



OBSTETRICS

The drive to do more and do it faster continues, leading to notable advances in prenatal diagnosis and fetal therapy, but is not sustainable over the long term



>> Jaimey M. Pauli, MD
Dr. Pauli is Assistant Professor, Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Penn State University College of Medicine, and Attending Perinatologist at The Milton S. Hershey Medical Center in Hershey, Pennsylvania.



>> John T. Repke, MD
Dr. Repke is University Professor and Chairman of Obstetrics and Gynecology at Penn State University College of Medicine. He is also Obstetrician-Gynecologist-in-Chief at The Milton S. Hershey Medical Center in Hershey, Pennsylvania. He serves on the OBG MANAGEMENT Board of Editors.

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If there have been overriding themes in obstetrics over the past year, they have been “more,” “sooner,” “faster,” “safer.” Advances in our field have thrilled our scientific curiosity and increased our ability to alleviate suffering—but at what cost? And who will pay that cost?

In this Update, we focus on recent advances in prenatal diagnosis and fetal therapy, as well as the ever-encroaching economic barriers that may limit our

ability to get what we want. In particular, we will discuss:

- two technologies in prenatal genetics: non-invasive aneuploidy testing using cell-free DNA and prenatal microarray analysis
- open fetal surgery to reduce mortality and improve the function and quality of life for fetuses with open neural tube defects
- the value and probable impact of bundled payments—that is, one payment for multiple services grouped into one “episode.”

Two noninvasive approaches to prenatal diagnosis offer promise—but practicality and cost are uncertain

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Genetic screening and testing are a standard part of prenatal care in most developed countries. We have come a long way since a maternal age of 35 years was the only variable separating patients into low- and high-risk categories. This year, two technologies have emerged that may change forever the way we approach prenatal genetics:

- noninvasive aneuploidy testing using cell-free DNA
- prenatal microarray analysis.^{1–4}

One argument for using more accurate genetic screening methods: They limit the number of invasive tests that are needed. Chorionic villus sampling (CVS) and amniocentesis, even when performed by the most experienced of operators, pose a small but real risk of fetal injury and pregnancy loss.

Noninvasive aneuploidy diagnosis is now a reality in high-risk population screening

The holy grail of aneuploidy diagnosis would be a noninvasive way to sample fetal cells. Although we have known for decades that fetal cells enter the maternal circulation, it has been impractical to use them for aneuploidy testing because of their scarcity and longevity. In the 1990s, however, cell-free fetal DNA (cffDNA), a compound of DNA fragments of uncertain origin, was identified in maternal plasma. CffDNA is more plentiful than fetal cells. It also disappears within hours of delivery, demonstrating that it is specific to the current pregnancy.

CffDNA is already used in fetal Rh typing and gender determination in disorders such as congenital adrenal hyperplasia. Several studies in high-risk populations have demonstrated high sensitivity and specificity for

the detection of Trisomies 21, 18, and 13. Several commercial tests are now available, although neither their accuracy nor their cost has been determined for use in low-risk population screening, compared with traditional testing.

Microarray analysis, paired with karyotyping, can elucidate ultrasound-identified fetal anomalies

Cytogenetic microarray analysis is also being explored in the prenatal period. Microarray analysis is currently used as a first-line test for infants and children who demonstrate developmental delay, autism spectrum disorders, dysmorphic features, and congenital anomalies. As many as 15% of patients with an otherwise normal karyotype will have a clinically significant copy number variant (CNV) on microarray. This finding has led to the use of microarray analysis in conjunction with karyotyping for fetuses with ultrasound-identified anomalies. Both targeted arrays (for syndromes associated with ultrasound anomalies) and whole-genome arrays are available.

Recent data from a study from the National Institute of Child Health and Human Development (NICHD) reveal that the prenatal detection rates for aneuploidy and unbalanced translocations are comparable between microarray analysis and karyotyping. Microarray analysis did not, however, detect triploidies or balanced translocations. As many as 6% of patients with a normal karyotype and structural anomalies and 1.7%

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As many as 15% of patients with an otherwise normal karyotype will have a clinically significant CNV on microarray analysis





WHAT THIS EVIDENCE MEANS FOR PRACTICE

We want an accurate, completely risk-free genetic test that can be used for anyone. What we have so far is a technology that must be tested before it can be used in most of our patients—that is, the low-risk ones. We also have access to the fetus' genetic code on a very specific level.

The total costs of such an approach—test, interpretation, counseling, and long-term follow-up of uncertain results—are unknown at this time and may prove to be unaffordable on a population-wide basis.

of patients with advanced maternal age or positive screening tests had either a known or potentially clinically relevant CNV. This large study concluded that microarray analysis not only provides equal detection of aneuploidy but also *more* information in the form of CNVs, compared with karyotyping alone.

Microarray analysis also has been used in the study of pregnancy loss and stillbirth because it does not require viable or intact tissue as a source of DNA—an advantage, compared with traditional karyotyping. A recent study from the Stillbirth Collaborative Research Network demonstrated that genetic results in cases involving stillbirth were obtained more frequently via microarray analysis (87.4%) than by karyotype (70.5%). In addition, more genetic

abnormalities (aneuploidy, pathogenic CNVs, and CNVs of unknown clinical significance) were detected by microarray analysis. Investigators concluded that microarray analysis may be especially useful in cases involving stillbirth (when a karyotype cannot be obtained) and structural abnormalities.

Should microarray analysis replace routine prenatal genetic testing?

A major dilemma associated with this technology is the significant amount of time that may be needed to counsel patients when the results are of unclear clinical significance.⁵ If the fetus has an anomaly, and a related CNV is identified, then counseling of the parents is fairly straightforward. However, if the fetus has an anomaly and a CNV that has not yet been defined, what should the parents be told? Some argue that this information should not be shared with the parents, whereas others recommend full disclosure of all results—even if we do not yet know what to make of them.

Another issue with microarray analysis is its inability to detect balanced translocations, triploidies, and low-level mosaicism, which require either a karyotype or whole-genome sequencing. Microarray analysis is also more expensive than karyotyping, although this may change in the future.

Fetal therapy involves a complex equation of potential benefits and risks

Adzick NS, Thom EA, Spong CY, et al; MOMS Investigators. A randomized trial of prenatal versus postnatal repair of myelomeningocele. N Engl J Med. 2011;364(11):993-1104.

Fetal therapy is broadly defined as any intervention administered to or via the mother with a primary indication to improve

perinatal or long-term outcomes for the fetus or newborn. The concept of intervening to prevent the death of a fetus by correcting an anatomic anomaly or halting a disease process in utero is not new. Liley performed the first intrauterine fetal transfusion for Rh alloimmunization in the 1960s. Today, we perform fetal interventions routinely to reduce mortality by giving medical



Microarray analysis has been used in the study of pregnancy loss and stillbirth because it does not require viable or intact tissue as a source of DNA

therapy to the mother, such as antenatal corticosteroids to enhance fetal lung maturity or anti-arrhythmics for supraventricular tachycardia. More invasive procedures have proved to be lifesaving (placental laser coagulation for twin-twin transfusion syndrome), ameliorating in the short term (shunting for lower urinary tract obstruction to relieve oligohydramnios), or ultimately not helpful (decompression of hydrocephalus).

Most recently, open fetal surgery has taken center stage as an intervention focused not only on reducing mortality but on improving function and quality of life for fetuses with open neural tube defects (ONTDs). This anomaly was targeted for fetal intervention because, although ONTDs are not generally considered lethal, a significant number of patients die before the age of 5, the majority of patients require shunts that leave them vulnerable to complications, and ONTDs generally impose lifelong intellectual and physical limitations. Repair during fetal life was proposed to prevent damage to the spinal cord and reverse hindbrain herniation, with the goal of improving long-term neurologic function.

The Management of Myelomeningocele Study (MOMS) is a prospective, multicenter trial that randomly assigned fetuses with isolated ONTDs to open fetal repair of myelomeningocele via hysterotomy or to postnatal repair of the defect. Forty percent of infants who underwent fetal repair required placement of a shunt, compared with 82% of those who had postnatal repair (relative risk, 0.48; 97.7% CI, 0.36 to 0.64; $P < .001$). Infants in the fetal-repair group also had significantly improved composite scores for mental development and motor function at 30 months ($P = .007$), as well as improvement in secondary outcomes such as hindbrain herniation and independent walking at 30 months.

As exciting as these results are, open fetal surgery still has significant limitations. The few centers that perform the most complex surgeries often have strict exclusion criteria,

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Although we may want to intervene as early in life as possible (that is, the fetal period) to achieve the best outcomes for the child, we need to weigh the short-term benefits of intervention against the known risks that intervention poses for the mother in the current pregnancy as well as the potential implications for future pregnancies (ie, the need for all future deliveries to be by cesarean section), not to mention the unknown long-term effects of intervention on both the child and society.

including maternal body mass index (BMI) greater than 35 kg/m² and other medical comorbidities. The surgery also poses real risks for both mother and fetus. In the MOMS trial, the risk of preterm labor increased in the fetal-repair group, compared with postnatal repair (38% vs 14%), as did the risk of premature rupture of membranes (46% vs 8%). The fetal-repair group delivered more than 3 weeks earlier than the postnatal repair group (34 vs 37 weeks). Twenty-five percent of the fetal-repair group had thinning of the uterine scar, with uterine dehiscence seen in 10%. When myelomeningocele is repaired during fetal life, mothers require two hysterotomies during pregnancy and face an increased risk of uterine rupture and preterm delivery in subsequent pregnancies. The use of tocolytics exposes these mothers to an increased risk of pulmonary edema (6% in the fetal-repair group vs 0% for postnatal repair).

Other issues that should be addressed:

- the need for rigorous study of open fetal surgery for other fetal anomalies
- prognostic factors for success and for complications
- long-term outcomes in neurologic development of children and fertility of mothers
- a comparison of costs between fetal and postnatal treatment.

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In the MOMs trial, 40% of infants who underwent fetal repair of myelomeningocele required placement of a shunt, compared with 82% of those who had postnatal repair

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Bundled payments may help us deliver higher-quality, more efficient, and less costly care

Centers for Medicare and Medicaid Services, US Department of Health and Human Services. Fact Sheet: Bundled Payments for Care Improvement Initiative. Washington, DC: DHS; 2011. <http://innovations.cms.gov/Files/fact-sheet/Bundled-Payment-Fact-Sheet.pdf>. Accessed December 6, 2012.

There is little question that health care in the United States needs reform. The culture of “more is better” is not sustainable economically—nor does our health as a whole reflect the amount of money that we spend on health care, compared with other countries. Although the future is not yet clear, one proposed mechanism for reform is the institution of bundled payments—the grouping of multiple services into one “episode” for payment purposes. An episode might include inpatient hospitalization for pneumonia, for example, or the grouping of surgery with post-discharge care. In obstetrics, all pregnancy care could be grouped into one episode. The concept behind bundled payments is to provide incentives to institutions and providers to deliver higher-quality, more efficient, and less costly care.

If bundled payments become the reality for obstetric care in the future, how will that affect the way we care for our patients? Instead

of blindly ordering all available tests, we need to consider thoroughly whether the patient truly needs a test to improve pregnancy outcomes. We also need to consider whether other measures might be avoided safely to keep costs within the bundle. A few examples:

- Is a screening fetal echocardiogram really necessary in a diabetic woman if the ultrasound anatomy scan is sufficient to rule out any cardiac anomaly that might require intervention in the delivery room?
- How will we integrate the expense of cell-free fetal DNA aneuploidy testing and microarray analysis, not to mention the extended counseling sessions that will be necessary to explain findings of uncertain clinical significance, into the bundle? Will “low-risk” patients need to pay out of pocket?
- Will a second ultrasound scan to visualize the fetal spine in a patient with a normal alpha-fetoprotein level be included in the bundle or paid for by the patient?

These issues may seem trivial, but we can no longer afford to order every test available. We will need to spend more time examining and counseling our patients so that they feel they are still getting the best care possible. ☺

FAST TRACK

As we work to reduce costs, thorough examination and counseling of patients is important to ensure the best care possible

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Few physicians entered medicine to worry about costs. Most of us want to worry about our patients. Yet, the reality is that scientific curiosity and a desire to do more—and to do it sooner, faster, and safer—are no longer sufficient justifications for many clinical decisions. We soon may need to figure out how to get what we need without spending as much in the process. In doing so, we may find ourselves moving away from the computer screen and back to the bedside—where we belong.

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