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Fully percutaneous fetoscopic repair of myelomeningocele: 30-month follow-up data

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KEYWORDS: fetoscopy; hydrocephalus; lower extremity neuromotor function; mortality; myelomeningocele; spina bifida aperta; VP shunt

CONTRIBUTION

What are the novel findings of this work?
This is the largest follow-up study to date evaluating the postnatal mortality and 30-month outcome of children who underwent fully percutaneous fetoscopic repair of myelomeningocele (MMC).

What are the clinical implications of this work?
Intrauterine repair of MMC by percutaneous fetoscopy, and via hysterotomy, result in a remarkably good outcome concerning mortality, prematurity, shunt-placement rates, motor and mental development and free ambulation, when compared to postnatal repair.

ABSTRACT

Objective *This observational study reports on the postnatal mortality and 30-month outcome of children who underwent fully percutaneous fetoscopic repair of myelomeningocele (MMC) at a single center in Giessen, Germany.*

Methods *Between October 2010 and August 2014, a total of 72 patients underwent fully percutaneous fetoscopic MMC closure at 21 + 0 to 29 + 1 (mean, 23 + 5) weeks' gestation. Of these, 52 (72%) participated in this study; however, 30-month mortality data are available for all 72 children. Children were examined at four timepoints: shortly after birth and at 3 months, 12 months and 30 months of corrected age. The patients underwent age-specific standardized neurological examinations and assessment of leg movements and ambulation at all timepoints. Cognitive and motor development were assessed using the Bayley Scales of Infant Development, second edition (BSID-II), at 30 months.*

Results *All 72 children survived the intrauterine procedure, however, four (5.6%) infants died postnatally (including two of the 52 comprising the study cohort). Of the 52 patients included in the study, 11.5% were delivered before the 30th week of gestation (mean, 33 + 1 weeks) and, of the survivors, 48.1% had ventriculoperitoneal shunt placement. Of the 50 infants that were alive at 30 months, independent ambulation, without orthosis, was feasible for 46%. At 30 months of follow-up, 46% of children presented with a functional level that was at least two segments better than the anatomical level of the lesion. At 30 months, 70% of the children presented with BSID-II psychomotor development index score of ≥ 70 and 80% with BSID-II mental development index score of ≥ 70.*

Conclusion *Intrauterine repair of MMC by percutaneous fetoscopy shows largely similar outcomes to those reported for open repair, with respect to mortality, prematurity, shunt-placement rates, motor and mental development and free ambulation.* © *2020 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

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INTRODUCTION

Since the 1980s, several studies have reported that the leg movements of fetuses with myelomeningocele (MMC) diminish continuously during pregnancy[1]. Additionally, Arnold–Chiari malformation and hydrocephalus have been reported to worsen during gestation in these cases[2]. Eventually a two-hit hypothesis was proposed to explain the sequelae of MMC; the first hit being the failure of the neural tube to close and the second hit the exposure of spinal neurons to neurotoxic agents in the amniotic fluid and mechanical alteration of the myelon[3,4]. Based on this theory, it was conceivable that early intrauterine repair might improve postnatal outcome. In 2011, the results of the Management of Myelomeningocele Study (MOMS) were published[5]. This groundbreaking randomized trial compared intrauterine MMC repair by open surgery, via hysterotomy, with traditional postnatal surgery. Prenatal repair was shown to reduce the need for shunt placement by about 50% when compared to postnatal repair, while independent walking increased from 24% in the postnatal-repair group to 45% in prenatally operated children[5].

Recently, the 30-month outcome data for the full MOMS cohort of 183 mother–child pairs were published[6]. When compared to postnatal surgery, prenatal repair by open surgery via hysterotomy resulted in a major improvement in independent ambulation and functional level of paraparesis compared to anatomical lesion level and Bayley Scales of Infant Development, second edition (BSID-II)[6]. A recent meta-analysis, which included the 30-months' report of the MOMs trial[6] and one additional study, reported slightly lower rates of independently walking children in the prenatal-repair group[7]. It was calculated that to detect a 4% difference in neurodevelopmental impairment between the prenatal- and postnatal-repair groups, with 80% power and 5% type-1 error, 1886 patients per group would be needed[7]. This underscores the fact that available data are vastly underpowered to detect significant differences at this level[8]. There is also a lack of studies comparing neurocognitive outcome of children with spina bifida who undergo surgery and those who do not[7,8].

As open fetal surgery by hysterotomy is an invasive procedure, fetoscopic surgical techniques aim to minimize surgical trauma. Early endoscopic studies included only a small number of patients and were complication prone[9–12]. Today, following significant technical improvements and a steep learning curve of the surgical teams, fetoscopic fetal surgery is considered by some authors to be on a par with open fetal surgery techniques, even though controlled head-to-head comparisons are still lacking[13–15]. It has also been shown that fetoscopic intrauterine repair does not affect negatively fetal or postnatal growth or fetal brain microstructure on magnetic resonance imaging (MRI)[13,16].

In the present observational study, we report the 30-month outcome of the patients who underwent percutaneous fetoscopic patch closure of MMC in Giessen, Germany, between October 2010 and August 2014. Details of the surgical procedures[17], maternal management and outcome[18] and neurosurgical intervention in the first postnatal year[19] were published recently.

METHODS

The regional institutional ethics board of the University of Giessen, Giessen, Germany, approved this observational, single-center follow-up study of children who underwent fetoscopic closure of their MMC at the University Hospital of Giessen between October 2010 and August 2014 (#113/12). All parents of the children who participated in this study provided written informed consent.

In the present study, we report perinatal mortality for all 72 children who underwent fetoscopic repair during the study period. Our follow-up protocol required the parents and their children to visit the Giessen clinic at all four study timepoints (shortly after birth and at 3 months, 12 months and 30 months of age), which was not acceptable for 20 parents, mostly because of the inconvenience of traveling. Of the remaining 52 patients, two children died within the first month after birth; therefore, 50 children completed the entire 30-month study protocol. The protocol focused on: mortality, prematurity, shunt-placement rate, independent ambulation at 30 months, functional level of paraparesis compared to anatomical lesion level and developmental and motor outcome assessed by the BSID-II[20].

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[17]. On ultrasound assessment, all included children had preserved or largely retained feet and knee movements prior to the fetoscopic intervention. However, normal leg function and foot position were not obligatory eligibility criteria for this procedure. Maternal eligibility criteria for the procedure were: (1) body mass index (BMI) ≤ 45 kg/m^2, if the placenta was posterior; (2) BMI ≤ 35 kg/m^2, 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[17].

Details of the surgical procedures have been described before[17]. Intrauterine percutaneous fetoscopic repair of MMC was performed between $21+0$ and $29+1$ (mean, $23+5$) weeks of gestation. Lesion levels ranged from T11 to S1.

Need for ventriculoperitoneal (VP) shunt placement within 1 year after birth was determined using the criteria provided in the MOMS trial[5]. At least two of the following criteria had to be present for shunt placement: (1) an increase in the greatest occipitofrontal circumference adjusted for gestational age, defined as crossing percentiles; patients who crossed percentiles and subsequently plateaued did not meet this criterion; (2) a bulging fontanel (defined as above the bone, assessed when the

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baby is in an upright position and not crying) or split sutures or sun-setting sign (eyes appear to look downward with the sclera prominent over the iris); (3) increasing hydrocephalus on consecutive imaging studies, determined by increase in the ratio of biventricular diameter to biparietal diameter, according to the method of O'Hayon *et al.*[21]; or (4) head circumference $> 95^{th}$ percentile for gestational age. Alternatively, a single criterion from the following prompted VP shunting: (1) presence of marked syringomyelia (syrinx with expansion of spinal cord) with ventriculomegaly; (2) ventriculomegaly (undefined) and symptoms of Chiari malformation (stridor, swallowing difficulties, apnea, bradycardia); or (3) persistent cerebrospinal fluid leakage from the MMC wound.

Follow-up examination

We report follow-up data for the 52 patients who agreed to the study protocol and participated in the study. These children were born between January 2011 and November 2014. Two children (2/52) died in the first month after birth (Figure 1). Examinations took place shortly after birth, at 3 months, at 12 months and at 30 months of age, with all timepoints corrected for gestational age. BSID-II assessment was performed at 30 months only. Examinations included detailed history, clinical neurological examination, video documentation of leg movements and ambulation, and additionally, a cranial ultrasound and an ultrasound of the kidneys and urinary tract. The timing of the examinations and the criteria were chosen in parallel to the MOMS trial[5].

The BSID-II is a widely used developmental assessment battery developed by Nancy Bayley[20]. The test is composed of three parts: a test scale on mental development (MDI), a scale on psychomotor development (PDI) and a behavioral assessment, which is not entered into a specified scale. The test is a used standard in many countries to measure development in children at risk for developmental problems (e.g. after prematurity or multiple pregnancy). A score of ≥ 70 is the limit for normal development. The Bayley scales were also used in the MOMS trial[5,6]. In our institution, it was applied by three specifically trained psychologists with extensive experience.

In addition, the patients underwent age-specific standardized neurological examinations. Muscle strength was graded on a scale from 0 to 5: 0, no movement at all; 1, trace of movement; 2, movement without gravity; 3, movement against gravity; 4, movement against resistance; and 5, normal strength. A score of at least 3 was needed for the functional level to be assigned[12]. In short[12], hip flexion corresponded to L1–L2, knee extension to L3–L4, ankle dorsiflexion to L4–L5, toe extension to L5–S1 and ankle plantarflexion to S1–S2. The anatomical level of the lesion was determined by fetal ultrasound (in 100% of children) and MRI of the spinal cord in the first year of age (in 85% of children). The neuromotor function of the patients was determined by the difference between the functional level and anatomical level of the lesion.

Statistical analysis

Statistical analysis was performed using R-project software, version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria)[22]. Categorical data are presented as *n* (%) and continuous data as mean ± SD. The results of the subgroup analysis were compared using odds ratios (OR) including 95% CI for categorical data based on Fisher's exact test or differences in mean and 95% CI, based on Student's *t*-test for normally distributed, continuous data. Mantel–Haenszel chi-square test with continuity correction was used for the subgroup analyses. Due to the exploratory nature of the analysis, no correction for multiple testing was applied and the focus lies upon the effect size.

RESULTS

Baseline characteristics of the 52 patients who participated in the study are shown in Table 1. In most respects, there is no notable difference in the level of the lesion, severity of medulla oblongata herniation, maternal BMI and age, placental position and gender between our cohort and those of other series[5,13]. However, foot deformities were documented in only 22% of fetuses in our series and a clubfoot in only two cases, which is much lower than that

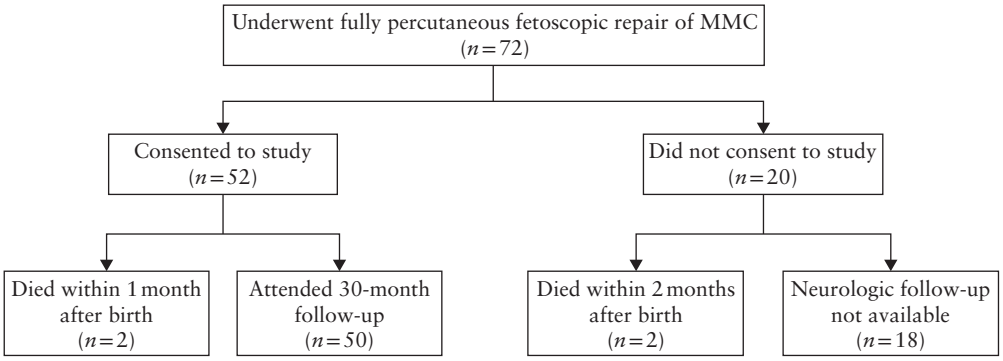

Figure 1 Flowchart showing inclusion in 30-month follow-up study of patients who underwent fully percutaneous fetoscopic repair of myelomeningocele (MMC) at University Hospital of Giessen, Germany, between October 2010 and August 2014.

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reported in other cohorts. This is because our cohort had preserved or largely retained feet and knee movements prior to the fetoscopic intervention, even though this was not a prerequisite for the procedure.

Infant mortality

Of the 72 patients who underwent intrauterine fetoscopic repair of their MMC between October 2010 and August 2014, four (5.6%) died in the first weeks after birth: one due to prematurity-related complications, two due to brainstem and Chiari malformation and one of trisomy 13, which was diagnosed in retrospect as the parents did not agree to prenatal karyotyping, despite our strong recommendation to perform it. The death of the latter child was in no recognizable context related to the conducted procedure and most likely represented the natural course of trisomy 13. All four children survived the fetoscopic procedure. Two of the deceased children belonged to the group of 52 patients who participated in the 30-month follow-up study.

Prematurity

Mean gestational age at delivery was 33 + 1 weeks, ranging from 27 + 5 to 38 + 3 weeks, in our cohort. Altogether 11.5% of children were delivered before the 30th week of gestation, which is in line with other reported series[5,13].

Need for shunt placement

Of the 52 patients included in the study, 22 received a VP shunt within the first 12 months of age. In parallel with the composite outcome of death or VP shunting used in the MOMS study[5,6], adding to this number the four deceased children (Figure 1) who did not undergo shunting would result in 26 of 54 (48.1%) infants in our cohort nominally receiving a VP shunt.

Table 1 Baseline characteristics of 52 fetuses that underwent fully percutaneous fetoscopic repair of myelomeningocele

Characteristic	*Value*
Gestational age at surgery (weeks)	23.69 ± 1.83
Maternal age at surgery (years)	31.58 ± 4.79
Maternal BMI at surgery (kg/m^2)	26.27 ± 3.71
Female fetal sex	27 (51.9)
Cervical length on TVS (cm)	4.23 ± 0.76
Anterior placenta	20 (38.5)
Level of lesion	
Thoracic	2 (3.8)
L1–L2	12 (23.1)
L3–L4	20 (38.5)
L5–S1	18 (34.6)
Lesion level ≤ L3	38 (73.1)
Clubfoot	2 (3.8)
Severe hindbrain herniation	13 (25.0)

Data are given as mean ± SD or *n* (%). BMI, body mass index; TVS, transvaginal ultrasound.

Thirty-month follow-up

The outcome data at 30 months are presented in Table 2.

The mental development of the children was evaluated using the BSID-II MDI. At 30 months, of the 50 patients who were alive, 46 (92%) had a MDI ≥ 50, 40 (80%) a MDI ≥ 70 and 36 (72%) a MDI ≥ 85.

With respect to motor development, 37 (74%) patients presented with a BSID-II PDI ≥ 50, 35 (70%) with a PDI ≥ 70 and 22 (44%) with a PDI ≥ 85. A PDI of ≥ 70 is considered normal, which therefore accounts for 70% of the children that underwent intrauterine repair of MMC. A functional lesion level ≥ 2 segments better than anatomically expected was observed in 46% of our patients and one segment better than anatomically expected in 34%. A functional level ≥ 2 segments worse than anatomically expected was found in only one (2%) patient (Table 3).

Table 2 Outcome at 30 months of 50 infants that underwent fully percutaneous fetoscopic repair of myelomeningocele

Outcome	*Value*
BSID-II mental development index	93.64 ± 17.43
BSID-II mental development index	
≥ 50	46 (92.0)
≥ 70	40 (80.0)
≥ 85	36 (72.0)
Difference between motor function and anatomical level of lesion	1.7 ± 1.59
≥ Two levels better	23 (46.0)
One level better	17 (34.0)
No difference	9 (18.0)
One level worse	0 (0)
≥ Two levels worse	1 (2.0)
BSID-II psychomotor development index	
Mean	78.08 ± 20.0
≥ 50	37 (74.0)
≥ 70	35 (70.0)
≥ 85	22 (44.0)
Walking status	
Not walking independently	8 (16.0)
Walking with orthotics or devices	19 (38.0)
Walking independently	23 (46.0)

Data are given as mean ± SD or *n* (%). BSID-II, Bayley Scales of Infant Development, second edition.

Table 3 Difference between motor function and anatomical level of lesion shortly after birth and at 3, 12 and 30 months of corrected age, in 50 infants that underwent fully percutaneous fetoscopic repair of myelomeningocele and were alive at 30 months

Difference in anatomical vs *functional level*	*Shortly after birth*	*At 3 months*	*At 12 months*	*At 30 months*
≥ Two levels worse	0 (0)	0 (0)	1 (2)	1 (2)
One level worse	0 (0)	0 (0)	0 (0)	0 (0)
No difference	7 (14)	6 (12)	6 (12)	9 (18)
One level better	14 (28)	14 (28)	14 (28)	17 (34)
≥ Two levels better	29 (58)	30 (60)	29 (58)	23 (46)

Data are given as *n* (%).

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Unaided independent ambulation (i.e. without orthosis) at 30 months was feasible for 46% of our cohort. Independent walking aided by orthosis was possible for 38% of patients, while 16% of children remained unable to walk independently (with or without orthotics). In our cohort, besides talipes equinovarus (clubfoot), pes adductus (sickle foot), pes calcaneus and split foot were quantified. A clubfoot was diagnosed if the adducted foot could not be freely redressed to a normal position. If careful manual redression was easily possible by the investigator, a pes adductus was diagnosed. A clubfoot was found in 4% of our cases and foot deformities were documented in 22%.

Subgroup analysis

A subgroup analysis was performed to evaluate the interaction of (1) independent ambulation, (2) difference between anatomical and functional level of the lesion and (3) BSID-II PDI ≥ 70 and MDI ≥ 70 with the superior level of the MMC lesion (T1–L2 *vs* L3–S1) and the need for VP shunt placement. Children with a low-level lesion (L3–S1), had a significantly higher probability of independent ambulation than those with a higher (T1–L2) lesion (OR, 22.30; 95% CI, 2.80–1039.81; $P = 0.0004$). In our cohort, 57% of children without VP shunt placement by 12 months of age acquired independent ambulation by 30 months *vs* 32% of children with a VP shunt (OR, 2.795; 95% CI, 0.773–10.937; $P = 0.092$). In addition, 85.7% of 28 children without a VP shunt presented with a PDI score ≥ 70 *vs* only 36.4% of those with a shunt (OR, 9.9; 95% CI, 2.285–54.22; $P = 0.0004$). A MDI score ≥ 70 was reached by 96.4% of children without a VP shunt *vs* 86.4% of those with a VP shunt (OR, 4.14; 95% CI, 0.306–231.59; $P = 0.307$).

DISCUSSION

To date, this is the largest study to report on the postnatal mortality and 30-month outcome of children who underwent fully percutaneous fetoscopic repair of MMC. Open intrauterine MMC repair has been shown to result in a significant improvement of long-term milestones when compared to postnatal repair[5–7]. Drawbacks of this approach include an increased risk for thinning of the hysterotomy scar and the need for Cesarean section. A fetoscopic approach offers reduced invasiveness, basically eliminating the risk of uterine rupture and providing an option for vaginal delivery. Controlled head-to-head outcome comparisons of these two techniques are lacking. Retrospective case series are difficult to compare because of diverging inclusion criteria, employed techniques and experience of the surgical teams. This observational study shows that intrauterine MMC repair by percutaneous fetoscopy results in an outcome improvement that seems to lie in the range of results reported for open intrauterine repair.

The mortality of patients with MMC has been reduced drastically during the last decades. In 1972, Lorber[23] reported that 22% of a cohort of 270 patients with spina bifida cystica died within the first 4 weeks after birth. The MOMS study reported a perinatal mortality of 4.4% in the prenatal-repair and 3.3% in the postnatal-repair group. A recent report by a consortium of six centers[13], one of which offered a percutaneous approach, reported an averaged mortality rate of around 4%. In our cohort, the mortality rate was 5.6%, which is roughly in line with these findings.

Our cohort of fetoscopically treated infants had a shorter mean pregnancy duration compared with the children in the MOMS trial who underwent prenatal open repair via hysterotomy ($33 + 1$ *vs* $34 + 1$ weeks; difference, 1.43 weeks; 95% CI, 0.36–2.5 weeks; $P = 0.009$)[5]. The number of children in our cohort who were delivered before the 30th week of gestation was similar to that in the MOMS prenatal-repair group (MOMS 13% *vs* Giessen 11.5%; OR, 0.85; 95% CI, 0.24–2.67; $P = 1$). The report of the International Fetoscopic Myelomeningocele Repair Consortium reported a rate of about 13% for delivery < 30 weeks of gestation[13]. It is known that prematurity is an important risk factor for long-term postnatal development in both early and late preterm infants[24,25]. Improving the rate of prematurity should therefore be a major aim for future studies. Promising possibilities may include the use of humidified and heated CO_2 for insufflation, amongst other technical variations[13].

The need for a VP shunt is one of the most common complications in patients with MMC. In a British long-term study of patients born with open spina bifida[26], 84% had a shunt at a mean age of 30 years, which is comparable to the 82% rate of shunt placement by the age of 12 months seen in the postnatally operated group of the MOMS trial, and hints to a shunting need predominantly in the first 12 months[5,27]. The MOMS study found a dramatically improved shunting rate of 43% in the prenatally operated group[5,27]. The VP shunt rate in our cohort was slightly higher, at 48%. In general, it is not easy to compare the rate of shunt placement between different cohorts. The MOMS trial employed an interdisciplinary panel of physicians who made the final decision on the need for VP shunt placement. We tried to reproduce the outlined criteria for shunt placement reported in the MOMS trial, however, there remains some room for interpretation on several features, such as bulging fontanel. The Consortium study[13] reported a VP shunt rate of 47% for a group of children who underwent intrauterine repair by a fully percutaneous approach like ours. A smaller number of children who underwent intrauterine repair using a hybrid approach (i.e. fetoscopic repair on an exteriorized uterus) showed even better results[13].

The anatomical level of the lesion is considered one of the key factors in predicting the neuromotor outcome of a child with MMC. In our cohort, 46% of children presented with a functional level of two segments better than anatomically expected and 34% with one level better than anatomically expected. A motor level of ≥ 2 levels worse than anatomically expected was found in only 2% of cases. These findings were paralleled by the results

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of the BSID-II PDI assessment, according to which 37 patients presented with a PDI ≥ 50, 35 with a PDI ≥ 70 and 22 with a PDI ≥ 85.

Independent unaided ambulation (i.e. without orthosis) at 30 months of age was feasible for 46% of our cohort and independent walking aided by orthotic devices was possible for an additional 38% of children. The rate of children who remained unable to walk independently amounted to 16% in our cohort. These numbers, however, cannot be easily compared with the results of any other trial or series. In our cohort, largely preserved movement of legs and feet was observed in all fetuses at the time of fetoscopic repair. This could bias our results towards a more positive outcome when compared to the results of other trials, in which some fetuses presented with markedly reduced, or even absent, legs and feet mobility[5,6]. Moreover, we found that children without a VP shunt were more likely to acquire independent ambulation and present with a PDI score ≥ 70 at 30 months compared with those that received a VP shunt. This is in line with findings in children that underwent open intrauterine repair of MMC[5,6].

A limitation of this study, besides its observational nature, is the lack of sufficient data on bladder function. Urologic follow-up of our cohort was not part of our study protocol and therefore was performed close to the home of the children, without following a standardized protocol. A long-term follow-up of urologic function at school age together with a spinal MRI to assess tethering is pending. In the presented study, a ventricular width ≤ 16 mm prior to intrauterine repair was an eligibility criterion and all fetuses had preserved or largely retained feet and knee movements prior to fetoscopic intervention (even though this was not a prerequisite for the procedure). This has to be considered when comparing our results to other series as it may bias our results towards a more positive outcome.

In conclusion, prenatal repair of MMC by fully percutaneous fetoscopy shows similar outcomes to those reported for open intrauterine repair, with respect to improved mortality, prematurity and shunt-placement rates and motor and mental development at 30 months of age.

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