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Cervical Interleukin-6 as a Predictive Test for Preterm Delivery in Symptomatic Women: Preliminary Results

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Eur J Obstet Gynecol Reprod Biol 2011;155:14–18

ABSTRACT

The outcome for babies delivered after 34 weeks' gestation is generally good, but deliveries at extreme prematurity between 24 and 32 weeks are at high risk of complications. Previous studies investigating risk factors predictive for premature delivery have demonstrated a clear association between ultrasonographic cervical length and preterm delivery. Another possible preterm delivery predictive risk factor is the concentration of cervical interleukin-6 (IL-6). Through increased production of prostaglandins, this cytokine seems to be involved in events leading to cervical ripening and uterine contractions.

This observational prospective study was designed to investigate cervical IL-6 presence and concentrations for preterm delivery, alone and in association with cervical length as a predictive diagnostic test for preterm delivery in high-risk symptomatic women. The study subjects were 100 women between 24 and 34 weeks of gestation with intact membranes but threatened preterm labor who had been admitted to a hospital in Spain from 2006 to 2008. Cervical fluid was analyzed with transvaginal scan to determine cervical length, and a cervical swab was taken for detection of IL-6. Statistical tests performed included χ^2 test, Cox and logistic regression, receiver operating characteristic curve analysis, and Kaplan-Meier survival analysis.

Preterm delivery occurred in 35% of the babies born before 37 weeks and in 5% before 32 weeks. Cervical length was <15 mm in 12% and <30 mm in 62% of the subjects. Receiver operating characteristic curve analysis showed that an IL-6 value >210 pg/mL and a cervical length <30 mm were useful predictors of preterm delivery within 48 hours, within 7 days, and at <32, <34, and <37 weeks; there was no difference between the predictive accuracy of IL-6 and cervical length. Their additive predictive value was greater than either alone.

These findings suggest that cervical IL-6 and cervical length are predictive risk factors for preterm delivery in symptomatic women at high risk and that when combined, the predictive accuracy of both is better than each test alone.

EDITORIAL COMMENT

(Preterm birth is a major cause of neonatal morbidity and mortality (*National Vital Statistics Reports*. 2010;58:1–32). Unfortunately, despite extensive efforts to understand and prevent preterm birth, the rate has continued to rise in the United States (NCHS Data Brief 2010;39:1–8). Although this rise may be due in part to iatrogenesis and certainly to the rise in multiple gestations secondary to assisted reproductive technologies, it certainly does not appear that

we have identified ways to systematically reduce preterm birth other than the use of progesterone for recurrent preterm birth (*N Engl J Med*. 2003;348:2379–2385). One hope is that the development of better preterm prediction tests will allow us to identify the women on whom to focus our prevention efforts. However, considering the minimal benefit from fetal fibronectin, this area is far from reaping potential rewards.

Additionally, delivery of a preterm infant may be more favorable than expectant management in a variety of clinical situations. For maternal reasons, we routinely recommend preterm delivery in the setting of severe preeclampsia. Similarly, this seems reasonable with placenta previa (*J Reprod Med.* 2010;55:373–381). Such recommendations are also made in the setting of IUGR and PPROM for fetal concerns. One recent study demonstrated that preterm infants who were IUGR and had absent or reversed umbilical artery Doppler flow had lower intelligence quotient score at 5 years of age as compared with gestational age-matched controls (*Pediatrics.* 2011;127:e874–e882). This suggests that perhaps prolonged exposure to chronic hypoxia may be worse than delivery in some situations. In the setting of PPROM, this is thought to be true; thus, it is common to recommend delivery at 34 weeks of gestation. However, with recent focus on the long-term complications related to late preterm birth, perhaps it would be reasonable to wait beyond 34 weeks of gestation in women with PPROM.

The challenge in such situations is balancing the risks and benefits of immediate delivery and expectant management. Historically, in the setting of PPROM or preterm labor, an amniocentesis has been performed to screen for chorioamnionitis. However, the commonly used tests, such as white blood cell count, leukocyte esterase, glucose level, and gram stain, are not particularly sensitive for infection. One biomarker, interleukin-6 (IL-6), was identified as evidence for intrauterine inflammation almost 20 years ago. IL-6 is a cytokine that induces the production of prostaglandins. It is produced at sites of both acute and chronic inflammation. In a groundbreaking study, Romero et

al demonstrated that IL-6 was elevated and predicted intra-amniotic infection and preterm birth (*Am J Obstet Gynecol.* 1993;169:805–816).

In this article, Brik et al utilized cervical IL-6 to predict preterm birth. They find that there is a strong association with cervical IL-6 levels and preterm birth in 48 hours, 7 days, and before 32 weeks of gestation. These findings are similar to a previous study (*BJOG.* 2001;108:875–881) that looked at IL-6, IL-8, and phosphorylated insulin-like growth factor binding protein 1 and found them to be correlated with preterm birth risk. With regard to the current study, an advantage of cervical collection as compared with amniocentesis is that it will not lead to iatrogenic preterm delivery from rupture of membranes or infection. An advantage of using IL-6 (and perhaps IL-8 and phosphorylated insulin-like growth factor binding protein 1) is that it might not only predict preterm birth but also identify those preterm (or perhaps even term) patients who might benefit from delivery.

What I find surprising is not that cervical IL-6 is associated with preterm birth, but rather that years after the identification of an association between this molecule and preterm birth and, moreover, intra-amniotic infection, that there still is no ready, bedside, or quick laboratory test for this and other related molecules. Certainly, this family of molecules and others related to inflammation deserve focused attention and then translational work to develop a better predictor for preterm birth. Moreover, if this test could help us identify fetuses at risk, this might be a way to triage both idiopathic preterm labor and PPROM. Until that time, I will continue to use 20th century technology (ie, amniocentesis) and will order the same tests that I did in residency.—ABC)

17-Hydroxyprogesterone Caproate for Twin Pregnancy: A Double-Blind, Randomized Clinical Trial

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Am J Obstet Gynecol 2011;204:221.e1–221.e8

ABSTRACT

Multifetal pregnancies carry a greater risk of serious neonatal morbidity and mortality than singleton pregnancies. Several clinical trials have suggested that prophylactic progestins, most prominently 17-hydroxyprogesterone (17-OHP), may reduce the risk of preterm birth among women with prior preterm birth, a short cervix, or after arrest of preterm labor. However, prophylactic progestins have shown little benefit for twin or triplet pregnancies.

The aim of this double-blind, randomized clinical trial was to investigate whether prophylactic administration of 17-OHP to pregnant mothers carrying twins reduces the rate of preterm birth and thereby reduces the risk of neonatal morbidity and mortality. All participants were randomly assigned to receive weekly injections of 250 mg of 17-OHP (17-OHP group, $n = 160$) or placebo ($n = 80$), starting at 16 to 24 weeks of gestation and continuing until 34 weeks. The main study outcome was composite neonatal morbidity; the secondary outcome of primary interest was prolongation of pregnancy.

There was no difference between the 2 groups in the frequency of composite neonatal morbidity (14% in the 17-OHP group and 12% in the placebo ($P = 0.62$)). Mean gestational age at delivery was not prolonged by 17-OHP compared with placebo (35.3 vs. 35.9 weeks, respectively, $P = 0.10$). However, the median gestation age in the placebo group was 3 days longer than in the 17-OHP group ($P = 0.02$). Three perinatal deaths occurred in the placebo and none in the 17-OHP group.

These findings show that progestins do not prevent preterm birth or reduce neonatal morbidity in twin gestations and may actually confer a higher risk of earlier birth.

EDITORIAL COMMENT

(The only treatment or medication that has been demonstrated to make a difference on the risk of preterm birth seems to be progesterone. Initially studied in the 1960s and 1970s (*N Engl J Med.* 1975;293:675–680), the drug has made a comeback with several studies in the past decade. Studies of both 17-hydroxyprogesterone caproate (17-OHP) and vaginal progesterone have demonstrated benefit in women with a prior preterm birth (*N Engl J Med.* 2003;348:2379–2385; 2007;357:462–469). This success led KV Pharmaceuticals recently to seek Food and Drug Administration approval for 17-OHP, and then to price the medication at \$1500 per dose, which would amount to approximately \$30,000 per pregnancy. This price, which is roughly 150 times the price that most compounding pharmacies were charging, is obvi-

ously outrageous and has led to outcries from ACOG and the Society for Maternal Fetal Medicine (SMFM). This prompted KV to lower the price to \$690 per dose. Unfortunately for them, and lucky for payers, most of us who prescribe the medication already have a compounding pharmacy to provide the medication at far less cost.

Although 17-OHP seems beneficial for women with a prior preterm birth, studies of other subgroups have had varied success. For example, there are promising recent data that progesterone may prolong pregnancies with a short cervix by ultrasound in the second trimester (*Ultrasound Obstet Gynecol.* 2011;38:18–31). However, there does not seem to be any benefit to women with multiple gestations, who are at very high risk of preterm birth.

This was first reported by Rouse et al from the MFMU in a large, prospective study of 17-OHP in twin gestations (*N Engl J Med.* 2007;357:454–461). In this study, there was no difference in preterm birth between the treatment and placebo arms. Subsequently, a study of triplets similarly found no benefit in preterm birth with 17-OHP (*Obstet Gynecol.* 2009;113:285–292). Similar to these prior studies, the study abstracted earlier finds that indeed, there is no benefit from 17-OHP in preventing preterm birth in women with twin gestations. In fact, they actually demonstrated a slightly longer median length of gestation in the placebo arm. And in another study of triplets, this same research consortium found the same thing—no benefit from 17-OHP (*Am J Obstet Gynecol.* 2010;203:248.e1–9). Thus, with multiple prospective randomized trials now in both twins and triplets, I believe we can definitively say there is no benefit from routine 17-OHP in women with multiple gestations.

So, what is the best way to prevent preterm birth in twin gestations? Prolonged oral tocolysis? Absolutely no evidence of benefit. Prolonged bed rest? No benefit, and likely harm in the way of increased risk of venous thromboembolism (VTE), deconditioning, and the potential for emotional

isolation and stress. Unfortunately, it seems that the best way to prevent preterm birth in twins is to not have twins in the first place. Now, some women have spontaneous twins, and it is controversial whether fetal reduction will help in that setting, and it may lead to a higher pregnancy loss rate. But, the vast majority of twins today are secondary to assisted reproductive technologies. Unfortunately, women and their partners who are paying out of pocket in many settings are desperate to get pregnant and so request the transfer of multiple embryos. Clinicians who are judged on their pregnancy success rate have little compunction about transferring 2 embryos—certainly an improvement on 4, 5, 6, or more. But, there is little incentive for anyone to recommend single embryo transfer despite the fact that for women <38 years of age, it appears to be the most cost-beneficial approach (*Obstet Gynecol.* 2006;108:593–602). Thus, those clinicians who provide care to women who may potentially undergo infertility treatment should discuss with their patients the increased risk of preterm birth and concomitant 20-fold increased risk of cerebral palsy in twin compared with singleton gestations. Now, that could potentially be a successful way to reduce our overall preterm birth rate.—ABC)

Challenging the Glucose Challenge Test

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ABSTRACT

The occurrence of gestational diabetes mellitus (GDM) during pregnancy is associated with adverse outcomes for both the baby and the mother. The oral glucose tolerance test (OGTT) is the gold standard for widespread diagnostic screening of GDM. A number of options for initial screening tests (assessing the need for OGTT) have been investigated with the goal of reducing the numbers of patients undergoing an OGTT. Any universal screening protocol needs to consider the risk of missing the diagnosis, patient comfort, and laboratory costs. Currently, the Australian Diabetes in Pregnancy Society (ADIPS) recommends initial screening for GDM with the glucose challenge test (GCT). Other groups have suggested that fasting plasma glucose (FPG) should be used as the initial screening test. Recently, the International Association of Diabetes and Pregnancy Study Group (IADPSG) recommended use of new diagnostic criteria for GDM using a one-step OGTT.

This retrospective study was designed to determine the number of patients with GDM who would be missed with the use of GCT/OGTT or FPG/OGTT compared with patients having OGTT alone without an initial screening, and also to assess the performance of GCT for diagnosis of GDM using the new IADPSG criteria. A search of the Austin Pathology database was conducted between 2005 and 2007, and it identified 8486 episodes of GCT and OGTT (2291 GCT only, 416 GCT, then OGTT and 5473 OGTT alone). Test characteristics were assessed for simulated GCT/OGTT (where the 1-hour OGTT value was considered equivalent to the 1-hour GCT value) and for simulated FPG/OGTT (which investigated different FPG values to indicate need for OGTT).

With the OGTT one-step procedure using ADIPS criteria, 14% of the patients (764/5743) had GDM. Among patients initially screened with a GCT, 17.3% (416/2407) had a positive test for GDM; subsequent follow-up with OGTT showed that 75% of the patients with a positive GCT did not have GDM. Using ADIPS criteria in the simulated GCT/OGTT, the sensitivity of GCT was 87% and specificity was 74%, showing that 13% of the subjects would be missed. Although the sensitivity of simulated FPG/OGTT was similar (82% for FPG ≥ 4.4 mmol/L), the specificity was only 42%. In the simulated GCT/OGTT using the new IADPSG criteria, the sensitivity of screening GCT was 83% and specificity was 75%, showing that 17% of the subjects would be missed.

These findings indicate that the most expansive test for the diagnosis of GDM is OGTT without prior GCT or other preliminary test if one wishes to utilize the broadest criteria. However, no study to date has determined whether such broad diagnosis would be beneficial to all such patients.

EDITORIAL COMMENT

(The International Association of Diabetes and Pregnancy Study Groups (IADPSG) consensus panel with representation from around world recommended last year that gestational diabetes be diagnosed with a single oral glucose tolerance test (OGTT) (*Diabetes Care* 2010;33: 676–682). Such a test would involve checking a fasting blood glucose level, followed by administration of a 75-g glucose load and checking 1-hour and 2-hour blood glucose levels. Gestational diabetes mellitus (GDM) would be diagnosed with only 1 of the following abnormal values: a fasting value of 92 mg/dL or greater, a 1-hour value of 180 mg/dL or greater, or a 2-hour value of 155 mg/dL or greater. Recently, the American Diabetes Association agreed with this recommendation. Interestingly, these recommendations are “based” on findings from the HAPO cohort study, which examined perinatal outcomes by patients’ glucose results on just such a 75-g OGTT. However, 2 things should be noted from HAPO study. First is that they did not identify any particular thresholds (many of the perinatal outcomes increased throughout the range of blood glucoses examined). Second is that the HAPO was a prospective cohort study, not one that examined whether an intervention may improve outcomes.

There are 2 large studies that have examined more mild versions of GDM to investigate whether intervention can improve outcomes. To be fair, both these studies did exclude women

thought to be at increased risk because of an elevated fasting blood glucose. The first study demonstrated improvement in a variety of neonatal parameters and a reduction in the composite severe neonatal outcomes (*N Engl J Med.* 2005;352:2477–2486). The second study, conducted by the MFMU, did not find a difference in their primary outcomes, but did find a reduction in neonatal growth parameters and other secondary outcomes (*N Engl J Med.* 2009;361: 1339–1348). However, these studies did not examine specifically what the IADPSG recommends, which would be specific diagnosis and treatment based on these new guidelines. One issue that remains unclear is whether the one-step OGTT or the use of a screening test, usually a 50-g glucose challenge test as is usually performed in the United States, is better.

In the article abstracted earlier, the authors attempt to address a similar question in their population in Australia. They wish to know how these new IADPSG thresholds for the diagnosis of GDM will affect those who are diagnosed with GDM and whether the screening test is useful. As noted, they found that one advantage of going straight to the OGTT is that it would identify approximately 29% of women with GDM who would otherwise not get diagnosed using a testing scheme that does not evaluate fasting plasma glucose values, the latter of which would lead to approximately 5.8% of the population not being diagnosed with GDM.

With these recommendations flying about, what should we do in the United States? Although I believe that we will likely eventually move to a single, 75-g OGTT, the research to demonstrate that our patients will actually benefit from us doing so has yet to be conducted. We need 2 studies (that could be combined). First, we need a study that compares the 2-step screening, followed by diagnostic test versus the single-step OGTT. This would provide us with information regarding how large the population of GDM patients would become. Then, we need a study that examines treatment versus usual care in the group of women who would be diagnosed by the OGTT, but missed by the 2-step screening and diagnostic test for GDM. With positive findings from such a study, only then do I believe that we should systematically change our practice. Until that time, to increase

sensitivity from our existing screening test, I would be inclined to use a lower screening threshold of 130 mg/dL with the 50-g screening test, particularly in higher risk women (e.g., overweight, obese, Asian, Latina, Native American, prior GDM, or positive family history of diabetes). Furthermore, I would also consider evaluating short-term (eg, 1 week) self-monitoring of blood glucose results in women with 1 elevated value on the 3-hour, 100-g OGTT to potentially identify women with impaired glucose tolerance while on their usual diets. Regardless of the testing strategy used, ultimately, one could argue that it is likely that all patients could benefit from meeting with a dietician and paying closer attention to diet and exercise during pregnancy. Although GDM may be “a diagnosis looking for a disease,” the lifestyle component of treatment is likely good for all of us.—ABC)

Travel Time From Home to Hospital and Adverse Perinatal Outcomes in Women at Term in the Netherlands

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ABSTRACT

Several studies have found a relationship between longer travel time from home to hospital and increased risk of mortality and other adverse outcomes for emergency/trauma care and cardiology. Few studies have investigated this issue in pregnant laboring women in transit to hospitals; none have reported a significant effect of travel time on perinatal mortality. Some investigators have hypothesized that increased travel time could have a negative effect on intrapartum/perinatal mortality, especially among women with higher risk pregnancies.

This population-based cohort study investigated the relationship between travel time from home to the hospital and risk of intrapartum/neonatal mortality, and with adverse neonatal outcomes among women delivering at term in primary and secondary care. Data were obtained from the perinatal registry of the Netherlands for 751,926 singleton term births without congenital anomalies and antepartum stillbirths.

Travel time by car was calculated using the postal code of the women's residence and the postal code of the maternity units and was classified as either less than 20 minutes or 20 minutes or more. The primary study outcome measures were intrapartum and neonatal mortality, and other adverse neonatal outcomes (Apgar <4 and/or admission to neonatal intensive care). Multivariable logistic regression analysis was used to adjust for confounding factors, including

gestational age, maternal age, parity, ethnicity, socioeconomic status, urbanization, type of hospital (tertiary care or other), and hospital volume. Among the 751,926 births during the 7-year study period, there were 1125 intrapartum/neonatal deaths and 4543 adverse outcomes (representing a mortality rate of 1.5 per 1000 births and an adverse outcome rate of 6.0 per 1000 births). Compared with travel times less than 20 minutes, there was a significantly higher risk for travel times of 20 minutes or more for total mortality (adjusted odds ratio [aOR], 1.17; 95% confidence interval [CI]: 1.00–1.36), for neonatal mortality within 24 hours (aOR, 1.51; 95% CI: 1.13–2.02), and for adverse outcomes (aOR, 1.27; 95% CI: 1.17–1.38). Other important risk factors for mortality were delivery at 37 and 41 weeks of gestation (aOR, 2.2; 95% CI: 1.81–2.73 and aOR, 1.5; 95% CI: 1.29–1.80, respectively).

These findings indicate that a travel time of 20 minutes or more by car from home to a maternity unit increases the risk of intrapartum/neonatal mortality and adverse outcomes among a population of Dutch women with term delivery.

EDITORIAL COMMENT

(With a number of obstetric conditions, being able to get to the hospital quickly may improve outcomes. Cord prolapse, placental abruption, and uterine rupture can lead to neonatal morbidity and mortality even when they occur in a hospital, but certainly one would suspect, if such events occurred at home, that being within some short distance to a hospital would be more favorable. In the study abstracted earlier, the authors demonstrate just that: travel time greater than 20 minutes from a hospital was associated with an increase in neonatal morbidity and mortality. Unfortunately, because these data were derived from a large national perinatal database, we don't have specific information about each case that might give us some suggestion about how distance may have played a role in the complication.

This study was conducted in the Netherlands, therefore one question that is raised is how generalizable is it to other countries and health systems? In the Netherlands, women are triaged to being low- or high-risk early during their prenatal care. The low-risk patients have the option to deliver at home, and approximately 20% of the women do deliver at home, a number greater than in the United States. However, these patients were excluded from the study. Thus, although the system is different, the direction of the effect is likely to be similar if it is due to obstetric emergencies. Another issue is the distributions of time/distance from a hospital. In the Netherlands, only about one-fourth of the women were 20 minutes or farther from a hospital. I wonder whether that number would be greater in the United States where a large minority of pregnant women live at great distances from the nearest hospital, particularly in the

western states. In that setting, perhaps the effect would be even greater, as a study conducted in Japan found a relationship similar to a dose-response in travel distance related to perinatal mortality (*Nippon Eiseigaku Zasshi*. 2004; 59:342–348). In Figure 1 of the current study, it seemed that the risks of both morbidity and mortality increased from 20 minutes of travel time to up to 60 minutes at which point it leveled off.

Going forward, this study is one that raises more questions than it answers. Should it become part of routine prenatal care to estimate the travel time to the hospital? Should we counsel those women who are farther than 20 minutes regarding the increased risk for morbidity and mortality? My personal practice would be no to both. However, I do think that for patients with obviously high-risk issues, such as placenta previa or advanced cervical dilation at a preterm gestational age, consideration of distance from a hospital and even distance from an appropriate hospital should be a component of the care and discharge planning we provide. Although a woman with 2 prior cesareans and a bleeding previa might live 15 minutes from her local hospital, if that hospital doesn't have the capability to provide a massive transfusion, her mortality risk is likely increased in that setting. Similarly, if a woman at 27 weeks with twins is 2 to 3 cm dilated, being close to not any hospital, but one with a level III NICU, is likely to be important. Now, in both of these scenarios, the easy, risk-averse approach is to keep the patients hospitalized. However, these prolonged hospital stays are expensive and are not entirely risk-free, as more intervention, increased risk of VTE, and deconditioning may occur.

Another approach that I have heard many clinicians discuss over the years is to have a place to stay that is near the hospital, but not in the hospital. On the pediatric side, the Ronald McDonald housing makes a huge difference for families with a baby in the NICU. However, there isn't a similar national program for antepartum patients where the medical need is even greater. As health systems become increasingly respon-

sible for their own costs, I believe that such programs to provide housing for high-risk patients to be within earshot of a hospital are going to become more prevalent. In fact, I have seen just such a program at the University of Arkansas, which utilizes a motel that is less than a mile from its hospital for those women who don't need to be in a hospital, but are likely to benefit from being near a hospital.—ABC)

Neonatal Diagnosis of Severe Combined Immunodeficiency Leads to Significantly Improved Survival Outcome: The Case for Newborn Screening

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ABSTRACT

Infants born with severe combined immunodeficiencies (SCIDs) develop severe and recurrent infections in the first few months of life that are fatal without hematopoietic stem cell transplantation (HSCT). There is a significantly poorer outcome for infants treated with HSCT after 6 months of age. A poor outcome is also likely with use of mismatched donors or the presence of pneumonitis before transplantation. It is believed that an early diagnosis soon after birth followed by HSCT is essential to protect the infant from respiratory infection and to improve survival outcome. There is little evidence, however, that diagnosis in the newborn would improve survival.

This retrospective cohort study was designed to determine whether SCID babies diagnosed at birth because of a positive family history have improved outcomes as compared with the first presenting family member. Data were obtained for infants born between 1982 and 2010 from 2 designated SCID transplantation centers in the United Kingdom.

A total of 60 SCID patients were diagnosed antenatally or at birth during the study period. The data showed that compared with the first presenting family member, SCID babies diagnosed at birth had a significantly decreased number of infections and markedly improved survival outcome (>90%) after HSCT, regardless of the donor match, conditioning regimen used, and SCID type.

These findings indicate that diagnosis at birth through neonatal screening for SCID would likely improve the outcome for infants born with SCID.

EDITORIAL COMMENT

(Severe combined immunodeficiency (SCID) is a disease that many of us haven't thought about since medical school. As a review, primary im-

mundeficiencies are related to genetic mutations that affect the immune system. They are termed "severe" when they lead to overwhelm-

ing infections and, if untreated, death in infancy or early childhood. The term “combined” refers to defects in both cellular and humoral immunity. Some of the genetic defects only affect T-cells, but without T-cell function, the humoral response of the B-cells is also blunted. SCID is rare, with an estimated incidence of 1/50,000 to 1/100,000, and is composed roughly equally of both autosomal recessive and X-linked etiologies. The most common, definitive treatment for SCID is a hematopoietic stem cell transplant (*JAMA*. 2006;295:508–518). Unfortunately, many children die before they can get such a stem cell transplant, and the mortality rate after such treatment is high as well.

For a decade or longer, the idea of earlier diagnosis, perhaps mediated through newborn screening, has been described in the literature. Currently, there are newborn screening programs in Massachusetts and Wisconsin that screen for lymphopenia. The Wisconsin experience was described recently (*JAMA*. 2009;302:2465–2470). They screened 70,000 newborns with 35 abnormal screens and only 119 inconclusive screens. The vast majority of the inconclusive screens were normal on repeat screening. From both the groups, there were 11 abnormal results on repeat testing that underwent flow cytometry that revealed 8 abnormal results. Of these 8, 2 had DiGeorge syndrome, 3 had extravasation of T-cells outside the vascular space, and 3 had idiopathic T-cell lymphopenia. Of these 3, one ended up requiring a hematopoietic stem cell transplantation (HSCT) early in infancy and another may require such in childhood. Although no classically defined cases of SCID were observed in this population, this likely represents the rare incidence of the disease as opposed to the lack of sensitivity of the test.

Because these children will eventually present to care with recurrent infections, what is the advantage of newborn screening, which may

have both financial and emotional burdens? The hope is that with earlier identification, the children will have less morbidity associated with their HSCTs. Additionally, because live or live-attenuated vaccines can be very dangerous to such children, these can be avoided, as can exposures to ill members of society. In the article abstracted earlier, the authors demonstrate the effect of early diagnosis. In a clever study design, they compared children who were diagnosed early because of early screens performed for positive family histories in their siblings to their affected siblings. The limitations of this study design are difficult to overcome. However, the strengths include the lack of confounders related to race and socioeconomic status, and so forth. As noted earlier, the mortality rates both pre- and post-transplant were markedly reduced in the children with the early diagnoses.

These findings suggest that there are likely benefits to be had from early screening. The Wisconsin study suggests that the screen-positive rates are quite low, about 0.2%, and the vast majority of these can be dismissed with repeat screening. The remaining question is whether the costs of such a program are outweighed by the benefits. For example, in an analysis of screening for spinal muscular atrophy, the program was not deemed cost-effective. However, a big difference between these 2 diseases is that SCID can be treated with HSCT.

The take-home message to clinicians is that patients may begin asking about this test as attention on screening for this disorder increases. Of course, such screening programs are usually administered at the state level, and are difficult and expensive to obtain at the individual level. After such newborn screening programs are developed, the next question will be whether such testing could occur prenatally.—ABC)

Maternal Selenium Status During Early Gestation and Risk for Preterm Birth

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ABSTRACT

Preterm birth is a leading cause of perinatal mortality and morbidity with both short- and long-term adverse health outcomes for the child. Excessive inflammation (elevated immune response) increases the risk of premature rupture of the membranes and preterm birth. Low maternal serum levels of the trace metal selenium in early gestation are associated with inflammation and increase the risk of premature delivery. Low serum selenium levels have also been found in women with preeclampsia, a condition with a strong inflammatory component. Previous small studies investigating selenium plasma levels in mothers with term and preterm delivery suggest a role for low values in preterm birth, but the data were inconsistent.

This prospective cohort study was designed to determine whether low maternal selenium serum levels in a large cohort of pregnant women followed up from early gestation to delivery are associated with preterm birth. The study was conducted over a period of 2 years in a population of 1197 Dutch women with singleton pregnancies who were followed up prospectively from 12 weeks of gestation to delivery. Women with known thyroid disease or type 1 diabetes were excluded from the study. Blood samples were drawn at 12 weeks' gestation for measurement of serum selenium.

Births were either term or preterm deliveries; preterm births were categorized as either iatrogenic, spontaneous preterm labor with intact membranes, or as resulting from preterm premature rupture of the membranes.

The incidence of preterm birth was 5.3% ($n = 60$); these 60 preterm deliveries included 21 with premature rupture of the membranes and 13 with preeclampsia. At 12 weeks of gestation, the serum selenium concentration was significantly lower among women who had a preterm birth ($n = 60$) compared with those who had term deliveries ($n = 1069$): the mean selenium serum concentration for preterm deliveries was 0.96 (standard deviation 0.14) $\mu\text{mol/L}$ compared with term deliveries (1.02 [standard deviation 0.13] $\mu\text{mol/L}$; $t = 2.9$, $P = 0.003$). Women were grouped into 4 quartiles using serum selenium concentration at 12 weeks' gestation. The proportion of women with premature birth differed significantly by quartile ($\chi^2 = 8.0$, 3 degrees of freedom, $P = 0.04$). Univariate logistic regression analysis showed that the overall risk of preterm birth was twice as high among women in the lowest quartile of serum selenium at 12 weeks' gestation compared with those in the 3 higher quartiles. These results persisted after controlling for the occurrence of preeclampsia, the adjusted odds ratio was 2.18, with a 95% confidence interval of 1.25–3.77.

These findings show that being in the lowest quartile of selenium concentration at 12 weeks' gestation is a significant independent risk factor for increased odds of preterm birth independent of having preeclampsia.

EDITORIAL COMMENT

(Spontaneous preterm labor and preterm premature rupture of the membranes have both been associated with infection and inflammation. Selenium, a trace mineral, plays a role in the immune response and resistance to infection. Enzymes that contain selenium, so-called selenozymes, have been shown to downregulate the expression of proinflammatory genes, and low concentrations of selenium have been found in women with preeclampsia (*Am J Ob-*

stet Gynecol. 2008;198:336). The authors of the abstracted article therefore hypothesized that low maternal selenium status during early gestation might increase the risk of preterm birth.

In this thoughtfully conducted study from the Netherlands, the authors recruited nearly 1200 Dutch women with singleton gestations early in their pregnancy. Serum concentrations of selenium were measured during the 12th week of pregnancy and correlated with birth outcomes,

specifically preterm delivery, preterm premature ruptured membranes, and preeclampsia. They found that women who went on to have a preterm birth had serum selenium concentrations at 12 weeks' gestation that were significantly lower than women who delivered at term. Adding to the credibility of their results, they further found that the number of women who had a preterm birth significantly differed by quartile, with women in the lowest quartile of serum selenium having twice the risk of preterm birth compared with women in the upper 3 quartiles. Furthermore, there was a dose-response, with the risk of preterm delivery increasing with decreasing levels of selenium. Although primiparity and preeclampsia were both also associated with preterm birth, the association of low selenium remained after adjustment for these and other confounders.

Selenium is incorporated into proteins to make selenoproteins, which are important antioxidant enzymes. The recommended daily allowance for selenium is 55 μg in adults, 60 μg in pregnancy, and 70 μg in breast-feeding women. Results of the National Health and Nutrition Examination Survey (NHANES III-1988–1994) indicated that diets of most Americans provide recommended amounts of selenium. Plant foods are the major dietary sources of selenium, but it is also present in some meats and seafood. The content of selenium in food depends on the selenium content of the soil where plants are grown or animals are raised. Soils in the high plains of northern Nebraska and the Dakotas have very high levels of selenium, and people living in those regions generally have the highest selenium intakes in the United States (*Am J Clin Nutr.* 1991;53:1288–1294). In contrast, selenium deficiency is more common in the Netherlands, the United Kingdom, and other parts of Europe, China, and Russia.

Selenium deficiency has been studied with regard to a number of health outcomes, including cardiovascular disease and cancer risk. Selenium deficiency itself does not usually cause illness; rather, it may increase susceptibility to illnesses caused by other nutritional, biochemical, or infectious stresses. Observational stud-

ies indicate that death from cancer, including lung, colorectal, and prostate cancers, is lower among people with higher blood levels or intake of selenium, although the benefit of supplementation has not been determined. In an analysis of NHANES III, it appeared that mortality rates from all causes decreased with increasing selenium levels up to a level of 130 ng/mL, above which there was a modest increase in mortality.

Some, but not all, prior studies have also associated low selenium levels with adverse pregnancy outcomes, including preterm delivery. However, it is not clear whether selenium status is causal in such adverse outcomes, or simply indicates a maternal physiological response to increased oxidative stress states. Women with nutritional deficiencies of various types and causes are at risk for a variety of poor health outcomes, including preterm birth. It is likely that selenium-deficient women lack other micronutrients, and thus this deficiency itself might not explain adverse fetal outcomes. A single study randomizing pregnant women to selenium supplementation versus placebo found a decreased risk of premature rupture of membranes (PROM) in women receiving additional selenium, but they did not specifically focus on preterm PROM, and the gestational age at delivery was comparable in the 2 groups without an impact specifically on prematurity (*J Obstet Gynaecol.* 2010;30:30–34).

Preterm delivery is a complex disorder, and there are clearly many contributors that vary from patient to patient. Attention to adequate nutrition, including appropriate vitamin and mineral supplementation, is important to optimizing health and may decrease the rate of adverse pregnancy outcomes. However, for factors such as selenium, it is clear that the risks are likely very different in different geographical regions and potentially with different racial/ethnic groups in which genotype and diet may be very different. The health risks associated with high selenium levels indicate the importance of determining risk factors in large, well-conducted studies, and not recommending supplementation to populations that may already have adequate nutritional stores.—MEN)

Racial, Ethnic, and Socioeconomic Disparities in the Prevalence of Cerebral Palsy

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ABSTRACT

Several population-based studies have found that the risk of cerebral palsy (CP) is higher among black infants than white infants. The underlying reason for this racial disparity is unclear. The rates of low birth weight (LBW) and prematurity are higher among blacks compared with whites suggesting that differences in birth weight or gestational age may explain ethnic disparities in the prevalence of CP. However, gestational age is unlikely to account for these differences in prevalence because black infants born at term or with normal birth weight have a 20% to 40% increased risk of CP compared with whites. Low socioeconomic status may also be risk factor for CP, but few studies have examined its impact on rates of CP.

This retrospective cohort study assessed the association of ethnicity and LBW with the prevalence of CP, and also investigated the impact of socioeconomic status on the risk of CP within racial/ethnic groups. Among the 6.2 million live births in California from 1991 to 2001, 8397 children (≥ 5 years of age) with CP were identified from a search of state databases, indicating a prevalence of 1.4 per 1000 live births. Univariate logistic analysis was used to compare possible ethnic disparities in CP rates among white (reference group), black, Asian, Hispanic, and other children. Multivariate analysis was used to control for covariables and to determine the independent contribution of risk factors for CP within each racial and ethnic group.

With univariate analysis, there was a 29% greater risk of CP among black children compared with whites; the relative risk (RR) was 1.29, with a 95% confidence interval (CI) of 1.19 to 1.39. However, a diagnosis of CP was 21% and 29% less likely among black infants born at moderately low (RR, 0.71; 95% CI: 0.59–0.85) and very low (RR, 0.79; 95% CI: 0.68–0.91) birth weight than among comparable white infants. This difference in CP risk between black and white infants found in crude analysis did not persist after adjustment for birth weight. Multivariate analysis showed that the risk of CP was twice as high among black, Hispanic, and white women who delivered without receiving any prenatal care compared with those who received early prenatal care. Decreasing maternal educational attainment among whites and Hispanics was independently associated with increased risk of CP in a dose-response manner. Adolescent childbearing (aged <18 y) was associated with increased risk of CP only among Hispanic women.

These findings are consistent with previous studies showing elevated risk of CP among black infants and suggest that the increased risk among blacks may be due to higher rates of LBW. The data also suggest that higher educational attainment and use of early prenatal care could reduce ethnic disparities in rates of CP.

EDITORIAL COMMENT

(It is an unfortunate fact of health outcomes in the United States that racial, ethnic, and socioeconomic disparities are prevalent. The underlying causes of such disparities are often unclear, making it difficult to identify and implement solutions. As is true of many adverse perinatal outcomes, black infants have an increased risk of cerebral palsy (CP) when compared with white infants. Although this has been

found in previous population-based studies, the reason for the disparity is unknown. Rates of prematurity, low birth weight (LBW), and lower socioeconomic status are all increased among US blacks, and it is possible that this contributes to the higher rates of CP in this group.

In this abstracted study, the authors investigated the relationship between race/ethnicity, socioeconomic status, birth weight, gestational

age, and risk of CP in a large, multiethnic population in California. As has been previously reported, black infants were 29% more likely to have CP than white infants. Paradoxically, however, black infants who had been born with LBW or preterm were actually less likely to have CP than their white, LBW, or preterm counterparts. Interestingly, in normal birth weight infants, the overall rates of CP were not different between racial and ethnic groups. However, the rate of spastic or dyskinetic CP, the form that is usually attributed to birth asphyxia, was significantly higher in blacks and Hispanics. This suggests differing rates of birth asphyxia in these groups, and may be related to the higher risks of CP that were found in patients with no prenatal care.

This study confirms previous findings of an increased risk of CP among black infants, and indicates that this increased risk is explained by increased LBW and prematurity. Black children have a 2- to -3-fold increased risk of LBW, and the association of LBW with CP has here been shown to account for the increased risk of CP in black infants. Paradoxically, black infants born preterm generally do better than white preterm infants, with improved survival as well as lower rates of CP (*J Pediatr.* 2009;155:482-487). However, because they are so much more likely to be born preterm and LBW, overall rates of CP are higher.

To address the racial disparity in rates of CP, it is necessary to focus efforts on reducing rates

of prematurity and LBW. The rate of preterm delivery in the United States has increased steadily in the past 2 decades, and most recent data indicate a rate of just over 12%. The majority of these preterm deliveries occur in the late preterm period, at 34 to 37 weeks' gestation. A steady decline in stillbirths has paralleled this increase in late preterm births, likely reflecting iatrogenic, indicated delivery in patients at increased risk of stillbirth before term (*Natl Vital Stat Rep.* 2007;56:1-19). Obviously, a desire to decrease the rate of preterm birth must be weighed against the need to intervene for the fetus at risk of in utero demise.

The increased rates of prematurity in black infants have been attributed to numerous factors, including suboptimal prenatal care, maternal education, neighborhood poverty and disparity, social stressors, and genetic differences. Interestingly, the rate of LBW in African-born black women in the United States is closer to that of American-born whites than of American-born blacks, suggesting that environmental factors play a key role in determining risk of prematurity and LBW (*Soc Sci Med.* 1996;42: 589-597). Given all the accumulating data on long- and short-term adverse outcomes of preterm and LBW infants, and the racial, ethnic, and socioeconomic predictors of such adverse outcomes, it is ever more important to address the social and health disparities in the United States.—MEN)

Multiplexed Analysis of Circulating Cell-Free Fetal Nucleic Acids for Noninvasive Prenatal Diagnostic *RHD* Testing

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ABSTRACT

The fetuses of RhD-negative pregnant women that are positive for the Rh blood group D-antigen gene (*RHD*) are at risk for hemolytic disease of the fetus and newborn. Prophylactic anti-D therapy is administered to Rh-negative pregnant women carrying *RHD*-positive fetuses. However, a substantial number of Rh-negative women carry Rh-negative fetuses, and are therefore subjected to unnecessary injections of anti-D therapy. Noninvasive molecular tests that have been shown to accurately identify *RHD*-positive fetuses through detection of fetal *RHD* sequences in serum DNA are already being used routinely in several European countries. Use of these tests would restrict administration of prophylactic anti-D therapy to women with *RHD*-positive fetuses.

The aim of this study was to evaluate the efficacy of a novel noninvasive multiplex assay to detect fetal *RHD* loci in the maternal plasma of pregnant women negative for *RhD*. This genotyping assay used the MassARRAY system to detect *RHD* exons 4, 5, 7, and 10, and *RHD* (pseudogene) of the *RHD* gene along with a Y chromosome-specific marker. A total of 150 plasma samples from *RHD*-negative pregnant women were analyzed with the multiplex assay for fetal *RHD* genotype. All 150 samples had been previously characterized for fetal *RHD* status using a real-time polymerase chain reaction amplification control.

The assay correctly identified fetal *RHD* status in 98.7% (148/150) of the samples based on comparison with the real-time polymerase chain reaction control results. Overall, 86 (57.3%) and 62 (41.3%) of the samples were correctly classified as positive and negative, respectively.

These findings show that the multiplex assay using the MassARRAY system has potential as a noninvasive prenatal diagnostic test for *RHD* typing.

EDITORIAL COMMENT

(Current management of Rh disease, and prevention of most cases of Rh isoimmunization through use of Rh immune globulin, has been a true public health success story. The concept of preventing isoimmunization by injecting the mother with antibody to fetal red blood cells was first proposed in 1960; this led to development of Rh immune globulin, which was introduced in the United States in 1968. By 1973, it was estimated that in the United States alone, >50,000 perinatal deaths had been prevented. Time magazine picked the development of anti-Rh(D) as one of the top 10 medical achievements of the 1960s.

The management of Rh blood type incompatibility and isoimmunization has witnessed numerous other important advances. These include techniques to predict fetal anemia, initially using amniocentesis and the Liley curve and later noninvasively using MCA Doppler, use of DNA testing to determine fetal blood type from amniocytes or fetal blood, and the use of in utero transfusion to treat the severely anemic fetus. Most recently, the burgeoning field of noninvasive prenatal diagnosis, and the ability to isolate circulating cell-free fetal DNA (cffDNA) from maternal plasma, has led to noninvasive prediction of fetal RhD type. This test is already

offered as a routine service to at-risk women in several European countries, although it is not yet available in the United States. In Europe, the noninvasive assay is used to restrict prenatal prophylactic treatment and use of anti-RhD to women at risk for alloimmunization and predicted to be carrying an Rh-positive fetus.

This abstracted study describes a series of Rh-negative women in whom fetal RhD typing was performed using cffDNA. The analyses were performed, and the study was published by an American company, although the samples were obtained in Germany. The authors report that they were able to correctly predict fetal blood type in 148 of 150 cases (98.7%). The other 2 cases were considered “indeterminate.”

Although this technique sounds on the surface like another exciting advance in this field, a few cautionary thoughts deserve some consideration. Anti-RhD is extremely effective in preventing Rh isoimmunization. It is estimated that the current strategy of administration of anti-RhD to all Rh-negative women results in a sensitization rate of 0.6 per 1000 women. A recent meta-analysis of use of cffDNA to predict fetal blood type, with anti-RhD only to fetuses predicted to be Rh positive, reported a sensitivity of 95% (*Am J Obstet Gynecol.* 2006;195:1163–1173). We performed (and presented at this year’s SMFM meeting) a decision analysis comparing

the current strategy of routine anti-RhD with triaging based on cffDNA results for Rh-negative women. Based on the published literature, we estimated that use of cffDNA would result in 13 sensitizations per 1000 cases, a 20-fold increased rate (*Am J Obstet Gynecol.* 2011;204:S1:A139). The primary benefit of cffDNA is elimination of unnecessary use of anti-RhD. However, it is important to remember that this is an extremely safe medication with few, if any, significant side effects or risks. Another potential benefit is in cost savings, although it is not clear how much this cffDNA assay might cost in the United States, and the cost of anti-RhD, at approximately \$150/dose, is not high.

Although the field of cffDNA for prenatal testing has advanced tremendously in the past decade, it is important that it be introduced in a thoughtful manner. All too often, we have developed, sometimes at great expense, tests and techniques that are exciting and innovative, but have limited indications. This “treatment in search of an indication” problem can result in a push to apply such technologies to increasing numbers of clinical scenarios that may or may not be appropriate. Careful consideration of the pros and cons of cffDNA in the setting of routine management of the Rh-negative pregnant woman is critically important before we jump on this bandwagon.—MEN)

An Interactive Computer Program Can Effectively Educate Potential Users of Cystic Fibrosis Carrier Tests

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ABSTRACT

A Consensus Statement (Genetic Testing for Cystic Fibrosis, NIH Consensus Statement, 1997) concluded that carrier testing for cystic fibrosis (CF) should be offered not only to adults who are at increased reproductive risk due to a positive family history of CF but also to their partners and to couples from the general population planning a pregnancy. Subsequently, several professional medical organizations issued similar recommendations for widespread genetic testing for CF. Education of any individual planning to undergo genetic testing on the nature of the disease, risk of genetic transmission, and the test itself is best achieved with a face-to-face genetic counseling (GC) session. However, GC is costly, time-consuming, and there are too few trained professionals to meet the demand for testing. With the continuing increase in the number of genetic tests available for clinical use, alternative educational and counseling methods are needed. Although health education materials such as booklets and videotapes are available, these are of limited value because the information provided is inadequate and they do not allow for interaction with the end user. In recent years, an interactive computer-based (IC) program has shown effectiveness for providing adequate information to individuals who were undergoing testing for a genetic disease or were scheduled for a medical or surgical procedure.

This interventional randomized clinical trial compared the efficacy of the IC program and a traditional GC session to educate potential users of the CF carrier test about the disease and benefits and limitations of carrier testing. Individuals undergoing an assisted reproduction protocol were randomly assigned to participate either in an IC-assisted session ($n = 22$) or a GC session ($n = 22$). A multiple-choice questionnaire was administered both before and after the educational intervention to assess improvements among the participants regarding knowledge and understanding of several issues related to CF carrier testing. The study was conducted for a period of 1 year, starting in 2008.

The precounseling knowledge level (baseline) was similar in both groups (IC group: 45% vs. GC group: 47%). After the counseling sessions, there was a statistically significant improvement from baseline in the proportion of correct answers in each group ($P < 0.0001$ for both), but no difference was found between the groups in the number of correct answers (85% in the IC group and 84% in the GC group). None of the participants in either group changed their intention to undergo testing.

These findings show that interactive education by computer is as effective an educational tool for potential users of the CF carrier test as individual face-to-face counseling.

EDITORIAL COMMENT

(In 2001, guidelines for prenatal cystic fibrosis (CF) carrier screening were developed by the American College of Medical Genetics, American College of Obstetricians and Gynecologists, and National Institutes of Health in response to a Consensus Development Panel report, indicating that CF carrier screening should be offered to couples planning a pregnancy or seeking prenatal care. Ideally, any genetic test

should be linked to an individual genetic counseling (GC) session, but in the context of population screening of all pregnant women, this is clearly not feasible. With CF, carrier testing is made more complex by the variability of the clinical involvement, the ambiguity of negative mutation analysis results, and racial and ethnic differences in detectable mutations and carrier frequency.

As the number of genetic tests available for clinical use continues to rise, the need for alternative educational and counseling methods is more pressing, for CF as well as other inherited diseases. Booklets and videotapes have been used with some success to provide patient education, and they are able to provide balanced information that can be periodically updated. However, these materials are limited in scope, often do not include sufficient information, and do not allow interaction with the end user.

This abstracted article describes an interactive computerized tool specifically geared at educating potential users of CF carrier testing. The authors found that the computer tool allowed the acquisition of knowledge regarding the test comparable to the comprehension acquired after traditional GC. Although it was not better than one-on-one GC, it was as good at improving knowledge. It is of some interest that patients having in-person GC did report that they felt more confident in their understanding of the issues, indicating perhaps that the human conversation and feedback provided some reassurance regarding their comprehension.

Interactive computer-based programs are an alternative to one-on-one counseling, and can help individuals understand risk, learn about options, clarify values, and examine the consequences of their decisions. Interactive multimedia systems have been used to educate patients regarding genetic testing for breast cancer predisposition, chemotherapy, plastic surgery, stem cell transplantation, chronic heart failure, and psychiatric disorders. In the area of prenatal testing, Miriam Kuppermann and colleagues at University of California, San Francisco (UCSF) developed and tested a computerized, interactive prenatal testing decision tool describing options for Down syndrome testing; this tool was found to result in more informed prenatal genetic testing decisions than viewing standard educational

booklets (*Obstet Gynecol.* 2009;113:53–63). Decision aids are particularly useful in allowing patients and providers to share in making informed decisions in situations that include more than one approach to care, uncertain outcomes, and benefits and harms that people value differently. Prenatal genetic testing is particularly value-laden, and therefore balanced, objective counseling is particularly important.

Clearly, providers should discuss testing options with their patients so that they can make informed decisions, but this recommendation poses significant challenges in most clinical settings. In addition to time constraints, in an increasingly multicultural society, there are often language and other barriers to adequately providing complex information. Sometimes, providers themselves do not have a good understanding of complicated genetic issues. One study in 2006 found that only 40% of prenatal care providers follow American College of Obstetricians and Gynecologists CF screening recommendations (*Am J Med Genet.* 2006;140:2464–2468). As in many other areas of medicine, it seems that innovative approaches, such as computerized education and decision tools, are potentially useful alternatives in the setting of prenatal genetic testing. Unfortunately, progress in this area has been somewhat hampered by poor economic incentives. The cost to create these decision aids is relatively small, but because they don't generate revenue, no one has a financial incentive to produce them. Meanwhile, they are an improvement, and a consistent one, on the brief time most clinicians have to educate patients. In 2011, with all of the technological advances in the computer and software development world, we should push to take advantage of these options and develop more innovative and cost-effective tools to assist our patients in making these decisions.—MEN)

Maternal Smoking and Congenital Heart Defects in the Baltimore-Washington Infant Study

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ABSTRACT

Previous studies have suggested that maternal smoking during pregnancy is a risk factor for birth defects, but the data are inconsistent. In the positive studies identifying smoking as a risk factor, the magnitude of the risk was generally modest. Two studies have presented evidence for an association of maternal smoking in pregnancy with congenital heart defects (CHDs). The first, a multistate population-based case-control study, found that self-reported maternal periconceptional smoking was associated with 4 cardiac phenotypes. The second, a large retrospective Swedish Child Cardiology Registry and Medical Birth Registry study, provided evidence for associations between first-trimester maternal smoking and risk of CHD.

This population-based case-control study examined associations between self-reported maternal smoking during the first trimester and the risk of CHDs among singleton infants. Data were obtained from the Baltimore-Washington Infant Study, a population-based case-control study of CHDs conducted between 1981 and 1989. After exclusion of infants with noncardiac birth defects (except for atrioventricular septal defects with Down syndrome), as well as those whose mothers had pregestational diabetes, the final analysis included 2525 case and 3435 control infants. The level of self-reported first-trimester maternal cigarette consumption was determined through in-person postdelivery interviews. The respondent reported levels of smoking were grouped as 0, 1 to 10, 11 to 20, 21 to 39, or ≥ 40 cigarettes per day. Logistic regression analysis was used to estimate associations between first-trimester maternal cigarette consumption and 26 different groups of CHDs, with adjustment for covariables.

The data showed statistically significant associations between first-trimester smoking and risk of several CHD phenotypes: truncus arteriosus (adjusted odds ratio [aOR], 1.90; 95% confidence interval [CI]: 1.04–3.45), levotransposition of the great arteries (aOR, 1.79; 95% CI: 1.04–3.10), right ventricular outflow tract defects (aOR, 1.32; 95% CI: 1.06–1.65), pulmonary valve stenosis (aOR, 1.35; 95% CI: 1.05–1.74), and secundum-type atrial septal defect (aOR, 1.36; 95% CI: 1.04–1.78). A suggestive dose-response association was observed for atrioventricular septal defects among infants without Down syndrome (OR, 1.50; 95% CI: 0.99–2.29).

These findings are consistent with previous studies, suggesting that first-trimester maternal cigarette smoking is a modest risk factor for selected CHD phenotypes.

EDITORIAL COMMENT

(Congenital heart defects (CHDs) are the most common type of birth defect, and are present in nearly 1% of live-born infants. CHDs can be associated with substantial morbidity and are a major cause of neonatal and infant mortality. Some CHDs result from recognized genetic, chromosomal, and teratogenic etiologies, but for most, the cause is not known. Isolated CHDs generally fall into the category of multifactorial disorders: those traits and birth defects that are

determined by multiple genes and environmental factors.

In this abstracted study, the authors investigated associations between maternal cigarette smoking and CHDs. Identifying such potentially modifiable risk factors is obviously appealing as a means to decrease the incidence of these disorders. They used data from the Baltimore-Washington Infant Study, a very large, population-based case-control study of CHDs that was

conducted in the United States between 1981 and 1989. The Baltimore-Washington Infant Study remains one of the largest and most robust epidemiologic studies of CHD; the original investigators were comprehensive in ensuring all cases of CHD in the region were identified, and a team of pediatric cardiologists confirmed and classified all cases. Smoking was ascertained by an in-person interview after delivery. They found that first-trimester maternal cigarette smoking was associated with a modest increase in risk for CHD, with odds ratio ranging from 1.32 to 1.9 for different cardiac anomalies.

These findings add to the existing body of evidence that first-trimester maternal cigarette smoking is associated with CHD. Another large, epidemiologic study, the National Birth Defects Prevention Study, had similar findings. Other studies have found that this association may only be present for specific cardiac phenotypes, or in particular maternal subtypes (e.g., women who did not use vitamins during the periconceptional period) (*Epidemiology*. 2002;13:625–630).

Although little progress has been made in preventing most birth defects, the folic acid and neural tube defect story is an example of a great success in public health. Adequate intake of folic acid in the periconceptional period has been shown to be protective against other birth defects as well, including CHDs. Recent studies have specifically investigated the interplay of genetic polymorphisms in genes associated with folate metabolism, environmental factors

including smoking, and CHD. A study this past year found that, among women who smoked, those who carried one or more copies of the G allele in the *TCII* polymorphism were 1.81 times (95% confidence interval: 1.06–3.11) more likely to have a CHD-affected pregnancy than women who smoked and carried the CC genotype (*Obstet Gynecol*. 2010;116;316–322). It seems that genetic factors, in conjunction with lifestyle factors such as obesity, cigarette smoking, and ethanol intake, may work in combination to increase the risk of CHDs as well as other birth defects.

However, multiple other epidemiologic studies have examined the association between CHDs and maternal smoking, with inconclusive results. Normal and abnormal cardiac development occurs in the context of both maternal and fetal genetic susceptibilities. Like other birth defects, development of these isolated, multifactorial disorders (such as cleft lip, neural tube defects, and CHDs) results from interactions of multiple genes and many environmental factors that are complex. As such, although identification of a single modest risk factor, such as smoking, may be helpful, with such small odds ratios even elimination of smoking in pregnancy altogether would not have a large impact on the rate of CHDs. Nevertheless, smoking obviously presents harm and risk for multiple poor health outcomes, and these current data should add to our armamentarium of evidence pointing to the need to eliminate this public health hazard.—MEN)