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Long-term neuroimaging and neurological outcome of fetal spina bifida aperta after postnatal surgical repair

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KEYWORDS: postnatal repair; prenatal diagnosis; spina bifida

ABSTRACT

Objective *Parents faced with the choice between postnatal management and prenatal surgery for spina bifida need to have up-to-date information on the expected outcomes. The aim of this study was to report the long-term physical and neurological outcomes of infants with prenatally diagnosed isolated spina bifida that underwent postnatal surgical repair and were managed by a multidisciplinary team from a large tertiary center.*

Methods *This was a retrospective cohort study of all cases of fetal spina bifida managed in a tertiary unit between October 1999 and January 2018. All cases of fetal spina bifida from the local health region were routinely referred to the tertiary unit for further perinatal management. Details on surgical procedures and neonatal neurological outcomes were obtained from institutional case records. Ambulatory status, bladder and bowel continence and neurodevelopment were assessed at a minimum of 3 years.*

Results *During the study period, 241 pregnancies with isolated spina bifida were seen in the unit. Of these, 84 (34.9%) women opted to continue with the pregnancy after multidisciplinary counseling by clinicians. Sixty-seven infants underwent postnatal repair of spina bifida aperta and were included in the analysis. After birth, hindbrain herniation was observed in 91.5% of infants with only seven requiring surgical decompression. Ventriculoperitoneal shunt placement was needed in 64.2% of infants, while normal cognitive development or mild impairment was demonstrated in 85.4% of cases with data for this outcome available, at a mean age of 8 years. Cumulatively, 40% of infants were walking independently or using minor support, and normal or mild impairment of bladder and bowel function was reported in 45.5% and 44.4% of infants, respectively.*

Conclusions *Neurodevelopmental and neurological outcomes between prenatal and postnatal repair are similar. As with fetal surgery, conventional postnatal surgery is associated with the reversal of hindbrain herniation. Similarly, postnatal ventriculoperitoneal shunt placement appears to be required mainly in fetuses without evidence of significant fetal ventriculomegaly. Copyright © 2019 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

In Europe alone, more than 4500 pregnancies per year are affected by neural tube defects, with a prenatal diagnosis of spina bifida being made before 22 weeks' gestation in about 90% of these cases[1,2]. In the past 50 years, the multidisciplinary approach to spina bifida care has improved significantly patient outcomes, leading to an increase in life expectancy and gain in the quality of life for patients and caregivers alike[3,4]. Even though survival to the age of 17 years has been reported to be 80%, neurological outcomes have apparently not changed significantly over the past few decades[5,6]. Neurological damage in spina bifida is thought to result primarily from the congenital spinal abnormality as well as from secondary damage from exposure to amniotic fluid and direct intrauterine trauma. This unproven 'two-hit' hypothesis is the rationale for fetal surgery, according to which *in-utero* repair of the spine may have the potential to prevent secondary damage to the spinal cord[7]. However, prenatal surgery for spina bifida can also be a harmful procedure; results from the MOMS trial showed a significantly increased risk of pregnancy complications,

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such as preterm rupture of membranes and early preterm birth before 34 weeks' gestation, in almost half of the cases that underwent fetal surgery[8].

Parents faced with the choice between postnatal management *vs* prenatal surgery need to have reliable and up-to-date information on the expected long-term neurological prognosis. A recent meta-analysis of two small prospective studies demonstrated comparable neurodevelopmental outcomes between prenatal *vs* postnatal repair, but paradoxically suggested improved independent ambulation at 30 months of age following prenatal repair[9].

The aim of this study was to report the long-term physical and neurological outcomes following postnatal surgical repair in cases of prenatally diagnosed isolated spina bifida managed by a comprehensive multidisciplinary team in a large tertiary center.

PATIENTS AND METHODS

This was a retrospective cohort study of all cases of fetal spina bifida managed in a tertiary unit between October 1999 and January 2018. Prenatally diagnosed cases of spina bifida from the local health region were routinely referred to the tertiary unit for further perinatal management. All cases with additional anomalies unrelated to spina bifida found on ultrasound or fetal karyotyping were excluded from the cohort. Fetuses with isolated spina bifida were referred to a multidisciplinary team and followed up during pregnancy and into late childhood by the same clinical team. Maternal and pregnancy characteristics, surgical procedures and complications as well as neonatal neurological outcomes were obtained from institutional written/digital case record/chart review and parental interviews.

Perinatal management

All fetuses underwent detailed serial ultrasound examination and birth was routinely scheduled in the tertiary center from 38 weeks' gestation. Cesarean delivery was carried out only for obstetric reasons unrelated to the diagnosis of fetal spina bifida. Surgical repair of the spinal defect was usually performed within the first few days postpartum for all neonates with open spina bifida[10–13]. The need for ventriculoperitoneal (VP) shunt placement and any associated surgical complications (shunt revision/blockage or infection) were recorded routinely. Neonates underwent cranial ultrasound and/or computed tomography and/or magnetic resonance imaging as clinically indicated. Neuroimaging reports were reviewed for the findings of ventriculomegaly, tonsillar descent, other hindbrain abnormalities and corpus callosum anomalies. Anomalies of the corpus callosum were classified as complete agenesis or hypoplasia/dysplasia (partial agenesis or dysplasia with or without hypoplasia). Postnatal follow-up was carried out by a multidisciplinary team of neurosurgeons, neurologists, urologists and orthopedic surgeons.

Postnatal outcome

Ambulatory status was evaluated in children aged between 3 and 5 years and was defined as normal in subjects able to walk independently with possible sensory or gait deficits. Ambulatory impairment was defined as mild or moderate in case of need of orthopedic support below or over the knees, respectively. Severe impairment of ambulatory status was defined by wheelchair dependency.

Bladder function was evaluated only in children over 3 years of age. Urinary function was considered normal when children were continent without the need for clean intermittent catheterization (CIC). Independent of the habitual use of CIC, mild incontinence was defined by occasional (< 3) episodes of incontinence per week, while moderate incontinence was defined by several but not daily episodes of incontinence per week. Severe incontinence was defined as urinary incontinence with or without the habitual use of CIC.

Bowel function was evaluated at 3 years of age and defined as normal when children were continent without the need for digital manipulation. Mild incontinence was defined by occasional (< 3) episodes of incontinence per week with occasional need for pharmacological therapy and/or no episodes of incontinence with antegrade colonic enema (ACE). Moderate incontinence was defined by several but not daily episodes of incontinence per week with daily need for pharmacological therapy and rare episodes of incontinence with ACE. Severe incontinence was defined as fecal incontinence or severe obstruction.

Information about the cognitive development of children above 5 years was obtained from clinical records and classified as normal when attending a mainstream school and as mild developmental delay when mild learning difficulties, speech delay and/or social interaction difficulties were recorded. Global developmental delay was assigned when special assistance was required for all daily activities.

RESULTS

During the study period, 241 pregnancies with isolated spina bifida were seen in our tertiary unit. Of these, 84 (34.9%) women opted to continue with the pregnancy and were eligible to be included in the study cohort. Thirteen pregnancies were excluded from this cohort because of fetal or neonatal/infant death and due to loss to follow-up (Figure 1). One further pregnancy was excluded from the analysis because the patient opted to have fetal surgery for spina bifida in another country. Maternal and pregnancy characteristics are shown in Table 1.

Surgical repair was performed in 67 (95.7%) cases. The other three babies did not undergo surgery because of a diagnosis of spina bifida occulta, and they were excluded from further analysis. There were no surgical complications recorded in 37 (55.2%) cases; a cerebrospinal fluid leak, wound infection or other surgical complication was recorded in 13 cases during the

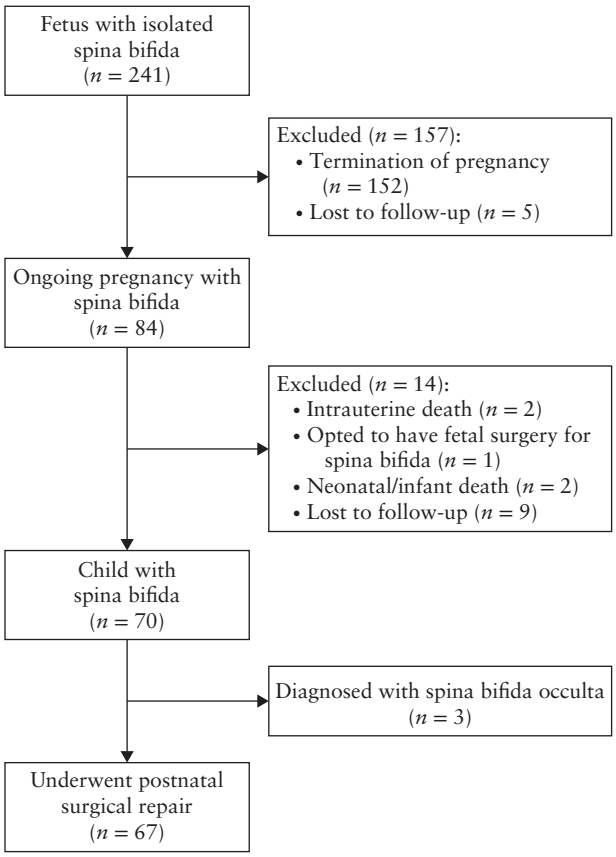

Figure 1 Flowchart showing inclusion in study of infants with prenatally diagnosed isolated spina bifida aperta that underwent postnatal surgical repair.

hospital admission; in 17 cases, no mention of surgical complications was made. VP shunt placement was needed in 43 (64.2%) patients, with at least one VP shunt revision being required in 20 (46.5%) cases. Postnatal neuroimaging findings are presented in Table 2.

Ambulatory, sphincteric and neurological outcomes were available for 55 babies with a mean length of follow-up of 8.1 ± 4.1 years (Table 3). Ambulatory, sphincteric and neurological outcomes according to upper spinal level of lesion are presented in Table S1. On urodynamic assessment, hydronephrosis was diagnosed in six (10.9%) and a neuropathic bladder in 45 (81.8%) cases. Pharmacological (anticholinergic) therapy for an overactive bladder was prescribed in 47 (85.5%) infants and CIC was used in 48 (87.3%). ACE was required in 16 (29.1%) infants and an anal plug was used for the treatment of severe fecal incontinence in one infant.

Table 1 Maternal and pregnancy characteristics of 81* pregnancies diagnosed prenatally with isolated spina bifida

Characteristic	*Value*
Maternal age (years)	30.1 ± 5.9
Ethnicity	
Caucasian	62/80 (77.5)
Asian	13/80 (16.3)
Black African	5/80 (6.3)
Primiparous	26 (32.1)
Gestational age at diagnosis (weeks)	20.8 ± 1.9
Gestational age at birth (weeks)	38 ± 2.0
Preterm birth (< 37 weeks)	9 (11.1)
Early preterm birth (< 34 weeks)	0 (0)
Mode of delivery	
Vaginal	27/77 (35.1)
Cesarean section	50/77 (64.9)
Birth weight (g)	3068 ± 604
Age of child at time of study (years)	6 (0–18)

Data provided as mean ± SD, *n*/*N* (%), *n* (%) or median (range). *Data are for women who opted to continue with pregnancy, excluding one who opted for fetal surgery and two cases of intrauterine death. Some data missing for ethnicity and mode of delivery.

Table 2 Neuroimaging and neurosurgical findings in 67 infants that underwent postnatal surgical repair of prenatally diagnosed isolated spina bifida

Finding	n/N *(%)*
Ventricles	
Normal	7/58 (12.1)
Mild ventriculomegaly	5/58 (8.6)
Moderate ventriculomegaly	18/58 (31.0)
Hydrocephalus	28/58 (48.3)
Cerebellum	
Normal	4/47 (8.5)
Arnold-Chiari malformation type II	43/47 (91.5)
Corpus callosum	
Normal	28/47 (59.6)
Dysplasia/hypoplasia	17/47 (36.2)
Complete agenesis	2/47 (4.3)
Gray matter	
Normal	37/43 (86.0)
Nodular heterotopia	6/43 (14.0)
Need for ventriculoperitoneal shunt	
No	24/67 (35.8)
Yes	43/67 (64.2)

DISCUSSION

This retrospective cohort study reports on pregnancy outcomes of 241 fetuses with a prenatal diagnosis of spina bifida in one of the largest spina bifida referral centers in the UK with more than 25 years of experience in multidisciplinary management of these patients. Parents chose to terminate the pregnancy in 65% of cases, a very similar rate to that reported in a recent systematic review[14]. The natural history and neurological findings of the 67 fetuses with open spina bifida managed with postnatal surgical correction in a single tertiary center suggest outcomes much improved compared with historical cohorts and comparable to those currently reported for fetal surgery.

Strengths and limitations

Bias introduced by case selection is a concern with retrospective studies. However, this was a patient-preference cohort determined by the parent's decision to continue with a pregnancy diagnosed with fetal spina bifida. This

Table 3 Ambulatory, bladder, bowel and neurological outcomes of 55 infants that underwent postnatal surgical repair of prenatally diagnosed isolated spina bifida, assessed at a minimum age of 3 years

Neurological outcome	n/N *(%)*
Ambulation	
Autonomous	13/53 (24.5)
Mild impairment	9/53 (17.0)
Moderate impairment	7/53 (13.2)
Severe impairment	24/53 (45.3)
Bladder continence	
Normal	6/55 (10.9)
Mild incontinence	19/55 (34.5)
Moderate incontinence	16/55 (29.1)
Severe incontinence	14/55 (25.5)
Bowel continence	
Normal	15/54 (27.8)
Mild incontinence	9/54 (16.7)
Moderate incontinence	15/54 (27.8)
Severe incontinence	15/54 (27.8)
Neurodevelopment	
Normal	35/55 (63.6)
Minor/mild delay	12/55 (21.8)
Global delay	8/55 (14.5)

cohort represents the very cases that would be given the option of fetal surgery, and therefore, the parents most in need of accurate information regarding the outcomes of spina bifida children undergoing conventional postnatal repair. Although infant neurodevelopmental evaluation, such as with Bayley's scale, is considered optimal, these assessments are known to be poor predictors of long-term outcome at school or adolescent ages[15,16]. In this context, school age attendance and educational attainment are used here as accurate and more relevant proxies of neurodevelopmental outcome[17]. An additional strength of the study is that long-term follow-up was conducted at an advanced mean age of 8 years.

Chiari malformation and callosal dysgenesis

A postnatal diagnosis of hindbrain herniation with Chiari malformation Type II was made in 91.5% of neonates with this outcome available prior to surgery, which is very similar to the rates reported in other postnatal series[18,19]. A purported advantage of fetal surgery is reduction in hindbrain herniation to about 62%[8]. However, the clinical benefits of a radiological diagnosis need to be judged taking into consideration that postnatal surgery is also associated with a 40% reduction in hindbrain herniation[19]. Furthermore, an analysis of long-term outcomes of 4448 individuals with spina bifida from a national registry demonstrated that symptoms of hindbrain herniation justifying surgery occurred in only 9% of cases despite the common occurrence of the radiological diagnosis[20]. The authors also demonstrated that clinical symptoms and surgery was more likely to be required with lesions rostral to a high lumbar functional level. Importantly, there was a strong temporal effect with more conservative management being adopted more recently. In keeping with the nebulous clinical significance of hindbrain herniation, only seven (10.4%) children in our cohort developed symptomatology requiring surgical decompression. Radiological defects of the corpus callosum were evident in 40.4% (19/47) of cases, with complete agenesis and hypoplasia/dysplasia reported in 4.3% and 36.2%, respectively. This finding is supported by previous studies that hypothesized that both primary malformations and a secondary destructive process (hydrocephalus) may result in callosal dysgenesis[21,22]. Despite this notable radiological diagnosis, there are data that demonstrate considerable developmental plasticity for callosal defects in spina bifida[23].

Ventriculoperitoneal shunt placement

In our population, shunt placement was required in 64.2% of children, which is midway between the reported rates of 41% and 83% for prenatal and postnatal surgical groups, respectively[9]. Specifically, in the only randomized controlled trial (RCT) on fetal *vs* postnatal surgery, the reported rate of shunt placement was 44% and 88%, respectively[8]. The latter finding is taken as evidence for encouraging a fetal surgical approach by proponents of the latter technique, given that USA registry data confirm shunt placement rates of 80% with postnatal surgery[20]. However, even within the context of a RCT, the MOMS trial guidance for shunt placement was subjective and open to the (unblinded) biases of the individual neurosurgeons caring for the infant. Furthermore, long-term follow-up of infants from the RCT has shown that fetal surgery did not reduce the need for shunt placement when fetal ventricular measurements were above 15 mm[24]. The latter guidance is in keeping with observational studies with postnatal surgery demonstrating that a fetal posterior horn lateral ventricular measurement of < 12 mm at diagnosis or < 15 mm in the third trimester was also associated with very low rates of postnatal shunting[25].

Neurological outcomes

In our cohort, 24.5% (13/53) of children could walk without any support and 17% (9/53) using only an orthopedic support below the knees; cumulatively, 41.5% of infants were walking independently or using minor support at a mean age of 8 years. This rate of ambulation is similar to that with fetal surgery in the MOMS trial, in which the assessment was at < 3 years of age and no distinction in the severity of the ambulatory impairment was made[26].

Normal bladder function or mild impairment was reported in 45.5% of our infants. A proactive approach in the urological management of spina bifida patients is preferred, leading to a higher rate (87.3%) of CIC use compared with in the MOMS trial (62%), as it is better tolerated and also decreases the need for surgical reconstruction and the risk of renal deterioration[27,28]. Normal or mildly impaired bowel

function was reported in 44.4% (24/54), which is similar to the 43% reported in the USA[29]. Importantly, both the MOMS trial and a subsequent systematic review failed to show any differences in bladder and bowel outcomes between prenatal and postnatal repair[8,9]. The cognitive development of children with spina bifida in our population was normal or mildly delayed in 85.5%, with global developmental delay reported in 14.5% of infants.

Conclusion

The long-term physical and neurological infant outcomes for cases of prenatally diagnosed spina bifida aperta managed by a comprehensive multidisciplinary team in a large tertiary center appear to be similar to those reported in emerging series of cases managed by fetal surgery. Neurodevelopmental and neurological outcomes between prenatal and postnatal repair are similar. Putative advantages of fetal surgery in reducing the rates of hindbrain herniation should be interpreted in light of the reversal of this finding with postnatal surgery and the infrequent need for surgical intervention. Similarly, the benefits of fetal surgery in reducing need for shunt placement appear to be restricted to cases without fetal ventriculomegaly, a finding apparent in cases managed with postnatal spina bifida repair.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Ambulatory, bladder, bowel and neurological outcomes of 55 infants that underwent postnatal surgical repair of prenatally diagnosed isolated spina bifida, assessed at a minimum age of 3 years, according to upper lesion level

