Effective Health Care Program

Technical Brief
Number 5

Maternal-Fetal Surgical Procedures

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Maternal-Fetal Surgical Procedures

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

This EPC evidence report is a Technical Brief. A Technical Brief is a rapid report, typically on an emerging medical technology, strategy or intervention. It provides an overview of key issues related to the intervention—for example, current indications, relevant patient populations and subgroups of interest, outcomes measured, and contextual factors that may affect decisions regarding the intervention. Although Technical Briefs generally focus on interventions for which there are limited published data and too few completed protocol-driven studies to support definitive conclusions, the decision to request a Technical Brief is not solely based on the availability of clinical studies. The goals of the Technical Brief are to provide an early objective description of the state of the science, a potential framework for assessing the applications and implications of the intervention, a summary of ongoing research, and information on future research needs. In particular, through the Technical Brief, AHRQ hopes to gain insight on the appropriate conceptual framework and critical issues that will inform future comparative effectiveness research.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this Technical Brief. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.hhs.gov.

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Ms. Allison Glasser provided research assistance on this report, including assisting with gray literature research on the Internet, carefully constructing many tables and efficiently coordinating key informant discussions.

Ms. Toye Spencer oversaw the completion and formatting of the summary tables, and other critical elements of the report as a whole.

Maternal-Fetal Surgical Procedures

Structured Abstract

Objectives. This report is intended to summarize the current state of practice and research in maternal-fetal surgical procedures, which is the surgical repair of abnormalities in fetuses in the womb.

Data Sources. We searched MEDLINE from 1980 forward for studies of fetal surgical procedures for the following seven conditions: congenital diaphragmatic hernia, cardiac malformations, myelomeningocele, obstructive uropathy, sacrococcygeal teratoma, twin-twin transfusion syndrome, and thoracic lesions. We also searched the Internet for sources of current practice, current insurance coverage of fetal surgery, and ongoing research (including the clinicaltrials.gov and NIH (National Institutes of Health) Reporter databases). We spoke with experts in the field regarding their knowledge of practice sites, ongoing training programs, research in the field, and considerations for the future of maternal-fetal surgical procedures.

Review Methods. We abstracted data on operational definitions of fetal diagnoses, type of procedure, maternal inclusion criteria, training of providers, study design, country, setting, comparators used, followup, outcomes measured, and adverse events. We summarized these data quantitatively. We attempted to identify all potential sources of care for maternal-fetal surgical procedures in the United States, and to summarize the state of the field.

Results. One hundred sixteen studies captured for this review were case series. There were 3 randomized controlled studies (RCTs) and the rest (47) were cohorts. Seventy-four studies were conducted in the United States; 68 were in Europe, and the rest in other parts of the world. One RCT was published as this report was in press; the study's findings add to the body of literature on maternal-fetal surgical procedures for myelomeningocele and are summarized in that section of the report. The most common outcomes measured across diagnoses were survival to birth, preterm birth, and neonatal death. Additional, longer term outcomes for infants were rare, but when reported included pulmonary and neurologic status as well as achievement of developmental milestones. Reports of maternal outcomes were exceedingly rare, and in particular, we note very few studies that addressed the issues of future reproductive function for the mother. There are few formal training programs and no system of accreditation or licensure.

Conclusions. While developing rapidly, research on fetal surgical procedures has not achieved the typical level of quality of studies and aggregate strength of the evidence used to reach definitive conclusions about care and policy. Overall momentum is toward more robust research and rigorous, more consistent documentation of outcomes over longer periods of time. Experts concurred in discussions as well as in the literature that they are eager to develop consensus measures as well as mechanisms to make implementation of common protocols and larger studies increasingly possible. Favorable signs include the substantive leadership of U.S. researchers across each of the topics considered. For each target condition, there are both fetal surgical centers and associated research enterprises engaged in the full spectrum of academic endeavor, from animal research and development of surgical interventions and refinements, to patient care, surgical training, bioethics forums, and reporting of results in the scientific literature.

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Introduction

Background

The purpose of this report is to describe the current state of research and practice of maternal-fetal surgical procedures; the report does not offer guidance on whether or when such procedures are appropriate.

Congenital abnormalities that can be repaired prenatally occur in a small percentage of full-term births, and because of advances in imaging techniques such as ultrasound, many more congenital abnormalities are being diagnosed in utero. As these abnormalities are increasingly frequently recognized prior to delivery, maternal-fetal surgical procedures have emerged as a potential option for treating some of these defects. Although postnatal intervention is best for most fetal abnormalities (particularly in light of risks associated with in utero surgeries), for a few conditions, the fetus' condition can deteriorate so rapidly in the womb as to make early intervention necessary either to avoid death or substantially higher morbidity after birth. Substantial questions remain about both the safety and efficacy of fetal surgical corrections. In some cases, the natural history of the conditions is poorly understood, making comparisons to no treatment or postnatal intervention difficult.

In addition, comparisons of fetal versus postnatal surgery must consider the safety of the mother, yet limited comparative data exist. The issue is particularly complicated because while congenital defects are relatively common in aggregate, individual congenital abnormalities occur infrequently, making effective study very difficult. Ongoing trials are evaluating some of the most common fetal surgeries (Appendix D).

The goal of this brief is to describe the current state of literature and practice of maternal-fetal surgical procedures for seven congenital abnormalities ranked of high importance by stakeholders:

- Sacrococcygeal teratoma
- Congenital diaphragmatic hernia
- Thoracic lesions: congenital cystic adenomatoid malformation and bronchopulmonary sequestration
- Obstructive uropathy
- Myelomeningocele
- Twin-twin transfusion syndrome
- Cardiac malformations

Key Questions Addressed in This Report

The key questions for this brief were as follows:

Key Question 1.

a. What fetal diagnoses are currently treatable with a maternal-fetal surgical procedure? For each fetal diagnosis that is potentially treatable with a maternal-fetal surgical procedure, what is the annual number of fetuses that could potentially benefit from the procedure?

b. What maternal-fetal surgical procedures are done in the United States? What is an estimate of the number of hospitals that perform each procedure and utilization of each procedure?
c. For each fetal diagnosis, which procedures or techniques are used?
d. For each maternal-fetal surgical procedure, what anesthesia is used? What are the potential harms to the fetus and mother from the anesthesia?
e. For each fetal diagnosis, what are the alternatives? For each fetal diagnosis, what are the theoretical advantages and disadvantages (including potential safety issues and harms to both the mother and fetus) of maternal-fetal surgical procedures relative to the alternatives?
f. What training programs exist for maternal-fetal surgical procedures? What special requirements are needed in hospitals that perform fetal surgical procedures?

Key Question 2.

Perform a systematic literature scan on studies on the use and safety of maternal-fetal surgical procedures for the selected conditions, with a synthesis of:

a. Operational definition of fetal diagnoses
b. Type of procedure
c. Maternal inclusion criteria
d. Training of providers of specialized expertise and equipment in the study hospital(s)
e. Study design or size/country or setting
f. Comparator used (if any)
g. Length of followup
h. Outcomes measured for both fetus and mother
i. Adverse events /harms/safety issues reported for both fetus and mother

We systematically searched, reviewed, and summarized the scientific evidence for each key question and any subsidiary questions.

A context section describing centers offering in utero procedures, training for such procedures, and access to care, and ethical issues surrounding maternal-fetal medicine is available in Appendix F. The state of the science sections for each condition, presented here, provide an overview of research in each area, including discussion of study designs, reporting of inclusion criteria, composition of comparison groups, and presence or absence of consideration of specific outcomes deemed important by the report team and expert consultants.

Methods

Overview

This brief combined standard systematic review approaches with Internet searches and key informant discussions.

Search Strategy

Search of the literature. We began our scan of the literature with a broad, general search query including key Medical Subject Heading (MeSH) terms and keywords related to fetal surgical procedures. The variability in subject term indexing among the retrieved citations in PubMed led to the development of additional search strategies to increase the comprehensiveness of our search retrieval.

From the combined retrieval of each of these search sets, we excluded publications that lay beyond the scope of the technical brief (letters, comments, editorials, reviews, news, practice guidelines), focusing on retaining items comprising primary data (case reports, prospective and retrospective studies).

We searched the Internet extensively to identify locations in the United States offering maternal-fetal surgical procedures; we also searched for insurance policies related to fetal interventions for a selected set of insurers. Searches were conducted across a number of fetal medicine-related Web sites as well as commercial databases including LexisNexis and ProQuest. We searched databases including Clinicaltrials.gov to identify current research. Appendix A includes further information about our search strategies and results.

Eligibility Criteria

Our inclusion/exclusion criteria for the research literature are shown in Table 1**.** All titles and abstracts identified through searches against our inclusion/exclusion criteria were reviewed by at least two investigators. When differences between the reviewers arose, we erred on the side of inclusion. For studies without adequate information to make the determination, we retrieved the full-text articles and reviewed them against the inclusion/exclusion criteria.

Table 1. Inclusion/exclusion criteria

Category	Criteria
Study population	Women and their fetuses with documented abnormalities on ultrasound that would require surgical correction
Publication languages	English only
Admissible evidence (study design and other criteria)	Admissible designs Randomized controlled trials, cohorts with comparison, case-control and case series with n ≥ 2 Other criteria • Original research studies that provide sufficient detail regarding methods and results to enable use and adjustment of the data and results • Studies must address one or more of the following for fetal procedures: – Treatment modality – Current medical practice of training – Short- and long-term outcomes, including maternal morbidity and mortality

We collected data from the studies to provide an overview of the status of research in the field by collecting the following information:

- Study design, country, and setting
- Research methods
- Type of procedure
- Fetal and maternal inclusion criteria
- Training of providers/specialized expertise and equipment in the study hospital
- Comparator used in comparative studies
- Length of followup
- Fetal and maternal outcomes measured
- Adverse events/harms/safety issues

Expert Panel Discussions

We consulted with experts selected because of their expertise in the following areas: expertise in each of the conditions of interest, those who could offer historical perspective on maternal-fetal surgical procedures, and individuals who had a particular subspecialty expertise, such as ethics. These three panels included a total of 17 experts with whom we held conversations via phone, lasting from 20 to 45 minutes. The conversations were unstructured and intended to elicit context and background related in particular to current practice of maternal-fetal surgery.

Describing the State of the Science

In text and tables through the report, we aimed to use counts to effectively describe the status of the available science on maternal-fetal surgical intervention. When possible, studies that include common participants from a single site are grouped together, and groupings are indicated. We recognize that duplications of individual mother-baby pairs nonetheless occur in the total counts. The total number of cases studied is certain to be lower than totals in tables

reflect. Our tables provide information that exceeds that in the text, and taken together within a section, they are the best source of a single view of the quality and strength of the evidence by topic.

Results

State of the Science

We present an overview of the state of the science for each of the seven conditions that are the focus of this report. As possible, we have attempted to either combine related publications in the citations or call the reader's attention to overlap. Total numbers of participants in text and tables overestimates the number of pregnancies because not all duplicate inclusions, especially those from registries and databases, can be deciphered from the information in the publications. Table 2 presents summary information for the studies included in this brief. Five studies were reported in the 1980s, 37 in the 1990s, and 121 since 2000.

Table 2. Overview of maternal-fetal surgical procedures literature

Study Characteristic	Cardiac malformations	Congenital diaphragmatic hernia	Myelomeningocele	Obstructive uropathy	Sacrococcygeal teratoma	Thoracic lesions (CCAM and BPS)	Twin-twin transfusion syndrome	Total Literature
Study Populations	(n=9)	(n=21)	(n=11)	(n=25)	(n=5)	(n=11)	(n=84)	(n=166)
U.S.	6	12	11	14	4	6	21	74
European	2	9	0	4	1	3	49	68
Asian	0	0	0	2	0	1	5	8
Other	1	0	0	5	0	1	9	16
Study Type								
Case series	9	12	4	14	1	3	73	116
Retrospective cohort	0	5	6	8	4	7	6	36
Prospective cohort	0	3	1	3	0	1	3	11
Randomized clinical trial	0	1	0	0	0	0	2	3
Approaches Assessed*								
Hysterotomy	1	8	9	3	3	3	4	31
Laparoscopic	0	12	2	0	1	2	7	24
Percutaneous	9	7	0	24	5	9	49†	103
Last Infant Outcome Assessment								
Birth	6	3	1	9	2	4	22	47
≤ 6 months	1	9	2	2	0	2	19	35
> 6 to ≤ 12 months	0	1	4	1	0	1	1	8
> 12 months	2	8	4	11	3	4	19	51
Unknown	0	0	0	2	0	0	23	25
Total Pregnancies:^	**90**	**503**	**262**	**450**	**130**	**414**	**2532**	**4381**

BPS=bronchopulmonary sequestration; CCAM=Congenital Cystic Adenomatoid Malformation

*Total is greater than number of studies, some publications report more than one approach. ^Minus duplication reported by authors. †Surgical approach is not clearly reported, therefore totals to less than 84 studies.

State of the Science: Cardiac Malformations

Background. In utero interventions are being performed for cardiac conditions including: Pulmonary atresia with intact ventricular septum (very narrow pulmonary valve without a connection between the right and left ventricles), critical aortic stenosis with impending hypoplastic left heart syndrome (HLHS) (very small, nonfunctional left ventricle, hypothesized by some investigators to be from underuse secondary to a severely narrow aortic valve), and

hypoplastic left heart syndrome with intact atrial septum (no connection between the left and right atrium). All of these conditions, if untreated either in utero or soon after birth, are lethal.

Critical pulmonary stenosis or atresia with intact ventricular septum. These anomalies portend a poor prognosis. A prospective prevalence study in Canada showed that overall survival was 77 percent at one month and 58 percent at 15 years.[1] Fetal intervention to relieve the stenosis and allow for ventricular growth could theoretically increase the number of patients who ultimately end up with a biventricular repair. There is some debate as to whether this is an adequate measure of success since the right ventricle in a two-ventricle repair still has abnormal diastolic dysfunction and may not lead to increased exercise capacity.[2] However, these studies were performed in patients who had not undergone in utero repair. It is possible that if the stenosis is relieved early enough in gestation that there may be adequate time before delivery for growth of the right ventricle. In fetuses with impending hydrops, in utero valvuloplasty could reverse the condition and prevent hydrops and death.

Included publications. We identified two published reports[3-4] of in utero fetal pulmonary balloon valvuloplasty in fetuses with pulmonary atresia of intact ventricular septum meeting our inclusion criteria (Table 3). Tulzer's case series[3] describes two patients who underwent in utero pulmonary balloon valvuloplasty at a specialty center in Europe. One fetus was diagnosed at 28 weeks and the other at 30 weeks gestation; both had imminent hydrops, which was not defined in the paper. Both fetuses showed successful valve perforations and immediate improvement in right ventricular function. Both fetuses sustained spontaneously resolving pericardial effusions.

No maternal selection criteria were noted. General maternal anesthesia was used in one case, and local maternal anesthesia was used in the second case. There was no additional fetal anesthesia used in the case with general maternal anesthesia. In the case with local maternal anesthesia, the fetus was given fentanyl, pancuronium, and atropine through the intrahepatic vein.

Table 3. Summary of case series of maternal-fetal surgical procedures for cardiac malformations

Author Year	With fetal procedure, N*	Fetal inclusion criteria provided?	Maternal inclusion criteria provided?	Comparison group	Outcomes beyond neonatal hospital stay?
Pulmonary atresia and intact ventricular septum					
Mizrahi-Arnaud et al.[4] 2007	8	No	No	None	No
Tulzer et al.[3] 2002	2	Yes	No	None	Yes
Aortic stenosis with developing hypoplastic left heart syndrome (HLHS)					
McElhinney et al.[5-6] 2009	70	Yes	No	Yes	Yes
Mizrahi-Arnaud et al.[4] 2007	50	No	No	No	Yes
Wilkins-Haug et al.[7] 2006	22	Yes	No	No	No
Marshall et al.[8] 2005	26	No	No	No	Yes
Tworetzky et al.[9] 2004	14	No	No	No	Yes (30 mos)
Kohl et al.[10] 2000*	12	No	No	No	Yes
Maxwell et al.[11] 1991	2	No	No	No	Yes
Intact atrial septum studies					
Marshall et al.2004[12] 2008[13]	19	Yes	No	No	No
Mizrahi-Arnaud et al.[4] 2007	20	Yes	No	No	No

*These totals represent an unknown number of duplicated cases; estimated total of unique cases is 93.

Both fetuses developed restenosis of the valve which prompted delivery, one at 38 weeks + 2 daysand the other at 35 weeks + 3 days. Both required postnatal balloon pulmonary valvuloplasty and systemic-to-pulmonary shunt. They were both reported to have biventricular circulation at 18 and 12 months of life.

Mizrahi-Arnaud's publication[4,8] regarding experience with fetal hemodynamic instability in 83 fetuses undergoing 3 different fetal cardiac surgeries included 8 patients with pulmonary atresia with evolving hypoplastic right heart syndrome (HRHS). Six of the eight fetuses experienced major fetal hemodynamic instability (defined as fetal heart rate $\leq$110 min^{-1} for $\geq$30 min with ventricular dysfunction of the dominant ventricle requiring resuscitation). There was no information provided on fetal inclusion criteria or survival of procedure, to birth, or beyond.

Critical aortic stenosis. Severe aortic stenosis, a very narrow aortic valve that develops early during gestation, may result in HLHS. In utero aortic balloon valvuloplasty has been suggested as a way to relieve aortic stenosis, thus preserving left ventricular growth and halting progression to HLHS.

The first described attempt at in utero balloon aortic valvuloplasty was reported by Maxwell in London in 1991. The same group reported the first survivor in a case report in 1995.[14] Since then, there have been scattered attempts at this procedure around the world, but the most

abundant work has been performed by the fetal surgery team at Children's Hospital Boston, Massachusetts.

Included publications. For this technical brief, we identified eight publications.[4-11] The fetal surgery team at Children's Hospital Boston has published several papers about its experience with a series of patients undergoing balloon dilation for severe aortic stenosis, some with additional participants and others with followup of the same participants. There is one publication from the United Kingdom[11] and one publication that pools data from six international centers,[10] including the aforementioned site in the United Kingdom. Two centers in Germany, two in Brazil, and an additional one in the United States (Pennsylvania) perform the procedures.

All publications are prospective case series that took place between 1989 and 2010. An estimated total of 90 fetuses underwent in utero balloon aortic valvuloplasty (the literature includes reports of 154 with some level of duplication). Seventy patients are from Boston. Technical successes have improved over time and appear to be related to center and team experience. In 2000, Kohl[10] reported on 12 cases in 6 different centers in Europe, Brazil, and the United States (the first 2 reported cases were also published separately by Maxwell in 1991). Technical success was achieved in 7 of 12 (58 percent), but 4 of 7 (57 percent) of those fetuses died within 24 hours of the procedure. By 2009, McElhinney[5] was reporting technical success in 52 of 70 (74 percent) cases with 5 of 50 (10 percent) of the technical successes resulting in fetal loss or stillbirth. Of the technical successes, 15 of 45 with live birth (33 percent) were born with a biventricular circulation, and 28 of 4,514 (62 percent) were born with HLHS. Of the 18 (26 percent) who had technical failures, 14 survived to birth, and all were born with HLHS. When the numbers of fetal deaths are included (excluding terminations for any reason), the rate of loss was 9 of 68 (13 percent) in those who underwent a procedure, whether successful or not, and 3 of 14 participants who declined procedures had neonatal deaths (21 percent). It is difficult to determine whether the procedure changes long-term outcomes, since it appears to increase risk of fetal loss but potentially prevent neonatal deaths

Table 4. Primary outcomes of maternal-fetal surgical procedures for cardiac malformations

Author, Year, Country	Key outcomes
Pulmonary atresia with intact ventricular septum	
Mizrahi-Arnaud et al.[4] 2007* **U.S.**	• Focuses on fetal hemodynamic instability (FHI), defined as fetal heart rate ≤110 min^{-1} for ≥30 min with ventricular dysfunction of dominant ventricle. Major FHI if required resuscitation. Minor FHI if no intervention required • 6 of 8 (75%) had major FHI. More likely in younger fetuses (p=0.03) and those with hemopericardium (p=0.07) • No fetal outcomes regarding procedure success, survival to birth or neonatal survival are available
Tulzer et al.[3] 2002 Austria	• 2 fetuses with imminent hydrops (undefined) had valvuloplasty • 35 weeks and 38 weeks at birth; follow up at 12 and 18 months

Table 4. Primary outcomes of maternal-fetal surgical procedures for cardiac malformations (continued)

Author, Year, Country	Key outcomes
Aortic stenosis with developing HLHS	
McElhinney et al.[5-6] 2009	• 59 of 70 (84%) with attempted procedures survived to viability at birth • 15 of 50 (30%) with successful procedures had biventricular circulation at birth • Of those without biventricular circulation at birth (n=30), 2 died without intervention, 1 had heart transplant and died, 3 died after neonatal procedures; 2 achieved biventricular circulation via surgeries in childhood. • Prenatal aortic valvuloplasty does not reverse abnormally low cerebrovascular impendence observed in studies of cerebral blood flow in fetuses with HLHS.
Mizrahi-Arnaud et al.[4] 2007* U.S.	• No differentiation in outcomes between pulmonary valvuloplasty and aortic valvuloplasty so many outcomes are overall for both • 45% had major FHI • More likely in younger fetuses (p=0.03) and those with hemopericardium (p=0.07) • No fetal outcomes regarding procedure success, survival to birth or neonatal survival available
Wilkins-Haug et al.[7] 2006* U.S.	• Only assessed factors affecting technical success • Descriptive series 22 fetuses
Marshall et al.[8] 2005* U.S.	• 14 of 26 (54%) performed percutaneously • 22 cases laparotomies • 20 of 26 technically successful. Neither gestational age nor annulus size associated with technical success
Tworetzky et al.[9] 2004* U.S.	• Technical success in 14 of 20 • 2 of 14 in utero demise • 3 of 14 (21%) born with 2 functioning ventricles, 2 required procedures in first week of life • 6 of 14 had HLHS; of the technical failures, 1 of 6 terminated, 3 of 6 HLHS, 2 of 6 fetal demise
Kohl et al.[10] 2000 Europe, Brazil, U.S.	• 12 fetuses in 6 different centers in Europe, Brazil, U.S. • 5 technical failures; 1 of 5 (20%) of these survived long-term • 1 of 7 (14%) who survived prenatal intervention survived long-term • Four fetuses died within 24 hours after procedure from bleeding, bradycardia and valvotomy following emergency delivery; two cesarean sections and one chorioamnionitis
Maxwell et al.[11] 1991 U.K.	• 2 fetuses with critical aortic stenosis. One fetal demise within 24 hours of technically unsuccessful procedure • One neonatal death from heart failure after one technically unsuccessful attempt and one successful attempt
Hypoplastic left heart with intact atrial septum	
Marshall et al.[13] 2008* U.S.	• 19 of 21 successful atrial septoplasty (excluded hydropic fetuses) • Fetal bradycardia, pericardial effusion, or pleural effusion in 8 of 21 (38%) • 12 of 19 required urgent intervention at birth • 7 of 19 underwent routine stage I postnatal surgery • Overall survival including two fetal demises 11 of 21 (58%)
Mizrahi-Arnaud et al.[4] 2007* U.S.	• Focuses on fetal hemodynamic instability defined as fetal heart rate ≤110 min^{-1} for ≥30 min with ventricular dysfunction of dominant ventricle • No major (requiring resuscitation) fetal hemodynamic instability from septoplasty; Minor FHI (no intervention required) occurred in 1 patient

FHI = fetal hemodynamic instability; HLHS=hypoplastic left heart syndrome
*Overlapping populations

Three successive papers were published by the same group, each focusing on different aspects related to the procedure: technical characteristics of successful balloon dilation,[8] examination of factors affecting technical success, and fetal hemodynamic instability during intervention. In all, they performed at least 50 attempts at in utero aortic valvuloplasty. Because

each of these subsequent studies has an independent focus, some during a very narrow time period, it is impossible to tell the overall success rate, survival to birth, and cardiac function and need for surgery postnatally. None of these publications focus on long-term outcomes, so it is difficult to determine whether there is an increase in biventricular function, and even whether any biventricular function is clinically superior to a univentricular circulation. There is also no published data discussing long-term survival and neurologic outcomes of these patients.

It does appear clear that technical success improves over time within a dedicated team and center. The group in Boston improved their success rate from 25 percent to 90 percent[8] over a period of several years. All procedures were performed percutaneously except for 12 laparotomies for failed percutaneous attempts (due to fetal positioning and maternal habitus). This is the only information available regarding maternal inclusion criteria, and there is limited information on maternal outcomes.

Hypoplastic left heart syndrome and intact atrial septum. The Centers for Disease Control and Prevention (CDC) estimates that each year about 975 babies in the United States are born with HLHS.[15-16] In other words, each year about 2 out of every 10,000 babies born will be born with HLHS. Given the high mortality of infants with HLHS and intact atrial septum, considered to be due to the pulmonary vasculopathy that develops before birth, in utero atrial septostomy has been performed in an attempt to improve postnatal survival. The first report of a balloon atrial septoplasty was in 2004. There is also a single case report using a laser to perform atrial septoplasty.[17] In two cases of balloon septoplasty, teams were unable to achieve technical success due to inability to reach the fetal left atrium.[17]

Included publications. We identified four publications reporting on the creation in utero of an atrial septal defect (ASD). Of these, three met criteria for inclusion.[4, 12-13] The fourth paper is the only published report using a laser to perform atrial septoplasty on a fetus but was excluded from evaluation since it was a single case report.[18] The first report of in utero creation of an ASD was published in 2004 by a large academic center that specializes in fetal cardiac surgery.[12] All publications included were case series from this group and represent one distinct population with additional participants in each subsequent publication for a total of 24 patients between 2001 and 2007.[13] There are no reports of this procedure being performed outside the United States.

Patients were consecutive fetuses diagnosed via fetal echocardiogram with HLHS and either an intact atrial septum or a ≤ 1mm ASD. Three patients had hydrops fetalis and were excluded from evaluation in the more recent publication. The fetuses were between 23 and 34 weeks gestation at time of intervention. The atrial septum was approached from the right in all but two of the cases.

Technical success was defined by documentation of passage and inflation of the balloon catheter across the atrial septum and echocardiographic flow across a new septal defect.[13] There was technical success in at least 19 of 21 cases (90 percent).[12-13] At least two of the three hydropic cases were a technical success. The two technical failures were because the introducer could not reach the fetal left atrium due to a combination of introducer length, maternal habitus, and fetal position.[13]

Fetal complications occurred in 8 of 21 cases (38 percent) and included bradycardia, pericardial effusion, or pleural effusion. Complications occurred in five of nine cases (56 percent) with a larger cannula compared to three of 11 cases (27 percent, p=0.36) with a smaller cannula. Two fetuses, both which developed hemopericardium, died within 24 hours of the

procedure.[13] At least one was hydropic. Another hydropic fetus died after delivery at 34 weeks due to respiratory compromise. All 19 underwent a stage I procedure, and overall surgical survival was 11 of 19 (58 percent). Of the non-hydropic fetuses, 12 of 19 (63 percent) required an urgent left atrial decompression and surgical survival was 5 of 12 (42 percent) compared to 5 of 7 (86 percent) in patients who underwent a routine stage I procedure.

No maternal selection criteria were provided. The average length of hospitalization was 2.4 ± 1 days.[12-13] One woman developed preintervention mirror syndrome (a form of severe preeclampsia) and postoperatively developed an oxygen requirement, which resolved with diuresis, and cellulitis. No maternal deaths or blood transfusion were reported. There is no report of long-term maternal outcomes.

HLHS with intact atrial septum has a poor prognosis, despite the availability of aggressive postnatal surgical options. The attempts to improve the outcomes by creating an adequate atrial septum in utero to allow for a routine stage I palliation have met with technical success. However, the mortality remains high, and there are no randomized controlled trials available to adequately compare the outcomes in patients treated prenatally with those treated postnatally, especially regarding need for definitive postnatal surgical repair. There is no data available on long-term neurologic outcomes.

Summary of fetal cardiac intervention literature. The procedures for severe fetal cardiac anomalies are in developmental stages. As is the history in most areas of new surgical interventions, preliminary work is based in a few highly specialized centers which are laying the groundwork for better understanding the feasibility and subsequent directions for outcomes research in this area. Key informants in our process identified as the most pressing challenge in this area the ability to identify the "right" patient whose care would be compromised by waiting to do a postnatal repair. They stressed the need for more work in developing tools for patient selection in this area. Future research should also include better controlled observational studies and investigate animal and other models to assist in the evaluation of fetal cardiac intervention.

State of the Science: Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia (CDH) results from abnormal development of the diaphragm which allows abdominal organs like the bowel, the stomach, and the liver to protrude into the chest cavity. CDH is an important, relatively common congenital malformation, with incidence in the United States of approximately one in every 2,500 births.[19-20] Fetuses diagnosed in utero as a result of maternal symptoms have mortality risk approaching 75 percent in some older reviews. One of the paradoxes of diaphragmatic hernia care is a trend toward improved outcome of fetuses not diagnosed before birth. This may reflect the fact that less severe lesions, without the findings of liver in the chest, stomach in the chest, or increased amniotic fluid volume are less likely to be detected by routine ultrasound.

Less invasive fetal procedures have more recently focused on methods to accomplish tracheal occlusion. Occluding the trachea of a fetus results in buildup of lung secretions in the pulmonary tree, gradually distending the lungs as well as triggering complex changes in maturation, including DNA synthesis, epithelial and endothelial proliferation, increased phospholipid metabolism, and surfactant synthesis. The growing lungs push the bowel and abdominal contents out of the chest cavity to an extent and promote improved lung growth.

Included publications. Our search for reports of fetal interventions for congenital diaphragmatic hernia identified 25 publications[21-45] with 21 unduplicated populations.

These 21 studies included data from 10 U.S. sites, 9 European, 3 multinational, and 5 from other countries. The Harrison group at the University of California, San Francisco is responsible for the largest number of papers that met criteria for this review, with seven of the publications reflecting their institution and approaches. Of the 21 reports summarized here, 1 is a randomized clinical trial with 3 publications;[21,29,38] 3 are prospective cohort studies;[25,31,45] 5 are retrospective cohorts;[22,35,37,41,43] and the balance are case series (Table 5).

Table 5. Summary of maternal-fetal surgical procedures for congenital diaphragmatic hernia

Author Year	Tracheal occlusion cases N	Other infants N	Fetal inclusion criteria?	Maternal inclusion criteria?	Comparison group	Outcome beyond neonatal hospital stay?
Randomized clinical trials						
Cortes et al.[21, 29, 38] 2005	11	13	Yes	Yes	No fetal procedure	Yes (24 mos)
Total	**11**	**13**	**1 of 1**	**1 of 1**	**1 of 1**	**1 of 1**
Prospective cohorts						
Cannie et al.[45]	40	18	Yes	No	No fetal procedure	No
Harrison et al.[31] 1998	8	13 (open repair) 13 (no procedure)	Yes	Yes	Open repair; no fetal procedure	No (unclear)
Harrison et al.[25] 1997	0	4 (open repair) 7 (no procedure)	Yes	No	Open repair; No fetal procedure	Yes (24 mos)
Total	**48**	**17, 38**	**3 of 3**	**1 of 3**	**23 of 3**	**2 of 3**
Retrospective cohorts						
Sinha et al.[43]	31	55 (no procedure)	Yes	No	No fetal procedure	No
Saura et al.[41] 2007	13	6	Yes	No	No fetal procedure	Yes (6 mos)
Jani et al.[35] 2005	24	37	Yes	No	No fetal procedure	No
Deprest et al.[22] 2004	21	17	Yes	No	No fetal procedure	No
Keller et al.[37] 2003	16	40	Yes	Yes	No fetal procedure	No
Total	**105**	**155**	**5 of 5**	**1 of 5**	**5 of 5**	**1 of 5**

Table 5. Summary of maternal-fetal surgical procedures for congenital diaphragmatic hernia (continued)

Author Year	Tracheal occlusion cases N	Other infants N	Fetal inclusion criteria?	Maternal inclusion criteria?	Comparison group	Outcome beyond neonatal hospital stay?
Prospective case series						
Jani et al.[36] 2006	28	NA	Yes	No	NA	No
Kohl et al.[39] 2006	8	NA	Yes	Yes	NA	No
Total	**36**	**NA**	**2 of 2**	**1 of 2**	**NA**	**0 of 2**
Retrospective case series						
Peiro et al.[44] 2009	18	NA	Yes	No	NA	No
Peralta et al.[40] 2008	30	NA	Yes	No	NA	No
Hee-rema et al.[33] 2003	17	NA	No	No	NA	No
Harrison et al.[27, 32] 1996, 2003	19	NA	Yes	Yes	NA	Yes (40 mos)
Harrison et al.[28] 2001	2	NA	Yes	No	NA	Yes (18 mos)
Flake et al.[23, 42] 2000, 2009	15	NA	Yes	Yes	NA	Yes (24-48 mos)
Gibbs et al.[24] 1998	11	NA	Yes	No	NA	Yes (48 mos)
Hubbard et al.[34] 1997	3	NA	No	No	NA	No
Harrison et al.[26] 1993	14	NA	Yes	No	NA	No (discharge)
Harrison et al.[30] 1990	6	NA	Yes	No	NA	No
Total	**135**	**NA**	**8 of 10**	**3 of 10**	**NA**	**4 of 10**

The 2003 randomized trial compared fetal tracheal occlusion to intervention at birth.[29] Entry criteria for the trial included a lung-to-head measurement ratio (LHR) of less than 1.4, which in historical cohorts had resulted in a survival rate of less than 40 percent. Participants were randomized into strata of severity as indicated by this ratio. The endoscopic procedure was successfully carried out in 11 fetuses, two with a tracheal clip procedure and nine with an intra tracheal balloon procedure. The study was stopped after 24 participants because the findings revealed similar survival rates to 90 days of life: 73 percent for tracheal occlusion recipients and 77 percent for the group that did not receive fetal intervention, with no anticipation that continued study would be able to confirm statistically meaningful differences in outcomes in an acceptable timeframe. Infants in the treated group were delivered at a mean gestational age of 30.8 compared to a mean of 37.0 in the standard care group. Survival was significantly greater

regardless of treatment group in infants with LHR >0.90. Consequently subsequent studies have focused on fetuses with LHR <1.0 predicting worse survival.

The fetal surgery trial group had higher rates of prematurity and lower birth weights. Follow-up of those infants has revealed more than half of both those with and without fetal treatment have growth failure and neurodevelopment status is not significantly different (Table 6). This study highlighted the importance of having a concomitant control group as the survival for CDH with postnatal repair had also improved over time from the predicted 38 percent, to 77 percent.

Table 6. Primary outcomes of maternal-fetal surgical procedures for congenital diaphragmatic hernia

Author, Year, Country	Comparison groups (N)	Key outcomes
Randomized trial		
Cortes et al.[21,29,38] 2005 U.S.	**G1:** balloon tracheal occlusion (11) **G2:** no fetal procedure (13)	• Lung-to-head ratios <1.4 enrolled between 22 and 27 weeks' gestation • 8 of 11 (73%) occlusion recipients survived beyond 90 days • 10 of 13 (77%) without fetal surgery survived • Infants with occlusion were more likely to be born preterm • Growth failure (<2 SDs below mean) occurred in 56% of controls and 86% of infants who had occlusion • No neurodevelopmental differences at 1 or 2 years of age between groups
Prospective cohorts		
Cannie et al.[45]	**G1:** balloon tracheal occlusion (40) **G2:** no fetal procedure (18)	• No data about fetal deaths; does not include infants born before 32 weeks • Fetuses with balloon occlusion had increase in lung volume in utero relative to untreated • Earlier balloon occlusion (<29 weeks) was associated with greater increase in lung volume • In multivariate models endoscopic occlusion was an independent predictor of survival
Harrison et al.[31] 1998 U.S.	**G1:** open tracheal occlusion (13) **G2:** fetoscopic occlusion (8) **G3:** no fetal procedure (13)	• All fetuses with isolated left CDH and poor prognosis • 2 of 13 with open surgery survived to discharge • 7 of 8 (88%) endoscopic occlusion recipients survived • 5 of 13 (38%) without fetal surgery survived • Endoscopic approach superior
Harrison et al.[25] 1997 U.S.	**G1:** open repair (4) **G2:** no fetal procedure (7)	• Repair at 25 weeks • 3 of 4 (75%) with in utero repair survived • 6 of 7 (86%) without fetal surgery survived • Fetal surgery was associated with preterm birth: mean gestational age attained: 32 weeks for surgery; 38 weeks for no fetal surgery
Retrospective cohorts		
Sinha et al.[43] 2009 U.K.	**G1:** balloon tracheal occlusion (31) **G3:** no fetal procedure (55)	• Balloon occlusion for fetuses with ratio ≤ 1.0 • Analysis includes only liveborn infants • 16 of 31 (52%) with in utero repair survived neonatal course • 35 of 55 (64%) without fetal surgery survived • Lung-to-head ratio and best oxygenation index on first day of life were correlated with oxygenation status best predictor of survival
Saura et al.[41] 2007 Spain	**G1:** balloon tracheal occlusion (13) **G2:** no fetal procedure (6)	• Balloon occlusion done for fetuses with ratio <1.1 • Comparison group: 3 with ratio >1.4 and 3 without antenatal diagnosis • 8 of 13 (61%) with occlusion survived • 5 of 6 (83%) with good prognosis or no antenatal diagnosis survived

Table 6. Primary outcomes of maternal-fetal surgical procedures for congenital diaphragmatic hernia (continued)

Author, Year, Country	Comparison groups (N)	Key outcomes
Jani et al.[35] 2005 Belgium	**G1:** balloon tracheal occlusion (24) **G2:** no fetal procedure (37)	• 12 of 24 (50%) with occlusion survived to 28 days of life • The no fetal surgery group included 5 decisions for termination • 3 of 32 (9%) without fetal surgery survived • Fetal surgery reduced gestational age at birth with mean of 33 weeks
Deprest et al.[22] 2004 Belgium	**G1:** balloon tracheal occlusion (21) **G2:** no fetal procedure (17)	• Median gestational age at balloon placement: 26 weeks • 10 of 21 (48%) with occlusion survived • 11 of 12 (92%) without fetal surgery survived • 5 cases ended in pregnancy termination
Keller et al.[37] 2003 U.S.	**G1:** balloon tracheal occlusion (16) **G2:** no fetal procedure (40)	• All fetuses with isolated left CDH and liver herniation and no other anomalies • 11 of 16 (69%) with occlusion survived to discharge • 17 of 40 (43%) of those without fetal surgery survived • Calculation of lung-to-head ratio in CDH is a strong predictor of survival; above ratios of 1.0 risk of death plateaus

CDH=congenital diaphragmatic hernia; SD=standard deviation

Among the cohort studies of tracheal occlusion, survival ranged from 48 percent to 75 percent among treated fetuses and 8 percent to 65 percent among the untreated (Table 6), with the high end likely reflecting less severe disease. The sole well-documented exception to these ranges was the note that a favorable prognosis, as gauged by higher LHR (>1.1), had an 83 percent survival among the untreated.[41] In that cohort there were no treated fetuses who did not have a ratio of less than 1, meaning they were all in the poor prognosis group.

Case series reflect the evolution of methods for treatment with consistent movement toward the improved outcomes observed in the cohorts and trials. In an initial report of eight fetuses using tracheal occlusion there was one survivor.[27] The first attempt was done using a foam plug to occlude the trachea in two fetuses which caused tracheomalacia in the first and did not create enough of a seal in the second to prevent hypoplasia.[27] In the same report, six subsequent fetuses were treated with a tracheal clip, all six delivered prematurely, and all died from complications of their disease or prematurity or a combination. Another series of 15 open procedures had 5 survivors, and studies of lung specimens suggested fetal lung growth increased but was not uniformly associated with normal tissue structure.[23,42] Subsequent patient series added further experience that lead up to the trial.[29]

A number of recent case series reports from Europe and the United States have been published. Endoscopic placement of a specialized balloon originally designed for vascular embolization was reported in 18 of 21 unique publications. Occlusions in Europe are now often performed by obstetric groups with expertise in endoscopic treatment using a new generation of detachable balloons.[39-41,43-45] Outcomes continue to trend toward favorable survival rates and lower risk of prematurity.

This literature has been focused primarily on short-term outcomes since congenital diaphragmatic hernia has such a high mortality. Long-term infant and maternal outcomes have been evaluated in few studies, with the longest followup of infant outcomes being between 24 months [21,25] and 48 months.[23-24,27] Long-term maternal outcomes were addressed carefully in the early U.S. series, and future maternal fertility was documented in one series.[30] For CDH, it is important to look at later outcomes since there is a significant postneonatal mortality reported in those groups that continue to follow their cohort.

All but one study provided good documentation of fetal inclusion criteria; only nine adequately described maternal inclusion criteria. The majority of studies did a thorough job of describing surgical approach. Though endoscopic devices are used, most of the procedures were done with a maternal laparotomy incision, often described as a minilaparotomy, prior to placement of trocars through the uterus. Open repairs were the primary use of full hysterotomy in 4 studies, and 6 of 21 papers described completely transcutaneous approaches. Use of both general and epidural anesthesia was common; some teams added fetal anesthesia and described their approach in publications; seven studies did not address anesthesia. A subset did not address details of the intraoperative and postoperative monitoring of mother and fetus; those that did were comprehensive and helpful in fully understanding the evolving standard of care. Outcomes assessed reflect lack of attention to longer term outcomes and maternal risks (Table 17).

Many questions remain including: What diagnostic approaches best predict prognosis? Which fetuses would benefit from treatment? When in gestation should the occlusive device be placed, and when in the gestation should the occlusive device be removed? The FETO Task group in Europe is using as a control group a multicenter study of 86 fetuses with left-sided CDH and liver herniation, which were managed expectantly and were live born after 30 weeks of gestation. In the control group, the survival rate increased from zero percent for those with LHR of 0.4 to 0.7 to about 15 percent for LHR of 0.8 to 0.9, 65 percent for LHR of 1.0 to 1.5, and 83 percent for LHR of 1.6 or more.[46] This European series, which continues to add participants, has an 11 percent survival for LHR <1 and can serve as an ongoing reference point for expectations among untreated poor prognosis pregnancies in Europe as it is not possible to directly compare outcomes between Europe and the United States, given the difficulty in reconciling different postnatal survival rates.[37] In the United States, multiple centers are working on device development or approval processes for an improved balloon to be used for tracheal occlusion.

Summary of congenital diaphragmatic hernia literature. Case reports comprise the bulk of the CDH literature and reflect movement toward improved outcomes for infants with CDH. The single randomized trial of in utero CDH therapy located for this review similarly reflects improved survival rates for fetuses treated with tracheal occlusion and infants treated at birth. Long-term outcomes, however, are not well reported, and significant questions about fetal treatment for CDH remain.

State of the Science: Myelomeningocele/Spina Bifida

Background. Myelomeningocele (MMC) is a congenital malformation in which the meninges and spinal cord protrude through a defect in the vertebral arches, muscle, and skin. It is the most commonly observed malformation of the central nervous system, affecting more than 1,000 fetuses in the United States annually.[47] MMC is the most common form of spina bifida, and although it is rarely fatal, individuals affected with it have a range of disabilities, including paraplegia, hydrocephalus, skeletal deformities, bowel and bladder incontinence, and cognitive impairment.

The standard treatment has been to close the defect postnatally, and shunting for hydrocephalus is common.

Table 7. Summary of studies of maternal-fetal surgical procedures for myelomeningocele (MMC)

Author Year	With fetal procedure N	Without fetal procedure N	Fetal inclusion criteria provided?	Maternal inclusion criteria provided?	Comparison group	Outcomes beyond neonatal hospital stay?
Randomized clinical trials						
None						
Prospective cohorts						
Tubbs et al.[48-49] 2003	37	40	Yes	No	No fetal procedure	Yes (36 mos)
Bruner et al.[50] 1999	29	23	Yes	No	No fetal procedure	Yes (6 mos)
Retrospective cohorts						
Danzer et al.[51] 2007	22	16	No	No	No fetal procedure and age matched controls	No
Adelberg et al.[52] 2005	14	39	Yes	No	No fetal procedure	No
Hamdan et al.[53] 2004	37	74	No	No	Other preterm infants	No
Tulipan et al.[54] 2003	104	189	Yes	No	No fetal procedure	Yes (>12 mos)
Bruner et al.[55] 2000	8	--	Yes	No	Endoscopic surgery	Yes (12 mos)
Prospective case series						
None						
Retrospective case series						
Wilson et al.[56-59,60,61-65] 2007	54	--	Yes	Yes	NA	Yes (36 mos)
Bruner et al.[66-71] 2004	177		Yes	No	NA	Yes (36 mos)
Farmer et al.[72-73] 2003	13	--	Yes	No	NA	Yes (45 mos)
Bruner et al.[74] 1999	4 (endo-scopic)		Yes	No	NA	No
Grand total	**262**	**413**	**10 of 11**	**1 of 11**		**8 of 11**

(All patients represented in the total for retrospective cohorts except the Adelberg study are part of the series of patients totaled in the case series.)

Animal research suggested that covering the defect early on could potentially result in better lower extremity and bladder function. Myelomeningocele repair was the first in utero surgery considered for a nonlethal malformation on the basis that its natural history was well known and leads to lifelong disability in the absence of intervention. Furthermore, the defect can be diagnosed prenatally in over 80 percent of cases by maternal serum alpha-fetoprotein and ultrasound; MRI is used to detect specific anomalies and disease process.

The procedure was initially performed by Bruner and colleagues as a closed laparoscopic covering of the spinal defect. The first case was reported in a letter, and a case series describing four fetuses was published in 1999 (the surgeries were conducted between 1994 and 1997).[74] Half of the fetuses survived, and both survivors required shunting. In a continuation of this work, four fetuses were operated on using an open approach and compared to four done endoscopically,[55] and the open surgery showed improved outcomes, while the endoscopic

approach had high mortality. The endoscopic approach has been abandoned, and therefore the rest of this overview will focus on literature related to open surgery for MMC repair. Since 1997, more than 200 fetuses with MMC have undergone open surgical repair in the United States.

Included publications. Our search identified 27 publications[48-74] that provided outcomes of surgery, two of which were on the use of endoscopic approach;[55,74] these publications comprise 11 unique studies. These surgeries have taken place at four academic centers in the United States, but to date have not been in the context of a randomized controlled study (RCT). All nine analyses of open surgery are based on four series of patients, although varying study designs were used to analyze the data. For that reason, there are duplicate patients represented in different studies of publications as represented in Table 7. Where authors have presented serial groups of overlapping patients as case series have grown, we focus our discussion on the most complete set, but where there are subanalyses with specific comparisons, those are indicated.

Two studies, including overlapping patients from one center, had concurrent comparisons.[48,50] The first study analyzed the first 29 cases of open MMC repair at Vanderbilt University Medical Center, and found significant reductions in the need for postnatal shunt placement (51 percent versus 91 percent; $p=0.01$) and reduced hindbrain herniation (38 percent versus 95 percent; $p<0.001$). However, the two prospective studies found greater rates of oligohydramnios among those with in utero repair (48 percent versus 4 percent; $p=0.001$), lower gestational ages in this group (33.2 weeks versus 37 weeks; $p<0.001$)[50] and no difference in lower extremity function.[48]

Six retrospective cohort analyses were conducted,[49,51-55] representing three patient populations. Of the five papers that included only open surgery, four used as their comparison group infants who had undergone postnatal repair.[49,51-52,54] Again, substantially lower rates of postnatal shunt placement were observed (58 percent versus 92 percent) as well as lower incidence of hindbrain herniation (4 percent versus 50 percent).[49] In a small series at one institution based on 14 repairs, no differences in ventricular progression were observed between the groups.[52] Two of the academic centers with larger series combined their data and conducted the largest retrospective analysis.[54] Although results of in utero repair were apparently positive in many of the prior studies, the question had been raised as to whether fetuses selected for in utero repair were fundamentally different than others in features affecting the risk of hydrocephaly, specifically lesion location. With this larger cohort, the investigators were able to stratify their results on lesion location and found statistically significant reductions in shunting relating to repairs of lumbar and sacral lesions, but not thoracic ones. They further observed an age effect whereby there was no improvement in fetuses whose repairs occurred after 25 weeks' gestation, supporting the theory that early intervention is essential.[54]

Case series in these sets of patients showed results generally in line with the comparative studies described above, including rates of shunting about half those seen in postnatal repairs, reversal of hindbrain herniation, and positive rates of cognitive language and personal skills after 3 years (67 percent).[53,56-71]

Table 8. Primary outcomes of maternal-fetal surgical procedures for MMC

Author, Year, Country	Comparison groups, (N)	Key outcomes
Danzer et al.[51] 2007 U.S.	**G1:** in utero repair **G2:** postnatal repair **G3:** age-matched non-MMC patients	• In utero repair was associated with increased normalization of the posterior fossa CSF spaces • Brain thickness was reduced in both pre- and postnatally repaired patients compared to age-matched comparators without MMC
Wilson et al.[56-65] 2007 U.S.	**G1:** in utero repair (58)	• 94% of fetuses survived, with a mean age at delivery of 34 weeks, 3 days • 100% demonstrated reversal of hindbrain herniation; 43% required shunting • Better than predicted leg function seen in 57% of thoracic and lumbar patients • At 2 years of age, 30 returned for neurodevelopmental testing • 67% had cognitive language and personal skills in normal range, 20% had mild delays and 13% has significant delays
Adelberg et al.[52] 2005 U.S.	**G1:** in utero repair (14) **G2:** postnatal repair (39)	• Study intended to measure ventriculomegaly in utero compared to that associated with postnatal repair • No difference in ventricular progression was observed
Bruner et al.[66,67-68,70-71] 2004 U.S.	**G1:** in utero repair (177)	• 61/116 fetuses with 12 mos followup required shunt (54%) • Strongest predictor of shunt requirement was upper level lesion, followed by greater gestational age (>25 wks) and ventricular size of >14mm • Among the first 95 infants, no difference in gestational age at delivery based on gestational age at repair (before or after 25 weeks) • Among 9 patients, ultrasound pre- and post- in utero repair showed reversal of preexisting hindbrain herniation
Hamdan et al.[53] 2004 U.S.	**G1:** infants born prematurely post in utero repair **G2:** infants born prematurely without MMC	• Rates of prematurity related complications (RDS, length of stay, IVH) were similar between infants born prematurely, post- in utero surgery and others without MMC born prematurely
Farmer et al.[72,73]2003 U.S.	**G1:** in utero repair fetoscopic (3); open (10)	• 56% required shunt by one year compared to 90% in historical controls at the site • 7 patients were examined for bladder function at 1 month • Urodynamic patterns were similar to patients in other studies undergoing postnatal repair
Tubbs et al.[48-49] 2003 U.S.	**G1:** in utero repair (37) **G2:** postnatal repair (40)	• No difference in lower extremity function between G1 and G2 • Substantially lower incidence of hindbrain herniation among in utero repair group compared to historical cohort of postnatal repair (4% vs. 50%)[49] • Lower incidence of shunting in in utero repair group compared with historical postnatal repair group (58% vs. 92%)[49]

Table 8. Primary outcomes of surgical repair of MMC (continued)

Author, Year, Country	Comparison groups, (N)	Key outcomes
Tulipan et al.[54] 2003 U.S.	**G1:** in utero repair (104) **G2:** postnatal repair (189)	• Combined data from Vanderbilt Medical Center and Children's Hospital of Philadelphia • Statistically significant reductions in shunting at lumbar and sacral lesion levels, but not for thoracic lesions • No statistically significant differences in fetuses older than 25 weeks gestation
Bruner et al.[55] 2000 U.S.	**G1:** endoscopic repair (4) **G2:** open (4)	• 2 survivors in the endoscopic group compared to 4 in the open surgery group • Both survivors in the endoscopic group required shunting compared to 2 of 4 in the open surgery group
Bruner et al.[50] 1999 U.S.	**G1:** in utero repair (29) **G2:** postnatal repair (23)	• First 29 cases of open surgery at Vanderbilt Medical Center • 51% of in utero cases required shunting compared to 91% of postnatal repairs (p=.01) • Reduced hindbrain herniation among in utero repairs (38% vs. 95%; p<.001) • Greater oligohydramnios among in utero repairs (48% vs. 4%; p=.001) • Gestational age for in utero patients 33.2 vs. 37 for postnatal repair patients (p<.001)
Bruner et al.[74] 1999 U.S.	**G1:** endoscopic repair	• 2 of 4 survived past 1 month after delivery

CSF=cerebrospinal fluid; IVH=intraventricular hemorrhage; MMC=myelomeningocele; RDS=respiratory distress syndrome

However, the procedure itself is not benign, and as with any surgery, the risk of maternal morbidity and mortality exists. Limited long-term data are available to assess maternal risks both in the immediate postoperative period and related to longer term fertility and none available in the studies that met inclusion criteria for this review. In addition, fetuses treated in utero routinely deliver prematurely, and outcomes related to prematurity may be the greatest challenge to evaluating the benefit of the surgical repair. Hamdan et al.[53] found that rates of prematurity-related complications were no higher among infants born prematurely with MMC after in utero repair compared to those without MMC also born prematurely, suggesting that the procedure is not associated with worse side effects. Nonetheless, absent the in utero repair, patients with MMC could very well have delivered at term. These reasons combined with concerns that past study designs simply do not ensure comparable groups for analysis led the NIH to fund an RCT, which is currently ongoing. Known as the MOMS trial, this study is taking place at three of the centers whose work is represented in this section. The trial will enroll 200 mother-fetus pairs, and at this time, there is a voluntary moratorium in the United States on conducting in utero repair of MMC outside of the trial. Several of our key informants and experts in the literature[75] suggested that this trial appropriately put a stop to a proliferation of centers doing in utero MMC repair based on enthusiasm but inadequate evidence.

Summary of the MMC literature. As is the case with other in utero repairs, evidence about MMC fetal surgical procedures from more rigorous studies is lacking; much of the MMC literature located for this review comprised retrospective cohorts and case series. Long-term followup of infants treated prenatally is limited, as are outcomes for mothers. No studies included in this review addressed long-term maternal fertility outcomes. Overall trends from

cohorts and case series include reduced shunting after fetal surgical repair of MMC and positive rates of language development and personal skills after three years. The ongoing MOMS trial should augment the MMC evidence base and help to inform families' and clinicians' decisionmaking.

Addendum. As this report was in press, results from the Management of Myelomeningocele Study (MOMS) were published in the New England Journal of Medicine (February 9, 2011). The study's findings add to the body of literature on maternal-fetal surgical procedures for myelomeningocele:

- The RCT reports results from 158 women participating between February 2003 and the trial's early termination based on evidence for the efficacy of prenatal surgery in December 2010. Among these 158 participants, 78 were randomized to prenatal surgery before 26 weeks gestation and 80 to postnatal repair after cesarean delivery at 37 weeks (if undelivered).
- Primary outcomes included a composite of fetal or neonatal death or the need for cerebrospinal fluid (CSF) shunt (placement or meeting criteria for placement) at 12 months of life and a composite score on the Mental Development Index of the Bayley Scales of Infant Development II and motor function at 30 months.
- There were 2 deaths in each group (relative risk [RR], 95 percent confidence interval [CI]: 1.03, 0.14 to 7.10). Overall, 68 percent of prenatal group infants and 98 percent of postnatal group infants either died or required CSF shunt/met shunt criteria by 12 months (RR, 95 percent CI: 0.70, 0.58 to 0.84, $p<0.001$). Forty percent (n=31) of infants in the prenatal group and 82 percent (n=66) in the postnatal group required shunt placement ($p<0.001$).
- Composite scores on the Bayley Mental Development Index were significantly better in the prenatal group compared with the postnatal group ($p=0.007$); motor function and ability to walk without orthotics were also better in the prenatal group as were parent-reported self-care and mobility.
- Prenatal surgery was associated with higher rates of preterm birth, intraoperative complications, maternal transfusion, and uterine scarring. Rates of chorioamniotic membrane separation, spontaneous membrane rupture, and spontaneous labor were higher in prenatal surgery participants.
- Though the trial was stopped early by the study's data safety monitoring board for positive results, the investigators note maternal and fetal risks including preterm delivery and uterine dehiscence.
- This RCT brings the total number of RCTs in the maternal-fetal surgery literature to four; it is the only randomized trial of assessing intervention for myelomeningocele. The study is of additional importance as a model for the field as investigators, working in collaboration with NIH, did not offer the procedure outside the trial during the duration of the study, helping to assure the feasibility of obtaining sufficient participants from around the country to obtain high quality data.

State of the Science: Obstructive Uropathy

Background. A variety of fetal malformations can lead to distention of the urinary bladder; these include urethral atresia (failure of the bladder stem to properly form so urine cannot exit), posterior urethral valves (which in male fetuses can prevent flow of urine through the full length

of the urethra); and megacystis-megaureter-microcolon syndrome (which results from malformation of the organs rather than frank blockage of urine flow), and prune-belly syndrome (which includes lack of development of abdominal muscles, undescended testicles, and urinary anomalies). Other urinary tract anomalies can result in distension of one or both ureters, such as blockage at the junction with the bladder or at any place along the ureter, which conveys urine from the kidney to the bladder. In this case when there is renal function and a ureteral impass, the distended portion of the urinary tract is the ureter or renal pelvis rather than the bladder.

Goals of fetal therapy have emphasized decompression rather than repair of the specific lesion. The goal of decompression of the distended portion of the urinary tract is to protect remaining renal function and to promote lung development. Challenges with increased preterm birth and comparable outcomes with open shunting procedures have resulted in a trend to percutaneous shunting procedures dominating the literature. After a small incision in the maternal skin, generally with local anesthesia only, the shunt is inserted through an introducer sheath into position within the fetal bladder. An internal guide or stylus within the shunt is withdrawn, allowing a prefabricated curl or "pigtail" to form at the distal end that helps hold the device within the fetal bladder. As the introducer is completely withdrawn, a second pigtail forms on the opposite end to hold the shunt outside the fetus and to assure drainage of urine into the amniotic cavity. When the shunt type or method was noted by authors to vary from this, we have indicated the difference.

Included publications. Our search indentified 26 publications representing 25 unduplicated reports about fetal interventions for obstructive uropathy. The publication that duplicates the same study population[76] is superceded in this summary by the original report.[77] We did not include reports that only focused on vesicocentesis, because this approach does not reach the degree of complexity to be considered a fetal surgical procedure and is most often reported as a diagnostic procedure to gauge renal function to inform decisions about choice of therapy. We recognize that the 25 identified publications include duplication of individual mothers and babies.

Table 9. Summary of studies of maternal-fetal surgical procedures for obstructive uropathy

Author Year	Shunt procedure N	Without this fetal procedure N	Fetal inclusion criteria?	Maternal inclusion criteria?	Comparison group	Outcome beyond neonatal stay?
Randomized clinical trials						
			None			
Prospective cohorts						
Welsh et al.[78] 2003	3	10	Yes	No	Hydroablation and/or guidewire passage	Yes
Quintero et al.[79] 1995	6	7	Yes	No	No fetal procedure (6); disruption of PUV (1)	No
Johnson et al.[80] 1994	15	8	Yes	No	No fetal procedure	Yes (18-66 mos)
Total	**24**	**25**	**3 of 3**	**0 of 3**	**2 of 3 include no treatment**	**2 of 3**
Retrospective cohorts						
Salam et al.[81] 2006	12	46	Yes	No	No fetal procedure	Yes (mean 47 mos)
Wilson et al.[82] 2003	3	3	No	No	No fetal procedure	No
Warne et al.[83] 2002	2	4	No	No	No treatment (All had suspected cloacal anomalies)	Yes (poorly specified)
Holmes et al.[84] 2001	9	5	No	No	Bladder marsup-ialization (2); ablations of PUV (2); cutaneous ureterostomy (1)	Yes (mean 139 mos)
McLorie et al.[85] 2001	9	3	Yes	No	No fetal procedure	Yes (mean 42 mos)
Freedman et al.[86] 1996	28	27	Yes	No	No fetal procedure	No
Cromble-holme et al.[87] 1990	19	21	Yes	No	No fetal procedure	No
Harrison et al.[77] 1982	5*	21	Yes	No	No fetal procedure	Yes (ad hoc)

Table 9. Summary of studies of maternal-fetal surgical procedures for obstructive uropathy (continued)

Author Year	Shunt procedure N	Without this fetal procedure N	Fetal inclusion criteria?	Maternal inclusion criteria?	Comparison group	Outcome beyond neonatal stay?
Total	**87**	**130**	**5 of 8**	**0 of 8**	**7 of 8 include no treatment**	**5 of 8**
Prospective case series						
Araujo et al.[88] 2007	13	NA	Yes	No	NA	No
Craparo et al.[89] 2007	12	NA	Yes	No	NA	Yes (3-36 mos)
Biard et al.[90] 2005	31	NA	Yes	No	NA	Yes (70 mos)
Makino et al.[91] 2000	5	NA	Yes	No	NA	Yes (0-48 mos)
Freedman et al.[92] 1999	14	NA	Yes	No	NA	Yes (54 mos)
Evans et al.[93] 1991	3	NA	Yes	No	NA	Yes (3-36 mos)
Manning et al.[94] 1986	73	NA	No	No	NA	No
Total	**151**	**NA**	**6 of 7**	**0 of 7**	**NA**	**5 of 7**
Retrospective case series						
Gehring et al.[95] 2000	3	NA	No	No	NA	No
Shimada et al.[96] 1998	6	NA	No	No	NA	Yes (1-14 mos)
Pinckert et al.[97] 1994	2	NA	No	No	NA	Yes (2-4 mos)
Bernaschek et al.[98] 1994	13	NA	No	No	NA	No
Robichaux et al.[99] 1991	2	NA	No	No	NA	No
Cromble-holme et al.[100] 1988	5	NA	No	No	NA	Yes (24-36 mos)
Manning et al.[101] 1983	2	NA	Yes	No	NA	Yes (6 mos)
Total	**33**	**NA**	**1 of 7**	**0 of 7**	**NA**	**4 of 7**

PUV=posterior urethral valves

* Varied therapeutic approaches (vesicoamniotic shunt, transcutaneous catheter drainage, hysterotomy with repair)

Of the 25 publications, 13 originate from research in the United States;[77,79-80,84,86-87,90,92-93,95,97,99-100] 4 from Europe;[78,83,89,98] 3 from Canada,[82,85,101] 2 from Japan,[91,96] and 1 each from Egypt,[81] Brazil,[88] and the International Fetal Surgery Registry.[94]

Three publications were prospective cohorts;[78,80,94] eight were retrospective cohorts;[77,81-87] seven were prospective case series;[88-94] and seven were retrospective case series.[95-101]

Prospective cohorts. Among the three prospective cohort studies,[78,80,94] none restricted to a single underlying pathology. Two groups[78-79] performed in utero cystoscopy to evaluate the urinary outflow tract and bladder. Each performed some maneuvers to attempt to establish patency of the urethra when applicable. One group placed transurethral shunts when possible during the cystoscopy[79] and the other used cystoscopy in a phased process in which recurrence or

persistence of obstruction was the indication for subsequent shunt placement.[78] Another publication reports the predictive value of urinary electrolyte and protein analysis obtained by vesicocentesis as a prognostic guide to likely disease severity; some fetuses with both poor and good prognosis (based on their hypothesis) received shunts.[80]

In total (Tables 13 and 14), 24 fetuses had placement of shunts in these studies; 11 had hydroablation or other disruption of posterior urethral valves (PUV); 14 fetuses had no fetal intervention; and another 13 pregnancies were terminated given clinical assessments of very poor prognosis. Overall, 53 percent to 66 percent of infants who had shunt placement survived short term (Table 10). Long-term data is scant and no longer than early childhood (Table 10). Prognosis was most easily established for dire cases without urine production and with poor lung development. For cases in which there was fetal urine production, diagnostic testing of fetal urine did not cleanly segregate those who would do well without intervention or the outcomes of intervention. The range of sensitivity for urine markers for predicting "absence of significant underlying renal damage" from last urine specimen obtained was 0.88 to 1.00; specificity ranged from 0.47 to 0.84, with positive predictive values between 0.47 and 0.77.[102] From another vantage point, ability to predict absence of renal dysplasia from urine markers in a related study was reported with sensitivity 0.17 to 1.00, specificity 0.27 to 0.91, and positive predictive value 0.43 to 1.00.[80] Small sample sizes significantly limit the ability to draw definitive conclusions, but it is helpful to have those cases that received no fetal intervention, or who had alternate interventions, receiving the balance of their care within similar protocols in the care of the same providers. These studies also provide evidence of feasibility of fetal cystoscopy for diagnostic evaluation and in some cases direct treatment of obstruction.

Each group reported on fetal eligibility criteria, none reported maternal inclusion criteria, none reported the approach to maternal anesthesia or analgesia, and none, other than noting ultrasound guidance, provided information about the monitoring of fetal well-being during or immediately after the procedure. One report[80] noted that 6 of 15 shunt placements required a second procedure to replace the shunt, while others did not comment on this aspect of care. Maternal complications were not systematically documented, and infections were only noted in the context of reasons for poor fetal outcomes on a case-by-case basis, such as noting that an infant died in utero secondary to chorioamnionitis. The status of renal function and need for transplant was well documented in these prospective cohorts, though duration of followup was varied within studies and overall limited. In contrast, pulmonary status was noted by only one report,[80] and neonatal and early childhood developmental status was not addressed in any of the publications. Table 17 summarizes the outcomes assessed by procedure type.

Retrospective cohorts. Eight studies[77,81-87] reported on cohorts from clinical medical or fetal surgery program records. One study reports on the urological outcomes of infants known to have been shunt recipients who presented for urologic care in infancy and for whom the denominator of total shunt recipients is unknown so direct comparisons to surgical cohorts are inappropriate.[81] All retrospective cohorts have small number of treated fetuses (2 to 28) and small comparison groups (3 to 46), with a total of 87 shunt recipients and 130 comparison group members in the eight cohorts. With one exception composed of small numbers of varied surgical approaches,[84] the comparison groups are affected pregnancies without fetal intervention.

Short-term survival to birth and/or hospital discharge ranged from 30 percent in a poor prognosis group, to 88 and 100 percent in the good prognosis group, and 57 to 75 percent for typical obstructive conditions not stratified by risk (Table 10). In the sole cohort of female

infants with cloacal anomalies, both infants who had a shunt placed survived.[83] A commonality across studies is that survival is not a sign that risk of renal compromise is low. Risk of renal compromise is 31 percent across all retrospective cohorts, with the majority of smaller cohorts closer to 50 percent (Table 10). Among those infants with renal compromise the plurality progressed to dialysis and transplant. The exceptions were noted early in the history of fetal intervention of obstructive urinary tract conditions—fetuses with unilateral ureteral obstruction do well without intervention, and the majority have normal renal function after postnatal intervention.[77] and infants with clusters of concomitant anomalies fare worse than those with isolated obstructive conditions.

Five of eight studies described the fetal eligibility criteria used to determine appropriateness for shunt placement; none reported use of any maternal eligibility restrictions. A subset of studies in this group have longer follow-up, one to an average of 11 years.[84] Three studies do not follow infants past the initial neonatal admission, and two studies poorly specify whether there was a systematic effort to achieve followup through a specific time in childhood; thus it is difficult to know if complete ascertainment of outcomes was obtained (Table 10). No single study in this group was large enough to conduct multivariable analysis to adjust for candidate confounders or modifiers of treatment outcomes; and in aggregate the number of participants would fall short of that needed for meta-regression.

No studies reported maternal inclusion criteria or outcomes in a systematic fashion. One study described the type of anesthesia of analgesia provided for procedures,[77] and no studies reported on monitoring of fetal well-being during or immediately after procedures beyond ultrasound during the procedure and to check shunt location and obstruction status after procedures. All studies reported on survival to birth and into infancy; seven of eight make note of preterm births and complications associated with prematurity; all make some note of assessment of renal function, and four of eight note pulmonary morbidity and sequelae. Pulmonary outcomes were overwhelmingly those close to birth, such as duration of ventilation. In individual cases, chronic pulmonary dysfunction was noted, but these assessments did not have any apparent uniformity. No retrospective studies had access to information about neurologic status in the neonatal period or later; and a single study reported that half of infants with a history of obstructive uropathy had abnormal growth patterns (diminished height and weight) into childhood.[85]

Table 10. Primary outcomes of maternal-fetal surgical procedures for obstructive uropathy

Author, Year Country	Comparison groups, (N)	Key outcomes
Prospective cohorts		
Welsh et al.[78] 2003 U.K.	**G1:** vesicoamniotic shunt after attempted hydroablation (3) **G2:** hydroablation and/or guidewire passage through cystoscope (7)	• 2 of 3 (66%) shunt recipients survived to infancy • 1 had normal kidney function, 1 poor function at 22 months • 1 of 3 died of complications of preterm premature rupture of membranes at 22 weeks • 6 hydroablation/guidewire procedures achieved technical success/patency of the bladder outlet • 4 of 7 (57%) survived to infancy; 1 pregnancy was terminated; 1 miscarriage (20 weeks), and 1 IUFD

Table 10. Primary outcomes of maternal-fetal surgical procedures for obstructive uropathy (continued)

Author, Year Country	Comparison groups, (N)	Key outcomes
Quintero et al.[79] 1995 U.S.	**G1:** vesicoamniotic shunt (6) **G2:** no fetal procedure (7)	• Fetal cystoscopy was possible in 11 of 13 cases, patency established in 1 case • 2 transurethral vesicoamniotic shunts placed • 4 of 6 (66%) shunt recipients survived to hospital discharge • 1 pregnancy terminated after shunt • Of the four survivors with shunts, no data is available about renal function at birth or longer term outcomes
Johnson et al.[80] 1994 U.S.	**G1:** vesicoamniotic shunt (15) **G2:** no fetal procedure (8)	• 8 of 15 shunt recipients (53%) survived to infancy • 3 deaths (one in utero) among those with good antenatal prognosis prior to shunt; 4 among those with poor prognosis • Among the 8 fetuses observed, 3 had resolution of obstruction and survived (38%) and 5 died in utero • Those shunted had better prognosis based on urinary analysis of fetal renal function • During evaluation, prior to decisions about intervention options, 11 pregnancies were terminated; 10 confirmed to have advanced renal fibrosis and dysplasia cloacal dysgenesis at autopsy
Retrospective cohorts		
Salam et al.[81] 2006 Egypt	**G1:** vesicoamniotic shunt for PUV (12) **G2:** no fetal procedure (46)	• 8 of 12 (66%) shunt recipients survived • 1 of 8 had renal insufficiency, 3 had renal failure and are transplanted or candidates • Comparison group reflects infants who survived to receive postnatal treatment; survival cannot be calculated • 43 of 46 (93%) infants treated achieved normal renal function after treatment of PUV • Urodynamic findings for those with antenatal vs. postnatal treatment
Wilson et al.[82] 2003 U.S.	**G1:** vesicoamniotic shunt for PUV (3) **G2:** other (not defined) (3)	• Therapy not sufficiently specified to distinguish outcomes across groups • 4 infants survived and one had renal failure
Warne et al.[83] 2002 U.K.	**G1:** vesicoamniotic shunt (2) **G2:** no fetal intervention (4)	• All fetuses had suspected cloacal anomalies • All survived • 2 of 2 shunt recipients survived to birth • 1 of 2 had renal failure
Holmes at al.[84] 2001 U.S.	**G1:** vesicoamniotic shunt for PUV (9) **G2:** bladder marsupialization (2) **G3:** ablations of PUV (2) **G4:** cutaneous ureterostomy (1)	• Outcomes are primarily grouped across all interventions • 5 of 14 (36%) infants died in utero; 1 pregnancy was terminated • 8 of 14 survived (57%) into childhood • 5 of 8 survivors had renal disease; 2 of those five had transplants, 1 was awaiting transplant
McLorie et al.[85] 2001 Canada	**G1:** vesicoamniotic shunt for PUV (9) **G2:** no fetal procedure (3)	• 6 of 8 (75%) shunt recipients survived into childhood; 1 pregnancy terminated after shunting • None of the untreated infants survived to follow-up • 5 of 6 survivors had growth in childhood less than 50% height and weight for age • 2 of 6 had long term pulmonary sequelae • 3 of 6 had renal impairment; 2 received transplants

Table 10. Primary outcomes of maternal-fetal surgical procedures for obstructive uropathy (continued)

Author, Year Country	Comparison groups, (N)	Key outcomes
Freedman et al.[86] 1996 U.S.	**G1:** vesicoamniotic shunt (28) **G2:** no fetal intervention (27)	• 17 of 28 (61%) shunt recipients survived to discharge • 3 of 17 (18%) survivors post shunt had end stage renal disease and 2 had renal impairment • 5 of 27 (19%) without fetal surgery survived • 1 of 5 survivors without surgery had renal impairment
Crombleholme et al.[87] 1990 U.S.	**G1:** shunt in good prognosis group (9) **G2:** no fetal procedure in good prognosis group (7) **G3:** shunt in poor prognosis group (10) **G4:** no fetal procedure in poor prognosis group (14)	• 8 of 9 (88%) shunt recipients in the good prognosis group survived hospital course, 1 pregnancy terminated • 5 of 7 without surgery and good prognosis survived • 3 of 10 (30%) shunt recipients in the poor prognosis group survived • Poor prognosis group without surgery included 11 terminations and 3 fetal or neonatal deaths • In the short term among those with good prognosis, 2 untreated infants have renal insufficiency and none of the shunted infants had renal impairment
Harrison et al.[77] 1982 U.S.	**G1:** no fetal procedure good prognosis (14) **G2:** decompression with equivocal prognosis (3) **G3:** no fetal surgery with equivocal prognosis (4) **G3:** decompression with poor prognosis (5) **G3:** no fetal procedure poor prognosis (3)	• 14 of 14 with good prognosis and no fetal intervention survived to birth • 2 of 3 (66%) with decompression and equivocal prognosis survived; one with renal disease • 4 of 4 with equivocal prognosis and no fetal surgery survived; two with renal disease • 2 of 5 (40%) with poor prognosis and intervention to decompress the outflow tract died, 3 pregnancies were terminated (no survivors) • 3 of 3 with poor prognosis and no surgery died • Infants with unilateral ureteral obstruction did well without intervention, 8 of 8 survived with normal renal function
Prospective case series		
Araujo et al.[88] 2007 Brazil	**G1:** vesicoamniotic shunt (13)	• 3 of 13 (23%) required replacement of shunt because the device did not remain properly placed (1) or obstruction was suspected (2) • 1 of 13, a fetus with trisomy 21, died in utero • 12 of 13 survived to one week of age
Craparo et al.[89] 2007 Italy	**G1:** vesicoamniotic shunt (12)	• 2 fetuses never re-accumulated amniotic fluid and pregnancies were terminated, both found to have renal dysplasia • 10 of 10 remaining reaccumulated fluid, all survived to discharge • Followup ranged from 3 months to 3 years • 6 had kidney failure with transplant or pending transplant; 4 had normal kidney function

Table 10. Primary outcomes of maternal-fetal surgical procedures for obstructive uropathy (continued)

Author, Year Country	Comparison groups, (N)	Key outcomes
Biard et al.[90] 2005 U.S.	**G1:** vesicoamniotic shunt (31)	• 8 of 31 were lost to followup • 23 of 23 live births in the group identified and followed • 21 of 23 (91%) survived to 1 year of age; 2 deaths from pulmonary hypoplasia • Average followup 5.8 years: 12 of 18 with data failure to thrive; 8 of 18 abnormal pulmonary function; 9 of 18 musculoskeletal conditions • 8 of 18 normal renal function; 6 of 18 required transplantation • 11 of 18 (61%) had normal bladder function • Self-reported health-related quality of life was comparable to healthy children
Makino et al.[91] 2000 Japan	**G1:** vesicoamniotic shunt (5)	• 2 of 5 (40%) survived • 1 survivor had hydrocephalus and normal renal function, the other had a seizure disorder • Both had developmental delay of unclear relation to obstructive syndrome
Freedman et al.[92] 1999 U.S.	**G1:** vesicoamniotic shunt (14)	• This paper included outcomes for 14 of 17 members of case series who are more than 2 years old • 3 were lost to follow-up or declined participation • 4 of 14 had pulmonary conditions; 6 of 14 did not have normal voiding function; 3 had renal insufficiency and 5 had renal failure • 3 of 14 had bladder augmentation surgeries
Evans et al.[93] 1991 U.S.	**G1:** vesicoamniotic shunt (3)	• 1 child with normal renal function at age 3 • 1 child with normal renal function and deafness at 3 months • Scheduled shunt placement was not required, decompression resolved megacystis and did not recur
Manning et al.[94] 1986 Multinational	**G1:** vesicoamniotic shunt (73)	• 30 of 73 (41%) survived • Procedure-related death rate was 4.6% • 11 pregnancies were terminated • Pulmonary hypoplasia (27) leading cause of death
Retrospective case series		
Gehring et al.[95] 2000 U.S.	**G1:** vesicoamniotic shunt (3)	• Reports a series of infants with abdominal wall hernia after shunt above the umbilicus; hernias repaired at birth • 2 of 3 required dialysis
Shimada et al.[96] 1998 Japan	**G1:** vesicoamniotic shunt (6)	• Infants entered this series at birth • 4 of 6 had normal pulmonary function • 5 of 6 had abnormal voiding function, including after surgical procedures • 4 of 6 had normal renal function • 2 of 6 had mild to moderate mental retardation
Pinckert et al.[97] 1994 U.S.	**G1:** vesicoamniotic shunt (2)	• 1 with peritoneal and nephrostomy shunts had normal growth and normal renal function at 4 months of age • 1 with nephrostomy had abnormal renal function at 2 months of age
Bernaschek et al.[98] 1994 Multinational	**G1:** vesicoamniotic shunt (13)	• 7 of 13 (54%) survived • 1 of 13 died in utero, 1 terminated pregnancy, and 2 died in neonatal period • 29 vesicoamniotic, thoracoamniotic, pleuroamniotic, or abdominoamniotic shunts (for a broader range of conditions included in aggregate in paper) required shunt replacement • Procedure-related mortality was 8%

Table 10. Primary outcomes of maternal-fetal surgical procedures for obstructive uropathy (continued)

Author, Year Country	Comparison groups, (N)	Key outcomes
Robichaux et al.[99] 1991 U.S.	**G1:** vesicoamniotic shunt (2)	• Reports cases of infants with abdominal wall hernia after shunt • Both had paramedian abdominal defects repaired at birth
Cromblehome et al.[100] 1988 U.S.	**G1:** open surgery (5)	• All open fetal surgery cases • 2 of 5 died at birth from pulmonary hypoplasia • 1 of 3 survivors had renal failure requiring transplant
Manning et al.[101] 1983 Canada	**G1:** vesicoamniotic shunt (2)	• 1 infant survived and had normal renal function at 6 months of age • 1 infant died of pulmonary hypoplasia within an hour of preterm birth at 30 weeks

IUFD=intrauterine fetal death/in utero fetal demise; PUV=posterior urethral valves

Prospective case series. Seven studies[88-93] including the report from the International Fetal Surgery Registry,[94] gathered prospective data about 151 treated fetuses, of which 73 were registry cases. Short-term survival ranged from 100 percent in a single report of 3 cases,[93] 92 percent in the Brazilian series of 13 cases;[88] and 91 percent in a larger U.S. series.[90] However, in that U.S. series, eight infants were lost to followup. Other groups reported less uniformly positive outcomes with survival in 83 percent,[89] 62 percent,[92] and 40 percent[91] among infants treated by vesicoamniotic, nephrostomy, or ureteral shunt placement. Need for shunt replacement was only reported by one paper, in which 23 percent of ongoing pregnancies required another procedure. The registry, which reflected care at 20 centers, reported 41 percent survival to birth with a 4.6 percent procedure-related death rate. This number takes into account pregnancy terminations that resulted after failure of the shunt to improve amniotic fluid volume and lung development. If terminations were not counted, the survival rate would be 48 percent.

Two larger studies focused on followup in childhood,[90,92] with findings consistent with those of smaller reports: shunted infants are at risk of poor growth in infancy; 34 percent to 40 percent will have severe renal disease and require dialysis and transplantation; one-quarter to nearly half do not have normal voiding function, with need for catheterization remaining common even after urologic surgery; one-third to half have pulmonary conditions; 25 percent have recurrent pulmonary infections, and 25 percent have asthma controlled by inhalers. The majority of children will have one or more surgeries for the condition that caused the obstruction. Among 14 parent-child pairs who completed health-related quality of life surveys, the scores were comparable to those of healthy children, suggesting children and families accommodate well to the challenges.[90]

While six of seven studies reported the criteria by which fetuses were selected for intervention, none reported maternal characteristics or eligibility criteria to allow assessment of whether the population of participants was similar to another setting or country. Two studies noted that local anesthesia was used; others did not provide details. None reported beyond ultrasound guidance on the protocol for fetal monitoring during or immediately after the procedure. No studies noted any information about maternal outcomes beyond route of delivery.

Retrospective case series. Seven studies[95-97,99-101] and one report from multiple European sites[98] gathered data retrospectively. Two are reports of abdominal wall hernias as a complication of shunt placement. These papers summarized outcomes for five infants, all of whom had repair of the defect at birth; other outcomes information is not the focus of these reports.[95,99] The remaining five case series include the early reports of these procedures including initial attempts

to define prognostic factors and protocols to select and care for pregnancies complicated by fetal obstructive uropathy. In total, these 5 publications report on 28 infants.

Reported survival was 50, 58, 60, and 100 percent, the last among two cases (Table 10). One of the studies began tracking infants at birth and cannot provide survival data. The studies are concordant with later and larger reports: shunt replacement is common; outcomes of open surgery were similar to percutaneous in a study with five cases; and residual renal impairment and need for dialysis and transplant is common. Details about infant status and childhood are the most limited in this literature. Likewise, details about inclusion criteria and content of care is typically narrative by case, variable, and difficult to compile as is common for case reports.

Summary of obstructive uropathy literature. Positive trends in this literature include larger numbers of participants and increasing momentum from small case series to larger cohorts that include fetuses that received intervention(s) and those that did not. Because the initial reports were in the early 1980s, and nearly a decade was spent in establishing which fetuses might be most likely to benefit, the literature does not yet include detailed comparative followup studies.

Across study designs common elements emerge: those fetuses who present later in gestational age with very little or no amniotic fluid, or those who have no urine production and/or with no lung development are not targets of intervention. With such restrictions, survival is enhanced but far from certain with 50 percent to 88 percent of treated fetuses surviving, and prognosis not predictable with confidence even among those fetuses who can be salvaged. Fetal intervention may not always change the long-term prognosis of renal function; sequelae of posterior urethral valves may not be preventable.[84] Projections of prognosis are further hindered because though karyotyping is generally required, a proportion of affected infants have clusters of syndromic features that are not readily diagnosed antenatally with confidence and that, when combined with renal or pulmonary compromise, have a synergistic effect in increasing mortality risk and amplifying morbidity experienced among survivors. More than one-third of otherwise normal infants who have only isolated bladder outlet tract obstruction and do not have multiple anomalies or syndromes do not recover normal renal function in childhood, and the majority of those with impaired renal function require dialysis and renal transplantation.

Critical gaps in the literature include complete lack of randomized trials among the groups in which there is clinical uncertainty, including lack of randomized trials making direct comparisons. Studies should continue to enhance description of fetuses enrolled, and must begin to present information about maternal characteristics and selection. Furthermore, multiple key informants expressed concern that intervening for obstructive uropathy may be seen as an "easy" in utero intervention and that therefore it may be escaping into practice in the absence of adequate evidence, methods for selecting patients, or training of physicians. They stressed the need for research and training around identifying appropriate surgical candidates. Finally, patient selection criteria should be carefully assessed and potentially updated.

Systematic and uniform assessments of early neurologic and health outcomes associated with critical illness and prematurity must be tracked, such as risk of ventricular hemorrhage and oxygen dependence. These need be extended to use of reliable tools for uniform assessment of growth and development in childhood. Given the importance of pulmonary sequelae as an outcome, it is quite concerning that little is known about pulmonary outcomes in the short and long term. Renal outcomes are being described and need to be pushed into later childhood and young adulthood; registries and pooled data will be required to gather this valuable information. Differences in needs for neonatal and childhood urologic surgical intervention need to be

examined as do continence outcomes. Health status, functional status, and quality of life will be important components of coordinated followup. A well-rounded picture of the lives of children who do and do not receive fetal intervention is required to fully support care teams and families in informed decisionmaking at a supremely difficult time in which decisions require some degree of dispatch.

State of the Science: Sacrococcygeal Teratoma

Background. Sacrococcygeal teratoma (SCT) is a relatively rare condition affecting approximately 1 in 40,000 fetuses or about 100 infants a year in the United States. As a result of ultrasound use, these tumors are increasingly recognized antenatally. The outcomes of prenatally diagnosed, uncomplicated survivors to term are generally good. However, those fetuses with large, vascular tumors have a high incidence of prenatal mortality from high-output cardiac failure or spontaneous hemorrhage into or rupture of the growing tumor. Fetal surgical procedures for SCT have focused on the small subgroup of fetuses with SCT and hydrops because untreated cases are expected to die in utero or at birth. All series report 100 percent mortality.[103-109] In severe cases, SCT with hydrops is associated with maternal risks. Mothers of fetuses with hydrops can develop mirror syndrome, which is a severe form of preeclampsia and can be associated with placentomegaly. Mirror syndrome is a maternal contraindication to fetal approaches since the mother is critically ill and delivery has been felt to be indicated for maternal health. Consequently, decisions to intervene need to be made when the fetus is documented to be critically ill while the mother is still in good health.

Table 11. Summary of studies of maternal-fetal surgical procedures for sacrococcygeal teratoma

Author Year	Open resection N	Other or no surgery N	Fetal inclusion criteria?	Maternal inclusion criteria?	Comparison group	Outcomes beyond neonatal hospital stay?
Randomized clinical trials and prospective cohorts						
			None			
Retrospective cohorts						
Grethel et al.[110] 2007	6	42	Yes*	No	RFA (7); no fetal procedure (35)	No
Danzer et al.[111] 2006 Hedrick et al.[112] 2004	4	26	Yes	No	No fetal procedure	Yes (20-72 mos)
Makin et al.[113] 2006	0	29	Yes	No	Varied interventions (8)‡;no fetal procedure (21)	Yes (8-86 mos)
Westerburg et al.[108] 2000 Schmidt et al.[107] 1989	7*	10	Yes	No	No fetal procedure	No
Total	**17**	**109**	**4 of 4**	**0 of 4**	**4 of 4**	**2 of 4**
Retrospective case series						
Paek et al.[114] 2001	0	4	Yes	No	No, all case RFA	Yes (12 mos)
Grand Total	**17**	**113**	**5 of 5**	**0 of 5**	**4 of 5**	**3 of 5**

RFA = radiofrequency ablation; * less detail for those without intervention; ‡ laser ablation, alcohol sclerosis, shunt placement for PUV

Included publications. We identified seven publications[107-108,110-114] that included fetal surgical procedures from five distinct populations of pregnancies affected by SCT. Procedures were associated with three fetal surgery groups based in an academic medical center. Two programs are in the United States, the other in the United Kingdom. Because this report is focused on surgical interventions, we have not included descriptions of percutaneous decompression of the SCT[115] without shunt placement or other concomitant fetal intervention. Randomized clinical trials and prospective cohorts have not been reported. Four retrospective cohorts and one case series (Table 11) have examined varied maternal-fetal interventions, including 10 cases of open fetal surgery,[110,112] 11 cases of radiofrequency ablation,[110,114] 4 of laser vessel ablation,[113]and 3 of alcohol sclerosis.[113] Another publication reports in the broad category of "fetal intervention" for seven cases without specific details.[108] In total, these studies include 130 fetuses with antenatal diagnosis of SCT, with 94 cases without fetal intervention or with only cyst aspiration. Overall, the expectant management cases are less severe (Table 12).

Table 12. Primary outcomes of maternal-fetal surgical procedures for sacrococcygeal teratoma

Author, Year, Country	Comparison groups, (N)	Key outcomes
Retrospective cohorts		
Grethel et al.[110] 2007 U.S.	**G1:** open fetal procedure (6) **G2:** percutaneous radiofrequency ablation (7) **G3:** no fetal procedure (35)	• 2 of 6 with open surgery survived; all 4 deaths were among fetuses with hydrops • 2 of 7 with RFA survived; 3 deaths were among fetuses with hydrops and 2 among those without hydrops • Among those without fetal intervention and no hydrops there were five terminations and 16 of 17 remaining survived • Among those without fetal intervention and hydrops there were four terminations and 1 survivor who was delivered preterm at 25 weeks at the onset of hydrops
Danzer et al.[111] 2006 Hedrick et al.[112] 2004 U.S.	**G1:** open fetal procedure (4) **G2:** no fetal surgery or cyst aspiration only (26)	• 3 of 4 fetuses survived open surgery (75%) and delivered between 27 and 31 weeks • 4 of 26 fetal deaths with 4 additional terminations. • 50% survived without intervention excluding terminations • 90% of fetuses with other procedures, amnioreduction, amnioinfusion, and cyst aspiration, survived
Makin et al.[113] 2006 UK	**G1:** laser vessel ablation (4) **G2:** alcohol sclerosis (3) **G3:** vesicoamniotic shunt (1) **G4**: no fetal procedure (21)	• 1 of 4 with laser ablation survived • 0 of 3 with alcohol sclerosis survived • 1 of 1 shunt recipient survived • 21 of 21 without fetal surgery for SCT survived ; 23 infants total survived to have definitive surgery including 2 of 8 with fetal surgery and 21 without • Median followup of 39 months
Westerburg et al.[108] 2000 Schmidt et al.[107] 1989 U.S.	**G1:** "fetal intervention" (7) **G2:** no fetal procedure (10)	• 3 of 7 with unspecified fetal intervention (43%) survived; all had hydrops • 1 of 5 fetuses with hydrops and no intervention survived; infant was delivered at detection of hydrops at 32 weeks • 2 of 5 with hydrops had pregnancy termination • 5 of 5 without hydrops and no intervention survived • Survival excluding terminations was 6 of 10 (60%)
Retrospective case series		
Paek et al.[114] 2001 U.S.	**G1:** radiofrequency ablation (4)	• 2 of 4 survived to birth • 2 deaths attributed to attempts to ablate larger portions of mass • 2 survivors had ablation targeted to only major feeder vessels

RFA=radiofrequency ablation

Alcohol sclerosis was the least studied, and all three reported cases died. Radiofrequency ablation was also rarely reported; four of seven infants survived (Table 12). Of the five fetuses or infants that died after radiofrequency ablation, death was associated with hydrops in three cases, occurred in two infants without hydrops, and was associated with aggressive use of radiofrequency ablation to debulk tumor rather than ablate vessels only in two cases. The group that examined outcomes of radiofrequency ablation reports subsequent cases have only targeted major vessels, and both fetuses treated after this change survived.[114] Laser vessel ablation in four cases with hydrops failed to salvage the fetuses and all died in utero or at birth.[113]

For open fetal procedures, the aggregate survival rates were 33 percent to 75 percent;[110,112] both reported fetuses without hydrops survived in one group, and three of three without hydrops survived in the other. All fetal and neonatal deaths occurred among those with hydrops or with prodomal cardiovascular changes concerning for developing hydrops. In the comparison groups without fetal intervention or with only cyst aspiration to facilitate delivery, all cases with hydrops died, with the exception of two infants who were delivered promptly near the time that progression to hydrops was detected by frequent ultrasound surveillance. These infants were delivered at 25 and 32 weeks, respectively.[108,110] Infants in both the intervention and no fetal intervention groups had complex hospital courses related to surgical intervention for the SCT. All who survived to surgery and who did not have fetal resection had surgery.

Long-term followup is limited; two groups provide only birth outcomes, and three provide longer term information out to 6 to 7 years of age.[112-113] Chronic lung disease related to prematurity and recurrence of tumor has been sporadically reported in both fetal intervention and no fetal treatment groups. Of 22 surviving infants in all groups of the British cohort, the median hospital stay was 14 days and median followup is 39 months. Three cases were lost to followup after one year and were alive at that time; the remainder were known to be alive. One child had developmental delay, one had chronic constipation, and three needed cosmetic scar revision. None of the children, including six who were younger than 2 years of age, had other urologic or neurologic sequelae.[113]

All studies provided sufficient detail to understand the status of the infants included for procedures. Less information about antenatal course was available in some cases about the SCT cases that did not have interventions. One report included insufficient information about the nature of the procedures done. The latter paper was focused on predicting the occurrence of hydrops and thus presented limited intervention and outcome data. No studies characterized maternal inclusion criteria, though three did provide some information about maternal obstetrical complications and perioperative complications.

Summary of the SCT literature. Consistent with other newer fetal interventions, this literature will benefit over time from the anticipated transition to uniform, prospective data collection. Standardized classification systems and consistent assessment of similar case features will allow aggregation across sites and ultimately enough cases will be compiled to begin to stratify outcomes by risk group and to design the next generation of research to fully understand infant, childhood, and young adult outcomes including use of multivariable models and clinical trials. Other challenges for SCT include a need to focus on the optimal timing of fetal interventions and early and reliable detection of fetuses which will or are developing hydrops or cardiac decompensation. The overriding comment from key informants was related to the importance of very careful patient selection. SCTs do not necessarily need to be addressed in utero, and in the absence of incipient hydrops, treatment should be postponed until the postnatal period. The

"right" patients for this procedure are extraordinarily rare—even the site with the greatest experience reports doing fewer than 10.

State of the Science: Thoracic Lesions

Background. Congenital pulmonary airway malformations (CPAM), which include congenital cystic adenomatoid malformation (CCAM) and bronchopulmonary sequestration (BPS), are congenital anomalies of the lung that share the characteristic of a segment of lung being replaced by abnormally developing tissue. CCAMs can have connections to the pulmonary tree and contain air. The tissue is served by blood vessels in the pulmonary circulation.[116] BPS does not connect to airway and has blood flow from branches off the aorta as well as the pulmonary circulation. Antenatal diagnosis is most often made by ultrasound.

Only a small subset of patients with congenital pulmonary airway malformations are candidates for in utero treatment. In this subset, the mass is large enough and in such an anatomically critical position that the fetal mediastinum is compressed, leading to impaired venous return with resulting fetal hydrops secondary to cardiac failure. When this occurs early enough in gestational age that delivery and postnatal treatment are not an option, in utero treatment is a possible solution. The majority of CPAMs, however, do not have an indication for prenatal treatment as the outcomes are excellent, with the tumors often regressing throughout pregnancy and causing no neonatal or early childhood symptoms.

Oftentimes the more difficult judgments to be made during pregnancy are the frequency with which these tumors should be monitored in order to detect the small percentage that will cause fetal harm in order to know when to intervene. Distinguishing between these conditions is difficult and some would argue clinically irrelevant until after birth. The final common pathway that leads to consideration of fetal intervention is the same—fetal hydrops—whether the lesion is considered a pure CCAM, BPS, or a hybrid lesion.

There are presently no useful predictors of outcome for thoracic lesions, and serial evaluations are essential to determine course. Hydrops in the fetus results from obstruction of the vena cava and cardiac compression caused by mediastinal shift.[117] The decision to intervene in utero is often based on the natural history reports that hydrops marks a transition to fetal demise. At times large pleural effusions occur without CCAM or BPS; the natural history of these effusions is even less well understood. We did not include interventions for isolated pleural effusions in this review; neither did we include papers that only reported thoracocentesis as a treatment.

Included publications. No randomized trials have focused on maternal-fetal intervention for CCAMS or BPS (Table 13). Our search identified 17 publications in which the authors focused on lesions thought antenatally to be CCAMs or in which the anomalies were simply classified as thoracic or pulmonary masses. They included: 13 publications about 6 distinct cohorts,[24,110,117-127] and 4 case series reports[88,98,128-129] about 3 distinct study populations from a total of 7 academic groups in the United States, South America, Europe, and Japan. Collectively, their participants represent approximately 401 fetuses believed to have CCAMs, of which 54 had thoracoamniotic shunting and 3 had open procedures, with the goal of decompressing the lung lesion. Two retrospective cohorts focused on a total of 13 fetuses with bronchopulmonary sequestration.[120,130] Fetal intervention for both CCAMs and BPS are summarized in Table 14.

Table 13. Summary of cohort and case series studies of maternal-fetal surgical procedures for thoracic lesions

Author Year	With fetal shunting N	Without this procedure N	Fetal inclusion criteria?	Maternal inclusion criteria?	Comparison group	Outcomes beyond neonatal hospital stay?
Cohorts						
Morris et al.[127] 2009	3 shunt 3 open	38	Yes	No	High risk lesion without surgery (7) All types of lesions who received steroids (9)	Yes (≥ 5 mos)
Merchant et al.[125] 2007*	9	19	Yes	No	Ineligible for fetal surgery (13); matched no fetal surgery (6)	Yes (1.5-9 mos)
Grethel et al.[110] 2007*	9	154	Yes	No	No fetal surgery (129); open fetal surgery (25)	Yes (1 mos)
Morikawa et al.[126] 2003*	2	2	Yes	No	No fetal surgery (2)	Yes (24-36 mos)
Adzick et al.[24,117,120-124] 1998*	6	114	Yes	No	No fetal surgery (101); open fetal surgery (13)	Yes (12-84 mos)
Adzick et al.[120] 1998	2	1	Yes	No	No fetal surgery	No
Dommergues et al.[118-119] 1997*	9	17	Yes	No	No fetal surgery	Yes (5-36 mos)
Becmeur et al.[130] 1997	1	9	Yes	No	No fetal surgery	No
Total	**44**	**354**	**8 of 8**	**0 of 8**	**8 of 8 include no fetal surgery**	**6 of 8**
Case series						
Araujo et al.[88] 2007*	2	NA	Yes	No	NA	No
Wilson et al.[128] 2004*	10	NA	Yes	No	NA	No
Golaszewski et al.[129] 1998* Bernaschek et al.[98] 1994*	4	NA	Yes	No	NA	Yes (mean 30 mos)
Total	**16**	**NA**	**3 of 3**	**0 of 3**	**NA**	**1 of 3**

*CCAM studies

The total literature available included 88 infants with untreated hydrops associated with CCAM. Of these infants, five survived (5.7 percent); four of these improved after a course of steroids. The intervention literature suggests a 54 percent overall survival to birth after maternal-fetal intervention, with survival as low as 20 percent to 33 percent among fetuses with hydrops.[110,120] In cohorts, 44 percent to 100 percent of infants who had thoracoamniotic shunts placed survived to birth or through neonatal hospitalization.[110,118,126-128]

Table 14. Primary outcomes of maternal-fetal surgical procedures for thoracic lesions

Author, Year, Country	Comparison groups (N)	Key outcomes
Prospective cohorts: CCAM		
Dommergues et al.[118] 1997 Revillon et al.[119] 1993 France	**G1:** thoracoamniotic shunt (9) **G2:** no fetal procedure (17)	• All 9 fetuses receiving thoracoamniotic shunt were hydropic • All 17 fetuses in no fetal surgery group were nonhydropic • 5 of 9 (55%) fetuses receiving thoracoamniotic shunt died; all had pulmonary hypoplasia at autopsy • 1 patient had PROM within 48 hours of shunt placement and delivered at 31 weeks (infant died) • 3 of 12 pregnancies assigned to receive thoracoamniotic shunt terminated the pregnancy • 17 of 17 nonhydropic fetuses assigned to no fetal surgery group survived • 11 of 17 (65%) of no fetal surgery cases the lesion was < 50% of the thorax • 11 of 17 of infants in no fetal surgery group had to undergo postnatal surgery
Retrospective cohorts: CCAM		
Morris et al.[127] 2009	**G1**: open fetal surgery (3) **G2:** thoracoamniotic shunt (3) **G3:** High risk no procedure (7)	• 3 of 3 fetuses with open fetal surgery died intraoperatively or in utero • 2 of 3 with thoracoamniotic shunt survived • 4 of 7 infants with hydrops survived without prenatal intervention • 4 of 4 survivors without procedure responded well to prenatal steroids; 3 who died did not respond
Adzick et al.[120-122] 1998, 1994, 1993 Cha et al.[123] 1997 Kuller et al.[124] 1992 Harrison et al.[117] 1990 Gibbs et al.[24] 1998 U.S.	**G1:** thoracoamniotic shunt (6) **G2:** open fetal lobectomy (13) **G3:** no fetal procedure (101)	• 3 of 3 nonhydropic fetuses survived after shunt placement, with 1 requiring ECMO for 4 days and 1 requiring high-frequency ventilation for 2 weeks • 2 of 3 (66%) hydropic fetuses survived after shunt placement • 8 of 13 (62%) fetuses undergoing open fetal lobectomy survived at up to 7 years follow-up • Mean postoperative pregnancy duration was 8 weeks (range: 2-13 weeks) • 76 of 101 fetuses in the no fetal surgery group did not have hydrops; 100% survived (66 of 76 received postnatal resection) • 25 of 101 fetuses in the no fetal surgery group were hydropic; 100% died • 4 of 4 infants who had open fetal surgery had normal neurodevelopment at up to 47 mos
Grethel et al.[110] 2007 U.S.	**G1:** thoracoamniotic shunt (9) **G2:** open fetal procedure (25) **G3:** no fetal procedure (129)	• 5 of 9 (45%) fetuses who received thoracoamniotic shunt survived (1 of 5 with hydrops survived) • 14 of 25 (56%) who had open fetal surgery survived (13 of 23 with hydrops survived) • 113 of 129 (87%) who were in the no fetal surgery group survived (0 of 14 with hydrops survived)

Table 14. Primary outcomes of maternal-fetal surgical procedures for thoracic lesions (continued)

Author, Year, Country	Comparison groups (N)	Key outcomes
Retrospective cohorts: CCAM		
Merchant et al.[125] 2007 U.S.	**G1:** thoracoamniotic shunt for macrocystic CCAM (9) **G2:** no fetal surgery-CCAMs did not require prenatal shunt (13) **G3:** gestation, volume, and CVR-matched CCAM who did not require prenatal shunt (6)	• All infants underwent surgical resection of CCAMs within first month of life • **G1:** 2 of 9 (22%) had significant chest wall deformity with rib deformity and rib thinning; 2 of 9 had rib fractures • **G2:** 13 of 13 had normal chest radiographs immediately after resection of CCAM without rib deformity, thinning, or fractures • **G3:** 2 of 6 had no rib deformity on chest radiographs; 4 of 6 had symmetric, minimal rib thinning
Morikawa et al.[126] 2003 Japan	**G1:** thoracoamniotic shunt (2) **G2:** no fetal procedure (2)	• **G1:** 2 of 2 infants survived and were well at 2 yrs • **G2:** 2 of 2 infants survived and were well at 2 and 3 yrs • **G1:** Gestational age was 37-40 weeks • **G2:** Gestational age 30-37 weeks • All 4 infants underwent postnatal surgery for CCAM
Retrospective cohorts: BPS		
Adzick et al.[120] 1998 U.S.	**G1:** thoracoamniotic shunt (2) **G2:** no fetal procedure (1)	• 2 of 2 infants with thoracoamniotic shunt survived but required ventilator support and postnatal extralobar pulmonary sequestration resection • 1 infant without fetal surgery was diagnosed at 34 weeks' gestation and died of pulmonary hypoplasia after postnatal resection and ECMO for 3 weeks
Becmeur et al.[130] 1997 France	**G1:** pleuro-amniotic shunt (1) **G2:** no fetal procedure (9)	• 1 infant received pleura-amniotic shunt at 30 weeks gestational age • 6 of 9 infants who received no fetal surgery had absolute or relative regression of the thoracic mass • Definitive diagnosis of BPS was done after birth (9) by MRI or US • 8 of 10 infants had other congenital malformations
Case series: CCAM		
Araujo et al.[88] 2007 Brazil	**G1:** thoracoamniotic shunt (2)	• 2 of 2 fetuses survived to one week of age
Wilson et al.[128] 2004 U.S.	**G1:** thoracoamniotic shunting (10)	• 7 of 10 (70%) infants survived • 2 of 10 (20%) infants died during the neonatal period • 1 of 10 fetuses died in utero • 6 of 10 fetuses were hydropic • 5 of 10 fetuses had polyhydramnios • 3 fetuses had both hydrops and polyhydramnios • All survivors had resection of CCAM in first 3 days of life
Golaszewski et al.[129] 1998 Bernaschek et al.[98] 1994 Austria, Germany	**G1:** thoracoamniotic shunting (4)	• 0 of 4 fetuses died in utero • 3 of 4 (75%) infants survived the perinatal period • 1 of 4 delivered preterm • 1 of 4 infants had occlusion of the shunt 1 week after shunt placement and required thoracocentesis four times in 10 days

BPS=bronchopulmonary sequestration; CCAM=Congenital Cystic Adenomatoid Malformation; ECMO=Extracorporeal Membrane Oxygenation; MRI=Magnetic Resonance Imaging; PROM=Preterm rupture of membranes; US=ultrasound

A team treating 13 fetuses with open fetal surgery achieved 61 percent survival through seven years of followup, with normal neurodevelopmental followup for the 4 infants with formal evaluation up to 47 months of age. In the same group of patients from this surgical group, all infants without hydrops survived, and 66 of 76 (87 percent) required postnatal resection.[24,117,120-124] This is similar to 56 percent survival reported for open surgery by another team who operated

on 25 fetuses, of which 23 had hydrops.[110] Another group reported intraoperative death or fetal demise in three cases of open fetal surgery in the setting of hydrops.[127] Uniform survival of infants without hydrops has been reported by several groups.[118-119,125-127]

Among fetuses with shunts for BPS three of three survived; however, as for CCAMs, a number of fetuses, in one series 67 percent, have spontaneous regression of the lesion in utero or after birth and do not require resection. The proportion of infants requiring surgery for resection of the lesions may not be reduced by fetal intervention. Outcomes beyond survival have been examined in only a few series. Merchant and colleagues[125] reported chest wall and rib deformities in two of nine patients treated with fetal shunts. Gibbs and colleagues[24] reported on neurologic outcomes of 11 infants with open fetal surgery for all types of lesions; 9 were developing normally.

Fetal inclusion criteria or detailed case descriptions are included in each of the identified publications; reporting of anesthesia approach is also well described. Subsequent surgical intervention in both those infants treated as fetuses and after birth is nearly complete. However, information about factors related to maternal selection and complications is meager. Length of followup is highly variable, with infants followed up past the newborn hospital stay in 7 of 16 publications; 4 provided any neurologic outcomes in infancy or childhood; and none provide formal evaluation of pulmonary function in childhood.

Summary of thoracic lesions literature. The literature on congenital lung lesions is dominated by reports of isolated or repeated use of thoracocentesis, which was not a maternal-fetal surgical intervention directly addressed by this report. This smaller body of literature about open maternal-fetal surgeries and thoracoamniotic shunt placement reflects a wide range of differences in spectrum of fetuses treated. Over time, interest has evolved in the direction of treating only those infants with poor prognosis as indicated by fetal hydrops. While logical, this creates lack of comparability of infants who received and did not receive fetal treatment. Other aspects of changes in contemporary care may also be influencing how cohorts and case series are interpreted. Recent advances in the CCAM literature include the report of three cases of a novel therapy involving percutaneous fetal sclerotherapy in 2008.[131] Additionally, some infants with large CCAMs may respond to in utero medical treatment with steroids.[110,127] Combined, the two teams have reported seven infants with CCAM and hydrops, with resolution of the lesion in all seven. Currently a multicenter trial is being organized at the University of California, San Francisco, the Fetal Care Center of Cincinnati, and the Children's Hospital of Philadelphia, which will randomize select infants with CCAM to steroid or no steroid treatment. Future interventions may also have failure to respond to steroids as an entry criterion.

State of the Science: Twin-Twin Transfusion Syndrome

Background. In twin-to-twin transfusion syndrome (TTTS), twins share a single chorionic membrane and therefore a single placenta, but have separate amniotic sacs. Approximately 15 percent of monochorionic, diamniotic twin pregnancies are affected by TTTS,[132] and therefore, estimates based on CDC data are that theoretical incidence of TTTS would be about 1.38 to 1.86 cases per 1,000 live births.[133] Although incidence studies have found lower numbers, these numbers are probably a reflection of early deaths of affected fetuses in utero that therefore do not get recognized as TTTS pregnancies.

Most pregnancies presenting with severe TTTS prior to 26 weeks and not undergoing some sort of therapy will end with dual fetal demise.[132] When both twins do survive, there is often

severe neurologic compromise in survivors as well as other organ failure, including cardiac conditions. Approximately 25 percent of surviving fetuses in a monochorionic twin pair in which one dies will suffer CNS injury.

Diagnostic criteria for TTTS have evolved to include: same-sex fetuses with a single placenta with lack of lambda sign in early pregnancy; oligohydramnios in the donor sac (<2 cm maximum vertical pocket); and polyhydramnios in the recipient sac (>8 cm maximum vertical pocket at less than 20 weeks or >10 cm after 20 weeks).

After diagnosis, the most common approach to assessing severity in TTTS is the Quintero staging system:[134]

- Stage I: The fetal bladder of the donor twin remains visible sonographically.
- Stage II: The bladder of the donor twin is collapsed and not visible by ultrasound.
- Stage III: Critically abnormal fetal Doppler studies noted. This may include absent or reversed end-diastolic velocity in the umbilical artery, absent or reverse flow in the ductus venosus, or pulsatile flow in the umbilical vein.
- Stage IV: Fetal hydrops present.
- Stage V: Demise of one or both twins.

In 1990, Baldwin and Wittman[135] presented three prenatally diagnosed twin pairs with in utero TTTS for which they attempted selective reduction. They postulated the importance of a vascular separation. Later that year, De Lia et al reported the first fetal surgery to treat the underlying pathology.[136]

Four primary approaches exist for intervening in TTTW:

- Serial amnioreduction to relieve intra-amniotic pressure and uterine size, and thus prolong the pregnancy. Although the mechanism by which it works is not entirely clear, amnioreduction has been associated with a 50–60 percent survival rate of at least one fetus.[137]
- Termination of the sicker twin, which is likely to rescue the healthier one and is accomplished by cord occlusion, radio frequency ablation, or ligation. This is only used in the presence of significant birth defects.
- Septostomy, in which the intervening membranes is punctured to attempt to increase amniotic fluid in the oligohydramniotic sac, was performed but has largely been abandoned as a therapy.[138]
- Laser ablation of communicating vessels is performed either selectively or non-selectively to attempt to protect one twin from hemodynamic disturbances in the other twin. In nonselective ablation, all vessels crossing the dividing membrane are ablated, whereas selective ablation is limited to vessels shown to be communicating between the two fetuses. Selective ablation is most common today, and is the focus of this section of the technical brief. Gaining access to the uterus can be accomplished in three ways: laparotomy to expose the uterus, laparoscopic placement of the fetoscope, and ultrasound-guided placement of the fetoscope.

Table 15. Summary of trials and cohort studies of laser ablation for twin-twin transfusion syndrome (TTTS)

Author Year	With laser ablation N	Without laser or other procedure N	Fetal inclusion criteria?	Maternal inclusion criteria?	Comparison group	Outcomes beyond neonatal hospital stay?
Randomized controlled trials						
Crombleholme et al.[139] 2007	20	20	Yes	No	Amnioreduction	Yes (30 days postnatal)
Senat et al.[140] 2004	72	70	Yes	No	Amnioreduction	Yes (7-12 mos)
Total	**92**	**90**	**2 of 2**	**0 of 2**	**2 of 2**	**2 of 2**
Prospective cohorts						
Chmait et al.[141-142] 2010	99	--	Yes	No	Sequential vs. nonsequential laser ablation	No
Quintero et al.[143] 2007	193	--*	Yes	No	Sequential vs. nonsequential laser ablation	No
Gardiner et al.[144] 2003	13	14	Yes	No	Symptomatic management	Yes (mean 11.1 mos)
Total	**305**	**14**	**3 of 3**	**3 of 3**	**2 of 3**	**1 of 3**
Retrospective cohorts						
Habli et al.[145] 2008	26	26	Yes	No	Amnioreduction (15), radio-frequency ablation (4), no fetal surgery (7)	No
Lenclen et al.[146-147] 2007	101	36	Yes	No	Amnioreduction	No
Middeldorp et al.[148-149] 2007	20	30	Yes	No	Conservative management	Yes
Santiago et al.[150] 2006	16	--	No	No	Prior amnioreduction	No
Quintero et al.[151] 2003	95	78	Yes	No	Amnioreduction	No
Quintero et al.[152] 2000	92	--	Yes	No	Selective vs. nonselective	No
Total	**345**	**160**	**5 of 6**	**0 of 6**	**6 of 6**	**1 of 6**

*These cohorts reflect differences in laser ablation approach (e.g. selective vs. nonselective) or prior intervention (e.g. with or without prior amnioreduction) as the basis for comparisons across groups.

Included publications. We searched specifically for literature on laser treatment for TTTS; therefore, we defined cohort studies as those that included comparisons either of types of laser to other types of treatment or to no treatment. Studies in which all participants received laser treatment were considered case series even if the data were presented for separate groups, such as by severity.

The treatment literature evaluating laser ablation for TTTS included 2 RCTs,[139-140] 3 prospective cohorts,[141,143-144] 7 retrospective cohorts[142,145-152] and 73 case series (Table 15). Although we attempted to group "families" of publications in which specific pregnancies may be reported in duplicate, we were unable to do so definitively, and there is likely substantial overlap

among the populations in the studies. Our best estimate is that approximately 1,790 pregnancies treated with laser ablation for TTTS have been reported in the literature. Of the 77 papers, 42 specified using selective laser ablation and 14 nonselective, including 3 that reported using both (sometimes in direct comparison). Of 54 studies reporting the type of anesthesia used, 15 used general, 26 used local and 13 used epidural.

Until 2000, all publications were case series, with the first RCT reported in 2004. The vast majority of studies (including all of the newer ones) that report surgical approach indicate that they used a percutaneous approach with a fetoscope. All but one of the reports using laparotomy to gain access to the uterus were by the same group, early in the series. This may reflect advances in instrumentation which improved minimally invasive access surgery during this time. Some laparotomy cases were done to gain access to an anteriorly placed placenta without transplacental fetoscope placement.

Both RCTs[139-140] used amnioreduction as their comparison group. One required that pregnancies first have an amnioreduction prior to randomization[139] The other excluded patients with prior invasive treatment.[140] Only pregnancies in which initial amnioreduction was non-therapeutic were enrolled in the study. Both studies were stopped before completion under standard stopping rules at planned interim analyses. The earlier study[140] had a higher rate of survival at 7 to 12 months of age of at least one twin in the laser group relative to the amnioreduction group (p=.002). Although survival rates were higher among lower Quintero-staged pregnancies in general, there was still greater survival among higher Quintero-staged pregnancies in the laser group. Cerebral lesions were also significantly less likely in the laser group compared to amnioreduction (7 percent of survivors in laser versus 35 percent of survivors in AR; p=.02).

In the Crombleholme study, there was a statistically significant increase in fetal mortality among recipient twins treated with laser (63 percent) versus amnioreduction (12.5 percent), but no difference in survival at 30 days. There was also no difference in survival among donor twins. Small numbers, however, make these results difficult to assess.

Nonetheless, the studies cannot be directly compared: the Senat study, which had more positive outcomes for laser intervention included women with any Quintero stage TTTS, whereas the Crombleholme study excluded women with stage 1 TTTS, thus focusing on a more severely impaired group. The Senat study also included pregnancies up to gestational ages of 26 weeks, compared to an upper limit of 22 weeks in the Crombleholme study.

Of the nine cohort studies, three were prospective and six were retrospective. Five included data that allowed comparisons of amnioreduction to laser ablation.[144-146,148,151] Two compared selective to nonselective approaches,[143,152] and one considered whether having had a prior amnioreduction conferred risk of worse outcomes on pregnancies undergoing laser ablation.[150]

The five studies that included data allowing for a comparison between amnioreduction and laser showed mixed results (Table 16), but because these studies were all nonrandomized, this could very well reflect unmeasured differences in study populations or differences in laser technique or experience. In one of the two studies that did not demonstrate a survival benefit for laser relative to AR,[148] however, substantially higher morbidity was observed among the neonates who had been treated with AR. One study[147] followed a subset of twins from another retrospective cohort[146] and found similar neurodevelopmental outcomes in survivors treated with laser as seen in a group of dichorionic twins. Survivors of amnioreduction had increased neurodevelopmental delay at 2 years, as measured by the Ages and Stages questionnaire.

Table 16. Primary outcomes of trials and cohort studies of laser ablation for TTTS

Author, Year, Country	Comparison groups, (N)	Key outcomes
Chavira et al.[142] 2009 U.S.	G1: very short cervical length, 0.5-1.9 cm (10) **G2:** moderate cervical length, 2-2.5 cm (13) **G3:** normal cervical length, >2.5 cm (76)	• 3/10 patients in the very short cervical length group had prior AR and 8/10 underwent cerclage • No significant differences among groups in gestational age at delivery, 30-day neonatal survival, or latency from time of surgery to delivery • Overall at least 1 neonatal survivor in 90 of 99 cases (91%), dual survival in 71/99 cases (72%)
Habli et al.[145] 2008 U.S.	**G1:** SFLP (26) **G2:** AR (15) **G3:** RFA (4), **G4**: expectant management (7)	• No significant difference in donor or recipient survival rate (p=0.058) or gestational age at delivery among treatment groups (p=.5)
Crombleholme et al.[139] 2007 U.S.	**G1:** SFLP (20) **G2:** AR (20)	• No significant difference in 30-day postnatal survival between donors or recipients by group • No difference in 30-day survival of one or both twins on a per-pregnancy basis • Significant increase in fetal recipient mortality in the SFLP arm, offset by increased recipient neonatal mortality in the AR arm • Echocardiographic abnormality in recipient twin; CVPS most significant (p=0.055) predictor of recipient mortality by logistic regression
Lenclen et al.[146-147] 2007 France	**G1:** laser ablation (101) **G2:** amnioreduction (36) **G3:**unattended dichorionic twins delivered at 24-34 weeks of gestation (242)	• Death or severe cerebral lesions more frequent in the amnioreduction group than laser or dichorionic groups • No significant difference in overall neonatal outcome between laser and normal dichorionic neonates • Neonatal morbidity higher in laser neonates delivered at <30 weeks' gestation when due to failed laser therapy • Neurodevelopmental delays greater at 2 years in G2 compared with the other 2 groups
Middeldorp et al.[148-149] 2007 Netherlands	**G1:** laser surgery, presenting after 26 weeks of gestation (10) **G2:** conservative management (30)	• No significant difference was found between groups in the median gestational age at birth • Long term neurodevelopmental delay in 0% of G1 vs.23% of G2 (p=.03) • Major neonatal morbidity occurred more often in the amniodrainage group (26%) than laser surgery group (7%), (p=0.04) • No significant difference in rates of severe cerebral injury (p=1.00), neonatal mortality (p=0.54), or overall adverse outcome (p=0.83) between groups
Quintero et al.[143] 2007 U.S.	**G1:**selective laser photocoagulation of communicating vessels (SLPCV) (56) **G2:** sequential SLPCV (137)	• Pregnancies in which sequential SLPCV (G2) was done were more likely (p=.02) to have 2 surviving fetuses (73% vs. 57%) • Differences for at least one surviving fetus were non-significant

Table 16. Primary outcomes of trials and cohort studies of laser ablation for TTTS (continued)

Author, Year, Study Type, Country	Comparison groups, (N)	Key outcomes
Santiago et al.[150] 2006 Spain	**G1:** laser without prior AR (10) **G2:** laser with prior AR (6)	• No substantial differences in survival rates between the groups, but the sample size was small
Senat et al.[140] 2004 France, Belgium, Switzerland	**G1:** selective laser SFLP therapy (72) **G2:** amnioreduction (70**)**	• Neonatal survival greater in G1 vs. G2 (p=0.0009) • Survival to 6 months of age was greater in G1 vs. G2 (p=0.002) • Incidence of cystic periventricular leukomalacia was lower in G1 vs. G2 at 6 months (p=0.003)
Gardiner et al.[144] 2003 UK, Germany	**G1:** TTTS treated symptomatically (14) **G2:** laser ablation (13) **G3:** pregnancies w/ monochorionic twins w/o TTTS (12) **G4**: normal dichorionic twins (11)	• Gestational age and birthweight slightly greater in G2 than G1 but no assessment of statistical significance for comparison • No significant differences in blood pressure or intrauterine growth between G1 and G2
Quintero et al.[151] 2003 U.S., Australia	**G1:** SFLP (95) **G2:** serial amnioreduction (173)	• Likelihood of at least one surviving infant was correlated inversely with stage in G2 but not G1 • G1 was 2.4 times more likely to have at least one survivor than G2 • Neurologic morbidity related to stage in G2 but not G1 • Neurologic morbidity significantly higher in G2 vs. G1
Quintero et al.[152] 2000 U.S.	**G1:** SFLP **G2:** nonselective laser	• Higher survival of at least one fetus in selective (83%) vs. nonselective (61%) (p=0.04)

AR=amnioreduction; CVPS=cardiovascular profile score; RFA=radiofrequency ablation; SFLP=selective laser photocoagulation; SLPCV= selective laser photocoagulation of communicating vessels; TTTS=Twin-twin transfusion syndrome

Two studies by the same group examined modifications to the general technique: selective versus nonselective[152] and sequential versus nonsequential approaches.[143] Both selective and sequential approaches were associated with greater survival rates. In a retrospective comparison of 16 patients referred for laser, some of whom had a prior amnioreduction, there was no difference between patients who had or had not had prior AR. Finally, one prospective cohort[142] found no difference in outcomes of laser treatment by cervical length at admission.

The many case series available in this literature are helpful in surveying the range of success rates and in identifying potential harms associated with treatment.[153] Preterm premature rupture of membranes is the most commonly noted short-term harm, with a range of 4 percent[154] to 28 percent.[155] Longer term developmental outcomes in the infants have been examined in a small number of studies, and although a high rate of neurodevelopmental impairment is noted,[156] none of these studies included a treatment comparison group, so the relative benefit or harm of laser treatment on these outcomes is unknown.

Experts in treatment for TTTS stressed the importance of very stringent techniques, particularly in mapping the vessels and incorporating checks and balances into the process; mapping techniques and the need for stringent processes, however, are not well evaluated in the literature and likely warrant further study. Two key informants spoke to their concerns that complications are substantially higher outside of the larger centers, but without a system for documenting outcomes and outside of the research enterprise, actual rates cannot be captured.

Summary of the TTTS literature. Case series comprise the bulk of TTTS literature discussed in this review. Two RCTs meeting our criteria compared amnioreduction to laser ablation; similarly, five of the eight cohort studies reported here compared laser ablation and amnioreduction. Consensus about the superiority of vascular ablation procedures versus amnioreduction is developing, but as in other fetal procedures, small sample sizes and differences between study groups limit comparisons. The TTTS literature also lacks substantial long-term fetal and maternal outcomes data.

Discussion

State of the Science

The crosscutting focus of this review is summarizing the state of the field of maternal-fetal surgical procedures, broadly defined to include topics such as training of providers, access to care, and strength of the research literature for understanding the anticipated effectiveness of fetal approaches in practice. Stakeholders requesting the report were specifically interested in instances in which strong comparative research suggests superiority of maternal-fetal surgical procedures over intervention at birth for reducing fetal, intrapartum, and neonatal mortality and for preserving organ function. However in compiling this literature it is apparent that, while developing rapidly, the research on fetal surgical procedures has not achieved the typical level of quality of studies and aggregate strength of the evidence used to reach definitive conclusions about care and policy.

Favorable signs include the substantive leadership of U.S. researchers across each of the topics considered. For each target condition, there are both fetal surgical centers and associated research enterprises engaged in the full spectrum of academic endeavor, from animal research, development of surgical interventions, and refinements, to patient care, surgical training, bioethics forums, and reporting of results in the scientific literature. The majority of fetal surgical innovations arose in the United States, and the momentum of the literatures suggest continued growth of expertise alongside a commitment to assuring forthright examination of the outcomes of maternal-fetal surgical care. All publications across both the United States and internationally reflected the involvement of tertiary care academic medical centers, and scholarly work is clearly woven into the fabric of maternal-fetal surgery care. Thus, available data are likely to be relevant to care and trends in the United States.

Randomized trials, a total of three published in two topics (CDH and TTTS), are rare. Experts and authors in this area rightly point out both the desirability of randomized trials and the factors that mitigate success of trials, including small numbers of fetuses with specific conditions, need for methodologic advancement for study of this topic, patients who span the country while academic research centers are sparsely distributed, insufficient mechanisms to absorb the costs of care for participants who are participating in research, lack of national research infrastructure to coordinate trials, and in some instances, competing availability of procedures outside the trial.[157-158] When conducted, the results have had influence in redirecting the field. The finding that open fetal repair of CDH did not improve outcomes compared to repair at birth, helped focus continued development of interventions on less invasive approaches that now include comparison of approaches for balloon tracheal occlusion. Trials suggesting superiority of laser ablation of vessels to serial amnioreduction also refocused the field on comparisons of less invasive approaches.

Prospective studies, with the potential to standardize protocols and elements of data collection and outcome measurement, are also few. Eleven of 166 total study populations (7 percent) were classified as prospective cohorts for this count. We erred on the side of inclusiveness, counting all use of research registries that prospectively capture individual case data, whether local or multisite, as prospective data collection. Retrospective cohorts, a total of 36, made up 22 percent of the total study populations reported in the literature. Retrospective

studies were less likely to compare to fetal interventions and most likely to have historical comparison groups.

Cohort studies have fundamental challenges with comparability of the comparison group because the decision to act or defer intervention until the postnatal timeframe is often entangled with clinically assessed prognosis. Infants who were expected to do well without intervention would be less likely to have fetal surgery and would potentially do better than those who received fetal surgery. Conversely, those who were felt to have grim survivability are often noted to have been offered termination or to have had treatment withheld secondary to perceived futility. The latter scenario overestimates the benefit of fetal intervention compared to those with extremely poor prognosis. The number of cases with similar characteristics between those who received surgery and those who did not accept referral to procedures is rarely reported. The total number in the literature is insufficient to make estimates that are legitimately comparable. Furthermore, data collection is often imbalanced, with greater detail available for the cases that underwent surgery than those that did not.

Few cohort studies were large and thorough enough to conduct appropriately powered multivariable analysis to adjust for candidate confounders or modifiers of treatment outcomes. TTTS was the exception, and findings from this area, which reflect greater numbers of pregnancies in individual studies available to aggregate, are more secure. Consensus is developing that vascular ablation procedures are superior to serial amnioreduction, and attention has turned to evaluating selective versus nonselective approaches to targeting vessels. For the majority of the conditions of interest, aggregating the number of participants would still fall short of that needed for metaregression, and key confounders and modifiers of outcomes appear not to be available uniformly across research groups.

Case series dominate the maternal-fetal surgical procedures literature, making up 70 percent of the included studies. This dominance of descriptive work is not an indictment, rather a natural consequence of the arrival of the fetus as a surgical candidate within the last 3 decades.

As expected, the literature for each type of approach reflects initial case reports of technical aspects of the surgery, followed by publications about selection criteria, then prognostics, and then conversion to including a comparison group and transitioning to cohort analyses. Increments of followup lengthen and the status of early cases is typically updated beyond infancy into childhood in later publications. This natural evolution of the field shows in the trend toward rising numbers cohort and prospective studies as we approach contemporary timeframes.

The strength of protocol-based research lies in gathering comparable information across an entire study population. The opportunity to use standardized timing of assessment, similar lengths of followup for those included in the analysis, or validated assessment tools for evaluation of characteristics such as neonatal and childhood developmental status is not yet being optimized. Twenty-eight percent of the publications report outcomes to birth only, and followup into childhood is meager. Outcomes of crucial interest such as neurodevelopmental status and quality of life for children and their families are rarely reported (Table 17). Complications of prematurity, a frequent sequelae of maternal-fetal surgical procedures or the conditions themselves, are not well reported. Surprisingly, gaps also exist in the reporting of the functional status of the target organ for which the procedure was done (i.e. need for renal transplant among infants with vesicoamniotic shunt placement).

Other notable gaps include sparse information about anesthesia care, intra-operative monitoring of mother and fetus, postoperative care, and specialized nursing considerations. Near-

absence of maternal outcome assessment, including a significant lack of data on future maternal reproductive health, is especially concerning.[159-161] The single publication that examined maternal outcomes across the spectrum of maternal-fetal surgical procedures for 187 women, reported 26 percent of women having open fetal procedures had an intensive care stay and 2.3 percent were intubated.[162] The team found across open, endoscopic, and percutaneous approaches combined that preterm labor resulting in birth affected 27 percent of pregnancies and preterm premature rupture of membranes 44 percent, with cesarean birth being the route of delivery for 70 percent. These and other details, such as the fact that 29 percent of women remained hospitalized until birth, are crucial to providing comprehensive anticipatory guidance during the process of informed decisionmaking about maternal-fetal surgical procedures.

Table 17. Counts of studies reporting outcomes of maternal-fetal surgical procedures

	Fetal and Infant						Maternal				
Procedure (total number of studies)	Survival to birth	Preterm birth	Neonatal deaths	Pulmonary status	Neonatal neurologic status	Developmental status in infancy or childhood	Mortality or intensive care	Infections and wound healing complications	Length of stay	Uterine rupture (index or later pregnancy)	Subsequent fertility or reproductive outcomes
Cardiac malformations											
Atrial septoplasty (3)	3	2	3								
Aortic valvuloplasty (8)	5	5	5				4	3			
Pulmonary valvuloplasty (2)	1	1	1								
Congenital diaphragmatic hernia											
Hysterotomy (8)	6	6	6	--	4	4	4	4	3	2	2
Laparoscopic (12)	10	10	10	--	2	3	4	4	2	2	1
Percutaneous (6)	6	6	6	--			3	2	1		
Myelomeningocele											
Hysterotomy (9)	6	7	6	--	7	3	4	1		1	
Obstructive uropathy											
Vesicoamniotic or other shunt (24)	24	23	24	10	1	5		1			
Hysterotomy with repair (3)	3	3	3	2				1			1
Sacrococcygeal teratoma											
Hysterotomy (3)	3	3	3				1	1			
Laparoscopic (1)	1	1	1								
Percutaneous (5)	4	4	4				2	1			
Thoracic lesions											
Thoracoamniotic shunt (9)	8	6	8	--	1	1					
Open resection (3)	3	2	3	--	1	1	1				
Twin-twin transfusion syndrome											
Laser ablation (84)	67	61	48	1	19	13	4	10			

NOTE: This table summarizes whether or not the publications considered these key outcomes, not the number of outcomes themselves. Some publications include more than one intervention and are counted under each intervention.

Despite these weaknesses, the overall momentum is toward more robust research and rigorous, more consistent documentation of outcomes over longer periods of time. All three trials

were conducted in the last decade, and each decade since the 1980s, the number of cohort studies has increased, with a threefold increase between 33 cohorts in the 2000s compared to 11 in the 1990s. Experts concurred in discussions as well as in the literature that they are eager to develop consensus measures as well as mechanisms to make implementation of common protocols and larger studies, both trials and prospective cohorts, increasingly possible.

The field is also benefitting from the contributions of groups like International Fetal Medicine and Surgery Society, the North American Fetal Therapy Network, and the International Fetal Surgery Registry. Large-scale collaborations promote not only aggregation of more participants but also standardization of measures, extended duration of followup, and emphasis on multisite trial research prioritization. Ongoing trials such as the National Institutes of Health Management of Myelomeningocele Study (MOMS) have also had beneficial effects on promoting strategies that enhance feasibility of study of rare conditions, such as commitments to provide the procedure under study only within trials and coordinating regional access.

Challenges and Opportunities

Fetal surgery teams, related research groups, professional associations, government agencies, and individual consumers with an affected fetus have a vested interest in the continued growth and sophistication of the study of outcomes of maternal-fetal surgical procedures. A number of challenges are presented, both individually and in combination:

- Relative rareness of specific anomalies, with no regional or national method to identify or consolidate new cases to be offered protocol involvement
- Need to accumulate cases over long periods of time, during which changes in other aspects of care such as innovations in neonatal care or pediatric surgery can change the benefit equation for fetal intervention or during which new surgical tools are introduced
- Variation in clinical care and research classifications of fetal anomalies and in accuracy of antenatal diagnosis, with limited diagnostic accuracy literature to draw on that reflects the general population of pregnant women in the United States
- Observation in some conditions that spontaneous regression or stabilization occurs
- Less than full agreement between staging or severity assessment systems and outcomes indicating prognosis is at present not fully discoverable from clinical assessments
- Changes in the spectrum of disease, to include previously undetected and possibly less severe cases, as imaging becomes more and more advanced with the result of reducing comparability to prior natural history studies of anticipated outcomes
- Continuing evolution of in utero interventions, which can complicate comparisons among interventions and outcomes
- Overrepresentation of higher socioeconomic status patients who have some or partial coverage for costs and may not have generalizable risks or outcomes compared to expected population-level outcomes
- Need for a strong assessment of models of care, including the potential for regionalization of care
- Training programs for the next generation of maternal-fetal surgeons, including assessment of whether formal training programs, accreditation or certification are appropriate

Strategies to reduce evidence gaps include:

- Continued development of consensus on operational definitions to uniformly classify and describe severity of conditions
- Enhanced attention to collection of common data elements using uniform approaches, especially for measurement of strong predictors of outcome and for the outcomes themselves
- Use of valid and reliable tools, common in pediatric and developmental biology research, to more globally assess infant and child health status with the long-term goal of ultimately having followup into young adulthood and later to include functional status and quality of life measures
- Cooperative data sharing with these common data elements to include plans for assessing issues of diagnostic accuracy, changing natural history, and prognosis, as well as large-scale multivariable data analysis comparing outcomes
- Use of such analyses to inform the conduct of the most pressing clinical trials in which there is scientific equipoise
- Investment in research infrastructure, external to any one site, that can facilitate achieving these aims
- New methods for funding and sharing cost and liability risk for the conduct of maternal-fetal treatment research
- Establishment of an accepted and consistent set of ethical standards for conduct of research in maternal-fetal procedures

In our discussions with experts across the country, they universally discussed the need for a considered approach to the potential for regionalized care, the need for appropriate and rigorous training, the potential for a move toward a nationally accredited field, and the desire to continue to push the science forward with as much rigor and ethical practice as possible. The coherence of the overall agenda157-158, 163 and the determination of those with a stake in understanding fetal surgical procedures are strong assurances that the scientific community will continue to build knowledge to inform care when infrastructure and consensus needs are overcome.

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Acronyms/Abbreviations

AHRQ	Agency for Healthcare Research and Quality
AR	Amnioreduction
ASD	Atrial septal defect
BPS	Bronchopulmonary sequestration
CCAM	Congenital cystic adenomatoid malformation
CDC	Centers for Disease Control and Prevention
CDH	Congenital diaphragmatic hernia
CM	Chiari malformation
CPAM	Congenital Pulmonary Airway Malformation
CSF	Cerebrospinal fluid
CVPS	Cardiovascular Profile Score
DNA	Deoxyribonucleic acid
ECMO	Extracorporeal membrane oxygenation
EPC	Evidence-based Practice Center
FETO	Fetoscopic tracheal occlusion
FHI	Fetal hemodynamic instability
G	Group
HLHS	Hypoplastic left heart syndrome
IUFD	Intrauterine fetal death/In utero fetal demise
IVH	Intraventricular hemorrhage
LHR	Lung-to-head ratio
MeSH	Medical Subject Headings
MMC	Myelomeningocele
mo/mos	Months
MOMS	Management of Myelomeningocele Study
MRI	Magnetic resonance imaging
NA	Not applicable
NIH	National Institutes of Health
PROM	Premature rupture of membranes
PUV	Posterior urethral valves
RCT	Randomized controlled trial
RDS	Respiratory Distress Syndrome
RFA	Radiofrequency ablation
SD	Standard deviation
SFLP	Selective fetoscopic laser photocoagulation
SLPCV	Selective laser photocoagulation of communicating vessels
TTTS	Twin-twin transfusion syndrome
U.S.	United States
UK	United Kingdom
US	Ultrasound

Appendix A. Exact Search Strings

Table 1. PubMed search strategies (last updated May 12, 2010)

Preliminary search terms		Preliminary search results
#1 General fetal surgery search	(fetus/surgery[mh:noexp] OR fetal heart/surgery[mh] OR fetal diseases/surgery[mh] OR fetal surgery[tiab]) AND eng[la] AND humans[mh]	1,426
#2 Sacrococcygeal teratoma	(sacrococcygeal teratoma OR sacrococcygeal region[mh]) AND (fetus[tiab] OR fetal[tiab]) AND (surgery OR surgical OR fetoscopy OR fetoscopic) AND eng[la] AND humans[mh]	138
#3 Congenital diaphragmatic hernia	(hernia, diaphragmatic[mh] OR diaphragmatic hernia[tiab]) AND (fetoscopy OR fetoscopic[tiab] OR "fetal therapies"[mh]) AND eng[la] AND humans[mh]	68
#4 Congenital cystic adenomatoid malformation, bronchopulmonary sequestration	(cystic adenomatoid malformation of lung, congenital[mh] OR bronchopulmonary sequestration[mh] OR adenomatoid[tiab] OR bronchopulmonary sequestration[tiab]) AND (intrauterine[tiab] OR in utero[tiab] OR fetoscopy OR fetoscopic[tiab] OR "fetal therapies"[mh]) AND eng[la] AND humans[mh]	136
#5 Obstructive uropathy	(uropathy[tiab] OR urologic diseases[mh] OR urinary tract[mh]) AND (fetoscopy OR fetoscopic[tiab] OR "fetal therapies"[mh]) AND eng[la] AND humans[mh]	39
#6 Myelomeningocele	(meningomyelocele OR myelomeningocele) AND (intrauterine[tiab] OR in utero[tiab] OR fetoscopy OR fetoscopic[tiab] OR "fetal therapies[mh]") AND eng[la] AND humans[mh]	127
#7 Twin-twin transfusion syndrome	fetofetal transfusion[mh] AND (laser therapy[mh] OR fetoscopy OR fetoscopic OR "fetal therapies"[mh]) AND eng[la] AND humans[mh]	300
#8 Cardiac malformations	(fetal heart[mh] OR heart[mh] OR heart septal defects[mh] OR hypoplastic left heart syndrome[mh] OR aortic valve stenosis[mh] OR pulmonary valve stenosis[mh] OR pulmonary atresia[mh]) AND (fetoscopy OR fetoscopic[tiab] OR "fetal therapies"[mh]) AND eng[la] AND humans[mh]	74
#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	2,020
#10	#9 AND letter[pt]	119*
#11	#9 AND comment[pt]	78
#12	#9 AND editorial[pt]	39
#13	#9 AND review[pt]	485**
#14	#9 AND news[pt]	9
#15	#9 AND practice guideline[pt]	4
#16	#9 NOT (#10 OR #11 OR #12 OR #13 OR #14 OR #15)	1,364***

Key: [mh] Medical Subject Heading; [tiab] title/abstract; [la] language; [mh:noexp] MeSH heading, not exploded

*Note: 34 of these letters include case reports; these have been included in the EndNote database

**Note: 52 of these reviews include case reports; these have been included in the EndNote database.

*** The EndNote database includes these 1,364 references, along with the 34 letters with case reports and the 52 reviews with case reports, bringing the overall pool of items retrieved by the PubMed searches to 1,450.

Update EndNote database from 5/12/10 includes 37 new items added to the database since the previous search update on 1/13/10.

Appendix B. Sample Data Abstract Forms

Technical Brief on Maternal-Fetal Surgery
Abstract Review Form

First Author, Year: _____ Reference #_____

Abstractor Initials: ___ ___ ___

Primary Inclusion/Exclusion Criteria			
1. Original research (exclude editorials, commentaries, reviews, etc)	Yes	No	Cannot Determine
2. Study published in English	Yes	No	Cannot Determine
3. Human study population	Yes	No	Cannot Determine
4. Eligible study size (N ≥ 2)	Yes	No	Cannot Determine
5. Related to one or more of the following:	Yes	No	Cannot Determine

a. ___Sacrococcygeal teratoma
b. ___Congenital diaphragmatic hernia
c. ___Congenital cystic adenomatoid malformation
d. ___Bronchopulmonary sequestration
e. ___Obstructive uropathy
f. ___Myelomeningocele
g. ___Twin-twin transfusion syndrome
h. ___Cardiac malformations
i. ___Hydrocephalus
j. ___Ovarian cysts
k. ___Amniotic band
l. ___Maternal outcomes of maternal-fetal surgery
m. ___Anesthesia care for maternal-fetal surgery
n. ___Intraoperative maternal and fetal monitoring for maternal-fetal surgery
o. ___Other_____

Retain for:

_____BACKGROUND/DISCUSSION
_____REVIEW OF REFERENCES
_____ETHICS
_____Other_____

COMMENTS:

Technical Brief on Maternal-Fetal Surgery
Full-Text Review Form

First Author, Year: _____ Reference #_____

Abstractor Initials: ___ ___ ___

Primary Inclusion/Exclusion Criteria			
1. Original research (exclude editorials, commentaries, reviews, etc)	Yes	No	Cannot Determine
2. Study published in English	Yes	No	Cannot Determine
3. Human study population	Yes	No	Cannot Determine
4. Eligible study size (N ≥ 2)	Yes	No	Cannot Determine
5. Related to one or more of the following (select all that apply):	Yes	No	Cannot Determine

a. ___Sacrococcygeal teratoma
b. ___Congenital diaphragmatic hernia
c. ___Congenital cystic adenomatoid malformation
d. ___Bronchopulmonary sequestration
e. ___Obstructive uropathy
f. ___Myelomeningocele
g. ___Twin-twin transfusion syndrome
h. ___Cardiac malformations
i. ___Hydrocephalus
j. ___Ovarian cysts
k. ___Amniotic band
l. ___Maternal outcomes of maternal-fetal surgery
m. ___Anesthesia care for maternal-fetal surgery
n. ___Intraoperative maternal and fetal monitoring for maternal-fetal surgery
o. ___Other_____

Does it provide any of the following data?

____ Operational definition of fetal diagnoses
____ Type of surgery_____
____ Maternal inclusion criteria
____ Training of providers/specialized expertise and equipment in the study hospital(s)
____ Study country_____
____ Study size (N= _____)
____ Study setting
____ Study design
a. ___RCT
b. ___Cohorts with comparison
c. ___Case-control
d. ___Case series
e. ___Case report
f. ___Literature review of case reports
____ Comparator used _____
____ Length of follow up _____
____ Outcomes measured for fetus
____ Outcomes measured for mother
____ Adverse events/harms/safety issues reported for fetus
____ Adverse events/harms/safety issues reported for mother

Retain for:

_____BACKGROUND/DISCUSSION
_____REVIEW OF REFERENCES
_____ETHICS
_____Other_____

COMMENTS:

Appendix C. Excluded Studies

Full-text Article Exclusion Criteria Codes for Database
X-1: Not original research
X-3: Non-human study population
X-5: Ineligible study size (N <2)
X-6: Not related to selected conditions and/or not related to fetal surgery for selected conditions
X-7: Unable to obtain full-text
X-8: Case series of twin-twin transfusion syndrome

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Appendix D. Ongoing Research

Study Name & Country	Outcomes	Maternal Criteria	Fetal Criteria
• **RCT of Fetoscopic Endoluminal Tracheal Occlusion with a Balloon vs Expectant Mgmt during Pregnancy in Fetuses with Left-sided CDH and Moderate Pulmonary Hypoplasia** • **Belgium**	Primary: Occurrence of broncho-pulmonary dysplasia at 28 days of life Secondary: • Survival at discharge, • Survival free of bronchopulmonary dysplasia at 28 days of life	• Patients aged 18 years or more, and are able to consent ; • Singleton pregnancy • Accepting of randomization or to comply with return to FETO center Exclusion: • Maternal contraindication to fetoscopic surgery or severe medical condition in pregnancy; • Technical limitations precluding fetoscopic surgery, such as severe maternal obesity, uterine fibroids or potentially others, not anticipated at the time of writing this protocol; • Preterm labour, cervix shortened (<15 mm at randomization) or uterine anomaly strongly predisposing to preterm • Diaphragmatic hernia	• Anatomically and chromosomally normal fetus; • Left sided diaphragmatic hernia; • Gestation at 32 wks plus 5 d ; • O/E LHR 25-34.9% ; • O/E LHR 35-44.9% (included) with intrathoracic liver herniation as determined by ultrasound or MRI

• **Management of Myelomeningo-cele Study (MOMS)** • **US**	Primary: • Infant death, • need for ventricular shunt by 1 year of life, • Bayley Scales of Infant Development MDI and functional-anatomical level of lesion at 30 months of age Secondary: • Chiari II malformation, • Neurodevelopmental status at 30 months • Ambulation status 30 months,neuro-muscular defects 30 months • Maternal psychological and reproductive functioning 30 months post-partum	Inclusion: • US resident • able to travel to study site for study • Singleton pregnancy Exclusion: • Insulin-dependent pregestational diabetes • Short or incompetent cervix or cervical cerclage, • Placenta previa, • BMI of 35 or more, • previous spontaneous delivery prior to 37 weeks, • HIV+ • Hepatitis B+ • Hepatitis C+ • Uterine anomaly	Inclusion: • Myelomeningocele lesion that starts no higher than T1 and no lower than S1 with hindbrain herniation present • Gestational age at randomization of 19 weeks 0 days to 25 weeks 6 days • Normal karyotype
• **Effect of Fetal Ovarian Cyst Aspiration to Prevent Torsion** • **France**	Primary: • To avoid neonatal surgery Secondary: • U/S pattern of neonatal ovarian cyst • maternal and fetal/neonatal safety of prenatal ovarian cyst aspiration	• Age 18-40 with singleton gestation	• Anechoic ovarian cyst (diameter at least 30mm)

• **Selective Fetoscopic Laser Photo-coagulation versus Amnioreduction Clincial Trial** • **US**	Primary: • Survival of donor twin at 30 days after birth and no treatment failure • Survival of recipient twin at 30 days after birth and no treatment failure Secondary: • Survival times of each twin in utero or after birth • Gestational age at delivery • Placental insufficiency • Cardiac outcome: echocardiographic evidence of cardiac compromise • Neurologic outcome: evidence of brain injury preceding birth by MRI • Postnatal comorbidity	Inclusion: • 16+ years • Diagnosis of TTTS prior to 22wks • Randomized at 24 wks • Both twins are alive • Mono-di twin pregnancy Exclusion: • Contraindication to general surgery • General anesthesia • Uterine anomaly • History of preterm labor • Sonographic evidence of fetal CNS injury at time of entry • Associated structural abnormalities	• Same sex with a thin intertwin membrane • Oligo in the donor twin (deepest vertical pocket of </= 2 cm) • Decompressed bladder in donor twin not seen to fill during US exam (state II, III, or IV) unless Doppler velocimetry changes and/or echo changes are already present • Polyhydramnios with deepest vertical pocket of >8 cm with or without Doppler or echocardiographic changes in the recipient twin (deepest vertical pocket of >6 if previous AR)
• **Percutaneous Endoscopic Tracheal Plug/Unplug for CDH** • **US**	Primary: • Neonatal survival at 90 days of life Secondary: • Fetal lung growth due to successful fetal tracheal occlusion/unocclusion as determined by serial LHR measurements btw 26 and 34 wks gestation	Inclusion: • 18+ • Meets psychosocial criteria • Pre-authorization from third-party pay or for fetal intervention or ability to self-pay Exclusion: • Preterm labor • Pre-eclampsia • Uterine anomaly • Unable/unwilling to stay in Providence, RI or San Francisco until removal of plug at 34 weeks	• Normal fetal echocardiogram • Normal karyotype • Fetal liver herniated into left hemithorax • LHR 1.0 or less as calculated btw 24-26 week's gestation • Fetus is btw 26 and 28 weeks' gestation • Singleton pregnancy

• **Selective IUGR with absent end-diastolic velocity in the umbilical artery in mono-di twin pregnancies: RCT of expectant mgmt versus laser therapy** • **US**		Exclusion: • Not able to make financial arrangements • Unwilling to be randomized • Unable/unwilling to be followed up	Inclusion: • IUGR defined as sonographic estimated fetal weight at or below the 10th percentile for gestational age • Single placenta • Thin dividing membrane • same gender • Absent twin-peak sign • Gestational age of 16-24 weeks • Absent or reverse-end diastolic flow in the umbilical artery in the IUGR twin • Absent or reverse-end diastolic flow in the umbilical artery in the IUGR twin Exclusion: • Not able to make financial arrangements • Unwilling to be randomized • Unable/unwilling to be followed up • TTTS • Major congenital anomalies • Unbalanced chromosomal complement • Ruptured or detached membranes • Placental abruption • Chorioamnionitis • Triplets • Active labor • Placenta previa
• **Effectiveness of Fetal Endotracheal Occlusion (FETO) in the Management of Severe Congenital Diaphragmatic Hernia** • **US**	• Neonatal survival rate after 90 days	Inclusion: • Age 16-45 years • Healthy enough to have surgery • Must fully understand and accept the maternal and fetal risks involved • Pre-authorization from third-party payor for fetal intervention, or ability to self-pay. Exclusion: • Contraindication to abdominal surgery or general anesthesia • Allergy to latex • Preterm labor, preeclampsia, or uterine anomaly (e.g., large fibroid tumor) • Family unable or refuse to stay in Denver for the duration of the tracheal occlusion period and for the duration of the pregnancy as medically necessary.	Inclusion: • Confirmed diagnosis of CDH • Normal fetal echocardiogram • Normal karyotype • Fetal liver herniated into the left hemithorax • Lung-head ratio (LHR) is 1.0 or less, calculated between 24-26 weeks gestation • Fetus is between 26 and 28 weeks gestation • Singleton pregnancy Exclusion: • Failure to meet all inclusion criteria • Other congenital anomalies detected on ultrasound

• **Randomized Clinical Trial in Order to Assess the Effect of Fetoscopic Tracheal Balloon Occlusion on the Postnatal Disease Course in Neonates With Left Congenital Diaphragmatic Hernia** • **Germany**	Primary: • Need for postnatal ECMO therapy in first 2 days of life Secondary: • Survival to discharge • Maternal morbidity • Fetal / Neonatal morbidity • Premature preterm rupture of membranes • Unintended preterm delivery • Days in intensive care • Days in hospital • Oxygen dependency on discharge	Inclusion: • Age 18-50 • Resident of European country carrying fetus with left diaphragmatic hernia Exclusion: • Any maternal disease or condition that would result in an increased risk to her health from the experimental procedure	Inclusion: • Normal karyotype, no further severe anomalies on prenatal ultrasound study • Fetal liver herniation into the chest; gestational age-related lung volume between 20-25% of normal as determined by magnetic resonance imaging between 30+0 - 34+0 weeks+days of gestation Exclusion: • Abnormal fetal karyotype, further severe fetal anomalies on prenatal ultrasound

Additional Studies

Study title & location:	Study Description:	Project Start:	Project End:
• **Mechanism of Vasopressin-Mediated Placental Vascular Resistance after Fetal Bypass** • **US**	**Investigation of vasopressin and cardiac fetal surgery; selective V1 vasopress**in receptor antagonism prevents increased placental vascular resistance and improves fetal gas exchange with fetal cardiac surgery and bypass	1-Apr-2009	31-Mar-2011

Appendix E. Peer Reviewers

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Appendix F. Maternal-Fetal Surgical Procedures: Background and Context

Overview

The purpose of the Maternal-Fetal Surgical Procedures report is to describe the current state of research and practice of maternal-fetal surgical procedures; the report does not offer guidance on whether or when such procedures are appropriate. Congenital abnormalities that can be repaired prenatally occur in a small percentage of full-term births, and because of advances in imaging techniques such as ultrasound, many more congenital abnormalities are being diagnosed in utero. As these abnormalities are more frequently recognized prior to delivery, maternal-fetal surgical procedures have emerged as a potential option for treating some of these defects. Substantial questions remain about both the safety and efficacy of fetal surgical corrections. In some cases, the natural history of the conditions is poorly understood, making comparisons to no treatment or postnatal intervention difficult.

In addition, comparisons of fetal versus postnatal surgery must consider the safety of the mother, yet limited comparative data exist. The issue is particularly complicated because while congenital defects are relatively common in aggregate, individual congenital abnormalities occur infrequently, making effective study very difficult. Ongoing trials are evaluating some of the most common fetal surgeries (Appendix D).

Therefore, there is substantial uncertainty about maternal-fetal surgical procedures for patients and their physicians in choosing a course of treatment as well as for stakeholders making coverage decisions. In order to reduce this uncertainty, it is helpful to describe the full scope of comparative outcome evidence for in utero precedures and conventional postnatal (neonatal) interventions. It is of particular importance to weigh benefits against harms of interventions because harms associated with fetal surgery vary with the level of invasiveness and pose risks to the health of the fetus and mother. Risks may include bleeding, infection, preterm labor, complications associated with anesthesia medications, prolonged hospitalization, and threatened maternal reproductive future. The overriding concern in any fetal operation must be maternal and fetal safety. Secondary goals include avoiding preterm labor and accomplishing the goals of the procedure for the fetus.

Maternal-fetal surgical procedures began with transfusions for hemolytic diseases in the 1960s,[1] but the field accelerated in the 1980s with advances in ultrasonography that allowed visualization of the fetus for surgical intervention–as well as earlier diagnosis of abnormalities.[2] In a 40-year time span, fetal procedures have moved from transfusion-focused work to open surgical repair of conditions such as obstructive uropathy, and is increasingly being done with minimally invasive approaches.[3] Although postnatal intervention is best for most fetal abnormalities (particularly in light of risks associated with in utero surgeries), for a few conditions, the fetus's condition can deteriorate so rapidly in the womb as to make early intervention necessary to avoid either death or substantially higher morbidity after birth.

Open surgery on the fetus was first done in 1981 for obstructive uropathy by Dr. Michael Harrison at the University of California, San Francisco (UCSF),[2,4] and endoscopic approaches have since evolved from largely diagnostic procedures to therapeutic modality over the last 30 years. Soon after the first open procedures, the International Fetal Medicine and Surgery Society (IFMSS) was founded to carefully support growth of the field through the sharing of data, a

registry of cases, and evolving principles for when fetal surgery should be considered. The IFMSS emphasized the need for research transparency through publishing in the peer-reviewed literature. In addition, this group established a set of principles recommended to guide fetal interventions:[5]

- The disorder should be significant
- The natural history (and postrepair development) should be known
- There is inadequate postnatal therapy
- Maternal risks are minor and acceptable
- An animal model exists for defect and procedure
- The defect is an isolated one for which there is a complete and accurate diagnosis
- There is superb parental counseling
- A multidisciplinary team is in agreement regarding the treatment plan
- Patients have access to high-level medical, bioethical, and psychosocial care

The field of maternal-fetal surgery has evolved tremendously. Some approaches are still in the experimental stage, while others have substantially more research or are being increasingly accepted as standard practice. The time is right to assess the status of surgical intervention on the fetus for those conditions most commonly treated in this way. Therefore, the goal of the brief is to describe the current state of literature and practice of maternal-fetal surgical procedures for several congenital abnormalities ranked of high importance by stakeholders:

- Sacrococcygeal teratoma
- Congenital diaphragmatic hernia
- Thoracic lesions: congenital cystic adenomatoid malformation and bronchopulmonary sequestration
- Obstructive uropathy
- Myelomeningocele
- Twin-twin transfusion syndrome
- Cardiac malformations

Key Questions Addressed in This Appendix

The key questions for this brief that are addressed in this appendix were as follows:

Key Question 1.

a. What fetal diagnoses are currently treatable with a maternal-fetal surgical procedure? For each fetal diagnosis that is potentially treatable with a maternal-fetal surgical procedure, what is the annual number of fetuses that could potentially benefit from the procedure?
b. What maternal-fetal surgical procedures are done in the United States? What is an estimate of the number of hospitals that perform each procedure and utilization of each procedure?
c. For each fetal diagnosis, which procedures or techniques are used?
d. For each maternal-fetal surgical procedure, what anesthesia is used? What are the potential harms to the fetus and mother from the anesthesia?
e. For each fetal diagnosis, what are the alternatives? For each fetal diagnosis, what are the theoretical advantages and disadvantages (including potential safety issues and harms to

both the mother and fetus) of maternal-fetal surgical procedures relative to the alternatives?

f. What training programs exist for maternal-fetal surgical procedures? What special requirements are needed in hospitals that perform fetal surgical procedures?

In addition, a systematic scan of the research literature is presented in the full report.

Overview of Methods

Search for Current Practice and Research Data

We searched the Internet extensively to identify locations in the United States offering maternal-fetal surgical procedures and verified identified sites with our key informants. Three primary Web sites contributed the bulk of the information: www.naftnet.orgwww.naftnet.org; www.fetalhope.orgwww.fetalhope.org; and www.tttsfoundation.orgwww.tttsfoundation.org. In addition, we searched Lexis Nexis and Proquest for lay articles on maternal-fetal surgical procedures that might point to locations from which we could gather additional practice information (final search 2/6/09). For these searches, we used the terms "fetal surgery" and "in utero surgery" as well as searched individually for each of the conditions being examined in this brief. For information on insurers' practices, we selected a set of insurers and used the Internet to search for their online coverage policies. Once identified, they were catalogued in a database and printed out for filing with the date of access. To identify current research, we searched Clinicaltrials.gov (clinicaltrials.gov) and the National Institutes of Health Reporter databases (http://projectreporter.nih.gov), and we worked with experts to identify any additional research we might have missed.

Expert Discussions

We consulted with experts selected because of their expertise in the following areas: expertise in each of the conditions of interest, those who could offer historical perspective on maternal-fetal surgical procedures, and individuals who had a particular subspecialty expertise, such as ethics. These three expert panels included 17 individuals, with whom we held conversations via phone lasting from 20 to 45 minutes. The conversations were unstructured and intended to elicit context and background related in particular to current practice of maternal-fetal surgery.

Results Regarding Current Practices

Our description of the current practice of maternal-fetal surgical procedures is limited to the United States and is derived from a combination of approaches, including internet sources and key informant discussions.

Geographic distribution and structure of maternal-fetal centers. There is no system of accreditation or certification that would make identifying all practitioners of maternal-fetal surgical procedures straightforward. As with all emerging technologies, there is a tendency for excitement generated around their potential to precipitate their adoption into practice, sometimes in the absence of strong, comparative research, but with the hope of helping infants with poor prognoses. Certain surgical procedures are farther along in their evolution and therefore are

relatively more common than others, in particular, use of shunts for obstructive uropathy (OU) and laser ablation for twin-twin transfusion syndrome (TTTS).

We attempted to identify as many locations currently providing the maternal-fetal surgeries as possible in this brief (Table 1); however, that number and those locations are a rapidly evolving group, and therefore, these data may quickly become out of date. A starting point for identifying centers providing maternal-fetal therapy is the North American Fetal Therapy Network (NAFTnet) (www.naftnet.org). This network is a voluntary association of centers in the United States and Canada that perform advanced in utero techniques (including surgical ones). A similar network exists in Europe and is called Eurofoetus. These centers have agreed to work cooperatively to advance the practice of in utero therapies, including sharing data and providing educational resources for patients. A number of the centers conducting the highest volume of in utero surgical procedures are members of NAFTnet, with some notable exceptions. For example, the USFetus group performs a number of laparoscopic procedures in utero. In addition, we searched the internet and queried experts about who they knew to be using these surgical approaches. Through a combination of methods, we snowballed the list in Table 1. Of note, our goal was to identify centers that provide services to patients beyond experimental attempts and that therefore would be clinically available to U.S. patients. It should be noted that several key informants indicated concern that interventions for TTTS with laser, and for OU with shunting were proliferating perhaps too rapidly without oversight. However, we were unable to identify many sites claiming to offer in utero treatment for OU.

Table 1. Clinical centers offering maternal-fetal surgical procedures by condition and NAFTnet affiliation

Clinical affiliation	Affiliated hospital	NAFTnet Affiliate	Sacrococcygeal teratoma	Congenital diaphragmatic hernia (CDH)	Thoracic lesions	Obstructive uropathy	Myelomeningocele (spina bifida)	Twin-twin transfusion syndrome (TTTS)	Cardiac malformations
Baltimore, MD University of MD Center for Advanced Fetal Care	University of Maryland Medical Center/University Hospital	√						√	
Boston, MA Brigham and Women's Hospital/ Children's Hospital Advanced Fetal Care	Massachusetts General Hospital/Children's Hospital Boston	√	√	√	√	√		√	√
Chapel Hill, NC UNC Maternal Fetal Medicine	Rex Hospital	√						√	
Cincinnati, OH Fetal Care Center of Cincinnati	Cincinnati Children's Hospital/Good Samaritan Hospital/ University Hospital	√	√	√	√	√		√	
Columbus, OH Ohio State University	Ohio State University Medical Center/Nationwide Children's Hospital	√				√		√	
Dallas, TX Southwestern Medical Center	UT Southwestern University Hospital/Parkland Memorial Hospital	√			√	√			
Detroit, MI* Wayne State University	Hutzel Women's Hospital	√							
Houston, TX Baylor: Texas Children's Fetal Center	Texas Children's Hospital/St. Luke's Episcopal Hospital	√	√	√	√	√		√	
Los Angeles, CA Institute for Maternal Fetal Health, University of Southern California	Hollywood Presbyterian Medical Center/ Children's Hospital Los Angeles		√	√	√	√		√	√
Milwaukee, WI International Institute for Treatment of TTTS	Wheaton-Franciscan Healthcare/St. Joseph Regional Medical Center							√	
Miami,FL University of Miami	Jackson Memorial Hospital		√	√	√	√		√	√
Minneapolis, MN Minnesota Perinatal Physicians	Abbott Northwestern Hospital							√	

Table 1. Clinical centers offering maternal-fetal surgical procedures by condition and NAFTnet affiliation (continued)

Clinical affiliation	Affiliated hospital	NAFTnet Affiliate	Sacrococcygeal teratoma	Congenital diaphragmatic hernia (CDH)	Thoracic lesions	Obstructive uropathy	Myelomeningocele (spina bifida)	Twin-twin transfusion syndrome (TTTS)	Cardiac malformations
Nashville, TN Junior League Center for Advanced Maternal-Fetal Care	Monroe Carell Jr. Children's Hospital/Vanderbilt University Medical Center	√			√	√			
New Haven, CT* Yale University Medical Center	Yale-New Haven Hospital	√							
New York, NY Columbia University Medical Center	New York Presbyterian Hospital/Sloane Hospital for Women	√				√			
Philadelphia, PA The Center for Fetal Diagnosis and Treatment	The Children's Hospital of Philadelphia	√	√	√	√	√	√	√	
Phoenix, AZ Phoenix Perinatal Associates	Arrowhead Hospital/Phoenix Children's Hospital	√						√	
Pittsburgh, PA* Magee-Women's Hospital of the University of Pittsburgh Medical Center	University of Pittsburgh Medical Center	√							
Providence, RI The Brown Fetal Treatment Program	Hasbro Children's Hospital/Women and Infants' Hospital of Rhode Island	√		√	√	√		√	
Salt Lake City, UT Maternal-Fetal Services of Utah	St. Mark's Hospital					√		√	
San Diego, CA UCSD Fetal Surgery Program	UCSD Medical Center							√	

Table 1. Clinical centers offering maternal-fetal surgical procedures by condition and NAFTnet affiliation (continued)

Clinical affiliation	Affiliated hospital	NAFTnet Affiliate	Sacrococcygeal teratoma	Congenital diaphragmatic hernia (CDH)	Thoracic lesions	Obstructive uropathy	Myelomeningocele (spina bifida)	Twin-twin transfusion syndrome (TTTS)	Cardiac malformations
San Francisco, CA UCSF Fetal Treatment Center	UCSF Children's Hospital	√	√	√	√	√	√	√	
Seattle, WA Evergreen Healthcare	Evergreen Hospital/Eastside Maternal Fetal Medicine at Overlake Hospital Medical Center	√			√	√		√	

*information on procedures offered not publicly available

Models of care. Although a range of modes of care exist, inevitably, maternal-fetal procedures require a team of physicians and staff who are knowledgeable and experienced at working together. Programs may be led primarily either by pediatric surgeons or by obstetricians or may be a collaborative effort between the two specialties in which the obstetrician gains access to the uterus and/or fetus and the pediatric surgeon does the repair. Table 2 presents examples of selected models of care currently in practice; this taxonomy is adapted from Harrison.[6] These examples are not exclusive or prescriptive; they are simply examples.

Table 2. Selected models of maternal-fetal surgical centers

Model	Description
Academic multidisciplinary	Academic multidisciplinary model with a large team reflecting expertise in perinatology, neonatology, pediatric surgical subspecialties, genetics, prenatal diagnosis, and anesthesia. Developed by pediatric surgeons and includes active participation of a large multidisciplinary conference and strong collaboration with basic sciences and animal research. Provides treatment for a range of conditions and may be led by a pediatric surgeon or maternal fetal medicine (MFM) specialist or both.
Export	Centralized care that travels to the patient; 2 physicians travel with fetoscopic equipment to other network hospitals to perform surgeries; may also train physicians and staff in those centers. In a system as large as Hospital Corporation of America (HCA), the need for availability of services, particularly for the more common conditions such as TTTS, is likely to increase. Rather than having many trained physicians at HCA hospitals, HCA opted to have a surgical team in one location that would go to the hospital where the patient was rather than having the patient come to them. Therefore, they export the program to other sites as needed. In addition, they have offered to participate in the establishment of centers at academic sites in several locations.
Perinatologist-led	MFM specialist alone or with other surgeons as needed (e.g., MFM specialist alone for laser ablation or with a neurosurgeon for myelomeningocele repair). Sometimes uses a "handoff" model where the obstetrician (OB) accesses the uterus, a different surgeon does the repair, and then the OB closes as per usual in cesarean section. In one example, the team includes 1 senior and 1 junior MFM specialist, and 1 senior and 1 junior pediatric surgeon. At least one of the senior physicians must be at each procedure.
Super specialist	An individual or group focuses on developing expertise in treating one condition in particular, or in using one approach. This can serve to centralize expertise.

Fetal surgery centers often also include the role of a "fetal board" or other conference that comprises a multidisciplinary group of individuals who meet regularly to discuss potential cases and review past cases. This approach has been described in the literature[6-8] and can be helpful in protecting the surgical team, who may have perceived gain (e.g., opportunity for an exciting procedure, increase in knowledge and scientific discovery, prestige from developing new techniques) from being perceived as the sole decisionmaker or source of information about the procedure's appropriateness. It is also an important opportunity to share experiences and to put in place mechanisms for tracking outcomes and processes both prospectively and retrospectively. This multidisciplinary approach has been evaluated[8] and supported as an appropriate model.[3]

Training to conduct maternal-fetal surgical procedures. No licensing or accreditation group oversees maternal-fetal surgical procedures and credentialing. Indeed, it is difficult to determine what governing group would oversee the training of a subspecialty that includes individuals from diverse medical specialties. Given the learning curve associated with any of these surgical approaches, several experts expressed concern over the practice of traveling to Europe to attend a number of cases over what may be a short period of time (up to several weeks) as the extent of training.[9] Absent traveling to Europe, there are two primary models of training in the United States: (1) in-house training in which experienced physicians invite other physicians to learn from them and (2) exported training in which experienced groups travel to other centers to train physicians and staff in their own environment and help them to establish the capacity for maternal-fetal surgical procedures.

The first approach (in-house) can either be established as a formal fellowship or as an "apprenticeship" that may serve as a precursor to having an individual physician join a given team. For example, as the site of the earliest open fetal surgeries, University of California San

Francisco (UCSF) has provided training for a number of physicians who have gone on to develop programs at other sites (e.g., Children's Hospital of Philadelphia, Fetal Care Center of Cincinnati). Physicians at several sites reiterated their openness to having fellow physicians join them to learn surgical procedure.

Three sites currently offer a fellowship: CHOP, Baylor College of Medicine–Texas Children's Fetal Center, and the Fetal Care Center of Cincinnati. To date, the fellowship at CHOP has produced three "certified fellows." Cincinnati has had three fellows since 2006, and faculty at Baylor are training their first fellow. Therefore, opportunities to obtain formal fellowship training are exceedingly rare, and the potential need for expanding opportunities has now been raised in the literature.[9] At both existing fellowships, significant emphasis is placed on the need to observe and understand cases, the selection of appropriate cases for intervention, and the counseling process for families. At CHOP, successful fellows are prepared to do laser ablation for TTTS or place shunts for OU; neither fellowship purports to produce "graduates" immediately prepared to conduct open fetal surgical procedures. CHOP is also home to the only NICHD-funded training grant (T32) in fetal biology and therapy, which provides strong integration of the clinical practice with research.

In the second model, established centers train physicians at other sites and/or help them to establish their program. Training may take place at the original center's site or at the learning center's site. For example, Cincinnati Children's Hospital has agreements in place to offer training in laser coagulation at four sites to selected maternal-fetal specialists with extensive experience in prenatal diagnosis and treatment. These specialists have not yet had the opportunity to learn fetoscopic techniques and invest up to 2 years in training before taking on their own cases. The agreements include an understanding that individuals at the extant sites will come to Cincinnati for training, then faculty from Cincinnati will go to the extant sites to supervise, and finally, that early in their practice, the extant sites will only attempt the procedure on the simpler case in which the placenta is posterior.

A third training model has been proposed in which telemedicine could be used to train and supervise laser coagulation, even internationally,[10-11] but issues of insurance liability and other logistics continue to be clarified. Finally, both informants and the literature stress the importance of integrating animal research with practice, both for training and practice purposes. In addition to furthering knowledge and techniques in the field, animal research is a practical way to develop and maintain surgical skills, particularly in the case of low-volume conditions. Some maternal-fetal medicine sites, particularly at academic centers, have ongoing animal research integrated into their programs, and some use these facilities for surgical training. A number of the papers reviewed in the literature review also described development and practice of techniques in the animal lab, with an eye toward describing the numbers of cases necessary to achieve proficiency before moving to human study and practice.[12-14]

Access to clinical care and research. A particular issue garnering discussion is the question of whether maternal-fetal procedures should be regionalized in "centers of excellence."[9] Evidence is strong that surgical skill improves with volume; for example, estimates of the number of cases needed to achieve proficiency in laser coagulation in TTTS range from 50[10] to 75,[15] with 20[15] per year suggested to maintain proficiency. Even with the most common conditions that are treatable in utero, the number of cases per year is likely to be low across the United States. Therefore, those cases centralized with surgical teams who would be most practiced, could theoretically

provide the best care.[9] The two most common of the candidate conditions for in utero repair (TTTS and myelomeningocele) present interesting examples.

In the case of myelomeningocele, prenatal treatment is limited to the Management of Myelomeningocele (MOMS) trial, currently being conducted at three sites (UCSF, CHOP, and Vanderbilt Medical Center). Even with a national agreement not to provide surgical repair outside of the trial, obtaining adequate numbers has been challenging, suggesting that if the treatment were available in more sites, adequate numbers to develop or maintain proficiency would be very difficult to achieve. Enrollment in the trial may have been affected by a drop in the number of U.S. cases, potentially resulting from the introduction of folate supplementation as well as the limited number of centers participating in the study, which may make patients reluctant to participate given that patients randomized to in utero treatment are required to stay at the fetal center for the duration of their pregnancy (potentially 2-3 months).

In the case of TTTS, several experts expressed concern that in utero treatment, specifically laser ablation, was proliferating too rapidly and with little oversight related either to training or practice—a particular concern in light of the learning curve described above. However, empirical evidence to this effect does not exist, so this idea is opinion only. Concerns about the rapidly expanding volume rest on expert opinion and analogies to other surgical fields.

There seems to be some support for regionalization of care, but we did not identify specific suggestions as to how the regional centers might be designated beyond the selection by insurers of centers of excellence where they might require that their insured population seek care. The number of centers necessary depends by condition on the prevalence of cases that are appropriate for intervention and should be determined with consideration of the number of cases needed to develop and maintain surgical proficiency, or other considerations including neonatal intensive care unit (NICU) level and other resource availability. These are metrics that are only beginning to be addressed in the literature, and only for the more common conditions. Conversely, regionalization of care could inhibit access for patients unable to travel, either for medical, financial, or logistical reasons. It should be noted that traveling to obtain in utero therapy most often includes a necessary hotel stay as surgeons prefer that patients remain close by for some period after surgery, even up to delivery. The export model described above is an attempt to mitigate these issues and increase access while keeping services within one system.

The question of distribution of and access to maternal-fetal surgical procedures is integrally connected to payment systems, specifically whether a given technique is in the realm of nonfunded early innovation, funded research, or reimbursed medical care. Early innovation most often takes place in academic medical centers as one time attempts to intervene in a grim clinical prognosis—enthusiasm spreads as surgeons share their experience before a study is necessarily developed. Academic centers may have the means to support innovation; however, for a medical practice to become available to many people, research must be strong enough to demonstrate benefit. An example is that of open surgery to repair myelomeningocele, which was gaining popularity before adequate research was conducted when concerns were raised about high rates of morbidity. The National Institutes of Health is sponsoring a randomized controlled trial (RCT), and all U.S. centers have agreed to a moratorium in the U.S. as part of which the surgery is only offered in the context of the trial.

It is likely that a system of outcomes reporting is necessary in this field, both from the perspective of being able to identify centers providing excellent care, and for transparency about the learning curve in doing this type of procedure. Who might develop such a system or manage it was less clear, but one strong message was that whoever did so would by necessity come from

a multidisciplinary perspective, given the range of disciplines working in this field. In other words, it will not work for a professional organization specifically representing obstetricians or pediatric surgeons to lead development of a reporting structure; conversely, a starting point may be an affiliation such as NAFTnet or the International Fetal Medicine and Surgery Society (IFMSS).

Nonetheless, the most comprehensive way to identify access to care at this point is to understand what care is available clinically and what is available to patients as research protocols. It is impossible to catalog the current level of innovative practice occurring in its pre-research stage. Therefore, currently funded trials are described in Appendix D. Interestingly, in some of the research reviewed, the ability to pay or be covered by insurance was an explicit inclusion criteria. The potential costs associated with a pregnant woman's care following in utero procedures are extremely high and unpredictable. A tension exists between the need to continue to expand research and study of these procedures and the availability of research funding, particularly since research funding would be unlikely to cover unlimited or unanticipated medical costs associated with the procedure or recovery.

Ongoing research studies may also offer an opportunity for patients to access maternal-fetal treatment. Our key informants consistently stressed their concerns that all maternal-fetal surgical approaches should be evaluated in rigorous research, although they had differing opinions on what that might look like. Nonetheless, the field is characterized by a commitment to publishing in order to advance methodology and share new knowledge with colleagues. One concern that was raised both by key informants and in our literature search, however, is the dearth of information on harms reported in studies larger than single cases. In addition to the research listed in the table below, leaders in the field continue to innovate at their respective sites, including new device development and evaluation under FDA jurisdiction. Several key informants who discussed research efforts stressed the importance of clinical innovation taking place with the oversight of a data safety monitoring board, IRB and/or fetal or appropriate review board, even in the earliest stages. The ethical and consent issues associated with development of new surgical approaches and of spread of innovation were of significant interest to many of our key informants, who work hard to straddle a line of enthusiastic innovation and cautious realism about the potential for these interventions.

Ethics and Issues of Consent

Indeed, as soon as physicians began performing maternal-fetal operations in the early 1980s, ethicists started weighing in on the moral, legal, and social implications of prenatal interventions.[16-18] Maternal-fetal approaches raise moral issues at the intersections of abortion debates, disability rights, and self-determination claims. Fetal interventions can be framed as providing an alternative to abortion when prenatal diagnosis reveals that a fetus has congenital abnormalities that would lead to severe morbidity.[16,19] While in utero surgeries can prevent elective abortions of some fetuses, the ability to correct certain fetal conditions during pregnancy may consequently exacerbate negative views in society of developmental and physical disabilities because they can become viewed as problems that should have been fixed or prevented.[20-21] Moreover, the extent to which pregnant women have the right to refuse treatment that benefits their fetuses but exposes the women to risk has been called into question.[22-25]

Initially, in the 1980s the ethics literature focused predominantly on the ability of the legal system to force women to undergo fetal surgeries. While there were no reported cases of conflict that emerged from women refusing to consent to treatment, there was significant concern that

fetal approaches were ripe for litigation. Some commentators predicted the inevitability of compulsory surgery being issued from the courts,[26] and they proposed preemptive legislation to avoid the courts' involvement.[27] The pervasiveness of the ethical debate about the rights of women vis-à-vis the rights of the "not-yet-born child" was a product of the legal atmosphere of the 1980s.[28] Specifically, the courts had become involved in legitimizing physicians' control over the behavior of pregnant women as part of a broader movement to promote child welfare by diminishing parental authority.[29] Courts issued orders forcing pregnant women to undergo cesarean sections, to consume drugs, or submit to prenatal screening, and they prosecuted women for drug and alcohol use.[30-31]

In large measure, the effect of these legal and ethical debates was to frame pregnant women and their fetuses in conflict,[32] but there is no evidence that pregnant women understand their self-interest to be at odds with those of their fetuses.[33-34] The conflict is more likely to arise between clinicians and pregnant women.[35] This can be due to care providers' perceptions that a pregnant woman is not appropriately willing to sacrifice her own interests for those of an "unborn child."[36] More likely, however, conflict occurs when physicians advise terminating the pregnancy in cases of fetal disability, but pregnant women desire to continue the pregnancy in spite of a grim prenatal diagnosis.[37] Religious beliefs and values often play into these decisions to continue the pregnancy and prompt the decision to undergo in utero procedures.[38-40]

Discussions about the conflicting rights of pregnant women and fetuses have subsided to some extent since the mid-1990s. In part, this shift could be attributed to the recognition that maternal-fetal approaches did not have the outstanding benefits to fetuses that ethicists had anticipated.[41-42] Taking a more measured view of existing interventions, ethicists began discussing the need to more thoroughly evaluate the therapeutic potential of fetal surgical treatment through the development of registries and clinical studies.[43-44] A major thrust to this viewpoint was that defining fetal interventions as "innovation" instead of "research" created a system of insufficient oversight,[45] particularly because innovation can be harmful and should be designed to minimize adverse outcomes.[46] In addition to traditional ethicists' involvement in these issues, social scientists began to take an active role in describing and analyzing practices that were actually occurring in fetal surgery centers.[34,38,47-49] This approach to ethics has focused more attention on the informed consent process, including the social and cultural components to decisionmaking.[38]

The ethics debates about maternal-fetal surgical procedures draw attention to the differing risks of the procedures to pregnant women and fetuses. In addition to the medical risks to fetuses, pregnant women are exposed to the risks of anesthesia and surgery during the procedure, drugs to prevent premature labor and delivery after the procedure, and the emotional burden of consenting to medical interventions with uncertain outcomes.[34] This means that the benefits of these surgeries always have to be considered within the context of the risks to both the pregnant woman and the fetus.

The practical implications of this are that informed consent procedures need to clearly explain all of the risks and benefits of the procedures and that benefits must be optimized through appropriate oversight of fetal interventions. For example, some ethicists have called for interdisciplinary teams to cooperate in the consent process by educating the pregnant woman (and her family) about her options, including but not limited to fetal interventions.[6] In particular, some ethicists have stated that informed consent should be obtained only by a more neutral member of the care team rather than the surgeon.[38] Because not everyone seeking fetal treatment is an appropriate candidate, the informed consent process should educate self-referring

individuals so that their expectations about likely outcomes match current clinical realities. This view of consent underscores recent calls for more oversight of surgical innovations (both prospectively and retrospectively), more precise information about the benefits of fetal approaches in the context of the natural history of the diseases or disabilities being treated, and disclosure of information about the skill sets, experience, and success rates of medical teams performing each procedure. These measures would ensure that pregnant women (and their families) would have more robust information to use in their decisionmaking about fetal intervention.

Background Information on Conditions Included

Cardiac Malformations

Cardiac conditions for which in utero interventions are being performed are those in which there is a severe narrowing in one of the outflow tracts (aortic valve or pulmonary valve), causing progressive damage to the heart muscle in utero. There are three types of cardiac conditions for which in utero intervention is being performed: pulmonary atresia with intact ventricular septum (very narrow pulmonary valve without a connection between the right and left ventricles), critical aortic stenosis with impending hypoplastic left heart syndrome (very small, nonfunctional left ventricle, hypothesized by some investigators to be from underuse secondary to a severely narrow aortic valve), and hypoplastic left heart syndrome with intact atrial septum (no connection between the left and right atrium). All of these conditions, if untreated either in utero or soon after birth, are lethal.

Fetal surgery teams have proposed that in utero intervention can change the progression of the disease, allowing for more normal muscle to grow which can preserve function of both the ventricles in pulmonary atresia with intact ventricular septum and critical aortic stenosis with impending hypoplastic left heart syndrome (HLHS) and could obviate need for emergent atrial septostomy at birth for those patients with HLHS and intact atrial septum.

Critical pulmonary stenosis or atresia with intact ventricular septum. These anomalies portend a poor prognosis. A prospective prevalence study in Canada showed that overall survival was 77 percent at one month and 58 percent at 15 years. Only 33 percent ultimately end up with biventricular repair, 20 percent with Fontan repair, 20 percent with 1.5-ventricle repair, 5 percent with heart transplant, and 38 percent die before reaching definitive repair. Two percent of patients survived without definitive repair.[50] Fetal intervention to relieve the stenosis and allow for ventricular growth could theoretically increase the number of patients who ultimately end up with a biventricular repair. There is some debate as to whether this is an adequate measure of success since the right ventricle in a two-ventricle repair still has abnormal diastolic dysfunction and may not lead to increased exercise capacity.[51] However, these studies were performed in patients who had not undergone in utero repair. It is possible that if the stenosis is relieved early enough in gestation, there may be adequate time before delivery for growth of the right ventricle. In fetuses with impending hydrops, in utero valvuloplasty could reverse the condition and prevent hydrops and death.

Critical aortic stenosis. Severe aortic stenosis, which is a very narrow aortic valve that develops early during gestation, may result in hypoplastic left heart syndrome. If the stenosis develops in the first trimester, the left ventricle may be tiny by the time a morphological ultrasound is

performed at around 20 weeks. However, if the stenosis develops closer to 20 weeks, the left ventricle may be hypertrophied or hypoplastic, but still visible. In utero aortic balloon valvuloplasty has been suggested as a way to relieve aortic stenosis, thus preserving left ventricular growth and halting progression to hypoplastic left heart syndrome.

The first described attempt at in utero balloon aortic valvuloplasty was reported by Maxwell in London in 1991. The same group reported the first survivor in a case report in 1995.[52] Since then, there have been scattered attempts at this procedure around the world, but the most abundant work has been performed by the fetal surgery team at Children's Hospital Boston, Massachusetts.

Hypoplastic left heart syndrome and intact atrial septum. A subset of patients with hypoplastic left heart syndrome (HLHS) with an intact or highly restrictive atrial septum will present with severe cyanosis and require immediate postnatal intervention in order to survive. This accounts for approximately 5.7 percent to 11 percent of newborns with HLHS.[53-54] CDC estimates that each year about 975 babies in the United States are born with HLHS.[55-56] In other words, each year about 2 out of every 10,000 babies born will be born with HLHS. The approaches that have been used include an emergent stage I palliation, the Norwood procedure, which has a poor survival rate in this scenario (10–28 percent)[54,57-58] or a neonatal catheter atrial septostomy. In Vlahos's study, patients requiring an urgent neonatal catheter septostomy to decompress the left atrium have a 21 percent mortality before stage I palliation compared to no mortality before a Norwood in patients with an unrestrictive atrial septal defect.[59]

Given the high mortality of infants with HLHS and intact atrial septum, considered to be due to the pulmonary vasculopathy that develops before birth, in utero atrial septostomy has been performed in an attempt to improve postnatal survival. The first report of a balloon atrial septoplasty was in 2004. There is also a single case report using a laser to perform atrial septoplasty.[60] The balloon atrial septoplasty is performed percutaneously with access usually to the fetal right atrium after traversing the maternal abdominal wall, uterine wall, and fetal chest wall using an 18- or 19-gauge introducer cannula mounted on a metal obturator.[57] The introducer is advanced into the right atrium and the atrial septum is punctured by the tip of the introducer or with a 22-gauge Chiba needle. A wire is then introduced through the Chiba needle into the left atrium or a pulmonary vein and the needle is exchanged for a balloon angioplasty catheter. The balloon is fully inflated twice. In two cases teams approached the atrial septum from the left atrium. In two cases teams were unable to achieve technical success due to inability to reach the fetal left atrium.[54]

Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia (CDH) results from abnormal development of the diaphragm, which allows abdominal organs such as the bowel, the stomach, and the liver to protrude into the chest cavity. CDH is an important, relatively common congenital malformation, with incidence in the United States of approximately 1 in every 2,500 births.[61-62] Fetuses diagnosed in utero as a result of maternal symptoms have mortality risk approaching 75 percent in some older reviews. One of the paradoxes of diaphragmatic hernia care is a trend toward improved outcome of fetuses not diagnosed before birth. This may reflect the fact that less-severe lesions, without the findings of liver in the chest, stomach in the chest, or increased amniotic fluid volume are less likely to be detected by routine ultrasound. Like all fetal diagnoses, the ability to detect less-severe lesions has improved over time, as has our

understanding of fetal lung physiology and advances in ventilator and NICU care, and thus the mortality estimates for defects detected during pregnancy, is continually changing.

After developing techniques for fetal surgical procedures in animal models, the initial attempts to repair CDH in utero were done via open hysterotomy followed by thoracotomy and repair of the defect. This work was hampered by technical challenges, including the inability to prevent preterm birth after a prolonged open uterus surgery and inability of the fetus to tolerate the surgical procedure, which included major manipulation of the liver through which the blood flow from the placenta is delivered. When the procedure was done in fetuses without liver involvement, it was learned that the group who received care at birth had 86 percent survival,[63] making the risks of preterm birth from in utero repair less acceptable. Subsequently, new understanding of the pathophysiology of lung fluid and growth suggested that a less invasive approach could be successful. Occluding the trachea of a fetus results in buildup of lung secretions in the pulmonary tree, gradually distending the lungs as well as triggering complex changes in maturation, including DNA synthesis, epithelial and endothelial proliferation, increased phospholipid metabolism and surfactant synthesis. The growing lungs push the bowel and abdominal contents out of the chest cavity to an extent and promote improved lung growth. Less-invasive fetal surgeries have more recently focused on methods to accomplish tracheal occlusion.

Myelomeningocele/Spina Bifida

Myelomeningocele (MMC) is a congenital malformation in which the meninges and spinal cord protrude through a defect in the vertebral arches, muscle, and skin. It is the most commonly observed malformation of the central nervous system, affecting more than 1,000 fetuses in the United States annually.[64] MMC is the most common form of spina bifida, and although it is rarely fatal, individuals affected with it have a range of disabilities, including paraplegia, hydrocephalus, skeletal deformities, bowel and bladder incontinence and cognitive impairment. It is generally associated with Arnold Chiari malformation (CM), which is often associated with the observed hydrocephalus in these patients. The genesis of CM and its association with the MMC lesion is not entirely understood, but may be due to leaking cerebrospinal fluid.

The etiology of MMC is not entirely understood, although it likely has a genetic component and may be environmentally driven as well.[65] There is good evidence that folate reduces the incidence of neural tube defects, including this one, but does not inevitably prevent them. The standard treatment has been to close the defect postnatally, and shunting for hydrocephalus is common.

In the early 1990s, animal experiments suggested that the neurologic damage to the spinal cord might be partially due to the exposure of the uncovered neural elements to trauma and amniotic fluid during the pregnancy. This is known as the "two-hit hypothesis" in which the first insult is the defect itself, and the second is the toxic effect of amniotic fluid on the exposed meninges and spinal cord. The hypothesis was supported by the observation that fetal leg movement may be observed up to about 17 weeks' gestation in fetuses with MMC, but subsequently ceases. Animal research suggested that covering the defect early on could potentially result in better lower extremity and bladder function. Myelomeningocele repair was the first in utero surgery considered for a nonlethal malformation on the basis that its natural history was well known and leads to lifelong disability in the absence of intervention. Furthermore, the defect can be diagnosed prenatally in over 80 percent of cases by maternal

serum alpha-fetoprotein and ultrasound; MRI is used to detect specific anomalies and disease process.

The procedure was initially performed by Bruner and colleagues as a closed laparoscopic covering of the spinal defect, with the first case reported in a letter and in a series of four fetuses published in 1999 (the surgeries were conducted between 1994 and 1997).[66] Half of the fetuses survived, and both survivors required shunting. In a continuation of this work, four fetuses were operated on using an open approach and compared to four done endoscopically,[67] and the open surgery showed improved outcomes, while the endoscopic approach had high mortality. The endoscopic approach has been abandoned, and therefore the rest of this overview will focus on literature related to open surgery for MMC repair. Since 1997, more than 200 fetuses with MMC have undergone open surgical repair in the United States.

Obstructive Uropathy

A variety of fetal malformations can lead to distention of the urinary bladder; these include urethral atresia (failure of the bladder stem to properly form so urine cannot exit), posterior urethral valves (which in male fetuses can prevent flow of urine through the full length of the urethra); and megacystis-megaureter-microcolon syndrome (which results from malformation of the organs rather than frank blockage of urine flow), and Prune-belly syndrome (which includes lack of development of abdominal muscles, undescended testicles, and urinary anomalies). Other urinary tract anomalies can result in distension of one or both ureters, such as blockage at the junction with the bladder or at any place along the ureter, which conveys urine from the kidney to the bladder. In this case when there is renal function and a ureteral impass, the distended portion of the urinary tract is the ureter or renal pelvis rather than the bladder.

Goals of fetal therapy have emphasized decompression rather than repair of the specific lesion. The goal of decompression of the distended portion of the urinary tract is to protect remaining renal function and promote lung development. While it is simplistic to attribute these resulting changes to a simple mechanism such as pressure relief on the developing kidney or movement of a column of amniotic fluid up and down the lower respiratory tree, the relief of urinary tract pressure and the presence of amniotic fluid are correlated with improved renal and pulmonary function at birth in some infants. Placement of an indwelling shunt to decompress fetal urinary tract distension was first reported in 1982.[68] The care team placed a shunt from the bladder to the amniotic cavity by insertion under ultrasound guidance through the maternal skin with a puncture, but not open surgery. This first case by a percutaneous approach was performed at 30 weeks gestation.[68] In rapid succession, clinical investigators began to intervene earlier in pregnancy with treatment before 18 weeks reported in 1983.[69] Open procedures to correct the urinary tract anomaly, using techniques similar to those used after birth, have also been reported in the earlier literature. Challenges with increased preterm birth and comparable outcomes with the shunting procedures have resulted in a trend to percutaneous shunting procedures dominating the literature. After a small incision in the maternal skin, generally with local anesthesia only, the shunt is inserted through an introducer sheath into position within the fetal bladder. An internal guide or stylus within the shunt is withdrawn allowing a prefabricated curl or “pigtail” to form at the distal end that helps hold the device within the fetal bladder. As the introducer is completely withdrawn, a second pigtail forms on the opposite end to hold the shunt outside the fetus and to assure drainage of urine into the amniotic cavity. When the shunt type or method was noted by authors to vary from this, we have indicated the difference.

Sacrococcygeal Teratoma

Sacrococcygeal teratoma (SCT) is a relatively rare condition effecting approximately 1 in 40,000 fetuses or about 100 infants a year in the United States. As a result of ultrasound use, these tumors are increasingly recognized antenatally. The outcomes of prenatally diagnosed, uncomplicated survivors to term are generally good. However, those fetuses with large, vascular tumors have a high incidence of prenatal mortality from high-output cardiac failure or spontaneous hemorrhage into or rupture of the growing tumor. Among fetuses followed in series without hydrops, survival ranges from 32 percent[70] and 48 percent[71]among infants with high output cardiovascular changes or associated anomalies to 83 percent,[72] 92 percent,[73] and 100 percent in uncomplicated cases.[74-75] Fetal surgical procedures for SCT have focused on the small subgroup of fetuses with SCT and hydrops because untreated cases are expected to die in utero or at birth. All series report 100 percent mortality.[70-76] In severe cases, SCT with hydrops is associated with maternal risks. Mothers of fetuses with hydrops can develop mirror syndrome, which is a severe form of pre-eclampsia and can be associated with placentomegaly. Mirror syndrome is a maternal contraindication to fetal approaches since the mother is critically ill and delivery has been felt to be indicated for maternal health. Consequently, decisions to intervene need to be made when the fetus is documented to be critically ill while the mother is still in good health.

Thoracic Lesions

Congenital pulmonary airway malformations (CPAM), which include congenital cystic adenomatoid malformation (CCAM) and bronchopulmonary sequestration (BPS), are congenital anomalies of the lung that share the characteristic of a segment of lung being replaced by abnormally developing tissue. CCAMs can have connections to the pulmonary tree and contain air. The tissue is served by blood vessels in the pulmonary circulation.[77] BPS does not connect to the airway and has blood flow from branches off the aorta as well as the pulmonary circulation. Antenatal diagnosis is most often made by ultrasound.

Only a small subset of patients with congenital pulmonary airway malformations are candidates for in utero treatment. In this subset, the mass is large enough and in such an anatomically critical position that the fetal mediastinum is compressed, leading to impaired venous return with resulting fetal hydrops secondary to cardiac failure. When this occurs early enough in gestational age that delivery and postnatal treatment are not an option, in utero treatment is a possible solution. The majority of CPAMs, however, do not have an indication for prenatal treatment as the outcomes are excellent, with the tumors often regressing throughout pregnancy and causing no neonatal or early childhood symptoms.

Oftentimes one of the more difficult judgments to be made during pregnancy is the frequency with which these tumors should be monitored to detect the small percentage that will cause fetal harm in order to know when to intervene. Distinguishing between these conditions is difficult and some would argue clinically irrelevant until after birth. The final common pathway that leads to consideration of fetal intervention is the same—fetal hydrops—whether the lesion is considered a pure CCAM, BPS, or a hybrid lesion. Evaluation of 40 infants classified as having BPS found 50 percent of infants had elements of CCAM on their lung pathology.[78]

The diagnosis of CCAM is likewise not always certain until after surgery. In separate series 4 of 33 suspected CCAMs had BPS upon pathologic exam;[79] six of nine had “hybrid lesions”(CCAM and sequestration present in the same lesion), and 16 of 37 were lesions other

than CCAM. In a report from a busy fetal center with 4,551 patients, 38 cases of thoracic lesions were identified, and three of them were BPS.[80] Based on this considerable overlap, Achiron and colleagues suggested a new classification of lung lesions based on vascular supply which has not yet been adopted.[81]

By convention CCAM lesions are grouped into three types: type one is a lesion composed of single or multiple large cysts (more than 2 centimeters in diameter); type two is multicystic composed of multiple small cysts (less than 1 centimeter in diameter); and type three is a solid lesion.[82] The potential for shunt placement depends upon the type of lesion. Cystic lesions may be drained, but other types are resected.

These lung malformations have a variable course in utero. Natural history reports suggest that the majority of CCAM lesions increase in size in midtrimester and either involute in the third trimester or cause a compressive effect on the fetal thorax resulting in hydrops in the fetus and occasionally a mirror syndrome illness in the mother.[83-84] There are presently no useful predictors of outcome, and serial evaluations are essential to determine course. Hydrops in the fetus results from obstruction of the vena cava and cardiac compression caused by mediastinal shift.[85] The decision to intervene in utero is often based on the natural history reports that hydrops marks a transition to fetal demise. In 1985, Adzick and colleagues reported on 11 fetuses with CCAM and hydrops with 100 percent mortality.[86] Hydrops in BPS may result from somewhat different mechanisms with tension hydrothorax increasing thepressure within the thorax and decreasing venous and lymphatic return to the heart. Hydrops in these fetuses has also been reported to usually be fatal if untreated in utero, with only 1 survivor in 33 cases.[87]

At times, large pleural effusions occur without CCAM or BPS, the natural history of these effusions is even less well understood. We did not include interventions for isolated pleural effusions in this review; neither did we include papers that only reported thoracocentesis as a treatment.

Twin-Twin Transfusion Syndrome

Background. In twin-to-twin transfusion syndrome (TTTS), twins share a single chorionic membrane and therefore, a single placenta, but have separate amniotic sacs. Approximately 15 percent of monochorionic, diamniotic twin pregnancies are affected by TTTS,[88] and therefore, estimates based on CDC data are that theoretical incidence of TTTS would be about 1.38 to 1.86 cases per 1,000 live births.[89] Although incidence studies have found lower numbers, these numbers are probably a reflection of early deaths of affected fetuses in utero that therefore do not get recognized as TTTS pregnancies.

In TTTS, one twin (the donor) transfuses the other twin (the recipient) through intertwin placental vascular anastomoses (or communications). When this occurs, the donor twin becomes hypovolemic, resulting in decreased renal perfusion. Decreased perfusion may result in renal pathology, thus reducing urinary output and amniotic fluid volume in the donor twin's amniotic sac (oligohydramnios). The recipient twin, conversely, is hypervolemic with increased renal perfusion resulting in polyhdramnios. As the overproduction of urine continues, the polyhydramniotic sac can expand and cause uterine distention, leading to premature labor and delivery. Most pregnancies presenting with severe TTTS prior to 26 weeks and not undergoing some sort of therapy will end with dual fetal demise.[88] When both twins do survive, there is often severe neurologic compromise in survivors as well as other organ failure, including cardiac conditions. Approximately 25 percent of surviving fetuses in a monochorionic twin pair in which one dies will suffer CNS injury. This is thought to be related to either transplacental passage of

cytokines and vasoactive compounds or a result of cerebral ischemia related to hypotension from exsanguinations of the survivor into the vascular bed of the dead twin.

The first reported case of twin-to-twin transfusion was in 1942[90] and was referenced in 1964, when DeMarco[91] postulated that some aspects of this disorder were explainable by an in utero placental shunt in monozygous twins. The early descriptions often depicted what is likely now known as acute twin-twin transfusion syndrome and were based on live born twins who had sometimes dramatically different hemoglobin levels and birth weights. With the development of ultrasonography, however, we have learned that the cascade of events leading to this outcome begins early, and classic TTTS findings are late manifestations of the condition.[92-93]

With this new information, diagnostic criteria for TTTS evolved to include: same-sex fetuses with a single placenta with lack of lambda sign in early pregnancy; oligohydramnios in the donor sac (<2 cm maximum vertical pocket) and polyhydramnios in the recipient sac (>8 cm maximum vertical pocket at less than 20 weeks or >10 cm after 20 weeks).

After diagnosis, the most common approach to assessing severity in TTTS is the Quintero staging system:[94]

- Stage I: The fetal bladder of the donor twin remains visible sonographically.
- Stage II: The bladder of the donor twin is collapsed and not visible by ultrasound.
- Stage III: Critically abnormal fetal Doppler studies noted. This may include absent or reversed end-diastolic velocity in the umbilical artery, absent or reverse flow in the ductus venosus, or pulsatile flow in the umbilical vein.
- Stage IV: Fetal hydrops present.
- Stage V: Demise of one or both twins.

In 1990, Baldwin and Wittman[95] presented three prenatally diagnosed twin pairs with in utero twin transfusion syndrome for which they attempted selective reduction. They postulated the importance of a vascular separation. Later that year, De Lia et al. reported the first fetal surgery to treat the underlying pathology.[96]

Four primary approaches exist for intervening in twin-to-twin transfusion syndrome:

- Serial amnioreduction to relieve intra-amniotic pressure and uterine size, and thus prolong the pregnancy. Although the mechanism by which it works is not entirely clear, amnioreduction has been associated with a 50–60 percent survival rate of at least one fetus.[97]
- Termination of the sicker twin, which is likely to rescue the healthier one and is accomplished by cord occlusion, radio frequency ablation, or ligation. This is only used in the presence of significant birth defects.
- Septostomy, in which the intervening membrane is punctured to attempt to increase amniotic fluid in the oligohydramniotic sac, was performed but has largely been abandoned as a therapy.[98]
- Laser ablation of communicating vessels; it is performed either selectively or nonselectively to attempt to protect one twin from hemodynamic disturbances in the other twin. In nonselective ablation, all vessels crossing the dividing membrane are ablated, whereas selective ablation is limited to vessels shown to be communicating between the two fetuses. Selective ablation is most common today, and is the focus of this section of the technical brief. Gaining access to the uterus can be accomplished in three ways: laparotomy to expose the uterus, laparoscopic placement of the fetoscope, and ultrasound-guided placement of the fetoscope.

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