contraindications for major surgery(= MOMS). | Open | N=49,  CSF diversion N=16, no diversion N=14 | 9 |
| 37 | Tulipan17 | 2002 | 1983-2000 | USA | Children's Hospital of Philadelphia | Retrospective cohort | Vanderbilt required only that the fetus have myelomeningocele,  have an estimated gestational age (EGA) of ^30 weeks (range 20–30 weeks), have a normal karyotype, and have no other appreciable congenital anomalies, while patient selection criteria at CHOP additionally require that fetuses demonstrate intact leg movements and no clubbed feet on prenatal ultrasound, that their EGA be ^25 weeks  (range 20–25 weeks) and that the ventricular size at the time of surgery be less than 18 mm |  | Open | N=104, CSF diversion N=47, no diversion N=57 | 8 |
| 21 | Bruner12 | 2003 | 1997-2002 | USA | Vanderbilt University Medical Center | Retrospective cohort | Criteria for the repair of spina bifida in utero include the absence of other major anomalies, a normal fetal karyotype, and the ability of the parents to fully comprehend the potential risks and benefits of the available treatment options. |  | Open | N=116, CSF diversion N=63, no diversion N=53 | 8 |
| 52 | Donepudi15 | 2020 | 2012-2018 | USA | The Fetal Center, Children's Memorial Hermann Hospital, Houston, TX, USA | Retrospective cohort | All women who underwent repair were included in the study. In addition, women whose neonates had prenatal repair were included if they were delivered at the operating institution. | Fetuses with other major anomalies were excluded from the study. | Open | N=110, CSF diversion N=69, no diversion N=41 | 7 |
| 27 | Corroenne13 | 2021 | 2011-2019 | USA | Texas Children's Hospital & Baylor College of Medicine, Houston, Texas | Retrospective cohort | All fetuses who underwent prenatal repair satisfied the MOMS trial inclusion | All fetuses who underwent prenatal repair satisfied the MOMS trial exclusion criteria. In addition, two cases in which MF could not be retrospectively evaluated were excluded. | open and laparotomy-assisted fetoscopy | N=103, CSF diversion N=71, no diversion N=31 | 9 |
| 54 | Lapa16 | 2021 |  | International multicenter | Eight centers in six different countries (in Sao Paulo (Brazil), Los ̃Angeles (USA), Petah Tikva (Israel), Santiago (Chile), London (UK), Milan (Italy), Miami (USA), and New York (USA)) | Prospective cohort | Centers perform prenatal OSB repair using the percutaneous. First, we used data from children at 12 months of age or older to determine the need for CSF diversion by 12 months of age; CSF diversion was defined as either insertion of a ventriculoperitoneal shunt or endoscopic third ventriculostomy. Second, we used data from children 30 months of age or older to determine the rate of and risk factors for the ability to ambulate without the need for an assistive device and the need for chronic intermittent bladder catheterization. Information on ambulation and the need for chronic intermittent bladder catheterization was obtained from the attending physician, medical records, and/or parents. fetoscopic SAFER technique |  | Fully percutaneous fetoscopy | N=170, CSF diversion N=48, no diversion N=55 | 7 |
| 57 | Diehl14 | 2020 | 2010-2014 | Germany | University Hospital Giessen-Marburg, Giessen, Germany | Prospective cohort | Fetal open spina bifida undergoing complete percutaneous fetoscopic repair, consenting to visit the Giessen clinic at all four study time points (shortly after birth and at three months, 12 months, and 30 months of age). The fetal eligibility criteria for prenatal fetoscopic MMC closure were: (1) no major anomaly detectable on prenatal ultrasound besides MMC and associated cranial abnormalities; (2) normal karyotype, if available; (3) defect located between vertebrae T1 and S1; (4) cerebral ventricles ≤ 16 mm; and (5) no severe kyphoscoliosis. Maternal eligibility criteria for the procedure were: (1) body mass index (BMI) ≤ 45 kg/m2 if the placenta was posterior; (2) BMI ≤ 35 kg/m2 if the placenta was anterior; (3) cervical length ≥ 15 mm; (3) singleton pregnancy; (4) no placenta previa; (5) no known coagulation disorder; and (6) no active hepatitis or HIV infection |  | Fully percutaneous fetoscopy | N=52, CSF diversion N=16, no diversion N=14 | 7 |
| 7 | Wille20 | 2021 | 2010-2017 | Switzerland | Zurich Center for Fetal Diagnosis and Therapy, Switzerland | Retrospective cohort | MOM inclusion criteria26 | MOM exclusion criteria were applied with some modifications (the criteria maternal BMI, hypertension, psychosocial background, as well as certain fetal anomalies such as irrelevant kidney anomalies and minor genetic anomalies were evaluated on an individual basis) | Open | N=61, CSF diversion N=19, no diversion N=27 | 7 |
| \*Risk of bias assessment was done using Newcastle Ottawa Scale for cohort and case-control studies or ROB2 for RCT. | | | | | | | | | | | |

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| --- | --- | --- | --- | --- | --- | --- |
| **Variable** | **Studies (n)** | **CSF Diversion**  **(n/N)** | **No CSF Diversion**  **(n/N)** | **Overall OR (95% CI) or MD (95% CI)** | **I² (%)** | **P(Z)** |
| **GA at surgery <25 weeks** | 512, 14, 16-18 | 75/233 | 148/250 | 0.3 (0.15, 0.6) | 67 | **0.001** |
| **GA at surgery ≥ 25 weeks** | 512, 14, 16-18 | 127/176 | 76/192 | 4.2 (1.8, 9.9) | 54 | **0.001** |
| **Myeloschisis** | 312, 16, 19 | 36/127 | 20/122 | 2.2 (1.1, 4.1) | 0 | **0.02** |
| **Preoperative LV ≥15 mm** | 712-16, 18, 20 | 136/274 | 48/227 | 4.5 (2.9, 6.9) | 0 | **<0.0001** |
| **Preoperative LV <15 mm** | 712-16, 18, 20 | 138/274 | 179/227 | 0.3 (0.2, 0.4) | 0 | **<0.0001** |
| **Predelivery LV width (mm)** | 312, 18, 19 | 96 | 118 | 8.3 (6.4, 10.2) | 0 | **<0.0001** |
| **Preoperative lesion level T12-L2** | 612, 14, 16-19 | 85/194 | 59/202 | 2.5 (1.03, 6.3) | 68 | **0.04** |
| **Preoperative lesion level L3-S1** | 612, 14, 16-19 | 225/375 | 203/374 | 0.83 (0.26, 2.67) | 92 | 0.75 |
| **Talipes** | 412, 14, 16, 19 | 25/127 | 15/126 | 1.7 (0.87, 3.9) | 0 | 0.11 |
| **Preoperative severe hindbrain herniation** | 312, 14, 18 | 27/113 | 24/116 | 1.3 (0.71, 2.6) | 0 | 0.37 |
| **GA at birth (weeks)** | 414-16, 19 | 147 | 153 | -0.4 (-1.07, 0.2) | 36 | 0.21 |

**Table 2.** Prenatal predictors of need for CSF diversion (shunt or ventriculostomy) in infants following prenatal repair of open spina bifida

**Figures legends:**

**Figure 1.** PRISMA flow chart of the search and selection process

**Figure 2.** Forest plot of the need for CSF diversion in children with fetal OSB repair when gestational age at repair < 25 weeks

**Figure 3.** Forest plot of the need for CSF diversion in children with fetal OSB repair when gestational age at repair ≥25 weeks

**Figure 4.** Forest plot of the need for CSF diversion in children with fetal OSB repair with Myeloschisis type of lesion.

**Figure 5.** Forest plot of the need for CSF diversion in children with fetal OSB repair when preoperative lateral ventricle width>15 mm.

**Figure 6.** Forest plot for the mean difference in post-operative (pre-delivery) lateral ventricle width in children with fetal OSB repair requiring CSF diversion.

**Figure 7.** Forest plot of the need for CSF diversion in children with fetal OSB repair when the level of lesion T12 to L2 (high lumbar).

**Figure 8.** Forest plot of the need for CSF diversion in children with fetal OSB repair when the level of lesion L3 to S1 (low lumbar).

**Figure 9.** Forest plot of the need for CSF diversion in children with fetal OSB repair with prenatally diagnosed talipes.

**Figure 10.** Forest plot of the need for CSF diversion in children with fetal OSB repair with prenatal severe hindbrain herniation.

**Figure 11.** Forest plot for the mean difference in gestational age at birth in children with fetal OSB repair requiring CSF diversion.