CORRESPONDENCE

Intrauterine Surgery—Choices and Limitations

by Dr. med. Anke Diemert, Werner Diehl, Peter Glosemeyer,
Prof. Dr. med. Jan Deprest, Prof. Dr. med. Kurt Hecher in volume 38/12

Intrauterine Surgery in Infravesical Obstruction

Regarding the subject of infravesical obstruction I would like to mention that the PLUTO study by Morris and Kilby cited by the authors (1) was stopped early: parents of affected unborn babies were given hope that intrauterine shunting of the bladder would result in improved fetal outcomes (lower mortality) because of prevention of pulmonary hypoplasia and not of improved renal function (morbidity).

The infants in whom shunts were placed using intrauterine surgery did not die from pulmonary hypoplasia any more but survived with very poor renal function, which means dialysis from an early age and transplantation later on. The fact that such critical nuances are explained to parents in the counseling has led to a situation in which increasing numbers of parents decide on a termination or non-intervention, not in favor of this randomized study. Due to the small number of cases the study was stopped before completion. All preceding studies on this subject showed that in this heterogeneous condition, patient selection is the decisive factor in order to reach a valid conclusion about which group might benefit from fetal surgery. Poor renal function has been described in the outcomes of all of these studies.

Parents and treating doctors should not be given false hopes. There is no proof that intrauterine shunting saves or preserves renal function.

The PLUTO study showed that the only sensible intervention in fetal infravesical obstruction is termination of the pregnancy. DOI: 10.3238/arztebl.2013.0134a

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Results Turned on Their Head

Diemert stated that the development of minimally invasive techniques should be promoted, as a consequence of the invasiveness of open fetal surgery for the treatment of unborn babies with myelomeningocele. She mentions a fetoscopic approach that I originally developed, but she attributes "sobering" results to it because of "a high rate of complications." Unfortunately she reports outdated information and therefore refers to merely the first 19 of almost 70 treated patients. This has certain consequences.

Diemert's description characterizes the clinical introduction period of this technically complex surgical procedure. For the present, the opposite is true (see also Kohl T, Kawecki A, Degenhardt J, Axt-Fliedner R, Neubauer B: Early neurological findings in 20 infants after minimally-invasive fetoscopic surgery for spina bifida at the University of Giessen 2010–2011. Ultrasound Obstet Gynecol 2012; 40(suppl 1): 9. and Degenhardt J, Schürg R, Kawecki A, et al.: Maternal outcome after minimally-invasive fetoscopic surgery for spina bifida. The Giessen experience 2010–2012. Ultrasound Obstet Gynecol 2012; 40(suppl. 1): 9.), (1). The early pediatric neurological results of the past two years are very encouraging as they have shown surprisingly good leg function in a majority of the children. Improvements of the type 2 Chiari malformation and a reduced need for postnatal shunt placement have also been observed regularly, along with a low rate of maternal and fetal complications, a fetal mortality of less than 3% (1/40) and delivery beyond 30 weeks of gestation in about 85% of cases.

Diemert and colleagues turned these results on their head—with grave consequences for pregnant women with sick unborn babies. In view of this faulty conclusion, large numbers of affected women will continue to opt for a termination. At least a proportion of the babies that are born in spite of the disorder, but without prenatal treatment, can be assumed to have a notably poorer start in life. DOI: 10.3238/arztebl.2013.0134b

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High-Quality Postnatal Care Is Essential

As explained in the article, those fetuses that are most severely affected by congenital diaphragmatic hernia (CDH) should be included for fetal therapy either in open observational studies or randomized studies at specialized centers. The inclusion criteria are met for one in four prenatally diagnosed fetuses with CDH, which means a maximum of 40 fetuses per year in Germany (assuming a total incidence of 1:3000 births). In the interest of sufficient routine experience, one or two specialized centers in Germany would be enough. Unfortunately, the authors did not explain the high importance of postnatal care given by specialized neonatologists.

The CDH-EURO-Consortium working group consists of European centers with more than 10 patients with CDH per year and has set out a guideline for standardized postnatal therapy (1). In an initial data analysis from Mannheim and Rotterdam, who both offer the option of extracorporeal membrane oxygenation (ECMO), the survival rate has improved significantly since a standardized therapeutic algorithm was introduced in November 2007 (2). The ECMO rate was falling. In order to avoid shifts in the prognosis children who had had fetal therapy and who had severe malformations were excluded. If a predefined standard exists, the treating team's attention and patient safety may just be higher.

Especially for the most severely affected fetuses that are referred for fetal therapy, Germany should follow the example of the Netherlands (two centers), and care for children with CDH should be provided only in highly specialized centers. As the example of the excellent results of the collaboration between the fetal surgery department at Giessen and the ECMO center in Mannheim illustrates for fetuses with right-sided CDH (80% survival rate), these results differ notably from those of the working group around Professor Deprest (3).

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In Reply:

In our opinion, fetoscopic treatment for myelomeningocele is a promising intervention that should be the subject of further research and should be promoted. Our assessment of the results is not based on outdated data, and we did not turn the results on their head, as Kohl says in his letter. The reference (e19) is from 2012 and therefore as up to date as it can be. The author of a commentary to this article (1) expresses grave concerns—namely, that valid statements about improved neurological and muscular function can only be made when the children are rather older, and that the proportion of children with dyspnea syndrome (12 out of 13) was very high. We do not share the view expressed by Shurtleff (1), that intrauterine endoscopic correction of myelomeningocele in human fetuses is still unethical, but we do see the urgent need for a randomized study. In this context it would be of particular interest to compare a group of babies who had intrauterine surgery with a group of babies who were operated on postnatally, where the pregnancy was ended in the 33rd gestation week by elective cesarean. This is the mean gestational age at birth in the studies on intrauterine surgery that have been published to date. It may be that shortening the term of the pregnancy—thereby shortening the exposure of nerve fibers to the toxic effects of amniotic fluid—is sufficient to improve the neurological results. The results mentioned by Kohl, which have improved thanks to greater and growing experience, have so far been published only in abstract form in conference proceedings. We look forward with some excitement to the publication of these data in the shape of original, peer-reviewed, articles.

Randomized studies are also urgently needed to evaluate the therapy of severe congenital diaphragmatic hernia. Comparing the results of observational studies from individual centers is not conclusive, owing to different selection criteria and small case numbers (2). We agree with Schaible that the treatment of fetuses and neonates with CDH should be given in highly specialized perinatal centers. It is hard to assess whether using extracorporeal membrane oxygenation (ECMO) significantly improves outcomes as no randomized studies have been undertaken so far. A follow-up study from two Dutch centers (Nijmegen and Rotterdam) showed the worst results for CHD, compared with other indications for ECMO: mortality 42%, 16% of surviving babies had severe handicaps, and only 37.5% had normal neurological test results (3). A multicenter randomized study of intrauterine tracheal occlusion with a balloon (www.totaltrial.eu) is currently being conducted in Leuven, headed up by J Deprest. In Germany, the prenatal medicine department at Bonn University Medical Center and our own group are participating.

We thank Reuss for reminding us that the PLUTO study was stopped early. Only 31 of 200 planned pregnancies were randomized, and data are available for a further 46 non-randomized cases (www.pluto.bham.ac.uk). The data are currently being analyzed. We

fundamentally agree with Reuss in her critical assessment of the prognosis in infravesical obstruction, but we do not think that total therapeutic nihilism is appropriate (4).

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Conflict of interest statement
The authors of all contributions declare that no conflict of interest exists