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

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ABSTRACT

Background: Parents faced with the choice between postnatal management versus prenatal surgery for spina bifida need to have up-to-date information on outcomes. The aim of this study is to report the long-term physical and neurological outcomes prenatally diagnosed spina bifida managed by a multidisciplinary team from a large tertiary centre.

Methods: A retrospective cohort study of all cases 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.

Results: During the study period, 241 fetuses with isolated spina bifida were seen in the unit, with 84 (34.9%) women opting to continue with the pregnancy after counselling by multidisciplinary clinicians. After birth, hind brain herniation was observed in 91.5% with only 7 infants requiring surgical decompression. Ventriculo-peritoneal shunt insertion was needed in 64.2% of infants who demonstrated normal or mild cognitive impairment in 85.4% of cases at a mean age of 8yrs. Cumulatively, 40% of infants were walking independently or using minor support and reported normal or mild impairment of bladder or bowel function in 45.4% and 44.5% of infants, respectively.

Conclusions: Neurodevelopmental and neurological outcomes between prenatal versus postnatal repair are similar. As with fetal surgery, conventional postnatal surgery is associated with the reversal of hind brain herniation. Similarly, postnatal ventriculoperitoneal shunts appear to be mainly required in fetuses without evidence of significant fetal ventriculomegaly.

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 cases[1,2] . In the last half century, the multidisciplinary approach to spina bifida care has significantly improved outcomes leading to an increase in life expectancy and gain in 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 last few decades[5,6]. Neurological damage in spina bifida is thought to result primarily from the congenital spinal abnormality as well as a secondary damage from exposure to amniotic fluid and direct intrauterine trauma. This unproven "two-hit" hypothesis is the rationale behind fetal surgery - in utero repair of the spine may have the potential to prevent secondary damage to the spinal cord due[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 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 versus 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 versus postnatal repair, but paradoxically suggested improved independent ambulation at 30 months of age[9]. The aim of this study is to report the long-term physical and neurological infant outcomes in cases of prenatally diagnosed spina bifida managed by a comprehensive multidisciplinary team in a large tertiary centre.

PATIENTS AND METHODS

This is a retrospective cohort study of all cases 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 their pregnancy and into late childhood by the same clinical team. Pregnancy and maternal 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 fetal ultrasound examination and birth was routinely scheduled in the tertiary centre from 38 weeks' gestation. Caesarean birth was only undertaken 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 of life for all neonates with open spina bifida[10-13]. The need for a ventriculo-peritoneal shunt and any surgical complications (shunt revision/blockage or infection) were recorded routinely. Neonates underwent cranial ultrasound and/or CT and/or MRI 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 orthopaedic surgeons.

Postnatal outcomes

Ambulatory status was evaluated in children aged between 3 and 5 years of age and was defined as normal in subjects able to walk independently with possible sensory or gait deficits. The ambulatory impairment was defined mild or moderate in case of need of orthopaedic 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 defined 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 faecal incontinence or severe obstruction. Information about cognitive development of children above 5 years was obtained from clinical records and classified as normal when attending a main stream 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 fetuses with isolated spina bifida were seen in the unit, with 84 (34.9%) women opting to continue with the pregnancy and eligible to be included in the current cohort. There were 13 further exclusions from this cohort because of fetal, neonatal/infant death and 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 babies that did not undergo surgery because of a diagnosis of spina bifida occulta were excluded from further analysis. There were no surgical complications recorded in 37 (55.2%) cases - a CSF leak, wound infection or other surgical complications were recorded in 13 cases during the hospital admission. Ventriculo-peritoneal (VP) shunt insertion 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). Supplementary table 1 presents ambulatory, sphincteric and neurological outcomes according to upper spinal level of lesion. Urodynamic assessment diagnosed hydronephrosis in six (10.9%) and a neuropathic bladder babies in 45 (81.8%) cases. Pharmacological (anticholinergic) therapy

for an overactive bladder was prescribed in 47 (85.5%) infants. Antegrade colonic enema (ACE) was required in 16 (29.1%) infants and an anal plug was used for the treatment of severe faecal incontinence in one infant.

DISCUSSION

This large 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 centres in the UK with more than 25 years of experience in multidisciplinary management of these patients. Parents chose to terminate the pregnancy in 63% of cases – an identical 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 centre, suggest outcomes much improved compared to historical cohorts and comparable to those currently reported for fetal surgery.

Research strengths and limitations

Bias introduced from by case selection is a concern with retrospective studies. However, this is a patient preference cohort determined by the parent's decision to continue with a pregnancy diagnosed with fetal spina bifida. The latter cohort represents the very cases that would be given the option of fetal surgery, and therefore parents most in need of accurate information regarding outcomes for spina bifida children undergoing conventional postnatal repair. Although infant neurodevelopmental evaluation such as with a 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 malformations and callosal dysgenesis

A post-natal diagnosis of hind brain herniation with Chiari malformation type II was made in 91.5% of neonates 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 hind brain 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 hind brain herniation[19]. Furthermore, an analysis of long-term outcomes of 4448 individuals with spina bifida from a national registry demonstrated that symptoms of hind brain herniation justifying surgery only occurred in 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 hind brain herniation, only 7 (10.4%) children in our cohort developed symptomatology requiring surgical decompression. Radiological defects of the corpus

callosum were evident in 40.5% of cases, with complete agenesis and hypoplasia/dysplasia reported in 4.3% and 36.2% of our cohort, respectively. This finding is supported by previous studies which hypothesised that both primary malformations and a secondary destructive process (hydrocephalus) may result in callosal dysgenesis[21, 22]. Despite this notable radiological diagnosis, there is data to demonstrate considerable developmental plasticity for callosal defects in spina bifida[23].

Ventriculo-peritoneal shunting

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 RCT on fetal versus postnatal surgery, the reported rates of shunt placement was 44% and 88%, respectively[8]. The latter finding is taken as compelling evidence for encouraging a fetal surgical approach by proponents of the latter technique, given that US register data confirms shunt placement rates of 80% with postnatal surgery[20]. However, even within the context of a RCT, the MOMS trial guidance for shunt placement were 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 shunt placement when fetal ventricular measurements were above 15mm[24]. The latter guidance is in keeping with observational studies with postnatal surgery demonstrating that a fetal posterior horn lateral ventricular measurement of <12mm at diagnosis or <15mm in the third trimester were also associated with very low rates of postnatal shunting[25].

Neurological outcomes

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

Normal or mild bladder impairment was reported in 45.4% of our infants, whose daily life is not affected by urinary incontinence. A proactive approach in the urological management of spina bifida patients is preferred leading to a higher rate (87.3%) of CIC use compared to 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 44.5%, which is similar to the 43% reported in the United States[29]. Importantly, both the MOMS trial and subsequent systematic review failed to show any differences in both bladder and bowel outcomes[8, 9]. The cognitive development of children with spina bifida in our population was normal or with mild delay in 85.4% of our patients, with global developmental delay reported in 14.6% of infants.

Conclusion

The long-term physical and neurological infant outcomes for cases of prenatally diagnosed spina bifida managed by a comprehensive multidisciplinary team in a large tertiary centre appear to be similar to those reported in emerging series of cases managed by fetal surgery cases. Neurodevelopmental and neurological outcomes between prenatal versus postnatal repair are similar. Putative advantages of fetal surgery in reducing the rates of hind brain 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 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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Figure legend:

Figure 1. Patient flow chart.

Table 1 - Maternal and population characteristics and demographics. Data provided as mean (±standard deviation), median (range) or number (%).

Maternal Age (years)	30.1 (±5.9)
Ethnicity	
Caucasian	62 (76.5%)
Asian	13 (16.0%)
Black African	5 (6.2%)
Parity	
Primipara	26 (32.1%)
Gestation at diagnosis	20.8 (±1.9)
Gestation at birth	38 (±2.0)
Preterm (<37/40 weeks) birth	9 (11.1%)
Early preterm (<34/40 weeks) birth	0 (0%)
Mode of delivery	
Vaginal Delivery	27 (33.3%)
Caesarean Section	50 (61.7%)
Birthweight (g)	3068 (±604)
Postnatal age at time of study (years)	6 (0-18)

Table 2. Neuroimaging and neurosurgical findings for all 67 study new-borns and infants. Data presented as number (%).

Ventricles	
Normal Ventricles	7 (12.1%)
Mild Ventriculomegaly	5 (8.6%)
Moderate Ventriculomegaly	18 (31%)
Hydrocephalus	28 (48.2%)
Cerebellum	
Normal cerebellum	4 (8.5%)
Arnold Chiari II	43 (91.5%)
Corpus callosum	
Normal	28 (59.5%)
Dysplasia/hypoplasia	17 (36.2%)
Complete agenesis	2 (4.3%)
Grey matter changes	
Normal	37 (86%)
Nodular heterotopia	6 (14%)
Ventriculoperitoneal shunting	
Not required	24 (35.8%)
Required	43 (64.2%)

Table 3 – Infant ambulatory, bladder, bowel and neurological outcomes in the 55 infants assessed at a minimum age of three years. Data presented as number (%).

Ambulation	
Autonomous	13 (24.5)
Mild impairment	9 (17)
Moderate impairment	7 (13.2)
Severe impairment	24 (45.3)
Bladder continence	
Normal	6 (10.9)
Mild bladder incontinence	19 (34.5)
Moderate bladder incontinence	16 (29.1)
Severe bladder incontinence	14 (25.5)
Bowel continence	
Normal	15 (27.8)
Mild bowel incontinence	9 (16.6)
Moderate bowel incontinence	15 (27.8)
Severe bowel incontinence	15 (27.8)
Neurodevelopment	
Normal	35 (63.6)
Minor/mild delay	12 (21.8)
Global delay	8 (14.6)