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# Open Spina Bifida: Why Not Fetal Surgery?

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Spina bifida · Myelomeningocele · Neural tube defect · Fetal surgery · Prenatal open spina bifida repair · Exclusion criteria · Prenatal counseling · Termination of pregnancy

**Abstract**
***Objective:*** The majority of patients counseled for prenatal open spina bifida repair (SBR) do not undergo fetal surgery. The aim of this study was to analyze the reasons for this phenomenon. ***Materials and Methods:*** The data of the first 160 patients seeking counseling or referred to the Zurich Center for Fetal Diagnosis and Therapy for prenatal SBR between December 2010 and March 2017 were retrospectively analyzed. ***Results:*** A total of 104 (65%) patients did not undergo prenatal SBR. Of this subgroup, 52% met the exclusion criteria, 35% decided to terminate pregnancy, 4% chose to continue pregnancy without fetal intervention, and 3% sought care in other European centers. In 6%, data about the ensuing course of pregnancy were not recorded. The main exclusion criteria were delayed presentation (30%), absence of hindbrain herniation (28%), and concomitant spinal anomalies (17%). ***Conclusion:*** The high percentage of patients not qualifying for prenatal SBR underscores the necessity of a standard evaluation of every single patient at a qualified referral center. To allow a higher proportion of women carrying a fetus with open spina bifida to be timely and correctly informed about a potential fetal intervention, much more effort is mandatory to spawn correct, objective, and understandable information among all groups of people potentially exposed to this topic.


## Introduction

The MOMS Trial has shown that prenatal open spina bifida repair (SBR) including myelomeningocele and its noncystic variant, myeloschisis, is beneficial for selected patients [1]. In comparison to postnatal repair, the overall percentage of prenatal repair patients requiring a ventriculoperitoneal shunt is reduced to half (from 80 to 42%, $p < 0.001$), and the percentage of patients walking independently is doubled (from 21 to 42%, $p = 0.01$). In addition, prenatal SBR leads to a reversal of hindbrain herniation in the majority of cases. Hindbrain herniation is a characteristic feature of Chiari II malformation and is practically always present in patients with open spina bi-



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fida (SB). In up to 33% of patients operated postnatally it causes cranial nerve, cerebellar, and medullary respiratory center dysfunction [2–4]. Reversal of hindbrain herniation after fetal SBR can largely prevent these potentially life-threatening dysfunctions. Further, persistent improvement of neurofunctional outcomes has been reported in a nonrandomized study that evaluated patients at a median age of 10 years after prenatal SBR [5].

However, despite these benefits, not all patients profit from prenatal SBR. Some will still require a ventriculoperitoneal shunt or have no improvement in motor function, and deficits in executive functions and adaptive skills are reported to be higher in patients undergoing prenatal SBR compared to a normal population [5]. In addition, the effect of prenatal repair on urological outcome, a crucial problem in patients with SB, is still unclear. A substudy of the MOMS Trial [6] demonstrated no significant reduction in the need for clean intermittent catheterization after prenatal SBR, but showed decreased bladder wall trabeculation and less open bladder necks. The significance of these findings in a long-term perspective is not known. However, some studies, including an own investigation, reported that prenatal repair may have a positive impact on lower urinary tract function [7, 8].

Seen in a critical light, the results of prenatal SBR are not perfect and beside that, a certain shadow falls over the possible benefits by the inherent risks of the procedure. Prenatal repair is associated with prematurity and with possible complications due to the uterine scar, including risk of uterine dehiscence and rupture [1]. Moreover, although studies have shown that prenatal SBR does not affect fertility, every subsequent pregnancy requires a cesarean section [9]. Despite these critical considerations, the undisputable benefits that can be achieved for a selected group of patients with prenatal SBR clearly outweigh the risks. Thus, prenatal repair by open fetal surgery is offered as a novel treatment option.

In light of the above problems associated with prenatal SBR and bearing in mind the relatively small incidence of SB, it is absolutely crucial that prenatal SBR be confined to a few high-volume and highly qualified fetal surgery centers worldwide where a multidisciplinary team of experts and an adequate infrastructure are readily available [10]. These places typically serve as referral centers for large areas not necessarily confined to geographic boundaries. For example, our Zurich Center for Fetal Diagnosis and Therapy (www.swissfetus.ch) is one of the very few established centers in Europe offering comprehensive prenatal evaluation and counseling, prenatal SBR, and a standardized long-term follow-up (up to 18 years of age) of all patients in a specific Pediatric Spina Bifida Center. Our fetal surgery program has been in existence for 7 years and gets requests and referrals not only from Switzerland, but also from most European as well as from many extra-European countries.

While we have accumulated a relatively large experience of over 80 operated cases so far, we are, in parallel, observing that a majority of patients referred to our center do not undergo prenatal SBR. Therefore, the aim of this study was to analyze the reasons for that phenomenon. We hypothesize that such an analysis will cast light on a number of crucial medical, social, and maybe also logistical issues. We further postulate that a detailed understanding of factors determining or influencing decision making is a precious resource for improvements, adaptations, and modifications regarding our system of care.

## Materials and Methods

The data of the first 160 patients referred to our center between December 2010 and March 2017 were analyzed retrospectively. Included were "classical" referrals, i.e., patients formally referred after evaluation and preliminary counseling by an outside specialist, but also self-referrals, i.e., patients that contacted us directly after having heard from us or found information on our program on the internet. Hence, we evaluated all charts of patients who had both on-site standard evaluation (according to MOMS [1]) and prenatal counseling at our center, but also notes of phone calls and e-mails as well as imaging material from patients not traveling to Zurich because they were excluded a priori (e.g., twin pregnancy) or because the information given by phone/e-mail was sufficient for them to choose another option (e.g., termination of pregnancy). Data were recorded and analyzed with Microsoft Excel 2013.

## Results

Of the 160 patients included in the study, 111 (69%) were evaluated on-site. The remaining 49 (31%) were patients whose basic information obtained by phone or e-mail revealed that they had exclusion criteria or who, after receiving preliminary basic information by phone or e-mail, decided to terminate pregnancy without an appointment at our center.

Of the 160 patients, 104 (65%) did not undergo prenatal SBR. In this subgroup, 54 cases (52%) met the exclusion criteria (Fig. 1), and 37 patients (35%) decided to terminate pregnancy. Four (4%) chose to continue pregnancy without fetal intervention, and 3 (3%) sought care in other European centers, among them a center offering

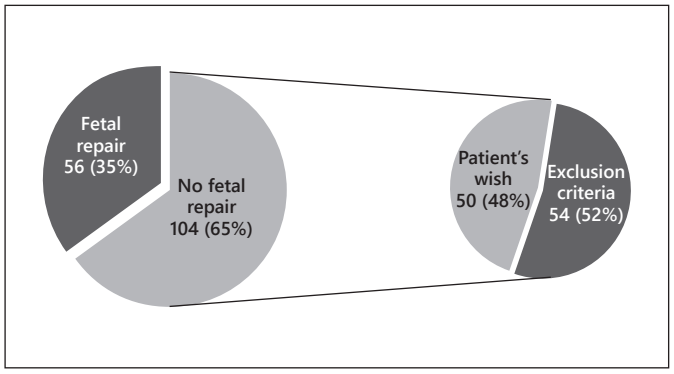


**Fig. 1.** Distribution of patients who were referred to us or contacted our center for possible prenatal spina bifida repair.

**Table 1.** Fetal and maternal exclusion criteria found in the 54 patients not qualifying for fetal spina bifida repair

| Exclusion criteria | *n* | % |
|---|---|---|
| *Fetal* | | |
| Absence of hindbrain herniation | 15 | 27.8 |
| Spinal anomalies | 9 | 16.7 |
| CRS with additional spine deformity | 3 | |
| CRS alone | 2 | |
| Kyphosis >30° | 4 | |
| Lesion below S1 and above T1 | 7 | 12.9 |
| Below S1[1] | 5 | |
| Above T1 | 2 | |
| Additional severe brain anomalies | 4 | 7.4 |
| Fetal cardiac anomalies | 2 | 3.7 |
| Genetic mutations | 2 | 3.7 |
| No spina bifida | 1 | 1.9 |
| Hydrops fetalis | 1 | 1.9 |
| *Maternal* | | |
| Presentation after 26 weeks | 16 | 29.6 |
| Multiple pregnancy | 4 | 7.4 |
| Prematurity in prior pregnancy | 3 | 5.6 |
| Body mass index >35 | 2 | 3.7 |
| Psychological issues | 2 | 3.7 |
| PA/PI, history of failed RU-496 abortion | 1 | 1.9 |
| HIV positivity | 1 | 1.9 |
| Hydatid mole | 1 | 1.9 |
| Combination of 2 criteria (fetal and/or maternal) | 12 | 22.2 |
| Combination of 3 criteria | 4 | 7.4 |

The sum of the percentages exceeds 100% due to presence of more than one exclusion criterion in some of the patients. CRS, caudal regression syndrome; PA, placenta accreta; PI, placenta increta. [1] All with concomitant missing hindbrain herniation.

fetoscopic repair. The records of 6 patients (6%) stated only that prenatal repair was declined (no details given).

The main exclusion criteria were presentation after 26 weeks of gestation ($n = 16$, 30%) and absence of hindbrain herniation ($n = 15$, 28%). Spinal anomalies were identified in 9 patients (17%), including 5 patients (9%) with caudal regression syndrome (CRS). Two of the 5 patients with CRS had CRS alone and 3 had additional spinal deformities. Four other patients (7%) were excluded for kyphosis (>30°). A lesion level below S1 was encountered in 5 patients (9%), all of whom also demonstrated absent hindbrain herniation. Two patients (4%) were excluded because of cervical location of the lesion. Severe brain anomalies (7%), heart defects (4%), genetic anomalies (4%), and a hydrops fetalis were other fetal pathologies found in excluded patients. One fetus had ventriculomegaly, aqueductal stenosis, agenesis of the corpus callosum, caudal displacement of the cerebellum, and talipes, but no SB was found on exams, whereupon the patient was excluded.

On the maternal side, exclusions were made due to twin pregnancies ($n = 4$, 7%), history of prematurity in former pregnancies ($n = 3$, 6%), body mass index >35 ($n = 2$, 4%), and psychological issues ($n = 2$, 4%). HIV positivity ($n = 1$, 2%) and a hydatid mole ($n = 1$, 2%) were other reasons. One woman did not qualify for fetal surgery due to a complicated index pregnancy with a history of failed abortion and placenta accreta/increta ($n = 1$, 2%). In 16 cases (30%), more than one exclusion criterion was present (two criteria in 12 patients and three criteria in 4 patients). These data are summarized in Table 1.

## Discussion

This is the first analysis explicitly looking in detail at the large group of women carrying a fetus with SB who do not undergo prenatal repair. A number of findings are worth commenting.

In our study, 65% of all patients did not have fetal surgery, and only a minority of 35% finally underwent prenatal repair. Similarly, the Children's Hospital of Philadelphia reported in their post-MOMS experience that only 17.2% of referred patients underwent fetal surgery [11]. These data highlight the fact that, apparently, a rigorous scrutiny takes place and that, consequently, only a meticulously selected group of patients with SB is ultimately eligible for and treated by fetal surgery.

Further, we speculate that a considerable number of patients never get in touch with a center that offers fetal

surgery. Therefore, the "true" percentage of all patients with SB undergoing prenatal repair is even lower.

Another important conclusion resulting from this study is that the exclusion criteria are met quite frequently. In fact, they were the most common reason why referred patients did not undergo fetal SBR. The fact that exclusion criteria are frequently present underscores the paramount importance of a vigilant and highly professional workup by an experienced expert team in order not to miss possible exclusion criteria as this may have deleterious consequences for the mother and the fetus. The total percentage of exclusion criteria found in our study (52%) is comparable to that reported in the MOMS Trial (56%) [1] and also in the post-MOMS experience (59%) [11].

Of note, most centers offering prenatal SBR have basically adopted and still vigorously impose the core exclusion criteria set forth by the MOMS Trial. Yet, this field is slowly changing, and disparate practices already exist among centers [12].

In our cohort, the most frequent exclusion criterion was presentation too late in gestation. Why is this, theoretically speaking, easily avoidable problem so dominant? From nonsystematic inquiries we guess that the option of fetal surgery is still not common knowledge among general practitioners and non-hospital-based specialists in obstetrics and gynecology. Furthermore, in larger hospitals and certainly in fetal-maternal medicine centers, the option is mostly well known, but there is still considerable skepticism with regard to this innovative therapy. As a consequence, patients may not be informed timely and correctly about a potential intervention before birth. In our experience, some patients develop an astounding self-initiative, sometimes after considerable trials and tribulations with doctors and insurance companies. They then contact our center directly, yet, at times too late. Thus, much more effort is mandatory to spawn correct, objective, understandable, and nondirective information among all groups of people potentially coming into contact with this topic. Obviously, this includes not only physicians and paramedical professionals, but also the public and the media.

In the context of timely referral, economic aspects may play an important role. Fetal surgery is expensive, and this is especially true for Switzerland. While patients from Switzerland get full coverage by mandatory health insurance, the financial aspects are sometimes complex for patients from abroad. Under EU law, European citizens have the right to obtain planned medical treatment in any EU country (including Switzerland) under certain circumstances and to be reimbursed by their national health insurance. However, prior authorization from the health insurer is needed. In most cases, this represents a serious challenge because of time constraints (intervention must often be done before coverage is ascertained). Consequently, we are often forced to operate without guaranteed cost coverage, and sometimes our "FetOpera" Fund must shoulder deficits. Thanks to this subsidize option, we did not have to turn down patients for financial reasons.

The second most frequent exclusion criterion was missing hindbrain herniation. Definitely, this seems to be a nondebatable exclusion criterion, as it indicates that the SB under examination in all likelihood belongs to the category of closed dysraphism (meningocele, myelocystocele, lipomyelomeningocele), i.e., that the lesion is covered by skin, meningeal, or connective tissue so that the spinal cord tissue is not directly exposed to amniotic fluid. Obviously, fetal intervention in such a situation would be futile. An important caveat is that sonography and MRI of the back lesion do not always allow for recognition of the dysraphism type beyond doubt, and here missing hindbrain herniation provides a very useful indirect, yet highly indicative, information. Fetal MRI allows to best visualize the presence or absence of hindbrain herniation and is thus mandatory for prenatal diagnostic workup [13, 14].

Spinal anomalies, including CRS as well as other severe malformations and deformities, were the third most frequent exclusion criterion identified. CRS is often associated with myelomeningocele. Even without myelomeningocele, CRS is per se often associated with devastating handicaps [15]. Comparing CRS patients with and without myelomeningocele, Balioğlu et al. [15] found that both groups were comparable in terms of ambulatory status, lower extremity deformities, and impairment of the genitourinary system. Therefore, a benefit of prenatal SBR for leg and lower urinary function cannot be expected. Hence, it is crucial that CRS is identified conclusively and timely.

Interestingly, patients qualifying for prenatal repair rarely opted for postnatal repair (4 patients in this study). It seems that patients counseled at our center do not really consider deciding between the three options prenatal repair, postnatal repair, and termination of pregnancy, but rather between having the "best possible" child or not having the child at all.

Two women decided for an endoscopic procedure even though this approach has not yet been proven to yield at least equivalent or, ideally, better results than open fetal surgery [16].

Given the high prevalence of exclusion criteria and the relatively large number of qualifying patients deciding to terminate pregnancy (Fig. 1), there is a preselection process before on-site evaluation and counseling. First, pre-

liminary information given by the referring physician and/or the patient is recorded on a checklist. Second, there is an expert interview over the phone with the patient. This procedure has led to almost one-third of all patients not coming "unnecessarily" to Zurich. Obviously, this kind of management spares resources for everyone involved. However and categorically, correct diagnostic workup comes first. Thus, in case of doubt, patients must come to our center to avoid exclusion based on wrong data or incorrect findings. For our future preselection practice, we are considering to use video calls instead of or in addition to e-mail and conventional phone calls.

Obviously, this study only reports a single-center experience. Thus, we cannot generalize our findings or translate them to other centers. On the other hand, there is only scarce detailed information from other centers, since these typically report on operated and not on excluded patients. Still, this analysis casts quite a comprehensive light on the overall recruiting activity of our center. It mirrors the entirety of our findings after evaluating patients and also the pattern of decisions made by our team and the mothers/couples.

## Conclusions

It appears that this is the first study which looked in detail at why fetal surgery is not performed. Here, a majority of 65% of potential candidates for fetal SBR were not operated. In 52% of this subgroup, one or more exclusion criteria were met (mainly delayed presentation, absence of hindbrain herniation, and concomitant spinal anomalies). This high percentage underscores the necessity of a standard state of the art expert evaluation of every single patient at the referral center. The remaining 48% of patients were eligible for fetal SBR, but chose another option (termination of pregnancy, postnatal repair, repair at another institution). Finally, fetal surgery was performed in only 35% of all patients.

Apart from a detailed understanding of the processes taking place before a final decision is made, we identify a need for more efficient information pathways regarding fetal surgery so that a higher proportion of women carrying a fetus with open SB have a chance to be correctly evaluated and counseled. This, in turn, will allow for a timely informed final decision making.

## Statement of Ethics

The study was approved by the local ethics committee on human research (KEK-ZH No. 2015-0172, PB_2016-00677).

## Disclosure Statement

The authors declare no conflicts of interest.

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