Maternal Allopurinol During Fetal Hypoxia Lowers Cord Blood Levels of the Brain Injury Marker S-100B EDITORIAL COMMENT

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Randomized Placebo-Controlled Trial of Outpatient (at Home) Cervical Ripening With Isosorbide Mononitrate (IMN) Prior to Induction of Labor—Clinical Trial With Analyses of Efficacy and Acceptability: The IMOP Study

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ABSTRACT

Several investigators have hypothesized that outpatient preinduction cervical ripening with nitric oxide donors such as isosorbide mononitrate (IMN) would reduce the elapsed time from hospital admission to delivery and improve women's experience of induction of labor. This double-blind randomized placebo-controlled trial investigated whether vaginal self-administration at home by woman at term would improve the process of induction of labor. The study subjects were 350 nulliparous singleton women with cephalic presentation at ≥37 weeks' gestation, requiring cervical ripening before induction of labor. The participants self-administered IMN (n = 177) or placebo (n = 173) vaginally at home without fetal monitoring at 48, 32, and 16 hours before the scheduled time of admission for induction of labor. The primary study outcome measures were the elapsed time interval from hospital admission to delivery and the women's experience of home treatment for cervical ripening. Maternal satisfaction was determined with a questionnaire, using a 10 point scale with 1 = extremely good and 10 = not at all good.

There was no statistically significant difference between the 2 study groups in the admission to delivery interval; the mean difference was 1.59 hours, with a 95% confidence interval (CI) of −5.08 to 1.89, $P = 0.37$. Compared to placebo, however, IMN was more effective in inducing a mean change in modified Bishop score from recruitment to hospital admission (mean difference: 0.65 [95% CI, 0.14–1.17, $P = 0.013$]). With regard to maternal satisfaction, the overall experience of home treatment was positive in both groups. Women in the placebo group reported it to be marginally more positive than those in the IMN group (placebo: 3.23 vs. IMN: 3.84; the mean difference was 0.61, with a 95% CI of 0.02–1.21, $P = 0.043$). No difference between the 2 groups was reported in either pain or anxiety levels or in the willingness to have the treatment in a subsequent pregnancy.

These data show that administration of IMN at home is effective in ripening the cervix but does not shorten the admission to delivery interval or improve maternal satisfaction. The investigators conclude from these findings that IMN in this setting has limited clinical value.

EDITORIAL COMMENT

(The appeal of the nitric oxide donor isosorbide mononitate (IMN) is its potential to induce cervical ripening without precipitating uterine contractions and thereby obviate the need for fetal heart rate monitoring, and allow cervical ripening to be conducted on an outpatient ba-

sis. Its utility for this purpose has been evaluated in 3 randomized trials.

In the first, 200 women at 42 weeks' gestation or beyond with an uncomplicated singleton pregnancy were randomly allocated to 40 mg of vaginal IMN or placebo inserted into the posterior vaginal fornix by an obstetrician the day before induction. The primary outcome was entry into spontaneous labor before the scheduled induction. Significantly more women in the IMN group achieved this outcome, 22% versus 8%. In the women who did not enter labor spontaneously, IMN was no more effective at improving the Bishop score than placebo. Overall, there were no significant differences between groups in mode of delivery, maternal bleeding complications, or infant condition at birth. There were no cases of abnormal fetal heart rate in the IMN group before the active phase of labor but many more women in the IMN group experienced headache, 88% versus 8% (Bullarbo M, et al. Am J Obstet Gynecol 2007;196:50e1).

In the second trial, 102 women were randomized to self-administration of 3 vaginal doses of 40 mg of IMN or placebo 36, 24, and 12 hours before scheduled induction. The primary outcome in this trial was time interval from hospital admission until delivery. This interval was significantly shorter in the IMN group, 13 versus 20 hours. The Bishop score from randomization was increased from 4 to 6 in the IMN group, but it was not increased in the placebo group. There was no difference between groups in the rate of spontaneous labor—8% in the IMN group and 6% in the placebo group. Fewer women in the IMN group received prostaglandins for cervical ripening, 63% versus 90%. Tachysystole, defined as two 10-minute windows with more than 5 contractions, was less frequent in the IMN group, 2% versus 16%. As in the Bullarbo trial, there were no significant differences between groups in mode of delivery, maternal bleeding complications, or infant condition at birth. Headache was less frequent than in the Bullarbo trial, and occurred exclusively in the IMN group, in which the rate was 12% (Habib S, et al. IJOG 2008;101:57).

The abstracted trial of Bollapragada et al is the largest trial yet to evaluate outpatient cervical ripening with IMN. In this trial, a self-administered, 3-dose, 40-mg vaginal IMN regimen had no meaningful clinical effect, even though it did improve the Bishop score by an average of 0.65 relative to placebo. IMN was not associated with maternal or perinatal harm, but again, caused more headaches, 66% versus 20%.

On the basis of these 3 trials, it is hard to get enthusiastic about the use of IMN for outpatient cervical ripening. The issue may be worthy of future study, but for now I am going to spare my patients the headache(s) of this intervention.—DJR)

Rapid Human Immunodeficiency Virus Testing in Obstetric Outpatient Settings: The MIRIAD Study

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ABSTRACT

This investigation was conducted as part of the Mother-Infant Rapid Intervention at Delivery (MIRIAD) study, a prospective, multicenter trial assessing routine rapid human immunodeficiency virus (HIV) screening of pregnant women in inpatient and outpatient settings. This study compared rapid HIV testing with conventional HIV testing in outpatient obstetric settings among a population of pregnant women who presented late in care with undocumented HIV status. The investigators hypothesized that rapid testing would provide results faster than conventional testing in this setting and would also be acceptable and feasible. The study was carried out in 285 nonlaboring pregnant women volunteers at ≥34 weeks' gestation, who presented at hospital clinics in 6 US cities between 2002 and 2005. Median times between conventional and rapid testing and between rapid point-of-care and rapid laboratory-based testing were determined. More than 90% of eligible women who were approached agreed to participate.

Results were available for rapid tests much sooner than for conventional tests: median time between blood draw and availability of results was 25 minutes (range, 20–110 minutes) among women with rapid HIV testing and 23 hours (range, 3.5 hours–43 days) among women with conventional testing ($P < 0.0001$). Most results for rapid testing (n = 273 or 96%) were available within 1 hour. Median test duration was shorter when the rapid tests were performed at the point-of-care (24 minutes) than when they were preformed in the laboratory (35 minutes) ($P < 0.0001$).

These findings show that rapid testing for HIV provides results far sooner than conventional testing in the outpatient obstetric setting and is acceptable and feasible.

EDITORIAL COMMENT

(Some 100–200 infants in the United States are infected annually with HIV, as are hundreds of thousands in less developed countries. If we are to reduce mother-to-child HIV transmission to its lowest possible level, we must maximize the identification of HIV-infected gravidas and offer them antiretroviral therapy. In select cases, prelabor, premembrane rupture cesarean delivery should be offered and performed.

Obviously, to identify HIV infection, one must test for it, and this testing is greatly facilitated by an "opt-out" approach, in which the patient is notified that HIV screening will be performed as part of her routine prenatal laboratory testing, as opposed to being performed only after specific assent for HIV testing is sought and given. The American College of Obstetricians and Gynecologists (ACOG), the American Academy of Pedi-

atrics, and the CDC recommend the opt-out approach.

In a perfect world, all women would get prenatal care early in gestation and be tested for HIV infection. Conventional testing consists of a screening enzyme-linked immunoabsorbent assay (ELISA) which, if positive, is followed by a confirmatory Western blot or an immunoflourescence assay (IFA). Although conventional testing may be accomplished in less than a day, it can take several days or even more than a week for the testing to be completed and reported. Early in gestation, this testing timeframe is acceptable. However, later in gestation, and in labor, it clearly is not, as the delay in the availability of the results may preclude or render less effective mother-to-child HIV transmission prevention interventions.

Fortunately, there are several reliable rapid HIV tests available, including the OraQuick rapid HIV antibody test (OraSure Technologies, Bethlehem, PA) utilized in the abstracted article of Tepper et al. This rapid test has a sensitivity of 100% and a specificity of 99.9%, and, in a previous study, was evaluated by the same investigators for its utility in diagnosing HIV during labor. In that study, it performed well, with a median time from blood collection to patient notification of 66 minutes, as opposed to 28 hours for enzyme immunoassay (Bulterys M. JAMA 2004;292:219). Not unexpectedly, in the Tepper study, rapid testing performed comparably well in obstetric outpatient settings, and thus can be considered for select women who are late in gestation and have not yet been tested for HIV infection.

Based on the performance of the rapid tests, ACOG recommends rapid HIV testing in labor for women with undocumented HIV status, and if the rapid test is positive, that antiretroviral prophylaxis be initiated (with consent) without waiting for the results of the confirmatory test (ACOG Committee Opinion 304, November 2004). The CDC recommends that HIV-infected women in labor who have not received antepartum antiretroviral drugs be given intravenous zidovudine (ZDV) during labor and that their infants receive 6 weeks of ZDV. In addition to ZDV, some experts recommend single-dose intrapartum/newborn neuiropine (available at: http://AIDSinfo.nih.gov).

Rapid test results should be confirmed by Western blot or IFA, because even with very high specificity, if the population tested has a low prevalence of HIV infection, a substantial percentage of positive rapid tests will be false positives. For example, at a prevalence of 1 per 1000, the OraQuick test, which has the lowest false positive rate of the available tests, has a false positive rate of 50%. But given that administering a short course of antiretrovirals to an HIV-negative parturient has little maternal or perinatal risk, and can cut the rate of mother-to-child transmission by one-half to two-thirds, this false positive rate seems acceptable. Better, clearly, would be definitively knowing all parturients HIV status before the onset of labor.—DJR)

Evaluation of Universal Antenatal Screening for Group B Streptococcus

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ABSTRACT

In 2002, updated national guidelines recommended universal culture-based antenatal screening of pregnant women during labor and delivery for detection of colonization with group B streptococcus. Four years later, a population-based surveillance study reported a 27% decrease in incidence of early-onset neonatal group B streptococcal (GBS) disease. It is unclear, however, whether there has been an increase in the rate of screening. This retrospective cohort study examined the medical records of a selected population of more than 800,000 live births to evaluate the implementation of the 2002 screening and chemoprophylaxis guidelines for the prevention of early onset neonatal GBS disease. It also assessed missed opportunities for prevention among the women who were not screened. The source of the data was the Active Bacterial Core Surveillance System, a 10-state network that monitors invasive GBS disease. Between 2003 and 2004, the investigators examined labor and delivery records of a stratified random sample of all live births (newborns without the disease) and of all cases (newborns with early-onset GBS disease). These data were compared with those from a similar study evaluating screening practices between 1998 and 1999.

Analysis of abstracted labor and delivery records identified 7437 newborns without GBS disease and 254 newborns with early-onset GBS disease. Between 1998–1999 and 2003–2004, the rate of screening of women for group B streptococcus before delivery increased from 48.1% (95% confidence interval, 46.7–49.5) to 85.0% (95% confidence interval, 83.9–86.0), and the percentage of mothers who received intrapartum antibiotics increased from 26.8% to 31.7%. The observed incidence of early-onset infections was 0.32 cases per 1000 live births. Among the women positive for group B streptococcus who delivered at term, the rate of administration of intrapartum antibiotics was 87.0%. Among women with unknown colonization status who delivered preterm, only 63.4% received intrapartum antibiotics. There was a higher incidence of early-onset GBS disease in preterm infants than term infants (0.73 vs. 0.26 cases per 1000 live births). Still, only 26% (65/254) of the cases of early-onset disease were preterm births. Of the infants delivered at term who had early-onset GBS disease, 18.0% (34/189) were newborns of unscreened women. Term infants born to women who had been both screened and tested negative for group B streptococcus accounted for 61.4% of the cases of early-onset disease.

These findings suggest that the rapid adoption of recommendations for universal antenatal screening for group B streptococcus may be responsible for the reported decline in the incidence of early-onset disease in newborn infants 4 years after the updated guidelines were issued.

EDITORIAL COMMENT

(The abstracted study of Van Dyke et al provides the most contemporary picture of the state of early onset neonatal group B streptococcal (GBS) disease prevention in the United States. We perform screening cultures on 85% of mothers, identify 24% as GBS carriers, and

provide intrapartum prophylaxis to 32%. The result is an overall rate of early onset neonatal GBS disease of 0.32 per 1000 live borns. The rate among term infants is 0.26 per 1000, and among preterm infants it is 0.73 per 1000.

How, then, are we doing? That is, absent our fairly intensive screening and treatment efforts, what would we expect the rate of early onset neonatal GBS to be? Previously, in a comprehensive decision analysis, we estimated that without maternal GBS screening or intrapartum antibiotic prophylaxis, the rate of early onset GBS sepsis would be 2.92 per 1000 births (Rouse, et al. Obstet Gynecol 1994;83:483). In the same analysis, we evaluated the current policy of maternal rectovaginal culture at 35 to 37 weeks, and intrapartum treatment of all women with positive culture results, GBS bacteriuria in the current pregnancy, or delivery of a previous child with early onset GBS sepsis. Women in whom a culture result was not available, and those delivering preterm, or with an intrapartum temperature of at least 38°C, or membrane rupture for at least 18 hours would also receive intrapartum prophylaxis.

We estimated that the current policy would result in 27% of gravidas being treated with intrapartum antibiotics (cf the rate of 32% in the Van Dyke report) and reduce the rate of early onset GBS sepsis to 0.41 per 1000 births (cf the rate of 0.32 per 1000 in the Van Dyke report). In short, we are doing about as well as could be reasonably predicted. Could we do better? Probably, but there is 1 fairly fixed impediment to achieving or even approaching the elimination of early onset neonatal GBS disease with our current approach: the imperfect correlation of maternal antepartum GBS culture results and intrapartum maternal culture status. Only mothers who are colonized intrapartum are at risk of giving birth to infants with early onset GBS disease. Maternal GBS carriage, however, is not constant, and thus the 35 to 37 week culture fails to identify all mothers who will be colonized intrapartum (and, conversely, labels some women as GBS positive who will not be colonized at the time of delivery).

The best study of the predictive value of the 35 to 37 week culture was by Yancey et al (Obstet Gynecol 1996;88:811). At a GBS carriage rate of 27%, they found a positive predictive value of 87% (i.e., 87% of mothers who are GBS positive at 36 weeks will be positive at the time of delivery) and a negative predictive value of 96% (i.e., 4% of mothers identified as negative at 36 weeks will actually be colonized intrapartum). The latter 4%, because they will not receive GBS prophylaxis, will inevitably give birth to some infants with early onset GBS sepsis.

A reliable, highly accurate, and universally available rapid intrapartum GBS test would obviate the problem of antepartum/intrapartum culture discrepancies. Such tests exist, but their wide-scale applicably has not yet been demonstrated. In the meantime, ensuring that cultures are obtained, performed, and reported appropriately, and that women without culture results receive prophylaxis if indicated (i.e., for current-pregnancy GBS bacteriuria, prior affected infant, and those delivering preterm, with fever, or after prolonged membrane rupture) will help to ensure that the rate of early onset GBS sepsis is as low as pragmatically possible.—DJR)

Maternal Allopurinol During Fetal Hypoxia Lowers Cord Blood Levels of the Brain Injury Marker S-100B

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ABSTRACT

It has been suggested that early postnatal administration of allopurinol, a xanthine oxidase inhibitor, might reduce perinatal brain damage because of intrapartum asphyxia. This double-blind randomized pilot study investigated whether maternal treatment with allopurinol in a population of pregnant women in late labor with signs of fetal hypoxia would reduce fetal cord serum concentrations of non–protein-bound iron, or other free radicals and S-100, a protein marker of central nervous system damage. The subjects of the study were 53 women in labor (54 fetuses) at >36 weeks' gestation, and who had signs of fetal distress (indicated by abnormal or nonreassuring fetal heart rate tracing or fetal scalp pH of <7.20). Each woman was given either a single intravenous dose of allopurinol 500 mg or a saline placebo. The plasma concentration of allopurinol and its active metabolite oxypurinol were determined from maternal blood and fetal cord samples obtained at the time of birth.

Median maternal allopurinol/oxypurinol concentrations were in the therapeutic range for xanthine inhibition (>2 mg/L for allopurinol and/or >4 mg/L for oxypurinol), and significantly higher compared with fetal arterial cord concentrations. Therapeutic concentrations were also found in the cord blood of 15 allopurinol-treated newborns. However, 12 had sub-therapeutic levels. For this reason, 3 treatment groups were created: therapeutic allopurinol (n = 15), sub-therapeutic allopurinol (n = 12), and placebo (n = 27). The therapeutic allopurinol group had significantly lower plasma S-100B concentrations compared with the subtherapeutic allopurinol and placebo groups ($P < 0.01$ for both). Moreover, the concentration of non–protein-bound iron was significantly less in therapeutic allopurinol cord blood cord samples than that in the subtherapeutic allopurinol and placebo groups ($P < 0.05$ for both).

The investigators believe that this is the first study to demonstrate that maternal allopurinol/oxypurinol can cross the placenta during fetal hypoxia, and that therapeutic concentrations can reduce serum levels of markers associated with brain asphyxia. These findings should be confirmed in a larger study using higher doses.

EDITORIAL COMMENT

(In the September 2009 Survey, I commented on the study of Bhat et al in which asphyxiated infants with moderate or severe encephalopathy were randomized to 3 daily infusions of magnesium sulfate or to placebo. In that small trial, short-term outcomes were better in the magnesium sulfate group. I opined that perhaps it was time for a trial of magnesium sulfate + whole body cooling versus whole body cooling alone for neonatal hypoxic ischemic encephalopathy (Pediatrics 2009;123:e764; SURVEY 2009;64:573).

Try as we might, and perform cesarean delivery on as many women as we will, there will always be some infants who suffer from hypoxic ischemic encephalopathy. Neonatal whole body cooling is a tremendous innovation, but even with it, asphyxiated infants with moderate or severe encephalopathy still face a 24% risk of death, and if they survive, a 19% risk of cerebral palsy (Shankaran, et al. NEJM 2005;353:1574). Thus there is a pressing need for co-interventions to improve the outcomes of asphyxiated, encephalopathic infants.

In 3 small trials that enrolled a total of 114 subjects, allopurinol has been given to newborn infants with suspected hypoxic-ischemic encephalopathy. The data from these 3 trials have been aggregated into a meta-analysis in which allopurinol had no statistically significant effect on the risk of death (relative risk: 0.92, 95% confidence interval: 0.59–1.45) or neonatal seizures (relative risk: 0.93, 95% confidence interval: 0.75–1.16). In one trial, neurodevelopment was assessed among survivors and was not affected by allopurinol. However, even when aggregated, the studies were statistically underpowered to detect meaningful differences between the allopurinol and placebo groups (Chaudari T, McGuire W. Cochrane Database of Sys Rev 2008;CD006817).

The rationale for evaluating allopurinol's potential to improve the outcome of perinatal hypoxic ischemic encephalopathy is that it is an anti-oxidant that may reduce or prevent free radical damage resultant from reperfusion/reoxygenation injury. Free radical generation is maximal in the first 30 minutes after injury (McCord JM. NEJM 1985;312:159), and thus the potential for therapy initiated in the neonatal period to mitigate hypoxic ischemic brain damage may be limited, especially if not given immediately upon birth.

Torrance et al in the abstracted pilot study, attempted to answer the question of whether earlier initiation of allopurinol therapy, ie in the intrapartum period via maternal administration to mothers whose fetuses were exhibiting signs of intrapartum fetal compromise, would be effective in achieving transfer of allopurinol to the fetus before birth, and in lowering the neonatal concentration of a marker of central nervous system damage, protein S-100B. As to the former, allopurinol did cross the placenta, and in approximately half of the perinates who received it, achieved serum concentrations that the authors considered therapeutic on the basis of previous work (in which the necessary concentration of allopurinol and its metabolite oxipurinol to inhibit xanthine oxidase was determined). As to the latter, S-100B concentrations were lower in the sub-group of allopurinol-exposed perinates who achieved therapeutic concentrations. This finding, however, is based on an inappropriate analysis—only the entire allopurinol group, not a sub-group defined post hoc, should have been compared with the placebo group.

Torrance et al are to be congratulated for taking on the challenge of attempting to identify fetal compromise, and initiate therapy before delivery. However, this approach is be-deviled by our inability to reliably identify fetuses who are in fact compromised. And if we do identify them, and delivery is truly urgent, in many cases there will not be time for the necessary informed consent and study drug administration. For now, intrapartum therapy to ameliorate the consequences of neonatal hypoxic ischemic encephalopathy is a bridge very far.—DJR)

Intramuscular Adrenaline Does Not Reduce the Incidence of Respiratory Distress and Hypoglycaemia in Neonates Delivered by Elective Caesarean Section at Term

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ABSTRACT

Although delivery of infants by elective cesarean section (CS) before active labor reduces the risk of perinatal asphyxia and birth injury, it is associated with the occurrence of respiratory distress and hypoglycemia in the newborn infant.

Previous studies suggest that neonatal respiratory distress and hypoglycemia after elective CS may be secondary to low catecholamine levels. This randomized, double-blind study investigated whether intramuscular adrenaline might reduce or eliminate morbidity from neonatal respiratory distress and hypoglycemia in term infants delivered by elective CS before active labor. The study took place between 2006 and 2007 at a university hospital in Denmark. The newborns of a total of 270 healthy women with a normal pregnancy at a gestational age of >37 completed weeks were randomized to receive an intramuscular injection of either adrenaline 30 mcg (n = 134) or saline (n = 135) immediately after birth. To determine potential changes in heart rate, hemoglobin oxygen saturation, and other potentially serious adverse events secondary to adrenaline therapy, the first 50 infants were monitored with pulse oximetry. Referral to the neonatal intensive care unit because of respiratory distress or hypoglycemia was the primary study end point.

Comparison of the incidence of respiratory distress and hypoglycemia in the 2 groups showed no decrease among infants treated with adrenaline. In fact, these morbidities were higher in the adrenaline group than in the control group (14% vs. 7%, $P = 0.048$). Monitoring with pulse oximetry during the first 10 minutes of life showed that the heart rate and hemoglobin oxygen saturation was significantly higher in adrenaline-treated infants compared to the controls ($P < 0.001$).

These findings show that adrenaline given intramuscularly to newborn infants does not reduce the risk of respiratory distress or hypoglycemia following elective CS.

EDITORIAL COMMENT

(Again this year, Tita et al have reminded us that if we are to perform purely elective cesarean delivery and are interested in minimizing neonatal morbidity, we should wait until 39 completed weeks of gestation. And almost 39 weeks is not the same as 39 weeks, as even those cesareans performed in the last half of the 38th completed week were associated with significantly more neonatal morbidity than those performed at or beyond 39 weeks (NEJM 2009; 360:111; Survey 2009;64:293).

Certainly, we obstetricians are aware that elective cesarean delivery before the onset of labor, especially if performed before 39 weeks' gestation, increases the risk of neonatal respiratory morbidity. Previously, I reviewed the trial of Stutchfield et al in which women undergoing elective cesarean delivery at or beyond 37 weeks' gestation were randomized to a predelivery course of betamethasone or to usual treatment (no betamethasone). Ironically, while that trial failed to establish that betamethasone was beneficial, it reinforced the wisdom of delaying the cesarean until 39 completed weeks, as there was a progressive decline in respiratory morbidity from the 37th to the 38th to the 39th week in

the control group: 11.4% to 6.2% to 1.5% (BMJ 2005;331:662; Survey 2006;61:157).

In the abstracted study of Pedersen et al, the potential of another intervention to blunt the risk of respiratory morbidity after elective cesarean delivery was evaluated: intramuscular epinephrine administered to the neonate immediately after birth. As described by the authors, the rationale for testing this intervention was that "adaptation to extra-uterine life is a complex process, and failure has been partially related to lack of fetal stress with low levels of circulating catecholamines." They note that "during successful transition from fetal to newborn life an appropriate catecholamine surge: (1) facilitates ventilation by enhancing water absorption from alveoli and by promoting surfactant secretion; (2) enhances pulmonary circulation by raising the systemic blood pressure; and (3) maintains blood glucose homeostasis by stimulating hepatic glycogenolysis."

The rationale for epinephrine, then, seems to be a good one. However, the epinephrine group fared worse, with a 14% rate of respiratory distress or hypoglycemia compared to a 7% rate in the control group. Moreover, an infant in the epinephrine group suffered a neonatal stroke which may or may not have been related to the epinephrine injection. This trial thus leaves little reason to suppose that neonatal epinephrine will ever be a routine, postelective cesarean delivery intervention, even though the observed differences might have occurred by chance, leaving open the possibility (albeit a slim one) that a higher dose of epinephrine might be effective.

So far, we have no proven, effective therapies for lowering the risk of neonatal respiratory morbidity after mid to late third trimester, prelabor cesarean delivery. Maternal corticosteroids such as betamethasone, the nondefinitive trial of Stutchfield et al notwithstanding, remain the most promising intervention, both for their ability to increase surfactant reduction, and for their potential to enhance alveolar water clearance (Jain L, et al. Am J Physiol Lung Cell Mol Physiol 2001;280:L646). They need to be tested in a well-done clinical trial, ideally from 34 to 38 weeks' gestation a range in which a large number of prelabor cesareans are currently being done, respiratory morbidity is appreciable, and predelivery corticosteroids currently not standard.—DJR)

Iron Deficiency Anemia, Cigarette Smoking, and Risk of Abruptio Placentae

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ABSTRACT

Some investigators have suggested that there is an association between maternal iron deficiency anemia and the occurrence of placental abruption. Previous studies investigating this association have had conflicting results or were compromised by failure to control for confounding variables. This retrospective case-control study investigated the possible association between maternal iron deficiency and placental abruption in a population of pregnant women from

a health care network in the Pacific Northwest. Between 1994 and 1998, medical records were used to identify 145 patients with a clinical diagnosis of abruption based on routine clinical examination. A randomly selected sample of 1710 women without a medical diagnosis of abruption served as the control group. Review of medical records provided data on maternal sociodemographic characteristics, reproductive and medical history, and history of smoking during pregnancy. Early pregnancy iron deficiency anemia was defined as first and/or second trimester hemoglobin <10 g/dL or hematocrit <30%. Adjustment was made by use of logical regression models for potential confounders including maternal age, gravidity, cigarette smoking during pregnancy, Medicaid payment status, and pregestational hypertension.

Iron deficiency anemia in early pregnancy occurred in 11.0% of abruptio placentae cases and 3.3% of controls. There was more than a 3-fold increased risk of placental abruption among women with a history of iron deficiency anemia in early pregnancy compared to those who did not have iron deficiency anemia (unadjusted odds ratio, 3.60; 95% CI, 2.01–6.04). Although the risk was reduced following adjustment for confounders, the difference remained statistically significant (adjusted odds ratio, 2.40; 95% CI, 1.22–4.73). The risk of placental abruption was also increased by maternal smoking during pregnancy but the abruption iron deficiency anemia association was not modified by maternal smoking status.

The investigators conclude from these findings that iron deficiency anemia in early pregnancy is a risk factor for placental abruption.

EDITORIAL COMMENT

(This retrospective case control study identified a significant relationship between iron deficiency anemia and placental abruption; 11% of women who suffered an abruption had iron deficiency compared to only 3% of controls, and iron deficiency in early pregnancy increased the risk of abruption more than 3-fold. Although smoking during pregnancy was independently associated with abruption, it did not interact with or modify the effects of iron deficiency. What is it about iron deficiency that would predispose to this adverse advent?

Interestingly, there is data indicating that iron deficiency strongly influences early placental development. Iron deficiency anemia results in reduced oxygen carrying capacity and increased oxidative stress, which prompts adaptive changes in placental morphology. Studies of placental morphology in anemic versus non anemic pregnancies have shown that the more severe the anemia as reflected by serum ferritin levels, the larger the placenta and the more abundant the placental vasculature (Hindmarch, et al. Lancet 2000;356: 719). Stereologic studies of placental morphology indicate that iron deficiency anemia results in placental hypertrophy with increased total capillary volume and surface area (Huang, et al. Eur J Obstet Gynecol 2001;97:59). These changes lead to increased gas exchange, which compensates for the reduced oxygen carrying capacity of iron deficiency, but the increased capillarisation likely also creates a more vulnerable uteroplacental interface.

There is another mechanism by which iron deficiency could predispose to abruption; both iron deficiency and abruption are associated with inflammation. Histologic chorioamnionitis, chorionic vasculitis, and other chronic inflammatory lesions of the placenta are significantly associated with abruption in both term and preterm pregnancies (Ananth, et al. Eur J Obstet Gynecol 2006;128:15; Nath, et al. Am J Obset Gynecol 2007;197:319.e1). There is evidence that iron deficiency adversely affects immune function, increases susceptibility to infection, and makes erthrocytes more vulnerable to oxidative stress (Allen LH. J Nutrition 2001;131:581s).

World Health Organization (WHO) data indicate that approximately 66% to 80% of the world's population are iron deficient (The WHO Health Report 2002. Reducing Risks, Promoting Healthy Life. Geneva, WHO, 2002). Two billion people are actually anemic, including 10% to 15% of the population of industrialized nations; anemia contributes to 20% of all maternal deaths worldwide. Hemorrhage is the leading cause of maternal mortality worldwide, accounting for 25% of all deaths (WHO "Make Every Mother and Child Count," 2005). Given how common both iron deficiency and hemorrhage are, it is not surprising that there is a causative link between the two. But if vulnerability to abruption is determined by early placental development, as the above data suggest, starting iron supplementation after pregnancy is rec-

ognized may be too late. Finding ways to increase the iron intake of reproductive age women and girls should be a priority for obstetricians, and should be addressed at the time of the annual exam and whenever preconception counseling is sought.—KDW).

Effects of Female Genital Mutilation on Birth Outcomes in Switzerland

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ABSTRACT

Worldwide estimates of the prevalence of female genital mutilation (FGM) indicate that well over 100 million women in more than 26 countries have undergone this procedure. Illegal in most western countries, FGM is primarily practiced in sub-Saharan Africa. Many women with FGM have migrated to Western countries where they constitute a significant proportion of the population. These women have special medical and psychological problems during pregnancy, and do not readily volunteer that they have undergone the procedure. Most physicians and other health professionals in Western countries have little knowledge of FGM and its management. There has been concern over reports of increased maternal and fetal mortality during childbirth among women with FGM. Little data is available on maternal expectations and wishes concerning antenatal, intrapartum, and postpartum care.

This retrospective case control study evaluated the desires and wishes of women with FGM regarding their external genitalia following delivery, and as a secondary aim investigated fetal and maternal outcomes among women with FGM compared to nonmutilated women. The study was conducted between 1999 and 2008 in a teaching hospital setting in Switzerland. The case subjects were 122 pregnant women volunteers with FGM. Controls were 110 women without FGM who were matched for maternal age and delivered at the same time. Most patients were from Africa. Defibulation, a corrective surgical procedure for infibulation, was performed in some patients before or during labor. The primary study outcome measures were patients' wishes concerning their FGM management before and during labor, their satisfaction with the postpartum outcome, and intrapartum and postpartum maternal outcome data including duration of labor and blood loss as well as fetal outcomes.

When given choices for managing their FGM during pregnancy, 6.5% (8/122) wanted to have antenatal defibulation, 43% (52/122) requested defibulation during labor, 34.4% (42/122) requested defibulation during labor only if deemed necessary by the medical staff, and 16.5% (20/122) patients were unable to articulate their expectations. No statistical differences between FGM patients and controls were found for maternal blood loss or duration of labor and fetal outcomes. Women after FGM did not have a longer duration of labor than the controls. Compared to controls, women with FGM had significantly more emergency Cesarean sections and third-degree vaginal tears, and significantly fewer first-degree and second-degree tears. Overall, 76% of patients were very satisfied (53%) or satisfied (23%) with the management of their FGM.

These findings suggest that appropriate management of women with FGM in pregnancy and its prevention requires an interdisciplinary team approach with special training in FGM issues.

EDITORIAL COMMENT

(Female genital mutilation (FGM), also improperly called "female circumcision," has been performed on over 130 million women and girls worldwide (Guidelines of Women's Health Care, 3rd edition, ACOG 2007, p243), but is especially prevalent in sub-Saharan Africa, the Middle East, and Southeast Asia. It is believed that FGM is performed for a combination of reasons,

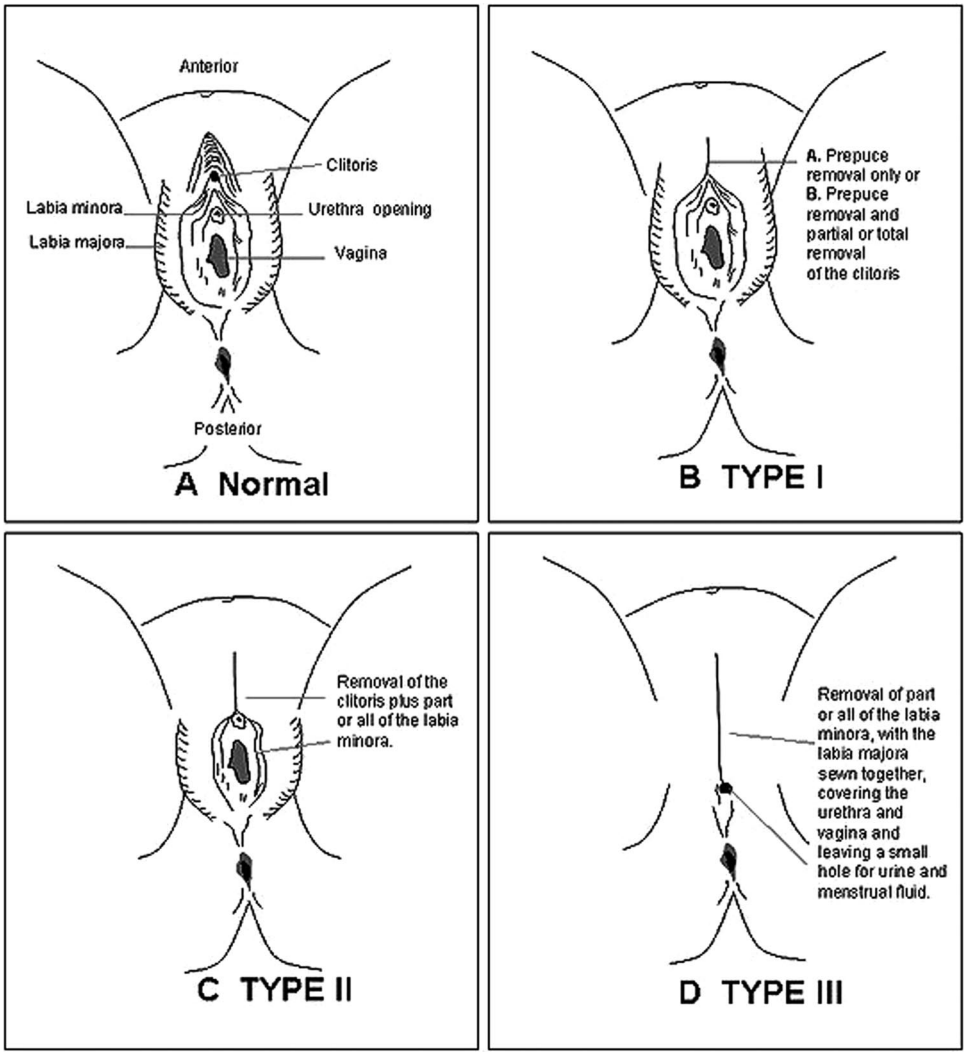

Fig. Types of female genital mutilation, reprinted from Wikipedia (http://en.wikipedia.org/wiki/Female_genital_cutting).

including attenuation of female sexual desire and insurance of chastity before marriage, social or cultural identification, or the belief that it enhances fertility. Although many western physicians may never see a case, those who practice in metropolitan areas that attract African and Asian immigrants may be called upon to provide obstetric or gynecologic care to such women. It is therefore important to understand the various types of FGM, the anatomic changes involved, and possible therapeutic options. As shown in the figure, the World Health Organization recognizes 4 types of FGM: removal of the clitoral hood or prepuce only, or removal of the prepuce and partial or complete removal of the clitoris (Type 1a and 1b); removal of the clitoris and part or all of the labia minora (Type 2); removing the clitoris and labia minora, and sewing the labia majora together over the urethra and most of the introitis, leaving only a small opening for the passage of urine and menses (Type 3, also called infibulation). The WHO also recognizes a fourth category of mutilation, which includes all other destructive genital procedures such as pricking, piercing, cauterizing, scraping, or incising the clitoris and labia, and/or traumatizing the vagina with corrosive substances or or tearing it to induce scarring that will result in vaginal narrowing (Type 4).

Such procedures are usually performed using unsterile instruments or even pieces of broken glass, and the resulting infections and scarring

can result in anatomic changes so severe the women often have difficulty urinating, severe pain with intercourse, menstrual irregularities, abscesses, or even fistulae or incontinence. When such women become pregnant and present for delivery, the scar tissue increases the likelihood of perineal tearing or may even preclude vaginal delivery.

Obstetrician–gynecologists caring for women with FGM are in the unique position of possibly being able to improve the appearance and function of the scarred perineal structures—if the woman so desires. The most disturbing data revealed in Wuest's study is that at least a third of infibulated women request defibulation only if necessary to allow vaginal delivery, although this may reflect their desire to minimize further trauma to that area rather than acceptance or approval of their altered anatomy. For women who do desire treatment of infibulation, there is evidence that carbon dioxide laser treatment may restore the vulvar opening and remove epithelial inclusion cysts, which are common after FGM and can become quite enlarged and painful. Penna and co-workers (Am J Obstet Gynecol 2002;187:1550) described a series of 25 cases of infibulation, 5 with epidermal inclusion cysts, in which the vulvar opening was successfully restored with laser and the cyst capsules were vaporized; the 7 women who were pregnant at the time were subsequently able to deliver vaginally without perineal trauma.

Women who have undergone FGM no doubt also require psychosocial support and counseling, although these may be difficult to provide given the many cultural barriers and the repressive home environments of many affected women. The first steps toward providing needed care include recognizing the anatomic changes of FGM, being sensitive to the cultural issues involved, being prepared to perform an atraumatic physical exam, and providing corrective surgery or referring the patient who desires it to an appropriate clinician.—KDW)

Effectiveness of a Multifaceted Strategy to Improve the Appropriateness of Cesarean Sections

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ABSTRACT

Studies evaluating methods to reduce cesarean sections have shown that multifaceted strategies and those adopted in a single hospital are more effective than centralized strategies and strategies applied in groups of hospitals. This report discusses the effectiveness of a strategy designed to improve the appropriateness of cesarean sections in 2 Spanish hospitals. The strategy employed included a protocol with indications for emergency and prescheduled cesarean sections, evaluating the appropriateness of the protocol, disseminating this evaluation through continuing education, and introducing measures for improvement. The evaluation was performed in 2 stages: The first stage (preintervention period) evaluated the appropriateness of the cesarean sections performed

over the 6-month period preceding the adoption of the strategy. In the second stage (postintervention period), the appropriateness of the cesarean sections performed during the first 6-months of the intervention was evaluated.

After intervention, there was an increase in overall appropriateness rates for emergency cesarean sections from 68.3 to 84.3% in the first hospital, and from 80.0% to 92.0% in the second hospital. There was a reduction (although statistically insignificant) in the overall cesarean section rates from 17.5% to 15.8% and from 29.0 to 22.0%, respectively.

The investigators conclude from these findings that implementation of such a multifaceted strategy may be useful to improve the appropriateness of cesarean sections and possibly lowering their rate.

EDITORIAL COMMENT

(Cesarean delivery rates have been increasing steadily since 1970, when the rate in the United States was—it's hard to believe—only 5.5% (MMWR 1995;44:303). As summarized by Ecker and Frigoletto (NEJM 2007;356:885), the increase has been promulgated by many factors. The advent of widespread fetal heart rate monitoring in the 1970s resulted in an increase in cesarean delivery performed to protect the fetus; it is disheartening to note that, despite this intervention, the rates of cerebral palsy, low birth weight, and perinatal mortality have not decreased significantly since then (Notzon F. JAMA 1990;263:3286). Women have gotten heavier in the last 40 years, resulting in a larger proportion of parturients who are obese or morbidly obese, and they have also gotten older, with many women postponing childbearing into their late 30's and early 40's; both these factors increase the likelihood of cesarean delivery for cephalopelvic disproportion and dysfunctional labor. The postponement of pregnancy has also lead to a higher reliance on reproductive technology to conceive, and thus a higher rate of multiple gestations that are delivered by cesarean due to malpresentation and/or prematurity. The general increase in primary cesareans since the 1970s has lead, inevitably, to a further bump in the cesarean rate due to repeat cesareans, which has been aggravated by the recent waning of enthusiasm for vaginal birth after cesarean. A relatively new factor is the advent of "cesarean on maternal request." Finally, liability concerns push the cesarean rate even higher, as more obstetricians fear being sued for "failure to perform a timely cesarean delivery."

Many hospitals and national organizations have weighed in on the runaway cesarean rates. The World Health Organization (WHO) has stated that the cesarean rate should be no higher than 15%. Some investigators and physician groups have created practice guidelines that reduce the number of cesareans, such as protocols for the active management of labor (Frigoletto FD, Lieberman E, Lang JM, et al. NEJM 1995;333:745) or programs that combine labor management protocols with physician feedback and peer review (Socol ML, Garcia PM, Peaceman A. Am J Obstet Gynecol 1993;168:1748). It has been suggested that managed care organizations could help to reduce the number of cesareans by employing physician—based options such as peer review, personal performance feedback, creation of practice guidelines, and the elimination of incentives for cesarean and creation of incentives for vaginal birth after cesarean (Mawson AR. Am J Manag Care 2002;8:730).

This article by Calvo et al describes a multifaceted strategy for improving the "appropriateness" of cesarean deliveries. The investigators intentionally designed their intervention with this goal in mind, rather than simply trying to reduce the cesarean rate, because they believed that if they succeeded in changing practice through compliance with specific consensus indications for cesarean delivery, it might ultimately result in a more lasting reduction in the number of cesareans performed. They created a list of approved indications for scheduled cesareans and for emergency procedures, scheduled a weekly discussion of all cesareans performed that week, and did another review every 2 months to specifically verify that all indications for cesarean had been appropriate over the previous 2-month period. They then disseminated the results of those evaluations to all clinicians and introduced measures for improvement. After the first 12 months, they noted an increase in the appro-

priateness of cesareans performed and a concurrent reduction in the cesarean rate.

The most interesting part of the study was that the investigators evaluated the appropriateness of cesareans for each indication on their list, and found that the physicians in one or both hospitals were good about complying with some indications—such as failed induction or arrested labor—but not so good about complying with "fetopelvic disproportion" or "risk of fetal distress." They noted that some physicians appeared to interpret fetal heart rate tracings subjectively rather than use uniform criteria—for which they proposed no remedy. But for cesareans performed for fetopelvic disproportion, they suggested stratifying the cesarean rates by maternal BMI and/or maternal age. If the likely rate of cesarean delivery could be predicted by maternal characteristics, the success or failure of each potential vaginal delivery could be judged by a patient-specific "expected cesarean rate" rather than by a single cesarean rate goal for all patients.

The data for such a predictive model are available. For example, Cnattingius et al (Obstet Gynecol 1998;92:501) used a dataset including more than 92,000 deliveries in Sweden to determine maternal age—and maternal weight—related cesarean rates. They found that, compared with teenagers, women age 30 to 34 were 2.6 times and those age ≥35 were 4.4 times more likely to be delivered by cesarean. Similarly, compared with lean women, those with a BMI 25 to 29.9 were 1.8 times and those with a BMI ≥30 were 2.4 times more likely to require cesarean delivery. Ecker et al (Am J Obstet Gynecol 2001;185:883) evaluated all deliveries in one year at Brigham and Women's Hospital in Boston, and found that the cesarean rate rose from 11.6% in women younger that 25 years to 43% for women age 40 or more. Chen and co-workers (Am J Obstet Gynecol 2004;191:617) actually developed an easy to use formula—which they turned into a Web-based calculator—for predicting the likelihood of cesarean delivery considering 6 factors: maternal age, maternal height, initial pregnancy BMI, pregnancy weight gain, gestational age at delivery, and expected birth weight.

Many obstetricians are conflicted about the burgeoning cesarean rate; on the one hand, they want to keep the cesarean rate as low as possible, but on the other, do not want to be driven out of practice by liability issues. The multifaceted strategy described in this article sounds like a reasonable approach to the problem.—KDW)

Placental Vascular Pathology Findings and Pathways to Preterm Delivery

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ABSTRACT

There is limited data on the role of specific maternal placental vascular findings in influencing preterm delivery. This prospective population-based cohort study examined possible associations between placental vascular pathology and preterm delivery in a subcohort of pregnant women enrolled in the Pregnancy Outcomes and

Community Health Study. The study was conducted between 1998 and 2004 in 5 Michigan communities. A total of 1053 placentas (239 preterm, 814 term) from pregnancies ending in both spontaneous and medically indicated preterm delivery <37 weeks' gestation and from women who delivered at term were analyzed. Histologic evaluation identified 29 placental vascular variables which were grouped into 5 pathology-based groups. Of the 5 groups, 3 were maternal lesions: vascular–obstructive lesions (MV-O); vascular–disturbance of integrity (MV-I); and vascular–developmental (characterized by abnormal or incomplete remodeling of maternal spiral arteries (MV-D). The remaining 2 groups were fetal lesions: vascular–obstructive (FV-O) and vascular–disturbance of integrity (FV-I). Within each group, pathology-based vascular continuous construct scores were obtained by adding the number of positive findings and calculating a dichotomous variable to approximate the top quintile, scored as "0" (high), and the bottom 4 quintiles, scored as "1" (not high). Polytomous logistic regression models were used to adjust for potential confounders.

High scores for each of the five groups were associated with medically indicated preterm delivery at <35 weeks, with unadjusted odds ratios ranging from 2.9 to 6.5. After adjustment for confounders, the association remained statistically significant. There was a significant association between the risk of spontaneous preterm delivery at 35 to 36 weeks and a high score for any one of 3 groups: MV-I, MV-D, and FV-I, with adjusted odds ratios ranging from 2.2 to 4.6. A significant association was found between the risk of spontaneous preterm delivery at <35 weeks and the presence of 2 or more high scores for 3 groups: MV-I, MV-D, and FV-I, with adjusted odds ratios ranging from 4.1 to 7.4. Neither MV-O nor FV-O was related to spontaneous preterm delivery.

These findings show that a model based on a grouping of pathology-based vascular placental lesions offers insights into pathways for medically indicated and spontaneous preterm delivery and support the evaluation in future studies of individual placenta vascular findings within each construct.

EDITORIAL COMMENT

(The American College of Obstetricians and Gynecology's (ACOG's) committee opinion on placental pathology, originally written in 1993 and reaffirmed in 2006 (ACOG Committee Opinion # 102, 1993), states that a skilled and systematic evaluation of the umbilical cord, membranes, and placenta may yield insight into antepartum pathophysiology and thus contribute to clinical-pathologic correlation under certain circumstances, such as when chorioamnionitis or oligohydramnios have been diagnosed clinically and are then confirmed by placental pathology. However, because the significance of other placental findings such as hemorrhagic endovasculitis and chronic villitis are not well delineated, and pathologists with the training and experience necessary to perform an accurate placental exam are not universally available, this document did not recommend submission of every placenta for pathologic examination. In fact, it has been estimated that 40% of placental diagnoses made by surgical pathologists who are not placental specialists are incorrect, of which 90% are errors of omission—failure to recognize a pathological lesion—and 10% result from the incorrect diagnosis of identified lesions (Sun CC. Arch Pathol Lab Med 2002;126:706). If true, the lack of widely available expertise in placental pathology is unfortunate, because this article by Kelly et al argues convincingly that placental pathology may reveal important information about the development of and damage to the placenta, and thus provide insight into the antenatal etiologies of several adverse obstetric outcomes.

Kelly et al devised a sophisticated scheme for classifying placental lesions, based on whether the lesions resulted from vascular obstruction (infarcts and atherosis), disturbance of vascular integrity (hemorrhage), or abnormal development (incomplete remodeling of the spiral arteries), and whether the abnormality was primarily of maternal or fetal origin. When this classification system was applied to 1371 women who had elevated MSAFP levels and delivered either before 37 weeks or at term, or had normal MSAFP levels and delivered at term, they found that 3 specific lesions were significantly associated with spontaneous preterm birth before 35 weeks: disturbance of vascular integrity of maternal origin, developmental abnormalities of maternal origin, and obstructive vascular lesions of fetal origin. Further, there were significant interactions between these 3 types of lesions, such that, after adjusting for maternal charac-

teristics such as age, race, BMI, parity, and insurance status, the presence of 2 of the 3 resulted in odds ratios for delivery before 35 weeks ranging from 4.1 (95% CI: 1.2 – 14) to 7.4 (95% CI: 1.3 –42). The presence of any of the 5 categories of lesions was also significantly associated with indicated preterm delivery before 35 weeks (OR: 2.9 [1.3–6.4] to 6.5 [2.8–15]), most likely for complications such as preeclampsia, growth restriction, abruption, and fetal distress. These results thus provide confirmation that several adverse pregnancy outcomes are set in motion weeks to months before delivery by specific pathological changes in the placenta.

Although these kinds of pathologic placental findings may help to deflect blame for obstetric complications away from intrapartum management, which can be important in certain cases, placental pathology identified after the fact does not assist antenatal management. However, there is data indicating that certain placental lesions are heralded antenatally by abnormal ultrasound findings. Infarction and other ischemic placental lesions are significantly associated with abnormal Doppler flow velocity waveforms in the umbilical artery, the fetal middle cerebral artery, and the ductus venosus; vascular lesions such as chorioangioma are easily detected sonographically; areas of intervillous thrombosis or subchorionic fibrin deposits are seen by ultrasound as "placental lakes" (echolucent areas with no blood flow within them) or appear as echolucent cavities within the placental mass; and areas of previous infarction or fibrin plaques are often calcified and echodense (Sebire NJ, Sepulveda W. J Clin Pathol 2008;61:1276). In fact, prenatal ultrasound has undergone sufficient advancement that antenatal identification of any of these defects is often the main reason for submitting the placenta for pathologic evaluation.

Although routine submission of every placenta for pathologic evaluation may not be justified, placental pathology is likely to be helpful in cases in which there has been as antepartum complication or a poor obstetric outcome, or there were abnormal ultrasound findings of the type listed above. Because a neonatal problem may not be obvious immediately after delivery, some experts recommend saving the placenta for 1 week before deciding to either submit it for evaluation or discard it. If more obstetricians request placental examinations, perhaps more pathologists will obtain the training necessary to perform such exams accurately.—KDW)

Lack of Association Between Folate-Receptor Autoantibodies and Neural-Tube Defects

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ABSTRACT

In a previous pilot study, autoantibodies against folate receptors were found in 75% of serum samples collected from pregnancies affected by a fetal neural-tube defect, compared to only 10% of samples collected from controls. Although these findings have been difficult to confirm, primarily due to the lack of suitable assays for folate-receptor autoantibodies, improved assays are now available. This case-control study investigated whether the presence of folate-receptor autoantibodies increased the maternal risk of having a pregnancy complicated by a neural-tube defect. The study subjects included pregnant women in an Irish population with a high prevalence of neural tube defects. This report is comprised of 2 studies. In study 1, the presence of autoantibodies against folate-receptors was determined through analysis of stored blood specimens obtained between 1993 and 1994 from 103 case mothers with a pregnancy complicated by a fetal neural-tube defect, 103 matched-control mothers without normal pregnancies, 58 women with no history of pregnancy, and 36 men. Study 2 used fresh blood samples to rule out the possibility that any differences found between cases and controls in study 1 could be due to protein degradation occurring during storage of the frozen specimens. Blood samples in study 2 were collected from 37 case mothers, 22 control mothers, 10 women who had never been pregnant, and 9 men. Assays for both blocking and binding autoantibodies against folate receptors were carried out.

In study 1, there was no significant difference between the cases and controls in the frequency of blocking or binding autoantibodies against folate receptors. Blocking antibodies were present in 17% of case and 13% of control women (odds ratio [OR], 1.54; 95% confidence interval [CI], 0.70–3.39) and binding autoantibodies were found in 29% of case and 32% of control women (OR, 0.82; 95% CI, 0.44–1.50). In study 2, similar results were obtained with fresh samples, indicating that there was little or no degradation of the stored samples.

These findings do not confirm the results of the pilot study and show no association between the presence of folate-receptor autoantibodies and a history of pregnancy affected by neural-tube defects in an Irish population.

EDITORIAL COMMENT

(The study that prompted this investigation included only 12 study patients and 20 control patients, 9 and 2 of whom, respectively, had antifolate receptor antibodies. The original investigators did not use commercially available assays, but rather developed assays in their own lab; these were fairly complicated, involving folate receptors isolated from placental tissue and an enzyme linked immunosorbent assay developed using cow's milk, making it difficult for other scientists to confirm the findings. Malloy et al, a group which has contributed greatly to the literature on neural tube defects (NTDs) were able to duplicate the assay techniques described in the original report, and tested them on both frozen and fresh serum specimens. They found that the incidence of folate-receptor blocking antibodies was similar in stored serum from case and control mothers (17% vs. 13%), as was the incidence of folate receptor binding antibodies (29% vs. 32%).

Was the idea that antifolate receptor autoantibodies could be contributing to the development of NTDs far fetched? A wealth of clinical and metabolic data collected by investigators around the world supports the link between folic acid deficiency and NTDs, and folic acid supplementation and a reduction in NTD incidence (MRC Vitamin Study Research Group. Lancet 1991;338:131; Czeizel AE, Dudas I. N Engl J Med 1992;327:1832); thus folic acid deficiency of some type is clearly associated with abnormal development of the neural tube. Folate occurs naturally in green and leafy vegetables and other common foods and in the United States, cereal and grain has been supplemented with folate since 1998, yet NTDs continue to occur even in well-nourished populations. Antifolate receptor autoantibodies have been identified in other conditions related to folate deficiency. Raemakers et al (N Engl J Med 2005;352:1985) studied 28 children with cerebral folate deficiency—a neurologic syndrome caused by low cerebrospinal levels of 5 methyltetrahydrofolate, and marked by irritability, slow head growth, psychomotor retardation, cerebellar ataxia, pyramidal signs in the legs, and occasionally seizures—and identified antifolate receptor autoantibodies in 24 (86%) of the affected children but in none of 28 control subjects with other neurological diseases. They also determined that pharmacologic doses of folinic acid (5-formyltetrahydrofolate) overcame the receptor problem and induced reversal of symptoms in some children. Interestingly, noting that the production of these autoantibodies began to appear at 4 to 6 months of life, these investigators

opined that they were likely induced by soluble folate-binding proteins in human and bovine milk.

When the initial report of antifolate receptor antibodies was published, it aroused great interest. An accompanying editorial by Nicholas Wald (N Engl J Med 2004;350:101), a leading authority on NTDs and folate nutriture, opined that these data suggested a mechanism through which folate deficiency could cause NTDs, and thus supported universal folic acid supplementation. The data presented by Malloy et al does not change that recommendation. Even if antifolate receptor antibodies are not causitive in neural tube defect development, perhaps because they develop later in life after exposure to human or bovine milk as suggested above, folic acid supplementation has been shown in prospective randomized double blind trials—the gold standard for research studies—to reduce the incidence of NTDs. Folic acid supplementation involves little or no risk and induces no side effects, thus can be recommended to everyone.—KDW)