Role of fetal surgery in spinal dysraphism

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ABSTRACT

Open spinal dysraphism is a common and clinically challenging organo-genetic malformation. Due to the well-known multi-organ affection with significant implication on the lives of patients and their families, abortion after prenatal diagnosis became reality in most parts of the world. After publication of the Management of Myelomeningocele Study (MOMS) results fetal surgery seems to be a new option and a broad discussion arose regarding advantages and risks of *in utero* treatment of spina bifida. This paper tries to evaluate objectively the actual state of knowledge and experience. This review article gives a historical overview as well as the experimental and pathophysiological background of fetal surgery in open spinal dysraphism. Additionally clinical follow-up experience of foetoscopically treated patients are presented and discussed. After carefully outweighing all available information on fetal surgery for spina bifida, one has to conclude, in accordance with the MOMS investigators, that *in utero* surgery cannot be considered a standard option at present time. But there is clear evidence of the hypothesis that early closure of the spinal canal has a positive influence on spinal cord function and severity of Chiari malformation type II, has been proven. A persisting problem is the fetal risk of prematurity and the maternal risk of uterus damage. There is also evidence that due to technical restrictions, fetal closure of the spinal canal bears unsolved problems leading to a higher postnatal incidence of complication surgery. Finally, missing long-term results make a definite evaluation impossible so far. At the moment, fetal surgery in open spinal dysraphism is not a standard of care despite promising results regarding central nervous system protection due to early spinal canal closure. Many technical problems need to be solved in the future in order to make this option a safe and standard one.

Key words: Fetal surgery, myelomeningocele, open spinal dysraphism

INTRODUCTION

Open spinal dysraphism is one of the most frequent congenital malformations with possible multi-organ manifestations. Therefore affected children develop significant disability and sometimes life-threatening complications. Lifelong medical support is needed. The fetal hit leading to spina bifida aperta happens during early organogenesis in neurulation phase 12 around gestational day (GD) 28, when the neural tube is formed from cranial down to the lumbar segments.

In utero ultrasound and magnetic resonance imaging studies have shown that in many cases of open neural tube defects lower limb development and movements are normal at early stages and tend to deteriorate toward late pregnancy.[1]

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This observation led to the hypothesis, that the amniotic environment secondarily damages the neural tissue and early closure could possibly prevent this. A second hypothesis was discussed related to the development of Chiari malformation type II, e.g., of hindbrain herniation, which most likely is a result of excessive cerebrospinal fluid (CSF) outflow from the spinal defect.

These observations lead to animal trials investigating the influence of *in utero* closure of experimental neural tube defects. Due to positive results in some of them, a multicenter trial to investigate the effect in human fetal surgery for open spinal dysraphism was conducted with some encouraging results.

After the publication of the Management of Myelomeningocele Study (MOMS) results, fetal surgery seems to be a novel option not only for treatment, but also in respect of long-term outcome of affected children. There is an ongoing discussion regarding advantages and risks of *in utero* treatment of spina bifida versus postnatal surgery, which becomes a crucial issue also in prenatal counseling. This paper tries to evaluate objectively the actual state of knowledge and experience.

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HISTORICAL BACKGROUND

During pregnancy follow up, the former diagnostic standard for spina bifida detection consisted of maternal serum screening for α-fetoprotein around gestational week (GW) 16-18, followed by amniocentesis and determination of amnion fluid acetylcholinesterase. Nowadays, fetal anatomical ultrasound with high resolution and fetal magnetic resonance imaging with a detection rate of 98% are screening standards.

In the 1980s the first animal models for *in utero* repair of congenital defects were conducted by Adzick and Harrison.[2] In 1994 a fetal lamb model was introduced by Meuli and Adzick,[3,4] in which a myelomeningocele (MMC)-like defect was created a GD 75 (term 145-150 days). The defect was covered with a latissimus dorsi flap at GD 100. After cesarean section prior to term, near-normal neurological functions and a well-preserved anatomy and histology was found in study animals compared with controls showing human-like defects.

Additionally, it could be demonstrated that lumbar myelotomy leads to Chiari type II like hindbrain herniation in a sheep model. After fetal closure of the spinal defect, normal hindbrain anatomy was found.[5]

The first human fetal MMC closure was performed foetoscopically in 4 fetuses by Bruner.[6] He covered the dysraphic defect using a maternal flap. Two of the fetuses died and the series was stopped.

In 1998 the first open fetal surgery was performed at Children's Hospital of Philadelphia (CHOP) in GW 22 by Adzick.[7] Tulipan started his series of open fetal surgery later during pregnancy (GW 28-30) and found that all 4 fetuses were born prematurely with evidence of reversed Chiari type II. Two of the babies needed an early CSF shunt. In later series he found that the most striking result was the positive effect on hindbrain herniation.[8] It could be shown that surgery later than GW 25 has no benefit for neurological function and Chiari type II. Other groups had similar results.[9]

Based on these results and experience a randomized controlled multicenter study was initiated by the National Institute of Health (USA) in 2003. Participants of MOMS were the three centers with the largest surgical experience in fetal MMC repair: CHOP, University of California, San Francisco (UCSF) and Vanderbilt University (VU). Study duration was 8 years and costs were US $22.5 million.

A total of 200 pregnancies/mothers were scheduled for inclusion. The study was terminated after 183 included cases after reaching significance level. Initially 1,087 fetuses and mothers were screened. CHOP treated 77 mothers, UCSF 54 and VU 52 (http://www.nejm.org/doi/suppl/10.1056/NEJMoa1014379/suppl_file/nejmoa1014379_protocol.pdf). In March 2011, study results were published and latest since then, a worldwide discussion is going on regarding the optimal treatment and prognosis for open spina bifida.

During MOMS, all other centers in North America discontinued comparable surgical activities. Parallelly open and foetoscopic surgery was performed in single centers around the globe, the largest series are reported from Poland[10] (open), Germany[11,12] (foetoscopic) and recently from Brazil,[13] but not under controlled study conditions.

Beside open spinal dysraphism a variety of other indications for *in utero* surgery exist and some of them are considered as standard treatment. Due to the essential sophisticated skills regarding anesthesia and surgery inside the amnion cavity and related problems in closing both amnion sac and uterus these operations remain reserved for highly specialized centers. The North American Fetal Therapy Network is a voluntary association of such medical centers with expertise in all kinds of fetal surgery in USA and Canada. In Europe major centers are located in Leuven (Belgium), Linz (Austria), Zürich (Switzerland) as well as Bonn and Hamburg (Germany).

RESULTS OF MOMS

The rationale of MOMS was to reduce amnion fluid toxicity in order to minimize a second-hit damage to the neural tissue and to stop CSF-outflow out of the spinal defect in order to minimize hindbrain herniation as major manifestation of Chiari malformation type II.

Accordingly a positive effect on postnatal paresis, bladder and bowel dysfunction, and development of hydrocephalus, secondary tethered cord and possible Chiari-related complications was expected and thus investigated. The trial compared open prenatal MMC closure versus open postnatal reconstruction in 158 pregnant women including postnatal neurological and radiological tests of the infants 12 months after birth as well as mental and motor development tests after 30 months. Fetal closure was performed without surgical neurulation of the spinal cord, postnatal surgery included standard plastic reconstruction of placode and all tissue layers. The primary outcome criteria were shunt rate

and death. In the fetal group both were 68% compared with 98% in the postnatal group ($P<0.001$). Tonsillar herniation has been found in 64% (fetal) compared with 96% (postnatal) [Table 1]. After 30 months a significantly improved mental and motor development was also found ($P=0.007$).

Fetal surgery resulted in all cases in preterm delivery, in average at GW 34. In 13% pregnancy was terminated before GW 30. The incidence of uterine dehiscence was 30% and both cases with fatal outcome occurred in the prenatal group. The causes were extreme prematurity at GW 23 and severe Chiari malformation type II. The authors found a higher incidence of surgical interventions due to early secondary tethered cord syndrome.[14]

The results need to be discussed and the authors themselves do not consider fetal surgery as standard of care yet, despite significant improvement of outcome parameters. So far, the long-term results in both groups are not available and bladder and bowel dysfunction were not study parameters. Looking at the reported shunt rate, a certain bias can be observed: Independent reviewers found that in the prenatal group an indication for hydrocephalus shunting was given in 65%, but only 40% received a shunt. In the postnatal group there was also a tendency to avoid a shunt, but not as pronounced as in prenatal patients (92% indicated vs. 82% shunted). The most important argument against considering fetal closure as a standard is the fact, that the presented data derive from three highly specialized centers and that expertise and technical background cannot be guaranteed in other centers.

Experience with foetoscopic MMC closure

Parallel to open fetal surgery endoscopic techniques were tested as well, mainly to reduce the uterine damage. Technical problems in respect of amniotic membrane and uterus closure and more important regarding the plastic covering of the dysraphic lesion itself remained unsolved until recently. Therefore foetoscopy was considered less promising and not tested in a major study.

Table 1: Results of primary outcome criteria death/shunt and extent of tonsillar herniation after fetal and postnatal surgery (management of Myelomeningocele Study, Adzick *et al.*[14])

	Fetal	Postnatal	
Death/shunt %	68	98	$P<0.001$
Death	2	0	
Shunt %	40	82	
Chiari II			
Tonsillar herniation %	64	96	
Mild	40	29	
Moderate	19	45	
Severe	6	22	

After the early experience with fetal surgery in North America and Europe, also with established foetoscopic procedures for other indications, a German pediatrician first developed a sheep model for foetoscopic MMC closure[15] and then started a series of individual treatment trials in human fetuses.[16,17] The fact that this ongoing series is not controlled, the true incidence of complications and the overall outcome remains obscure, e.g., there is no matched population of postnatally treated patients in a comparable medical and social environment. The endoscopic interventionalist himself indicates that he is offering endoscopic treatment to a very select group of patients.[11,12] In order to get more evidence regarding the clinical results of this technique, several independent colleagues, pediatric neurologists as well as neurosurgeons collected data from patients followed by them with those who were primarily treated foetoscopically. In these randomly collected patient groups the shunt incidence was as high as in regularly treated patients, although shunts were put in many cases after the sixth month. Severe courses with early need for Gardner decompression due to excessive tonsillar herniation were seen, and numerous patch complications and early detethering procedures in secondary tethered cord syndromes were also noticed. On the other side, good motor development with only moderate bladder dysfunction could be observed in good-risk patients, which means low and smaller lesions, with intact patch closure. In this foetoscopic series, at least in the beginning, fatal outcome and maternal problems, e.g., uterus and amniotic cavity complications were reported. All children were premature, some of them extremely.

There is one independent paper reporting upon patients from this series. Verbeek *et al.*[18] could demonstrate that segmental neurological function after foetoscopic repair was better preserved compared with matched pairs with standard postnatal treatment, some of them after natural birth. A total of 13 pairs were investigated regarding segmental neurological function and leg muscle ultrasound density (MUD), a technique developed by Verbeek for functional muscle evaluation, e.g., in small children with dysraphic disorders.[19,20] Additionally they determined the inter-individual difference in MUD (dMUD), which describes the difference between affected myotomes cranial and caudal to the MMC level. This parameter was interpreted as extent of neuronal damage. The results show a better neurological functioning in respect of preserved knee-jerk ($P=0.006$) and anal reflex ($P<0.05$) in the fetal group, the dMUD

Table 2: Results of fetoscopic myelomeningocele closure performed at Department of Obstetrics, University of Bonn, Germany, between 2003 and 2009 (Verbeek *et al.*[18])

n foetoscopic MMC interventions	19	
n fetal death	3	
n interruption by iatrogenic hemorrhages	3	
Matched pairs analysis	**Fetal**	**Postnatal**
n	13	13
Mean age	14 months	
F/M ratio	1.6	
GW at birth (median)	32	39 (P=0.001)
Preserved knee-jerk reflex	↑	↓ (P=0.006)
Preserved anal reflex	↑	↓ (P=0.032)
dMUD (mean 24, 95% CI 15-33)	↓	↑ (P<0.05)
Complications*	↑	↓

MMC – Myelomeningocele; GW – Gestational week; dMUD – Difference in muscle ultrasound density. *(chorioamnionitis, premature rupture of amniotic membranes, oligohydramnios, respiratory distress syndrome, in premature baby)

was smaller as well (P<0.05). An overview of the results is given in Table 2. Out of 19 pregnancies 3 fetal deaths and 3 interruptions due to iatrogenic hemorrhage resulted. The complication rate was high [Table 2].

DISCUSSION

In general the standard treatment for open spinal dysraphism is postnatal plastic reconstruction after cesarean section, if possible. From neurosurgical point of view surgical neurulation and careful closure with sufficient CSF space around the placode is the best option for prevention of secondary tethering. Hydrocephalus shunting in due time is also recommended for optimal long-term mental and motor development. Beside Chiari-related circulation disorders, malresorptive hydrocephalus due to chemical CSF reactions caused by the open tube defects is also present in 80-90% of the patients.

Theoritically, fetal defect closure is able to reduce the negative impact of the amniotic fluid on neural tissue and CSF and also minimizes CSF-outflow with positive effect on hindbrain herniation formation. Due to the fact that the time window for fetal intervention lies between GW 22 and 25, some early damage of the neural structures cannot be prevented and potential fetal and maternal risks exist related to the early gestational state. Anesthesia as well as obstetric techniques must be very sophisticated and performed by a team with high expertise[21] in specialized centers. Even in good-risk patients treated under best clinical conditions fetal surgery for MMC inevitably results in significant prematurity and bears a 30% rate of uterus lesions. The *in utero* defect closure itself seems to be less appropriate both in open and in endoscopic surgery compared with postnatal treatment, as the increased rate of early interventions due to secondary tethering shows. Endoscopic coverage is technically more demanding and *in utero* and persisting postpartal CSF leakages frequent with significant complications and less successful prevention of hindbrain herniation have been reported.

No long-term outcome data exist so far as well as on bladder dysfunction. The fact that secondary tethering is an unsolved problem and hydrocephalus of later onset might be expected, secondary evaluation of the preliminary MOMS outcome data has to be awaited. Probably the best treatment for spina bifida will be prevention, e.g., folic acid supplementation and stem cell repair somewhere in the future.[22,23]

CONCLUSION

Taking into account all available evidence, fetal surgery in open spinal dysraphism cannot be considered as standard of care despite promising results regarding central nervous system protection due to early spinal canal closure and less severe hindbrain herniation. Many technical problems need to be solved in the future in order to make this option a safe and standard one.

The ethical conflicts related to prenatal counseling and different treatment modalities in open spina bifida potentially affecting two individuals, the mother and the (unborn) child, are complex and cannot be addressed here. But they should always be considered when decisions are to be made.

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