

Twenty-five years after the first fetal surgery was performed, doctors and ethicists are trying to learn whether and when the drastic procedures work—and whether they're worth the frightening risks

Desperate Measures

ON 23 JANUARY 2002, SURGEONS CUT A 30-centimeter incision in Lorie Barber's abdomen, peeling away layers of tissue to reach her 23-week-old fetus. Delicately removing the uterus and slitting it open, the doctors at Vanderbilt University Medical Center in Nashville, Tennessee, stitched closed a gaping hole at the base of the fetus's spine. That opening was the signature left by spina bifida, which can cause paralysis, hydrocephalus, and other lifelong disabilities.

Thirteen days after the surgery, Nicole Eva Barber was born, more than 3 months early and weighing in at 1 pound and 10 ounces (740 grams). Nearly all fetal surgeries, the Barbers had been warned, carry a risk of premature birth. That hadn't deterred them.

Lorie Barber and her husband had come to Vanderbilt from their home in Ohio, desperate and devastated. Weeks earlier, a genetic counselor had discussed the diagnosis and presented two options: terminate the pregnancy or have the baby. The Barbers reached for a third choice they'd learned of over the Internet: fetal surgery that might offer their child a better life.

But for the Barbers, as for hundreds of other couples who have endured fetal surgery for a variety of conditions, there were no guarantees that the benefits of this treatment would outweigh its risks to both mother and fetus. Although roughly a dozen medical centers

worldwide now offer fetal surgery, it remains highly experimental. Few fetal surgeries have been tested systematically in clinical trials, and for those that have, the results are decidedly mixed—suggesting anything from no advantage to robust benefit.

Part of the problem is that fetal surgeries are maddeningly difficult to evaluate in clinical trials. That's true of surgical interventions generally, and many enter mainstream practice without rigorous testing. But as diagnostic imaging advances, making it possible to visualize still more fetal anomalies potentially amenable to surgery, a growing number of physicians and ethicists are calling for trials to measure fetal surgery's worth against standard postnatal care. Perhaps more than anything, they fear that fetal surgeries, once confined to the most dismal cases, are becoming

routine before their safety and effectiveness can be rigorously tested.

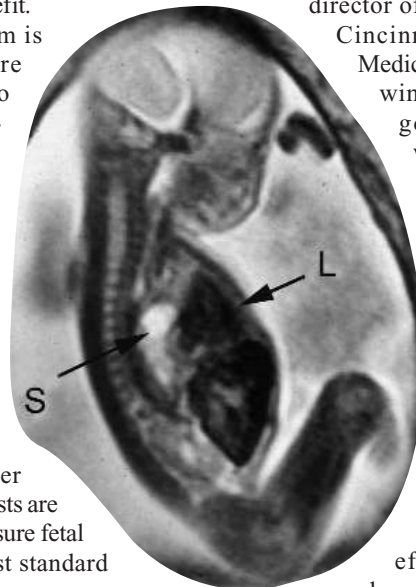
"Oftentimes, these therapies kind of take on a life of their own," says Timothy Crombleholme, a pediatric surgeon and director of the Fetal Care Center at Cincinnati Children's Hospital Medical Center in Ohio, "and the window to evaluate them ... goes away." To keep that window open, fetal surgery centers banded together last spring to form a clinical trials network that they hope will speed testing of various fetal treatments, before they become entrenched.

First breaths

Fetal surgery began in 1981 at the University of California, San Francisco (UCSF), as a last-ditch effort to save otherwise doomed fetuses. The hope was

that by correcting a life-threatening defect early, surgeons could prevent further damage and save the fetus's life.

The first successful surgery, to repair a urinary obstruction that triggers kidney and lung failure after birth, resulted in a boy born



Hazardous motion. In a fetus with congenital diaphragmatic hernia, the stomach (S) and part of the liver (L) have migrated toward the chest, inhibiting lung development.

Diagnosis. A woman undergoes a high-resolution ultrasound at the Children's Hospital of Philadelphia to help determine whether her fetus could benefit from surgery.

alive who recently celebrated his 25th birthday. In the hands of UCSF pediatric surgeon Michael Harrison and his colleagues, rare conditions considered fatal sometimes proved no longer so. By following the natural history of certain diseases—in other words, how babies fared with standard, postnatal care—the physicians felt they could gauge fetal surgery's effectiveness.

As word spread about what the UCSF team was doing, "people would present [us] with a problem, often in the form of a patient, and say, 'Do something,'" says Mitchell Golbus, an obstetrician and geneticist, now retired, who helped develop the UCSF program. In this way, the surgeries gradually spread to other life-threatening conditions. Among them was twin-twin transfusion syndrome, an often fatal circulatory disorder that strikes twins.

Another, congenital diaphragmatic hernia (CDH), occurs when abdominal organs migrate through a hole in the diaphragm to the chest in utero, compressing lung development and leaving newborns with inadequate lung capacity. The disease afflicts about 1 in 2500 babies worldwide, and all require surgery early in life. Intervening during fetal development, it was thought, might leave babies with larger, healthier lungs at birth and thus a much better chance of survival. When pediatric surgeons first began exploring fetal surgeries for CDH, about 30% of infants born with the condition survived.

In 1989, after 5 years of failed attempts in fetuses who died from the disease, UCSF performed the first successful CDH fetal surgery, closing the hole in the diaphragm. Although buoyed by their victories, even the most enthusiastic recognized that although they might be saving some very sick fetuses, the early surgeries had unsettling downsides. Some fetuses died from surgery itself, and others were born extremely prematurely. Moreover, some of the healthy women who underwent fetal surgery ended up in intensive care, hit danger-

ously hard by side effects from drugs given to prevent early labor.

"You have to make sure you have very good justification" for these surgeries, says Golbus, "because you're taking a healthy mother and running the risk of making her unhealthy."

With that in mind, Harrison pushed for and led the first-ever clinical trial of fetal surgery. Begun in the early 1990s, the trial was designed to test so-called open surgery for CDH, the surgical approach that Lorie Barber endured for spina bifida. In CDH cases, the mother's womb is opened and the fetus partially removed for the operation.

Behind the scenes, the trial was a nightmare. Uneasy about the treatment's novelty,

ending 8 years after Harrison first proposed it. The randomized trial eventually compared the survival of four fetuses who had open surgery with seven who did not.

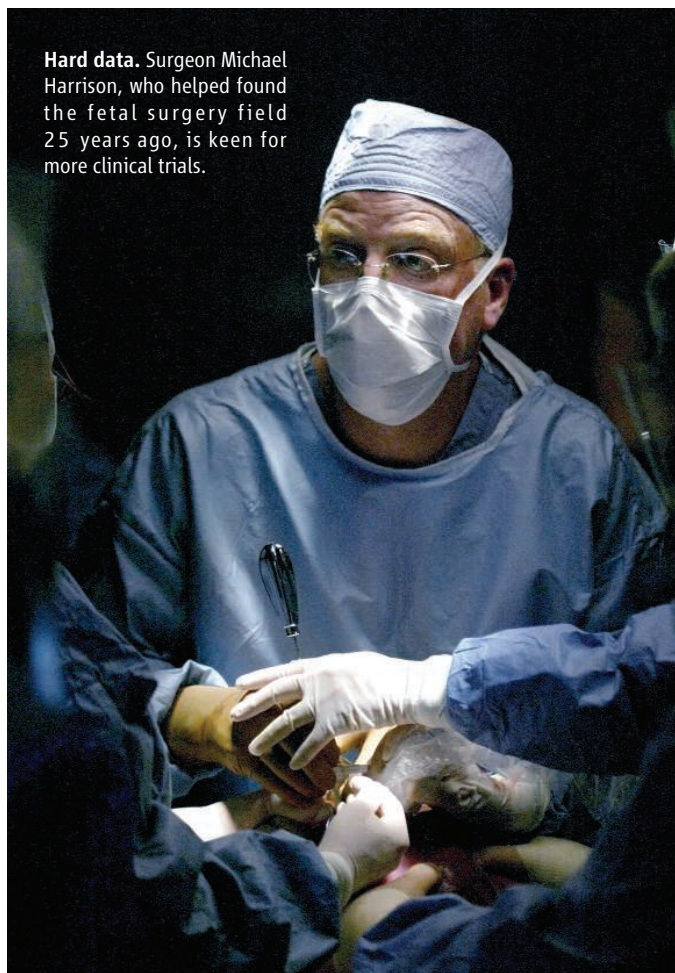
Logistics aside, Harrison and colleagues were convinced going in that CDH surgery would prove beneficial. "We thought for sure the randomized trial couldn't fail," says Russell Jennings, then a fellow with Harrison and now head of the Advanced Fetal Care Center at Children's Hospital Boston. The truth was less kind. In a paper published in 1997 in *The Journal of Pediatric Surgery*, Harrison and colleagues reported that survival rates were 75% in the treated group and 86% in the control group, a difference that was not statistically significant, given the small numbers involved. One baby in each group died.

But around that time, two teams working with fetal lambs—one led by Harrison and the other by Jay Wilson of Children's Hospital Boston—found that they could correct the defect by blocking the trachea. This less invasive mechanical fix had a dramatic effect, keeping fluid pressure in the lungs high and forcing them to grow more rapidly. (The herniated diaphragm, surgeons found, could be repaired after birth.) "Right after our first sheep, we said, 'This is it; we have cured diaphragmatic hernia,'" recalls Jennings.

A second trial testing this endoscopic technique, however, met with disappointment. Published in 2003 in *The New England Journal of Medicine*, that study found that 8 of 11 treated fetuses survived. But so did 10 of 13 in the control group. The treated babies who lived did have larger, healthier lungs, as the sheep studies had predicted, but those benefits were often muted by prematurity.

Although they didn't show survival advantages from fetal surgery, the trials did underscore risks to the fetus and the mother.

Both open and endoscopic surgery greatly boosted the chance of premature birth. Babies in the open-surgery trial were born at 32 weeks, on average, and at 31 weeks in the endoscopic trial, roughly 6 weeks earlier than babies in both control groups. Since then, other risks have surfaced. Roughly 5% to 15% of women undergoing endoscopic fetal surgery experience a rupture in their uterine membrane, which puts the mother at risk of



Hard data. Surgeon Michael Harrison, who helped found the fetal surgery field 25 years ago, is keen for more clinical trials.

officials at the National Institutes of Health (NIH), which funded the trial, and UCSF's human subjects oversight committee took 2 years to approve it. Soon after the trial began, it was abruptly halted amid reports that women inside and outside the study who had undergone fetal surgery suffered pulmonary edema. The cause was traced to nitroglycerin, given experimentally to prevent early labor. The study restarted, finally

infection and may force early delivery of the baby—a complication that can also strike subsequent pregnancies. The risk is lower, about 4%, in open surgeries, says Scott Adzick, who runs the Center for Fetal Diagnosis and Treatment at the Children's Hospital of Philadelphia (CHOP).

Another reason for the confounding CDH results is that while the trials chugged along, survival odds were trending upward for CDH babies given postnatal respiratory support and surgery. At major pediatric centers such as Children's Hospital Boston, 95% of babies with CDH now survive, says Wilson, although many suffer long-term gastrointestinal and respiratory complications.

At least some surgeons still believe CDH fetal surgery offers the best hope for a healthy life. A variant on the endoscopic surgery tested in the second trial is now practiced regularly in Europe. More than 90 fetuses have been operated on so far, says Jan Deprest, a gynecologist at University Hospital Gasthuisberg Leuven in Belgium. Deprest says that his technique improves survival by 50%—but in Europe, say U.S. surgeons, CDH survival rates are lower than in North America (an assertion Deprest disputes). The surgeries, which focus on fetuses with the worst prognoses, have generated controversy, in part given the failure of other CDH fetal surgeries to show benefit. Both Deprest and Harrison are eager for yet another trial, to, as Deprest puts it, “have this discussion finished.”

Regardless, as postnatal medical care advances, many babies with CDH and other conditions who once perished now pull through. But often, they're left with lingering disabilities. That has physicians considering fetal surgery's power to enhance life's quality.

A better life?

As the CDH trials continued, fetal surgery was stretching to accommodate its first non-life-threatening defect, spina bifida. “It really shifted ... fetal treatment into another realm,” recasting the benefit-risk balance irrevocably, says Nancy Chescheir, an obstetrician at Vanderbilt.

Spina bifida arises very early in pregnancy, when the fetus's spinal cord fails to close. Children with the disability rarely die from it, but they often need shunts to drain fluid from their brains and suffer mobility, learning, and bladder and bowel problems.

Experiments on fetal lambs in the 1980s and early 1990s suggested that closing the wound in utero could reduce these complications. Fetal surgeons believe that sealing the opening may protect the spinal cord from continuing damage, perhaps by preventing exposure to amniotic fluid and normalizing fluid dynamics in the fetus's brain. Physicians at Vanderbilt proclaimed the first open fetal surgery for spina bifida in 1997, and hundreds of families streamed into Nashville.

The University of North Carolina, Chapel Hill, also offered the surgery. Sue Estroff, an anthropologist who chairs the university's maternal-fetal intervention advisory group, says that families typically came determined to proceed and weren't swayed by discussions of risks and benefits. “Our concepts of [informed] consent didn't fit what we saw,” she says. “People brought ideas about what it means to be a good parent.”

One was Lorie Barber. She imagined eschewing the surgery, only to have her child later grow up to say, “Mom, you knew about this, and it was available back then. Why didn't you try, why didn't you go for it?”

Barber was also encouraged by preliminary data from Vanderbilt suggesting that surgery might lessen the need for a shunt. In a paper published 2 years ago (although details were shared with families earlier as they accrued), Joseph Bruner, who oversaw spina bifida fetal

surgeries at Vanderbilt and now works in Tennessee, and his colleagues reported that of 116 fetuses who had the surgery, 54% required a shunt before 1 year of age. The shunt rate for children who don't have fetal surgery has been estimated at as high as 85%, although it's thought to be drifting downward as neurosurgeons shunt more conservatively.

Even so, substantial questions about the surgery's benefit remained. For one, “spina bifida in humans happens at 8 weeks' gestation,” says Harrison. “We cannot work [on a fetus] at 8 weeks.” It's possible that by the time technology permits surgeons to operate—at about 20 weeks—the bulk of the damage has already occurred, making the drastic surgery largely futile. At the same time, because babies with spina bifida have an excellent chance of survival, life-threatening fetal surgery was creating ethically tenuous scenarios. At CHOP, says Crombleholme, who trained there before moving to Cincinnati, three babies with spina bifida who underwent fetal surgery were born so prematurely that they died. “These are three patients who would have survived,” he says.

Many physicians and ethicists became convinced that the only way to assess this surgery was in a clinical trial with a control group. With that in mind, NIH launched a trial in 2003, based at Vanderbilt, CHOP, and UCSF. Originally slated to end next year, the trial randomly assigns 100 mothers to surgery and 100 more to standard care. Success is measured by survival, the need for a shunt in the baby's first year, and neurologic function at 30 months.

By the time the trial began, physicians had performed more than 200 spina bifida fetal surgeries, and demand showed no signs of abating. To ensure that women would sign up for the trial, all hospitals halted spina bifida fetal surgeries outside the study.

Despite these efforts, recruitment has been sluggish. The trial was supposed to have begun a full year ago, but so far just 99 women have signed on. Explanations include a reluctance to be randomly assigned to either fetal surgery or a control group and a mother's unwillingness to remain at the surgical center until birth, as the trial mandates. But one thing is apparent: Continuing to recruit at this pace, “we're up to a 10-year trial,” double the time anticipated, says Chescheir. So far, NIH has allotted more than \$14 million to it.

Some surgeons quietly question whether spina bifida fetal surgery will survive. “The surgery itself is dying a slow death because of the length of the trial,” says Bruner. Unlike a drug, “surgery is a living, evolving entity,” he says. Doing a trial means “you have to freeze it in time,” halting the subtle enhancements surgeons routinely make. Safer, endoscopic



Riding high. Born 3 months early after spina bifida fetal surgery, 4-year-old Nicole Barber has few spina bifida symptoms—but it's difficult to know whether the experimental procedure made a difference.

CREDIT: COURTESY OF THE BARBER FAMILY



Fetal Surgery Trials

Disease	Lead Clinical Site(s)	Surgery Type	Total Size (women)	Status
Congenital Diaphragmatic Hernia	UCSF	Open surgery	11	Published in 1997, no survival benefit
Congenital Diaphragmatic Hernia	UCSF	Endoscopic	24	Published in 2003, no survival benefit
Twin-Twin Transfusion Syndrome	Hospitals in France, Belgium, and the U.S.	Endoscopic	142	Published in 2004, fetal surgery helped survival
Twin-Twin Transfusion Syndrome	*Children's Hospital Medical Center, Cincinnati	Endoscopic	42	Halted early after European trial
Spina Bifida	UCSF, Vanderbilt, CHOP	Open surgery	200	Still recruiting

* Trial began at CHOP.

approaches have not yet been effective at repairing spina bifida lesions, for example. As a result, in Europe, where open fetal surgeries are considered too aggressive to the mother, the procedure is not offered.

The heart of the matter

Some physicians are converging instead on another new frontier: fetal heart surgery. In the operating suites at Children's Hospital Boston, doctors now regularly perform procedures on fetuses with heart defects, 77 and counting since 2000. Although Boston is the only center in the world to have done more than a handful of these surgeries, says Wayne Tworetzky, a cardiologist there, other centers are considering whether to follow suit. Heart defects are ideal candidates for fetal surgery, Tworetzky and others say. High-tech fetal imaging has made diagnosis easier, and heart defects are a common and serious scourge in babies. The surgery to address them involves inserting a needle into the mother's abdomen and guiding it via ultrasound into the fetus's heart.

But as with other fetal surgeries, the cardiac procedures are raising difficult questions of their own—in particular, whether cardiologists understand enough about the defects they're trying to fix in utero. Nor is it clear that they can identify the fetuses most likely to benefit.

Take hypoplastic left heart syndrome (HLHS), the defect that the Boston team most commonly targets. Babies with HLHS are born lacking a functioning left ventricle, which leaves them with “only one pumping chamber,” says Tworetzky. Soon after birth, the infants turn ashen and struggle to breathe and feed normally. HLHS is not curable, and although most children can be treated with a series of operations or a heart transplant, their long-term prognosis is still shaky.

Strategies to fix HLHS in utero, however, are complicated by questions about what's driving the disease. In some babies, HLHS

seems to begin with a problem that is straightforward enough to fix: a blocked heart valve. Sophisticated tests on a pregnant woman can determine whether her fetus has this blocked valve. The surgery targets this obstruction in the hope that clearing it gives the left ventricle time to develop.

However, although a blocked valve is certainly associated with the heart defect, it's not yet clear that it's the key culprit. Fixing it, then, might be less likely to help than it would be if the blocked valve were causative. “It's possible that these lesions which we consider primary ... could be secondary, [and] relieving those would not necessarily improve muscle growth,” says Abraham

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—Timothy Crombleholme, Cincinnati Children's Hospital Medical Center

Rudolph, a former chief of pediatric cardiology at UCSF who spent decades studying fetal circulation.

And there's a second catch. Only a subset of fetuses with the blocked valve develop HLHS. Others are born with just the blockage, which can be corrected postnatally. Physicians at Children's Hospital Boston such as Tworetzky and cardiologist James Lock have done a number of studies to try to identify which fetuses with blocked heart valves go on to develop HLHS, because the risks of fetal surgery cannot currently be justified for the others. “We have strict criteria; you have to have this and this and not that,” says Tworetzky. In March, he and his colleagues published a

paper in *Circulation* suggesting that certain types of blood flow in fetal hearts can predict HLHS—and thus which mothers and their fetuses are best suited for surgery.

But other hospitals are hanging back. “There's logic to it, it makes sense, but it hasn't been rigorously tested,” says Jack Rychik, the head of CHOP's Fetal Heart Center, of the work in Boston. Last month, CHOP performed its first fetal heart procedure—but that fetus had multiple heart defects and an especially poor prognosis. Rychik wants firmer guarantees that he can pick the right mothers and fetuses for surgery and for now is not comfortable operating on all the same classes of women and fetuses treated in Boston.

Instead, Rychik is working to bring together eight centers, including Boston, to create a registry of fetuses with various heart defects who would be followed until birth. “The Boston experience has given us a kick in the pants” to examine the natural history of HLHS and other defects before fetal heart surgery becomes routine, says Rychik, who adds that the therapy may soon merit a clinical trial. In April, 17 centers in North America launched the North American Fetal Therapy Network to create a single voice to advocate for and help develop fetal treatment trials. It hopes its endorsement of certain trial proposals will encourage NIH and other funders to supply the millions of dollars these studies can cost.

Rychik and others are treading cautiously in part because families seek fetal surgery wherever possible. Even the Barbers, whose daughter spent 6 weeks on a ventilator and 103 days in a neonatal intensive care unit, say the price of surgery was worth it. Now 4 years old, Nicole's moderate hydrocephalus has not required a shunt. She's a strong-willed, talkative little girl who walks unassisted, attends a typical preschool, and enjoys bringing in the mail. Her mother has no regrets.

—JENNIFER COUZIN